Nucleophilic substitution reactions of some polyhalogenated compounds

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entitled

NUCLEOPHILIC SUBSTITUTION REACTIONS OF SOME POLYHALOGENATED COMPOUNDS

submitted by

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(Van Mildert College)

A candidate for the degree of Doctor of Philosophy

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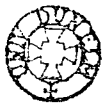

For Liam and Jamie

MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1978 and October 1981. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

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An Abstract from a Thesis entitled

Nucleophilic Substitution Reactions of Some Polyhalogenated Compounds.

By P.A. Martin. BSc.

Submitted for the Degree of Doctor of Philosophy

Durham University (1987)

Rate measurements for the reactions of a series of polyfluoro- and polychloro-pyridines with aniline and ammonia in 60/40 dioxan/water at 25°C has shown that chlorine, when ortho and para to the position of attack, is activating with respect to fluorine, but at the position meta to the point of attack, chlorine and fluorine are virtually equivalent in their effect on reaction rate. The trifluoromethyl and nitrile groups were found to be activating relative to fluorine when ortho and para to the position of substitution and the nitrile group was thus found to be ortho/para directing. The ortho/para orienting effect of ring nitrogen was shown to be dominant in heterocyclic systems.

It has been demonstrated for several different nucleophiles that nucleophilic attack in polyfluorinated heterocycles occurs so as to maxmise the number of ortho and meta fluorines with para fluorine being of little significance.

Of the nucleophiles examined aniline and ammonia were found to be similar in their behaviour. Benzylamine however showed some propensity for substitution at positions ortho to ring nitrogen whilst N-methylaniline showed strong steric effects due to the N-methyl group, most notably when the heterocylic ring substituents were chlorine, trifluoromethyl and nitrile.

Sodium was shown to have a 'salt effect' in the reactions of methoxide and phenoxide, and, a catalytic effect on the reactions of aniline affecting both the rate and position of substitution.

The use of transition state, and molecular orbitals to explain the patterns of substitution is discussed.

The trifluoromethylsilyl group was found to undergo nucleophilic attack at silicon and the series of mono, di and tri-fluoromethyl-pentafluorobenzenes were used to examine the concept of negative ion hyperconjugation.

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INTRODUCTION

CHAPTER 1

NUCLEOPHILIC AROMATIC SUBSTITUTION

CHAPTER 1

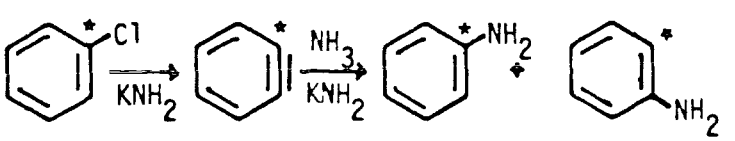
NUCLEOPHILIC AROMATIC SUBSTITUTION

Compared with nucleophilic aliphatic substitution, nucleophilic aromatic substitution is much less common. The electron clouds of aromatic rings protect them from the approach of all but the strongest of nucleophiles and, essentially, unless the aromatic ring contains an electron withdrawing group it may be considered immune to nucleophilic attack under normal conditions. Perhaps the most important feature of substitution in aromatic hydrocarbon systems is the nature of the leaving group which must be capable of accepting an electron pair and forming a stable anion. It is not surprising, therefore, that reactions involving elimination of hydride ion (e.g. the Tschitschibabin reaction) occur only in highly activated aromatic rings,[1] whilst halogen atoms are perhaps the most common of all leaving groups.

1.1 Mechanism of Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution occurs by three principal mechanisms.

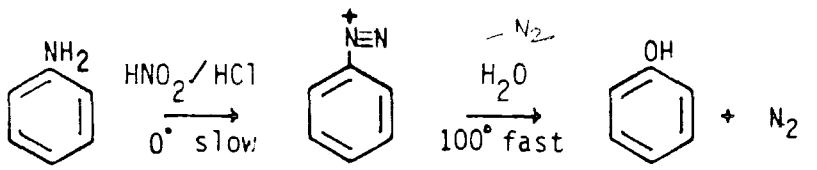
i) A two step elimination-addition (EA) reaction or 'benzyne/aryne' process, encountered for reactions of unactivated substrates and powerful nucleophiles - e.g. scheme (1.1). This is supported by ^{14}C labelling,[2,3] halobenzynes not possessing ortho hydrogen atoms being unreactive towards strongly basic nucleophiles.[4]



(1.1)

The discovery of benzyne or dehydrobenzene has led to the development of a new field of organic chemistry which reaches far beyond the scope of nucleophilic aromatic substitution. Arynes can be generated under non-basic conditions and the thus formed intermediates used in a wide variety of cyclo-additions, Diels-Alder additions and others.[5-8]

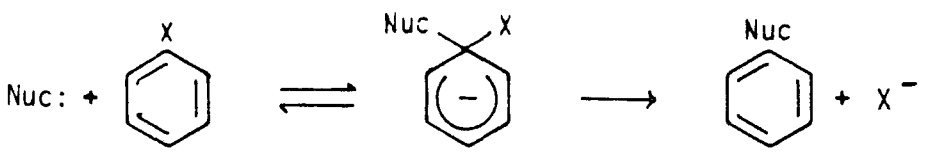
ii) A unimolecular or S_N1-mechanism for the thermal decomposition of diazonium ions in aqueous solution, usually represented as in scheme (1.2).



(1.2)

The driving force behind these reactions appears to be the stability of the elemental nitrogen displaced.[9]

iii) A bimolecular (S_NAr) process which appears to be the most common process for reactions in 'activated systems' e.g. scheme (1.3).



(1.3)

The first two mechanisms are rarely encountered in work with fully halogenated systems and will not be discussed further - the bimolecular mechanism will be given a fuller discussion later (see 1.1.1).

Of the several less important mechanisms of nucleophilic aromatic substitution two are worth mentioning here.

The copper catalysed mechanism outlined in scheme (1.4) is typical of the rapid displacement of iodine by ammonia in the presence of cuprous trifluoromethylsulphonate or the nucleophilic substitution of bromine by cuprous cyanide.[10]

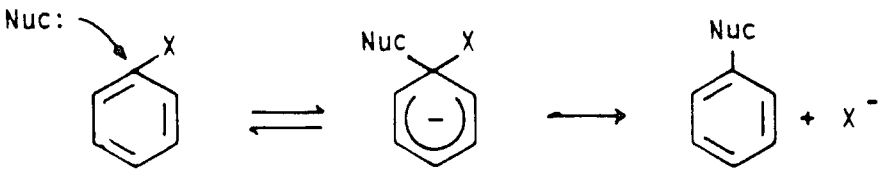
$$\begin{aligned} \text{Ar-X} + \text{Cu(I)} &\longrightarrow \text{Ar-Cu-X} \\ \text{Ar-Cu-X} + \text{Nu:} &\longrightarrow \text{Ar-Nu} + \text{Cu(I)} + \text{X} \end{aligned} \qquad (1.4)$$

The $S_{RN}1$ radical mechanism of scheme (1.4) is often found competing with the benzyne process, as for example with the reactions of the 5- and 6-iodopseudocumenes with potassium amide in liquid ammonia.[11]

$$\begin{aligned} \text{electron donor} + \text{ArI} &\longrightarrow \text{ArI}^{-\bullet} \\ \text{ArI}^{-\bullet} &\longrightarrow \text{Ar}^{\bullet} + \text{I}^{-} \\ \text{Ar}^{\bullet} + \text{NH}_2^{-} &\longrightarrow \text{ArNH}_2^{-\bullet} \\ \text{ArNH}_2^{-\bullet} + \text{ArI} &\longrightarrow \text{ArNH}_2 + \text{ArI}^{-\bullet} \\ &\text{termination steps} \end{aligned} \qquad (1.5)$$

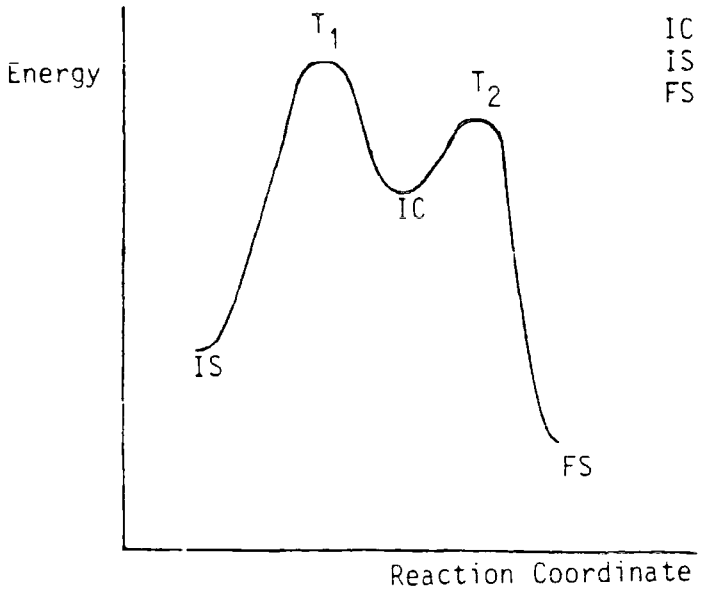
1.1.1 The Bimolecular Addition-Elimination Mechanism

Although a one-step process was originally proposed, the most widely encountered mechanism for nucleophilic aromatic substitution is a two-step addition-elimination mechanism (AE,S_NAr) in which the attacking nucleophile forms a fully bonded intermediate [1] with the aromatic system, the central carbon is sp^3 hybridised and the negative charge is delocalised into the ring as in the scheme (1.6).



[1] (1.6)

This mechanism will involve two transition states (T_1 and T_2), one on each side of the intermediate complex as represented by the energy profile of figure (1.7).



(1.7)

The structures of T_1 and T_2 are represented by [2] and [3] respectively (see overleaf). The relative energies of the two transition states will depend upon the reaction. If the activation energy of T_1 is greater than that of T_2 the formation of the intermediate will be rate determining. Alternatively if the activation energy of T_2 is greater than T_1 the rate limiting step will be the dissociation of the intermediate to give the product.

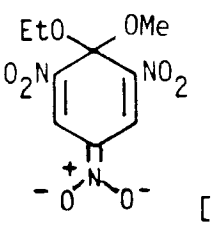
The addition-elimination mechanism is now generally accepted to account for the bulk of aromatic nucleophilic substitution reactions where strong activation and very mobile groups are involved; this mechanism is therefore particularly attractive in reactions involving polyhalogenated compounds where the halogens represent both good activating and good leaving groups.

[2] [3] (1.8)

1.1.2 Evidence for the General S_NAr Mechanism

1.1.2.1 Intermediate Formation

The best evidence for the S_NAr mechanism comes from the isolation of stable intermediates - the Meisenheimer complexes - from nucleophilic attack on highly activated substrates.[12] The original Meisenheimer complex [4] was a red salt isolated from the addition of potassium ethoxide to 2,4,6-trinitroanisole. This salt [4] was also obtained on adding potassium methoxide to 2,4,6-trinitrophenetole.[12]

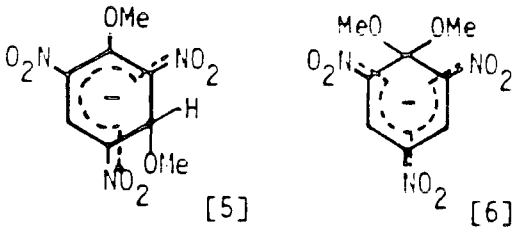


[4] (1.9)

1.1.2.2 1-σ versus 3-σ-complexes

In recent years, several hundreds of Meisenheimer complexes have been isolated and substitution at positions other than on the carbon bearing the leaving group has been observed. The first example of this was found with the reaction 2,4,6-trinitroanisole with methoxide in dimethyl sulphoxide;[13,14] many highly activated aromatic ethers undergo a rapid reversible nucleophilic addition of methoxide to a

non-substituted position to give [5] which is followed by the slower formation of the thermodynamically stable adduct [6].



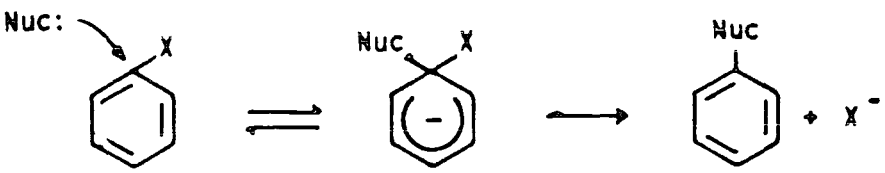
[5] [6] (1.10)

This process has also been shown to occur in nitro-activated benzene,[15,16] naphthalene[17,18] and pyridine[19] derivatives bearing a variety of substituents. Until recently direct evidence for 3-σ complexes could only be obtained in dimethyl sulphoxide or dimethyl sulphoxide/methanol mixtures due to their short lifetimes in pure methanol; evidence is now available for the 3-σ complex [5] in methanol via calorimetric studies[15,20] and more direct evidence (UV/visible spectra) for [5] and [6] is available from temperature jump stopped flow studies.[19]

1.1.2.3 Leaving Group Mobilities

If some mechanism other than S_NAr were to apply to nucleophilic aromatic substitution, then we might expect to find that the leaving group order was related to the carbon leaving group bond strengths. When halide ion is the leaving group the observed ease of substitution in Nucleophilic Aromatic Substitution is generally F>Cl>Br>I; one of the many examples of this order of reaction being found is in the reaction of ortho and para nitrophenylhalides with methoxide ion in methanol.[21-23] The difference in reactivity between fluoride and the corresponding chloride can be very great. The rate constant for the reaction of 2,4-dinitrofluorobenzene with ammonia in methanol at 50° is

some 1000 times greater than that of 2,4-dinitrochlorobenzene.[24] This order of mobility is the reverse of the order of the carbon-halogen bond strengths[25] and is incompatible with a one-step mechanism, in which bond breaking in the transition state should lead to the order of leaving group mobility being directly related to the carbon-halogen bond strengths, as is observed with S_N2 aliphatic nucleophilic substitution.[26] If no carbon-halogen bond breaking is occurring in the rate determining step the mechanism can only be explained by a two-step process (scheme 1.11) in which the rate determining step is intermediate formation.[27]



(1.11)

The rate of reaction, being determined by the rate of formation of the nucleophile-carbon bond, is dependent on the polarity of the carbon-halogen bond under attack; thus the more electonegative the halogen, the faster the rate of reaction, i.e. an observed reactivity order of F>>Cl>Br>I.[23,28]

1.1.2.4 Unusual Halide Ion Mobilities

For some reactions such as that between the 1-halo-2,4,-dinitro-benzenes and N-methylaniline in nitrobenzene,[29] the rate of halide ion displacements is reversed and the order becomes I>Br>Cl>F. Similarly the reactivity order I>F is found for the reaction of iodide ions with 1-halo-2,4,-dinitrobenzenes in acetone[30] and the

reaction of thiophenoxide and the 1-halo-2,4,dinitrobenzenes in methanol. It has been proposed[30,31] that these reactions operate by a one-step concerted mechanism in which carbon-halogen bond breaking is occurring in the rate-determining step. They are not inconsistent however with a two-step process i.e. the S_NAr addition-elimination mechanism, in which the rate determining step is now dissociation of the intermediate to give the product.[32,33] It has been suggested that in the case where the nucleophile is iodide ion the intermediate complex of reaction 1.11 would lose iodide ion faster than fluoride (difference in bond strengths) thus lessening the value of k_2 to such an extent that the second step in which the C-F bond is broken becomes rate determining.

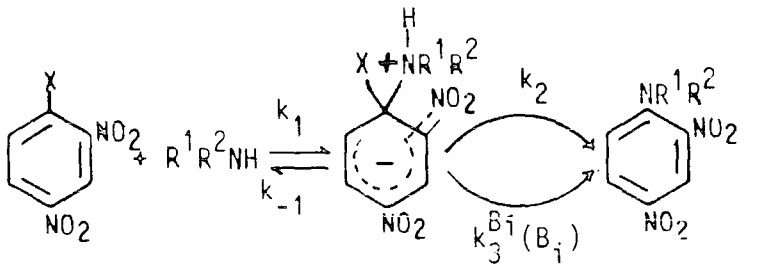
1.1.2.5 Other Group Mobilities

Studies on the reaction of 1-substituted 2,4-dinitrobenzenes with piperidine,[32] in which the substituents are Cl,Br,I,SOPh,SO_2Ph and $_pNO_2C_6H_4$-O- have shown that the rate constants for the reactions vary less than a factor of five. The carbon bearing group bond strengths differ greatly, hence the similarity in rate constants indicates that there is no appreciable bond cleavage in the rate determining step, which implies a two-step process as above.

1.1.3 Base Catalysis

1.1.3.1 The Role of Amines

Kinetic studies involving primary and secondary amines as the nucleophiles have played a key role in confirming the two- or multi-step nature of the mechanism of Nucleophilic Aromatic Substitution and have also helped in answering questions as to the relative rates of intermediate complex formation and decomposition. This is most easily seen by reference to the reaction scheme (1.12)



(1.12)

[7]

In contrast to the situation where the nucleophile is an anion (scheme 1.11) the intermediate [7] can proceed to products either spontaneously (k_2) or through general base catalysis (k_3^{Bi}) The bases B_i are typically lyate ions, tertiary amines or others which may be specifically added to the reaction mixture or are frequently the nucleophiles themselves. Hence by adding or omitting bases in the reaction mixtures we may sometimes exert considerable control over the relative rates of product formation versus reversion to reactants or the intermediate, and thus on the overall rate controlling steps.

1.1.3.2 Rate Laws and their Information Content

The overall rate expression for the reaction of Scheme 1.12 is:

$$\frac{\text{rate}}{[ArX]\,[R^1R^2NH]} = k_A = \frac{k_1k_2 + k_1\sum_i k_3^{Bi}[B_i]}{k_{-1} + k_2 + \sum_i k_3^{Bi}[B_i]} \qquad (1.13)$$

which is obtained by applying the Bodenstein[34] or 'Steady State'[35] approximation.

Since in the study of base catalysis the concentration of all bases except one is generally held constant, eqn (1.13) may be rewritten as eqn (1.14) where k_2' represents the true uncatalysed rate constant, k_2, plus the sum of all the $k_3^{Bi}[B_i]$ terms where i=j, i.e.

for which base concentration is held constant. We can now examine this equation for reactions under special conditions.

$$k_A = \frac{k_1 k_2' + k_1 k_3^{Bj}[B_j]}{k_{-1} + k_2' + k_3^{Bj}[B_j]} \qquad (1.14)$$

Low Concentration

If k_2' is smaller than k_{-1} then at low concentrations $k_3^{Bi}[B_i] \ll k_{-1}+k_2'$ and eqn (1.14) becomes eqn (1.15) which describes a straight line .

$$k_A = \frac{k_1 k_2'}{k_{-1} + k_2'} + \frac{k_1 k_3^{Bj}}{k_{-1} + k_2'}[B_j] \qquad (1.15)$$

$$k_A = k' + k_i'[B_i] \qquad (1.16)$$

High Concentration

At high concentration, $k_3^{Bi}[B_i] \gg k_{-1}+k_2'$ and eqn (1.15) becomes eqn (1.17) i.e. the overall reaction is no longer sensitive to base catalysis.

$$k_A = k_1 \qquad (1.17)$$

Medium Concentration

At medium concentration of base, eqn (1.14) holds which describes a curved dependence of k_A on base concentration. Only a limited number of aminolysis reactions have shown such a characteristic curved

plot.[19,36] In the majority of cases no base catalysis is observed, or where there is base catalysis k_A depends linearly on $[B_j]$ over the whole concentration range.

In terms of the addition- elimination mechanism, absence of base catalysis can mean that either $k_2 >> k_{-1}$ or that one has reached the region where levelling off takes place ($k_3^{B}i[B_i] >> k_{-1}$). Since at low amine concentration base catalysis is unlikely to be very great we may conclude that failure to observe base catalysis under these conditions means that $k_2 >> k_{-1}$.

For example the reactions of 2,4 dinitrobenzene with n-butylamine and aniline in alcohol or dioxan/water solvents are not base catalysed[37] hence $k_2 >> k_{-1}$, whilst for the reactions of 2,4-dinitrofluorobenzenes with amines in benzene,[19,38] where catalysis is so great that there is an almost second order dependance on base concentration that $k_3^{B}j[B_j] >> k_{-1}+k_2'$.

The linear response to base concentration, characteristic for the majority of base-catalysed reactions, is rationalised by assuming $k_3^{B}j[B_j] >> k_{-1}$ as well as $k_2' << k_{-1}$ which converts eqn (1.15) into eqn (1.18)

$$k_A = \frac{k_1 k_2'}{k_{-1}} + \frac{k_1 k_3^{Bj}[B_j]}{k_{-1}} \qquad (1.18)$$

It is apparent that a considerable body of information can be obtained from the way a reaction responds to the addition of base. When the response is curvilinear and the dependence of k_A on all bases including the nucleophile is determined, k_1 and the ratios k_2/k_{-1}, $k_3^{B}i/k_{-1}$ can be calculated from eqn (1.14). When the response is linear the

inference that $k_2/k_{-1}>>1$ follows.

1.1.3.3 Small Accelerations

A number of reactions, particularly those involving activated chlorobenzenes in non-polar solvents, undergo mild accelerations with increasing amine concentration,[39,40] or by addition of other substances.[39]

$$k_A = k' + k_i'' [B_i] \qquad (1.19)$$

The second-order rate constant usually obeys eqn (1.19) and typical k_i''/k' ratios vary between 0.5 and 5 though interpreted as base catalysis by some authors.[39] Such an interpretation has been critisized by Bunnett[41] mainly on the grounds that to change to a stronger base did not bring about more efficient base catalysis and suggests that k_i''/k' should be greater than 50 for the inference of base catalysis to be warranted and that small accelerations in rate may be due to medium effects.

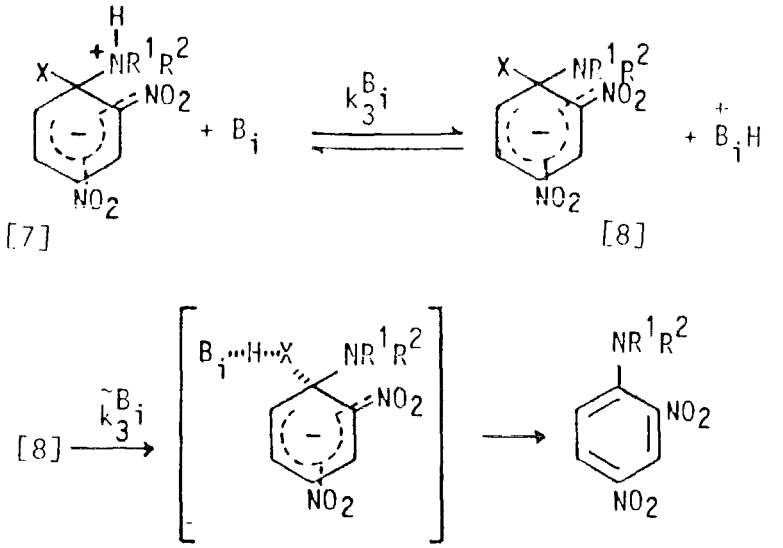
1.1.3.4 Mechanism of Base Catalysis

Three alternative mechanisms have been proposed for the base catalysed step:

i) Rate limiting proton transfer from [7] to the base, with subsequent rapid leaving group removal.[32]

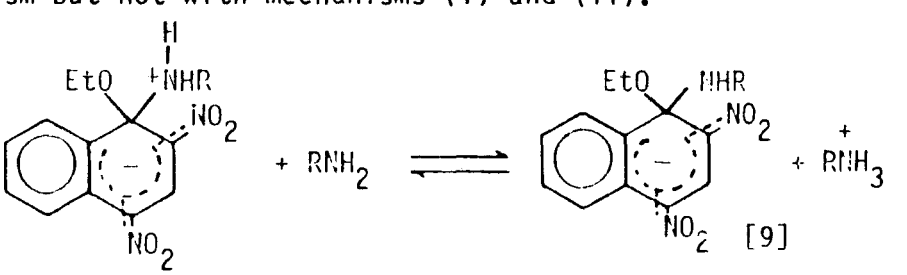
ii) Concerted breaking of the N-H and C-X bonds of [8] bought about by attack of base on H.[32,42]

iii) A fast acid-base catalysed equilibrium between the initially formed Zwitterionic intermediate [7] and its conjugate base [8] followed by rate limiting expulsion of X with general acid catalysis by BH.[43]



(1.20)

This latter theory, the specific-base-general acid (SB-GA) catalysis mechanism, is the one favoured by most authors. The kinetics of intermediate complex formation and decomposition were followed separately[44] in the reaction of 2,4-dinitro-1-naphthyl ethyl ether with n-butyl and t-butylamine in dimethyl sulphoxide. It was shown that the equilibrium (1.20) lies strongly over to the right and that removal of the ethoxide ion from [9] is first order with respect to the concentration of RNH_3^+. This is in complete agreement with the SB-GA mechanism but not with mechanisms (i) and (ii).[44]

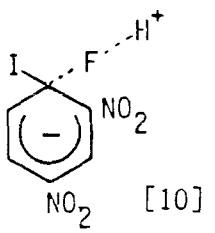


(1.21)

1.1.4 Acid Catalysis

The observation of acid catalysis is only possible when reactions are studied for which the nucleophile is practically unaffected by the

presence of hydrogen ions. It has been found[45] that the rate of reaction of 2,4-dinitrobenzene with iodide ion in methanol increases by a factor of $5x10^5$ in using hydroiodic acid instead of potassium iodate. This is explained[45] by invoking a two-step mechanism in which the second step, i.e. the one in which carbon-fluorine bond cleavage occurs, is rate determining, and that protons hydrogen bond to the fluorine in the transition state, increasing the rate of fluorine displacement. A model [10] for the transition state is shown below.



[10] (1.22)

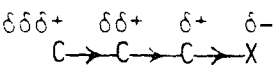
1.2 Electronic Effects of Substituents in Bimolecular Nucleophilic Substitution Reactions

1.2.1 Types of Effects

There are two principal modes of action for the electronic effects of ring substituents (i) Inductive and (ii) Mesomeric.

i) Inductive

Inductive effects are those which are directly related to the electronegativity differences between the carbons of the ring skeleton and the substituent X. The difference in electronegativity results in a polarisation of the C-X σ bond. This polarisation may then be transmitted through the carbon skeleton, but in practice this transmission of inductive effect falls off sharply with distance from the substituent and is very weak by the third carbon[46].



(1.23)

The inductive effect (-I effect) may be electron withdrawing or donating relative to the carbon skeleton depending on whether the substituent is respectively more or less electronegative than carbon. Recently the inductive effect has been considered as having two components, an effect transmitted through the electrons of the σ bond, and a through space or 'Field Effect' transmitted via space or the solvent molecules. In practice it is difficult to separate these two components and although claims have been made that the inductive effect may in fact have a very small or negligible σ component for some molecules, most authors prefer to talk of the inductive effect as operating through the σ bonds and this is the convention used here. Typical examples of inductively active substituents are shown in Table 1.1[47] together with their Hammett σ values (a measure of their inductive power relative to Hydrogen.)

Table 1.1[47]

	σ_{m-x}	σ_{p-x}
H	0.00	0.00
MeO	0.12	-
HO	0.12	-
F	0.34	0.06
Cl	0.37	0.23
MeCO	0.38	0.50
Br	0.39	0.23
CN	0.56	0.66
NO_2	0.71	0.78

Table 1.2.[47]

	σ_{m-x}	σ_{p-x}
Me_3C	-1.00	-0.20
Me	-0.07	-0.17
MeO	-	-0.27
HO	-	-0.37

ii)Mesomeric

Mesomerism is where a group is able to undergo resonance by donating (or accepting) an electron pair to (or from) a conjugated system as represented by:[46]

$$X—C{=}C—C{=}O \quad —— \quad {}^{+}X{=}C—C{=}C—O^{-} \qquad (1.24)$$

Substituents which are mesomerically active are shown in Tables 1.3 and 1.4 together with their σ and σ^{-} values (a measure of their mesomeric electron donating/withdrawing ability relative to hydrogen.)

Table 1.3 [47]

	σ_{p-x}
C_6H_6	-0.18
Me	-0.13
MeO	-0.78
NH_2	-1.30
NMe_2	-1.70

Table 1.4[47]

	σ^-
CO_2Et	0.68
COMe	0.84
CN	0.88
CHO	1.03
NO_2	1.27

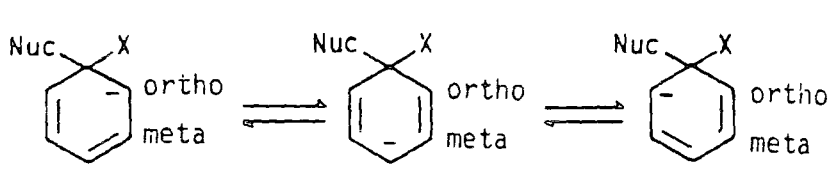
Therefore, anything which will stabilize/destabilize these resonance forms will enhance/retard intermediate formation.

1.2.2 Electronic Effects in the Ground State

In the ground state of an aromatic system, a group which acts to increase the positive charge on a carbon will increase its susceptibility to nucleophilic attack and vice versa, whilst any group which acts to decrease the positive charge on a carbon will decrease its susceptibility to nucleophilic attack. Thus in the ground state, since inductive effects fall off with distance we would expect electron withdrawing groups to be activating in the order o>m>p and similarly electron donating groups will be deactivating in the order o>m>p.

1.2.3 Electronic Effects in the Intermediate

The intermediate state may be considered to consist of several forms, (scheme (1.25).



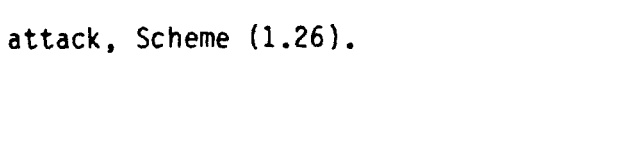
(1.25)

Inductive Effects

Since negative charge in the resonance structures is located at the positions ortho and para to the site of attack we would expect that groups which are inductively electron withdrawing/donating will enhance/retard the reaction when at positions ortho and para to the site of attack. Also since groups at the meta position can have an inductive effect on charge centred at the ortho and para positions, we would expect meta substituents to have an effect on the intermediate stability and thus we might predict the order of activating/deactivating effects for electron withdrawing/donating groups to be o=p>m.

Mesomeric Effects

In a manner similar to that for the ground state, mesomeric interactions between a substituent and the charged ring of the intermediate can only occur in positions ortho and para to the position of nucleophilic attack, Scheme (1.26).



(1.26)

Hence, as with the ground state, we would expect mesomeric effects in

the ortho and para positions to be approximately equal. However mesomeric effects will be much more important in the transition state since there is no loss of aromaticity to be overcome.

1.2.4 Electronic Effects in the Transition State

1.2.4.1 The Hammond Postulate

The Hammond postulate states that ''If two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganisation of molecular structure.''[25] Applying this to nucleophilic aromatic substitution, since we consider the transition state to be nearer the intermediate in energy than the ground state, we may reasonably take the intermediate as a model for the transition state. Thus, the electronic effects which we have discussed for the intermediate will apply to the transition state also. In practice of course, the transition state must represent some 'mix' of the ground state and intermediate and the electronic effects contributed by each to this 'mix' will be difficult to separate. The implications of this will be discussed in more detail later.

1.2.5 Ortho/Para Substituent Effects

1.2.5.1 Inductive Effects

Taking the substituted benzene ring [11] as an example, we can see that any group which is ortho to the leaving group X, being only one carbon removed, may have a strong inductive effect upon the carbon under attack.

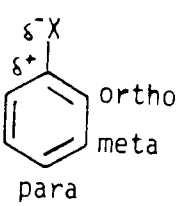
Groups which are para to the position of attack (being three

carbons removed) probably have little or no inductive effect in the ground state, but an effect similar to an ortho substituent in a transition state model.

Activation

In both the ortho and para positions, groups which are inductively electron withdrawing will activate the ring towards nucleophilic attack, whilst groups which are inductively electron donating will deactivate the ring towards nucleophilic attack.

A group which is able to interact with a negative charge solely by inductive effects is NMe_3^+. A measure of its activating effect in the para position has been obtained by comparing the rate constants for the reactions of 4-trimethylammonium-2-nitrochlorobenzene and 2-nitrochlorobenzene with methoxide in methanol at 25°C.[48]



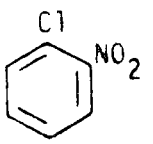
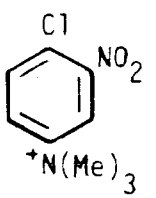
(1.27)

[11]

The data of Table (1.5) show NMe_3^+ to be ~5500 times more activating than hydrogen in the para position. Similarly the CF_3 group has also been found to be inductively activating. Table (1.6) shows the rate constants for the reaction of 2-nitrochlorobenzene with methoxide ions in methanol at 50°C. These show CF_3 to be inductively 1000 times more activating at the para position than hydrogen.

Table 1.5

Rate Constants for Reaction with MeO^- in MeOH at 25°C[48]

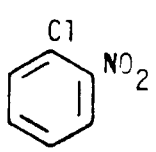
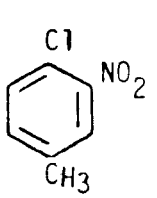
Substrate	$k/(1\ mol^{-1}s^{-1})$
	1.5×10^{-7}
	8.23×10^{-4}

Deactivation

Deactivation is found for a para methyl group as compared with a para hydrogen. The rate constants for the reactions of 2-nitrochlorobenzene and 2-nitro-4-methylchlorobenzene with methoxide ion in methanol at 50°C[51] are shown in Table (1.6).

Table 1.6

Rate Constants for the Reaction of 2-Nitrochlorobenzene with MeO^- in MeOH at 50°C[51]

Substrate	$k/(1\ mol^{-1}s^{-1})$
	2.52×10^{-6}
	2.99×10^{-7}

1.2.5.2. Mesomeric Effects

Any group ortho and para will have comparable mesomeric activating/deactivating effects since both positions are equally capable of undergoing resonance.

Activation

Table (1.7) shows the values of rate constants obtained for reaction of para-substituted systems with nucleophiles. In each case halogen is displaced.[49,50]

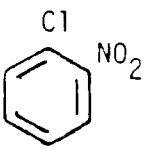
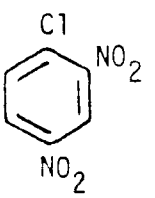
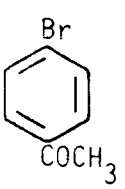
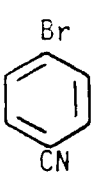
The first two values show the great activating effect of the NO_2 group as compared to hydrogen. Rate constant values for the reactions of the para-substituted bromides compare the relative activating effects of the substituents; the nitro-group is generally found to have the greatest activating effect.

Deactivation

Mesomeric deactivation is illustrated by the rate constants of Table (1.8) for the reactions of some para-substituted 2-nitrobromobenzenes with piperidine in piperidine at 25°C.[52]

Table 1.7

Rate Constants for Reactions of various substituted benzenes.

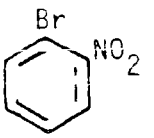
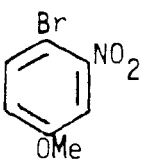
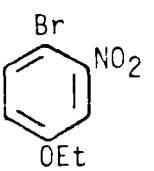
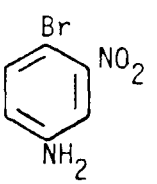
Substrate	$k/(1\ mol^{-1}s^{-1})$	
	0.363×10^{-5}	a
	14.9×10^{-2}	a
	64.5×10^{-7}	b
	0.86×10^{-7}	b
	1.98×10^{-7}	b
	3.40×10^{-7}	b

a reaction with MeO^- in MeOH at 50°C

b reaction in piperidine at 99°C

Table 1.8

Rate Constants for the Reactions of para-substituted 2-nitrobromobenzenes with Piperidine in Piperidine.[52]

Substrate	$k/(l\ mol^{-1}s^{-1})$
	2.9×10^{-3}
	5.22×10^{-5}
	4.38×10^{-5}
	3.60×10^{-7}

1.2.5.3 Steric Effects

A group which is ortho to the position of substitution may be able to interact sterically with the incoming nucleophile or the outgoing leaving group. Ortho steric effects of 2-COX-4-nitrochlorobenzenes have been investigated by comparing the relative rate constants for the reactions of 2-COX-4-nitrochlorobenzenes and 2-nitro-4-COX-chlorobenzenes with methoxide ion in methanol at 50°C. The results are shown in Table (1.9.)[53]

Table 1.9

Relative Rate Constants for the Reactions of Substituted Nitrochlorobenzenes[53,54]

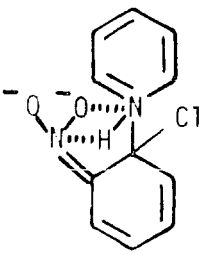
Substituent	Relative Rate Constant[53,54]	
	Para	Ortho
H	1	1
CO_2Me	1560	174
COMe	1990	246
COPh	1655	21.6
CHO	2240	285

The lower relative rate constant for a substituent ortho to the leaving group compared to a para substituent is accounted for by steric effects.[54]

The nitro group has been found to be less activating (by factors of 2 to 4) in the ortho position than in the para position.[21,22] Again this can be accounted for by steric effects.

1.2.5.4 Substituent-Nucleophile Interactions

Reactions of piperidine with ortho-nitrochlorobenzene have been shown to be faster than para-nitrochlorobenzene in a variety of solvents.[55,56] In changing solvent from 75% methanol to benzene the rate constant of the ortho nitro compound remained virtually constant while that of the para-nitro compound was reduced by a factor of 200.[55] This can be explained by an interaction between the nitro group and piperidine in the transition state for the ortho substituted compound leading to an 'internal solvation' which lessens the effect of solvent solvation.[55,56] [12]. For para-nitrochlorobenzene such an interaction is not possible so that its rate constant will be more susceptible to the degree of solvation which will be greater for 75% methanol than benzene.



(1.28)

[12]

1.2.6 Meta-Substituent Effects

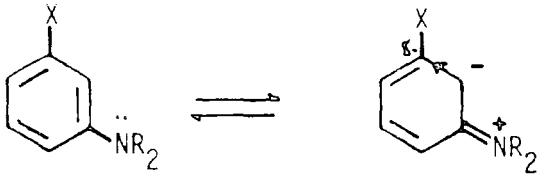
Substituents in the meta position cannot interact mesomerically with the ring in either the ground or transition state thus the primary effect of a meta substituent is via an inductive effect. The inductive effect is probably not very strong in the ground state since the meta substituent is 2 carbons removed from the site of attack. However, inductive stabilisation/destabilisation of charge in the transition state is possible as represented by structures [13],[14]

(1.29)

Stabilisation [13]

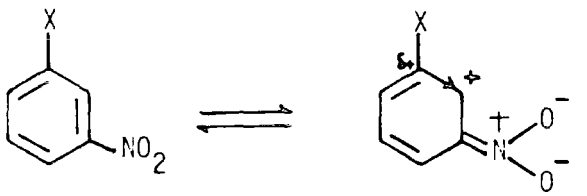
Destabilisation [14]

Inductive relay of resonance effects is also possible, as shown by [15] and [16] for meta amino and nitro substituents in ground state resonance.



[15]

(1.30)



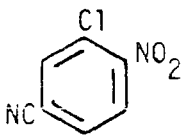
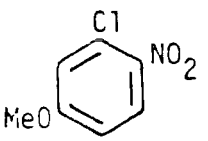
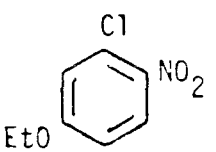
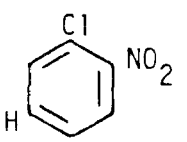
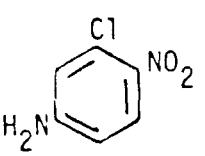
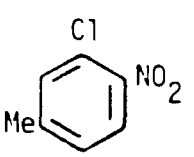
[16]

The rate constants for the reactions of piperidine in benzene at 45°C with a series of meta substituted 2-nitro-5-substituted chlorobenzenes[49] are shown in Table (1.10)

The MeO and EtO groups, in contrast to their ortho and para effects, are slightly activating with respect to hydrogen, indicating that their inductive effects are dominant - whereas the amino group is slightly deactivating as it is in the ortho and para positions due to its inductive effect.

Table 1.10

Rate Constants for Reactions with Piperidine in Benzene at 45°C

Substrate	$k/(1\ mol^{-1}s^{-1}) \times 10^5$
	21.2
	1.52
	1.34
	0.363
	0.311
	0.312

CHAPTER 2

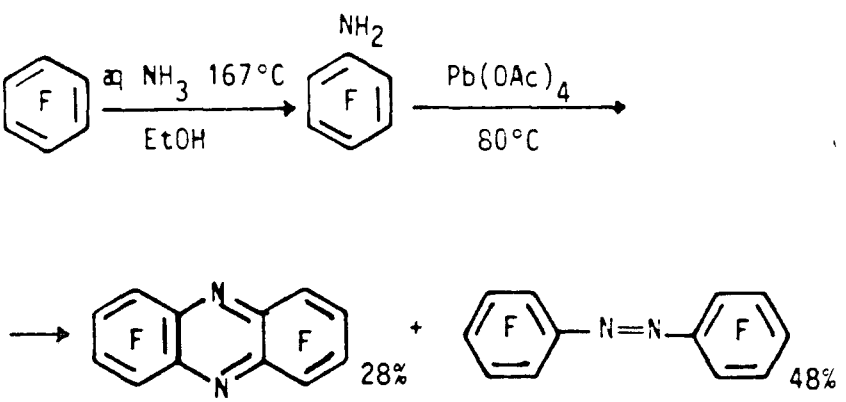
NUCLEOPHILIC AROMATIC SUBSTITUTION IN POLYHALOAROMATIC COMPOUNDS

CHAPTER 2

NUCLEOPHILIC AROMATIC SUBSTITUTION IN POLYFLUOROAROMATIC COMPOUNDS

2.1 Nucleophilic Aromatic Substitution in Polyfluoroaromatic Compounds

Halogen, as a substituent in Nucleophilic Aromatic Substitution, is not only a good leaving group, but also because of its inductive electron withdrawing effect, a good activating group. Polyfluorinated and chlorinated benzenoid compounds will readily undergo nucleophilic substitution reactions with a variety of nucleophiles e.g. HO^-,MeO^-, HS^-,NH_3,NH_2NH_2,NC^-,$C_6H_5^-$,CH_3^-.[57,58,59] Many of these nucleophilic reactions have proved to be useful as the first step in a variety of synthetic procedures in which more complex ring systems are produced, for example:

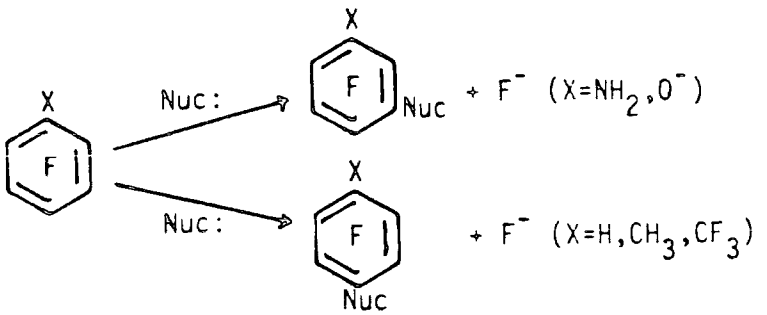


(2.1)

2.1.1 Polyfluorobenzenes

Pentafluorobenzene derivatives, C_6F_5-X, react with nucleophiles[57] such as methoxide to give substitution almost exclusively (>90%) <u>para</u> to the substituent group X (for example, where X=H,CH_3,SCH_3,CF_3, $N(CH_3)_2$,SO_2CH_3,NO_2,C_6F_5,OC_6F_5, etc.[57,58,59]); In a few cases (X=NH_2,O^-) <u>meta</u> replacement predominates while for X=OCH_3 and $NHCH_3$,

comparable amounts of meta and para replacement occur.[57,59]



(2.2)

The reactions of the polyfluorobenzenes are of great interest because of the way in which the position of substitution is relatively insensitive to the nature of any non-fluorinated substituents.

2.1.2 Effects of Substituents on the Rate of Reaction

In contrast to the situation with monofluoro and chlorobenzenes, very little kinetic data are available for the reactions of polyfluorinated and chlorinated systems. The halogens are, as expected, activating due to their electron withdrawing effect, while electron donating groups such as NH_2 and O^- are strongly deactivating. Tables 2.1, 2.2a, and 2.2b show the relative rate constants for reactions of substituted benzenes with sodium methoxide in methanol.[60,98] Except where shown, attack is para to the substituent X. Similarly Table 2.3 shows a comparable set of results for the reaction of sodium pentafluorophenoxide ion in dimethylacetamide at 106°C.[58]

Table 2.1

Rate Constants for Reactions of Substituted Polyfluorobenzenes with NaOMe at 60°C. in Methanol [60]

Substrate		Relative Rate Constants	
C_6F_5H	X=F	0.90	-a
C_6F_5Cl	Cl	1	
C_6F_5Cl	Cl	1.9	-b
$C_6F_5CF_3$	CF_3	4.5×10^3	
$C_6F_5NO_2$	NO_2	2.3×10^6	
C_6H_5F	H	5.2×10^{-8}	
$p\text{-}FC_6H_4NO_2$	NO_2	28	

a - corrected for statistical factors

b - for attack ortho to Cl

Table 2.2a

Rate Constants for Reactions of Substituted Polyfluorobenzenes with NaOMe in Dioxan/Methanol 5:1,(v/v) at 50°C. [118]

Substrate			$k/l\ mol^{-1}s^{-1}$
C_6F_6	X=F		3.50×10^{-3} - a
C_6F_5H	H		4.00×10^{-3}
C_6F_5Br	Br		6.42×10^{-2}
C_6F_5I	I		3.85×10^{-2}
$C_6F_5OCH_3$	OCH_3	all positions	2.71×10^{-4}
$C_6F_5NH_2$	NH_2	meta to NH_2	2.15×10^{-5}
$C_6H_5O^-$	O^-	meta to O^-	8.11×10^{-8}

a - corrected for statistical factors

Table 2.2b

Rate Constants for Reactions of Substituted Polyfluorobenzenes with NaOMe in Methanol at 50°C. [118]

Substrate		$k/l\ mol^{-1}s^{-1}$
C_6F_6	X=F	5.02×10^{-5} - a
C_6F_5H	H	8.66×10^{-5}
$C_6F_5CF_3$	CF_3	3.70×10^{0}
C_6F_5CN	CN	3.45×10^{1}

a - corrected for statistical factors

Table 2.3

Rate Constants for Reactions of Polyfluorobenzenes with Sodium Pentafluorophenoxide in DMA at 106°C [58]

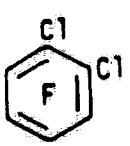
Substrate		Relative Rate Constants
C_6F_5X	X= F	0.91
	H	1
	Cl	32
	Br	39
	C_6F_5	7.3×10^2
	$CO_2C_2H_5$	2.9×10^3
	CF_3	2.4×10^4

The data of the previous few tables clearly show the wide spread of rates found in nucleophilic aromatic substitution, this is comparable to the case for electrophilic substitution but here we have the contrasting feature that the orientation pattern is relatively insensitive to the substituents other than fluorine. Consequently, it becomes important to try and establish the exact nature of the unusual orientating effects of fluorine.

Kinetic data for the reactions of the chlorofluorobenzenes with methoxide ion have been obtained in methanol at -7.6°C. The rate constants are shown in Table 2.4 together with those for hexafluorobenzene under the same conditions. Similarly kinetic data for the reactions of the tetrafluorobenzenes and methoxide ion in methanol has also been obtained, this is presented later in Chapter 3. (Table 3.4)

Table 2.4

Rate Constants for the Reactions of Chlorofluorobenzenes with Sodium Methoxide in Methanol -7.6°C[51]

Substrate	$k/(1\ mol^{-1}s^{-1})^a$
	8.49×10^{-8}
	3.12×10^{-6}
	2.14×10^{-6}
	1.00×10^{-5}

a - values of k are corrected for statistical factors

Table 2.5

Second Order Rate Constants and Relative Rates for -OMe attack upon C_6F_5X MeOH 333K [120]

X	10^4k_2*	10^4k_o*	10^4k_p*	$k_o$rel	$k_p$rel
H	3.0+.01	0.05	3.0	1	1
F	4.7+0.2	1.68	1.68	34	0.6
Cl	-	6.8	53.2	130	17
Br	58+1.2	3.6	50	70	17
I	120+1.0	3	114	60	38

* = /l $mol^{-1}s^{-1}$

It can be seen from Tables 2.4, 2.5 and from Table 3.4 in Chapter 3, that the activating influence of the halogens appears to increase in the order F<Cl<Br for the ortho and para positions, moreover that para-fluorine is actually deactivating with respect to hydrogen and that chlorine is more activating when it is ortho, rather than para, to the fluorine being replaced.

2.1.3 Base Catalysis

Base catalysis has been observed for the reaction of hexafluorobenzene with piperidine in n-hexane, dioxan and methanol at 100°C.[61] The measured rate constant, k, was found to be sensitive to piperidine concentration and was analysed as a combined rate constant of the form:

$$k=k' + k"[B] \qquad (2.3)$$

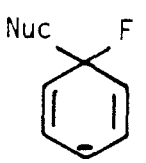
The extent of catalysis (k"/k') decreased along the solvent series

hexane - methanol - dioxan i.e. in the sequence of increasing specific solvation. By specific solvation we mean the ability of a solvent to coordinate to the reaction centre of a molecule and in these cases, to act as basic catalyst in removal of the proton from the amine nitrogen. The occurrence of base catalysis is an indication of a two-step addition-elimination mechanism for substitution in these systems.

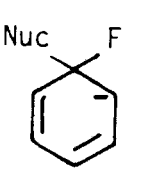
2.1.4 An Early Rationalisation of Orientation of Substitution

It seems a reasonable assumption that displacement of fluorine from highly fluorinated systems is a two-step process, as discussed previously. Since the order of halogen mobility in displacement from polyfluorinated aromatic compounds is F>Cl>Br>I we may argue that the rate determining step, in general, does not involve much C-F bond breaking and hence that the 1st step is rate determining. It has been argued that the magnitude of certain substituent effects is also consistent with this process.

Taking the intermediate complex as a model for the Transition State we need to make an assumption, that is, that the charge is greatest at the position para to the point of attack by a nucleophile. In valence bond terms [1] is more important than [2].



[1]

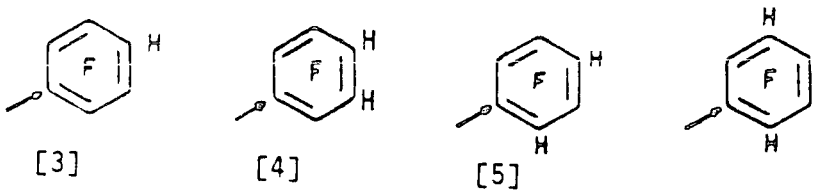


[2]

(2.4)

This assumption is supported by calculations and is also indicated by the orientation of attack in pentafluorobenzene and the three

tetrafluorobenzenes. These four compounds react with nucleophiles in the positions arrowed.



[3] [4] [5] (2.5)

For [3],[4] and [5] attack occurs only para to a hydrogen, which it has been suggested stabilizes a negative charge on an ortho carbon atom to a greater extent than fluorine. The fact that no ortho product is formed suggests a non equal distribution of charge in the transition state at positions ortho and para to the point of attack. If it is accepted that [1] is a model for T_1 then our discussion is essentially concerned with the relative effects of halogen and other substituents on carbanion stabilities.

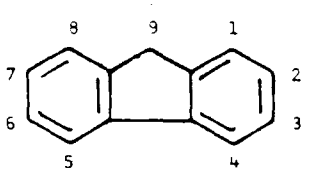
2.1.5 Directing Effect of Halogen

The halogens are often found to destabilize a negative charge on an alpha carbon atom in the order F>Cl>Br>I-H, when the geometry of the carbanion is planar, for a tetrahedral carbanion F is found to be slightly stabilizing[61]. This order of the capacity to destabilize a negative charge has been explained in terms of the I-pi effect,[62] which is a measure of the inductive repulsion between the non-bonding electrons of the halogens and the negative charge on carbon in a pi system.

For the halogens the I-pi effect is in the opposite direction to the -I-sigma effect arising from their electronegativities and in the same direction as, but different from, their mesomeric (+M) effects.

The I-pi repulsion results from a coulombic interaction between the

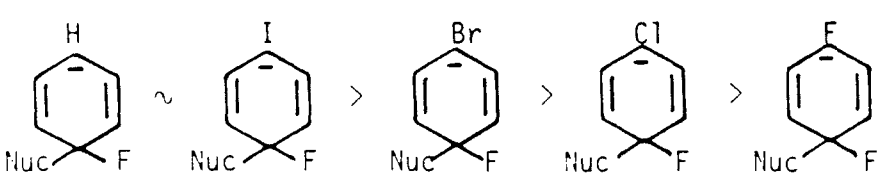
lone pairs on halogen and the electrons on the alpha carbon atom. The effect will be greater for fluorine than for the other halogens as it results from an interaction with the 2p orbitals of ring carbon. Hence for fluorine the interaction is 2p-2p where as for Cl,Br and I it is 2p-3p, 2p-4p and 2p-5p, respectively. This effect is likely to increase with increasing charge on the carbon. Hydrogen will have no I-pi effect. The dependence of the magnitude of the I-pi effect of an alpha fluorine upon the conformation of the carbanion and hence the degree of orbital overlap can be seen in the following examples. Measurements of the kinetic acidities of $CHFX_2$ compounds, which give tetrahedral carbanions, shows them to be 10^4 to 10^5 times more acidic than the corresponding CH_2X_2 compounds.[63] However, the sodium methoxide catalysed isotope exchange of fluorene [6] is reduced by a factor of 8 by a 9-fluoro substituent.[64] in this case planar geometry is enforced.



(2.6)

[6]

Thus by considering the I-pi interactions, the following order of stability has been proposed for the various transition states.[65]

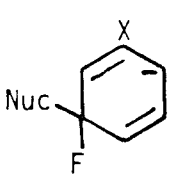


(2.7)

Hence the I-pi effect successfully explains the positions of substitution in the simple pentafluorobenzenes.

2.1.6 Directing Effects of Other Substituents

Following on from the above, this simplistic argument can also be used to explain the meta directing effect of $-NH_2$ and $-O^-$ substituents in pentafluorobenzenes. It has been argued[59] that the lone pairs on the nitrogen and the full charge on the oxygen in pentafluoroaniline and pentafluorophenoxide interact with the charge in the transition state more strongly than fluorine: this is in line with the previous argument as the electrons on both nitrogen and oxygen result in a 2p-2p interaction with carbon and being less electronegative than fluorine will have a greater tendency to donate their lone pair electrons to the ring. Hence the most stable transition state for these compounds is one in which the attack is at the meta position and the negative charge of the transition state is on the carbon beta from - NH_2 or O^-

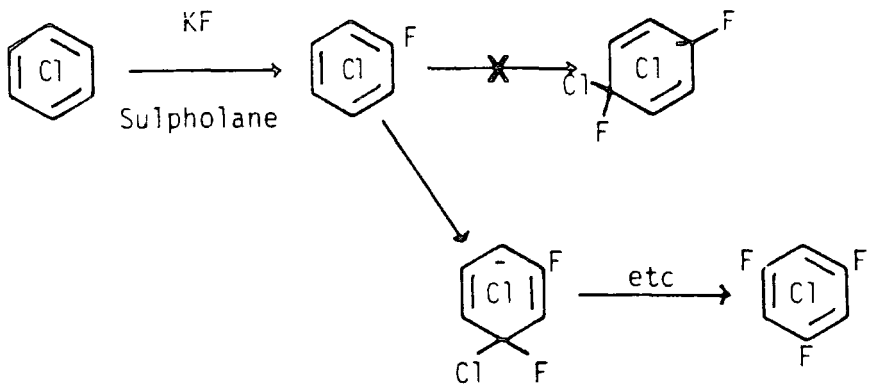


$X=NH_2$ or O^- (2.8)

2.1.7 Application of this Approach to More Complicated Benzenoid Systems

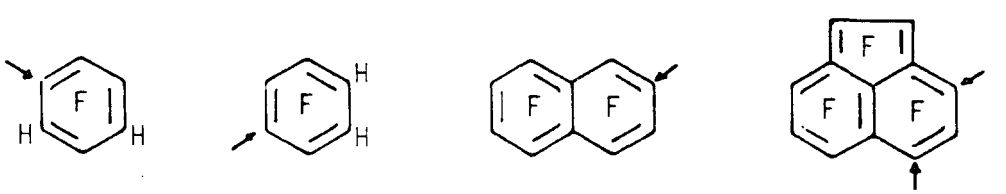
The same approach to explaining the positions of substitution can be applied to a number of other more complex systems. For example it

explains the formation of 1,3,5-trifluorochlorobenzene from perchlorobenzene and potassium fluoride in sulpholane.



(2.9)

Similarly this approach may be used to explain substitution in the following benzenoid systems.



(2.10)

This simplistic approach however ignores the evidence available from the rate data (Table 2.6) which suggests a more complicated situation exists involving initial state effects as well as a transition state effect, we must regard the limited success obtained in explaining the position of substitution in these more complex benzenoid compounds as being to some extent due to a fortuitous choice of the compounds themselves. A more sophisticated rationalisation will be discussed later in this chapter and expanded on in chapter 3.

Table 2.6

Substituent Effects in Methoxydefluorination of 2-X-Heptafluoro-naphthalenes and C_6F_5X (NaOMe - MeOH 323.3 K) [59]

X	srf. 2-X-naphthalene	srf. C_6F_5X
H	1.0	1.0
F	1.1	0.75
Cl	5.2	26
Ph	1.2	1.6
OMe	6.3	0.08

srf = substituent rate factor

2.1.8 Conclusion

Although the discussion above relates the course of reactions to electronic effects in the transition state of the rate determining step, initial state effects must also be taken into account. It has been stated,[59] taking hexafluorobenzene as the standard, that substituents which can reduce the electron deficiency of the ring by electron donation through a +M effect such as NH_2 and OCH_3, will increase the initial state stability of the system making it less reactive, while substituents which increase the electron deficiency of the ring, such as NO_2 or CF_3, will destabilize the initial state of the system, relative to hexafluorobenzene, making the molecule more susceptible to nucleophilic attack.

2.2 Unusual Substituent Effects

2.2.1 Ortho Attack

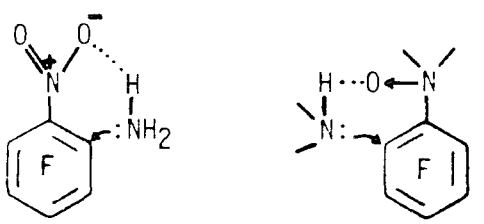
A special case of preferred ortho attack has been found in reactions of pentafluoronitrobenzene with ammonia and, to a lesser

extent, other amines in ether,[65] whereas with other reagents such as methoxide in methanol *para* attack is preferred.[67,68] These results are summarised in Table 2.7.

Table 2.7

Nucleophile	NH_3	$MeNH_2$	Me_2NH	NaOMe/MeOH
ortho attack	69	65	19	8
para attack	31	35	81	92

The high *ortho* ratios have been attributed to hydrogen bonding of the nucleophile to the nitro group leading to a lower energy transition state for *ortho* than *para* substitution.



(2.11)

The reduced *ortho* substitution with dimethylamine was attributed to steric effects inhibiting hydrogen bonding. The situation is more complicated than this however, for sodium methoxide in ether containing only 3.8% of methanol gives a 1:1 ratio of *ortho* to *para* substitution.[69].

2.2.2 Meta-para Attack

Attack by a series of nucleophiles on pentafluoroaniline and methyl derivatives each gave a smooth gradation in *meta*/*para* ratios for substitution of fluorine, as indicated, *ortho* substitution being <6%

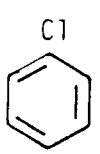
in any case.[66]

	$C_6F_5NH_2$	$C_6F_5NHCH_3$	$C_6F_5N(CH_3)_2$
meta/para ratio	7	1	0.07

This variation, with the N,N-dimethyl derivative leading to essentially para replacement, has been attributed to steric inhibition of resonance of the dimethylamino group with the ring by interaction with adjacent fluorine atoms.

Table 2.8

Rate Constants for Reaction with Methoxide/Methanol at 50°C.[69,70]

Substrate	$k/(1\ mol^{-1}s^{-1})$
	1.20×10^{-16}
	3.47×10^{-6}
	8.19×10^{-7}

2.3 N-Heterocyclic Compounds

2.3.1 Effect of Ring-N

Polyhalogenated nitrogen heterocyclic systems are all activated, relative to the corresponding benzenoid compounds, towards nucleophilic aromatic substitution. The activating effect of the aza group is found to be similar in magnitude to that of the nitro group in aromatic compound systems and like the nitro group the aza group has its greatest activating effects ortho and para to itself.[69,70] A comparison of the activating powers of the the aza and nitro groups is shown in Table 2.8

2.3.2 Mechanism of Substitution

The majority of nucleophilic substitution reactions in N-heterocyclic systems appear to proceed via the two-step addition elimination mechanism. Evidence for this is the same as for the benzene compounds. The order of halogen mobilities is often found to be F>>Cl as for the reactions of the 2-halopyridines and 2-haloquinolines with piperidine in a variety of solvents.[70] Base catalysis has also been found for the reactions of 2-fluoro and 2-chloro-5-nitropyridines with aniline and piperidine in acetone.[71]

A number of reactions, however, appear to operate by the elimination addition mechanism, when the substrates are unreactive and the nucleophiles are strongly basic. An example is the reaction of 3-bromopyridine with sodamide in liquid ammonia which gives a mixture of 3- and 4- aminopyridine.[72]

The I-pi effect must obviously be considered but high electron densities on nitrogen in the transition state, as in [7] and [8], reduce the electron densities on carbon atoms compared to substitution in polyfluorobenzenes and hence may lessen the importance of I-pi

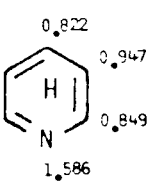
destabilizations.

[7] [8] (2.12)

We shall now discuss nucleophilic substitution in several heterocyclic systems in relation to the rationalisation proposed for the benzenoid systems, Monosubstituted heterocycles will be used to illustrate the effects of nitrogen on the ground and transition states, while polyfluorinated heterocycles will be used to show the additional influence of the ring substituents.

2.3.3 Pyridines

Calculation of pi electron densities of the carbon atoms of pyridine in the ground state give the following values.[73]

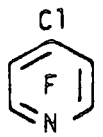
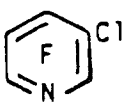
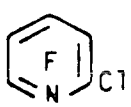


(2.13)

The electron density on the nitrogen is heightened at the expense of the ring carbons and from these electron densities we would expect the order of susceptibility to nucleophilic attack in the ground state to be 4>2>>3. This is supported by the observed rate constants for the reactions of the 2,3, and 4-chloropyridines with sodium methoxide in methanol.[73]

Table 2.9

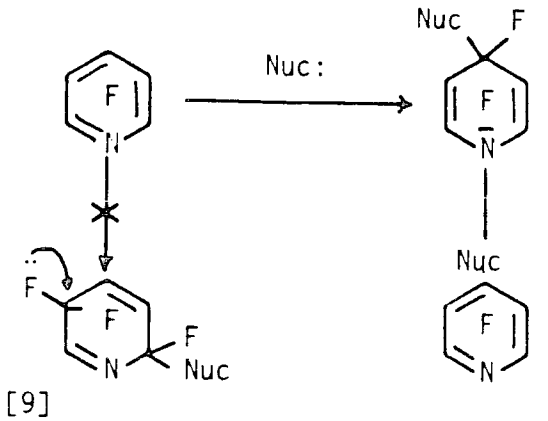
Rate Constants for Reaction with Methoxide/Methanol at 50°C.[73]

Substrate	k/(l mol-1s^{-1})
	8.91×10^{-7}
	1.09×10^{-11}
	3.31×10^{-8}

Pentafluoropyridine reacts with nucleophiles e.g. MeO-, NC-, HO- and amines, to give almost exclusively 4-substituted products,[75,60,76] Further substitution in the case of methoxide ion gives 2,4,dimethoxytrifluoropyridine and 2,4,6-trimethoxydifluoropyridine.

These results are consistent with the model described in the previous section on benzenoid systems; a transition state leading to 4-substitution and resembling the intermediate complex is favoured because nitrogen becomes the position of maximum charge density, whereas attack at the 2-position through [9] is inhibited by electron pair repulsions arising from fluorine at the 5 position.

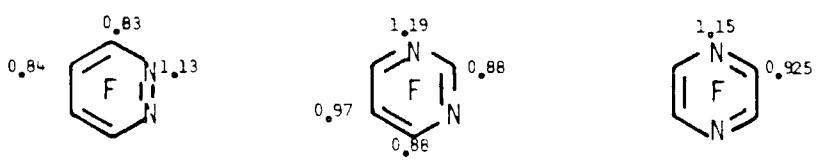
Both 4-chloro and 4-bromo[77] tetrafluoropyridine react with nucleophiles to replace the 2-fluorine. The fact that neither bromide nor chloride is displaced is indicative of the one-step mechanism.



(2.14)

2.3.4 Diazines

Adding a second aza group to the aromatic nucleus would be expected, from the previous arguments to increase the susceptibility of the system towards nucleophilic attack. The pi-electron densities for the three diazines have been calculated to be as follows.[78]



(2.15)

Table 2.11 shows the results of rate measurements for various chlorodiazines with p-nitrophenoxide in methanol at 50°C in the presence of added nitrophenol.[78,79] As expected the results show a great increase in reactivity in going from the pyridine to the diazo compounds. On the assumption that ortho and para nitrogen are more activating than meta nitrogen it would be predicted that the reactivity of the diazines would be:

Table 2.10

Rate Constants For Reaction With para-Nitrophenoxide/Methanol at 50°C. [78,79]

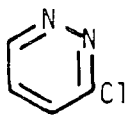
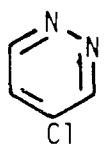
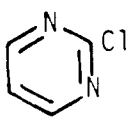
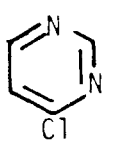
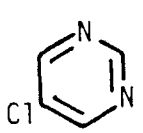
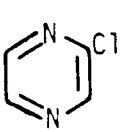
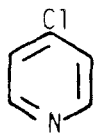
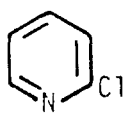
Substrate	$k/l\ mol^{-1}s^{-1}$
	1.3×10^{-6}
	2.1×10^{-6}
	6.9×10^{-4}
	1.2×10^{-5}
	1.3×10^{-7}
	4.5×10^{-6}

Table 2.10 continued

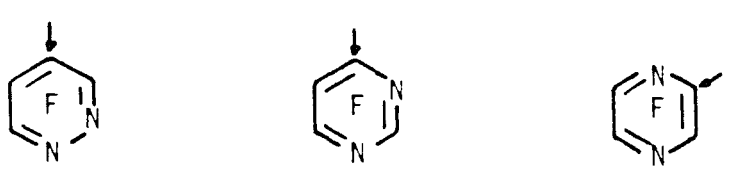
Rate Constants For Reaction With para-Nitrophenoxide/Methanol at 50°C. [78,79]

Substrate	k/l $mol^{-1}s^{-1}$
	3.0×10^{-12}
	8.1×10^{-11}

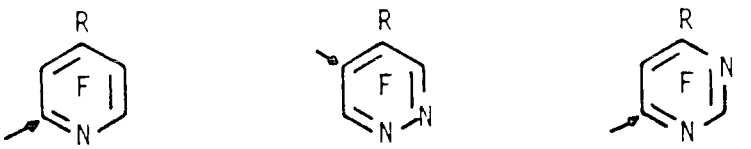
4-chloropyrimidine ~ 2- chloropyrimidine > 3-chloropyridazine ~ 4-chloropyridazine ~ 2 - chloropyrazine > 5-chloropyrimidine

This order of reactivity is reflected reasonably well in Table 2.10, except that 2-chloropyrimidine is more than 50 times as reactive as 4-chloropyrimidine. This is accounted for by the fact that the reactions are mildly acid catalysed, owing to the presence of added p-nitrophenol in the reaction mixture,[73] and this catalysis is likely to be more effective at positions ortho to the ring nitrogen.

Tetrafluoropyridazine,[80,81,82,83] pyrimidine[84,85,86] and pyrazine [87,88] react with nucleophiles in the positions indicated, i.e para to the ring nitrogen where possible.

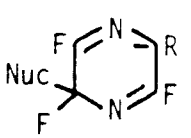
 (2.16)

Subsequent substitutions in the 4-substituted pyridazines[80] and pyrimidines[85] are explainable entirely in terms of the activation caused by second ring nitrogen but for the pyridines,[81] we must also consider the activating effects of the fluorine substituents.



(2.17)

Orientation of substitution in monosubstituted trifluoropyrazines is dependent on the nature of the substituent.[88] In most cases e.g. for chlorine and alkyl groups, substitution is para to the substituent, leading to the transition state in which the negative charge is located on the carbon atom bearing the substituent R. Where the substituent is methoxy, substitution is ortho to the methoxy group leading to a transition state where the negative charge is localized on a carbon bearing fluorine.



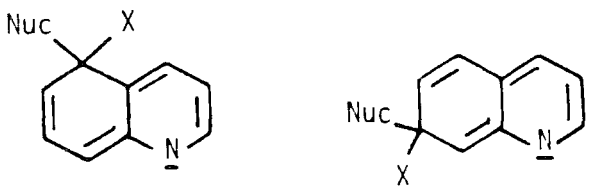
(2.18)

2.3.5 Quinolines and Isoquinolines

2.3.5.1 Quinolines

For nucleophilic attack in halogenopyridines, the rate of reaction ought to be greater for halogens in the heterocyclic ring than in the

alicyclic ring, with an order of reactivity 4-2>3, as in positions 2 and 4 negative charge can be accommodated on the nitrogen. For attack in the benzene ring, substitution at the positions 3 and 7 can lead to a transition state in which the charge is placed on nitrogen.



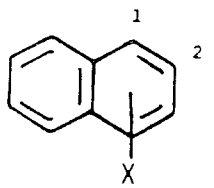
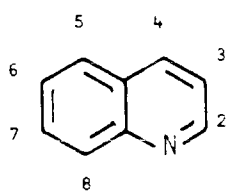
(2.19)

[10] [11]

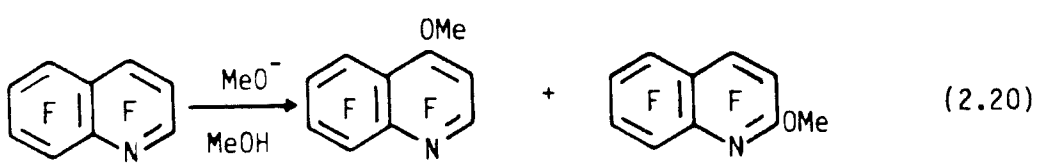
One would then predict an order of reactivity for the benzene ring of 5~7 > 6~8. As there is only weak conjugation between the two rings formation of [10] and [11] would not be expected to be very favourable and hence attack should be preferentially in the heterocyclic ring. The measured rates for various halogeno-quinolines with piperidine as both nucleophile and solvent bear out these arguments.[89] The rates are shown in Table 2.11 corrected to 50°C by Miller.[89] The values for the naphthalenes are given to show the activation resulting from the ring nitrogen.[90]

Table 2.11

Rate Constants for Reaction with Piperidine at 50°C [58]

Substrate		k/(1 mol^{-1}s^{-1})
	X=1-Br	5.62×10^{-13}
	2-Br	1.15×10^{-12}
	2-Cl	3.52×10^{-6}
	3-Br	3.20×10^{-10}
	4-Cl	6.10×10^{-7}
	5-Br	7.29×10^{-11}
	6-Br	5.67×10^{-11}
	7-Br	6.55×10^{-10}
	8-Br	5.66×10^{-10}

Heptafluoroquinoline reacts with nucleophiles, including methoxide ions and ammonia, to give a mixture of products resulting from substitution in the 2 and 4-positions.[91]



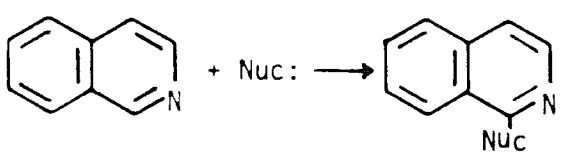
(2.20)

Steric effects due to fluorine in the 5-position appear to be

important. The reaction of methoxide ion in methanol gives 75% of the 2-substituted product (25% of the 4-isomer), while methoxide ion in t-butanol >95% of the 2-methoxy product.[91]

2.3.5.2 Isoquinoline

By analogy with the quinoline system, the positions most susceptible to nucleophilic attack in isoquinoline ought to be those alpha to the nitrogen (i.e. positions 1 and 3). Rate measurements for the reactions of ethoxide ions in ethanol at 20°C with 1-chloroisoquinoline and 3-chloroisoquinoline give rate constant values of 6.9×10^{-7} l $mol^{-1}s^{-1}$ and 1.20×10^{-1} l $mol^{-1}s^{-1}$ respectively.[38] Heptafluoroisoquinoline reacts with nucleophiles to give exclusively the 1-substituted product.[91]

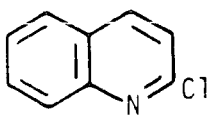
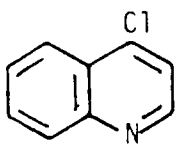
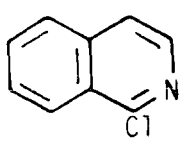


(2.21)

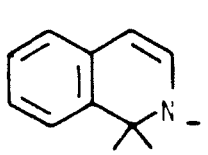
The overwhelming activating influence of the ring nitrogen in mono-substituted compounds is shown by the remarkable similarity in the rates of reaction for 2-chloro- and 4-chloroquinoline and 1-chloroisoquinoline with ethoxide in ethanol at 20°C.[38]

Table 2.12

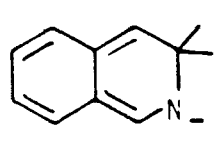
Rate Constants for Reaction with Ethoxide in Ethanol at 20°C [38]

Substrate	$k/(1\ mol^{-1}s^{-1})$
	6.30×10^{-7}
	6.50×10^{-7}
	6.90×10^{-7}

The much lower rate constant for attack at the 3-position in the mono-chloroisoquinoline and the total absence of 3 attack in the heptafluoroisoquinoline can be explained be a consideration of the transition states. In the transition state for attack at position 1 [12] negative charge can be localized on nitrogen without loss of aromaticity in the benzene ring, whereas localization of negative charge on nitrogen for attack at the 3 position [13] destroys the aromaticity of the benzene ring.



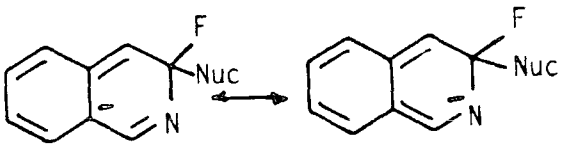
[12]



[13]

(2.22)

On the basis of the fluorine electron pair repulsion effect, however, it would be argued that heptafluoroquinoline would react in the 3-position, analogous to octafluoronaphthalene passing through a transition state[14].



(2.23)

[14]

Instead, we find the substitution gives entirely 1, indicating the control of the orientation rests with the nitrogen.

2.3.6 Substrate Basicity

A property of N-heterocyclic compounds which differentiates them from benzene compounds, is that the aza group of the former renders them basic. Table 2.14 shows the pKa values for some heterocyclic compounds and their derivatives.[32]

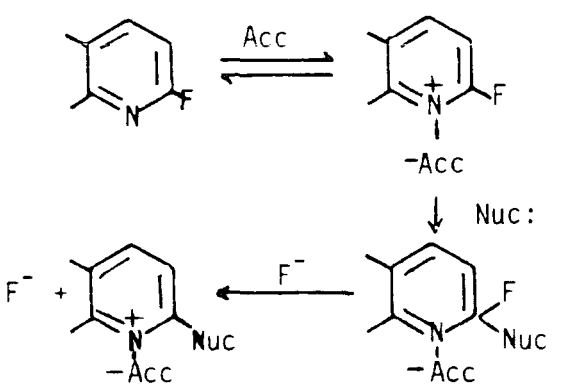
Table 2.13

Substrate	pKa
Pyridine	5.17
Pyrimidine	1.30
Quinoline	4.81
2-fluoropyridine	-0.44
4-chloropyridine	0.72
4-chloropyridine	3.71

It can be seen that the presence of halogens in the heterocyclic ring reduces the basicity of the system.

2.3.7 Acid Induced Processes

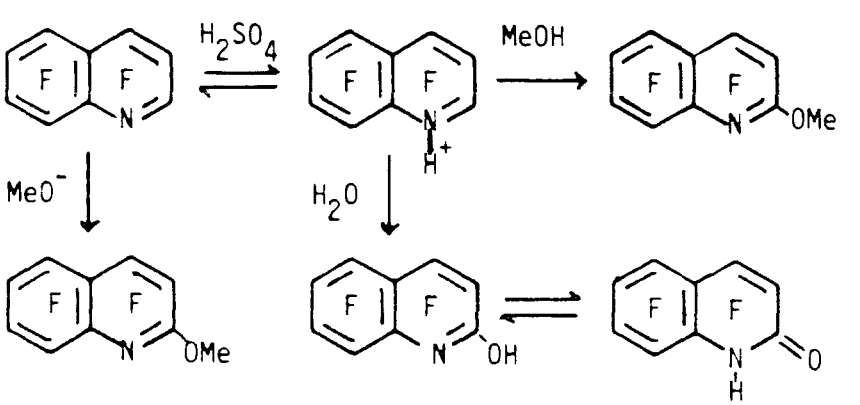
Although perfluoroaromatic nitrogen heterocyclic compounds are only weak bases, nucleophilic substitution can be induced by protonic or Lewis acids, as outlined below, and interesting contrasts in orientation can sometimes be achieved because attack ortho to the nitrogen is often preferred under these conditions.



(2.24)

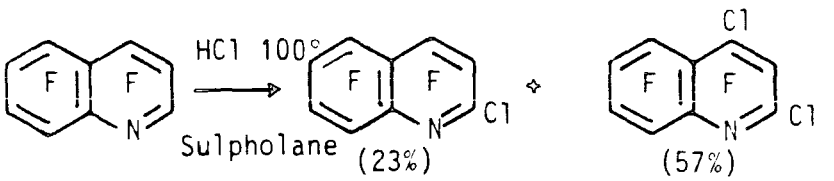
Acc=electron acceptor

An example of preferred ortho attack is shown in the reaction scheme:



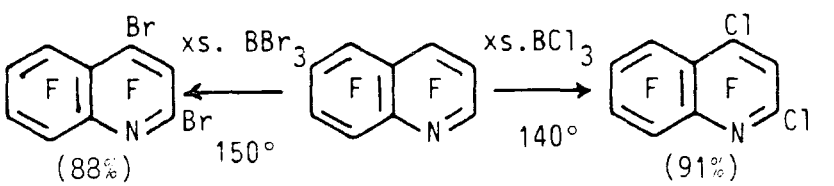
(2.25)

Hydrogen halides give products where substitution para to nitrogen occurs almost as readily as at the ortho position while Lewis acids



(2.26)

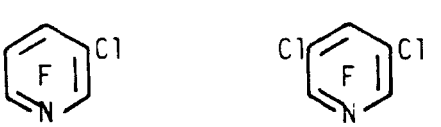
are even less discriminating.



(2.27)

2.3.8 Steric Effects of Halogen

Both 3-chlorotetrafluoropyridine [15] and 3,5-dichlorotrifluoropyridine ([16] react with aqueous ammonia, hydrazine hydrate and methoxide ion in methanol to give a product resulting from exclusive replacement of fluorine in the 4-position.



(2.28)

[15] [16]

Steric effects in these two compounds, arising from the presence of chlorine, are evident. Aqueous potassium hydroxide with [15] gives a

mixture of products with the hydroxyl group in the 4- and 6-position (90% and 10%, respectively) and the same composition is given for the analogous reaction with [16]. In contrast to this, attack by hydroxide ion in t-butanol on [15] gives a mixture of the 2-,4- and 6-hydroxy compounds (10%,50% and 35% respectively), and the same reagent with [16] gives a product consisting of 70% of the 2-hydroxy isomer, i.e. with hydroxide ion in t-butanol, attack at the sterically hindered 4-position is less favourable than attack at the 2- or 6- positions. This has been attributed to solvation of the hydroxide ion in t-butanol leading to an effectively larger nucleophile which would react preferentially at the sterically hindered 6-position.

2.4 Polychloroaromatic Compounds - Chlorine as a Leaving Group

2.4.1 Hexachlorobenzene

Chlorine has a Van der Waals Radius of 1.80A compared to that of 1.35A for fluorine. The carbon-carbon bond length in pentachlorobenzene is only 2.8A. This leads us to expect that steric effects in the chlorobenzenes will be greater than those in the fluorobenzenes. This is exemplified by the fact that unlike pentafluorobenzene, which is planar, the steric effects of the chlorine atoms in hexachlorobenzene cause the aromatic ring to exist in a buckled form.[92] Hexachlorobenzene, readily reacts with nucleophiles[93] including alkoxide, thioalkoxide and amines to give the monosubstituted product, although its low solubility in common organic solvents causes problems. Under the same conditions hexachlorobenzene reacts more slowly than hexafluorobenzene, and this has been attributed solely to the greater ease of displacement of the fluoride ions.

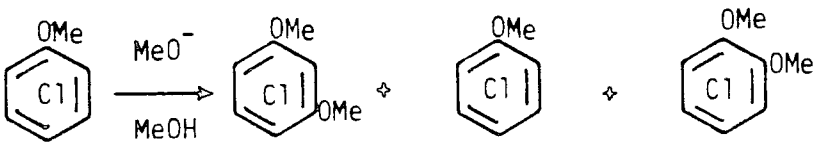
Table 2.14 shows the rate constants for nucleophilic attack on hexachloro and fluorobenzene by hydroxide ion in dioxan/water (90:10,v/v) at 160°C.

Table 2.14

Substrate	$k/(1\ mol^{-1}s^{-1})$
C_6F_6	1.03×10^{-2}
C_6Cl_6	7.40×10^{-5}

2.4.2 Monosubstituted Pentachlorobenzenes

Little data is available for these compounds, unlike the situation with the corresponding pentafluorobenzenes. Pentachloronitrobenzene reacts with aqueous ammonia at 200°C giving as the major product, pentachloroaniline (60%) plus a mixture of 2- and 4-aminotetrachloronitrobenzene. The displacement of the nitro-group is in contrast to the the analogous reaction with pentafluoronitrobenzene in which the nitro group is not displaced. Yakobson and co-workers[90] have studied the orientation of substitution in pentachloroaniline and pentachloroanisole and in both cases it is the same as for the corresponding pentafluoro compounds. Pentachloroaniline reacts with both methylamine and methoxide ion to give only the 3-substituted product (meta to the NH_2 group), while pentachloroanisole with methoxide ion gives products arising from attack at positions ortho, meta and para to the OMe group.



(2.29)

Pentachlorobenzene reacts with nucleophiles in the position para to hydrogen, as does pentafluorobenzene. This has been interpreted through the I-pi effect in terms of the relative stabilities of transition states [17] and [18] i.e. attack para to the hydrogen gives a more stable transition state than for attack para to chlorine.

[17] [18]

(2.30)

Comparison between the rates of displacements of fluoride ion from hexafluorobenzene and pentachlorofluorobenzene has shown the latter to be more reactive. Table 2.15 shows the relative rate constants for reaction with methoxide in methanol at 60°C.

Table 2.15

Substrate	Relative Rate Constant
C_6F_6[a]	1
C_6Cl_5F	40

a - corrected for statistical factors

2.4.3 Pentachloropyridine.

In contrast to pentafluoropyridine, pentachloropyridine reacts with nucleophiles in both the 4- and 2- positions. Steric factors are important, as large nucleophiles give a greater proportion of the 2-substituted product, the 2-position being less sterically hindered than the 4-position. Table 2.16 shows the ratio of 2:4 substitution with various nucleophiles.[123]

Table 2.16[123]

Nucleophile	Solvent	Ratio of 4/2 substitution.
NH_3	EtOH	40/30
Me_2NH	EtOH	20/80
Et_2NH	EtOH	1/99
MeO^-	MeOH	85/15
EtO^-	EtOH	63/35
n-BuO^-	n-BuOH	57/43

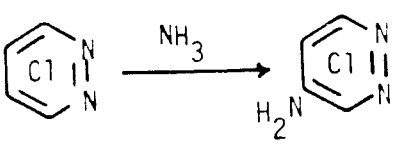
The monosubstituted products are also subject to disubstituted, with the possibility of forming either the 2,4 or 2,6-disubstituted product. Again the position of substitution appears to depend on the size of the nucleophile.[123] Table 2.17 shows the ratio of 2,6-:2,4-disubstituted products obtained for further substitution.[123]

Table 2.17[123]

Nucleophile	Solvent	Ratio of 4/2 substitution.
NH_3	EtOH	0/100
Me_2NH	EtOH	70/30
MeO^-	MeOH	0/100
EtO^-	EtOH	1/99

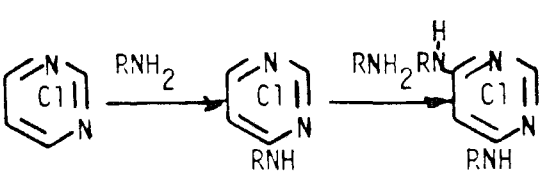
2.4.4 Tetrachlorodiazines

Tetrachloropyridazine reacts with aqueous ammonia in ethanol and sodium hydroxide in water to give 4-amino- and 4-hydroxy-trichloropyridazine respectively[125] i.e. substitution occurs *para* to the nitrogen. No other isomer was reported formed.



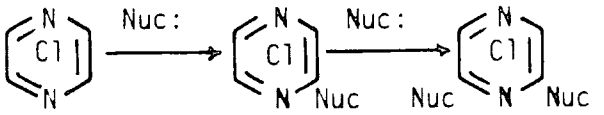
(2.31)

Tetrachloropyrimidine reacts with aqueous ammonia and primary aromatic amines in aqueous acetone to give the 4-substituted product.[125] Further substitution with amines leads to the 4,6-disubstituted product,[125,126] i.e. for both mono- and di-substituted compounds attack occurs *para* to a ring nitrogen as for tetrafluoropyrimidine.



(2.32)

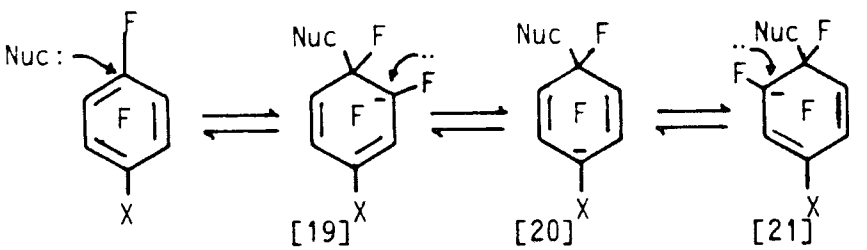
Tetrachloropyrazine has only one position for monosubstitution. Recent work has shown that for disubstitution, attack occurs meta to the first substituent whether the nucleophile is an anion (methoxide ion) or neutral (amine).[96]



(2.33)

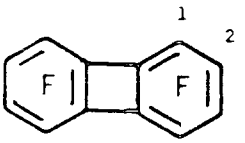
2.5 Rationalisation of Position of Substitution in Polyfluoroaromatic Compounds.

As has been discussed previously, the earliest rationalisation of the orientation of substitution, in polyfluoroaromatic compounds, considered only the I-pi deactivating effects of fluorine on the Wheland intermediates [19] to [21]. Substitution occurring at the position which gave the least number of para fluorines.



(2.34)

This rationalisation fails to explain the activating effects of fluorine when it is ortho, meta, and para to the position of substitution for instance.



(2.35)

Where 2-substitution is predicted but 1-substitution occurs.

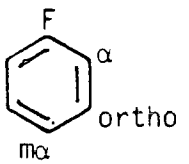
Also, this rationalisation fails to explain why ortho-fluorine is activating relative to hydrogen - when on the basis of the Wheland intermediates alone, we would expect ortho fluorine - like para fluorine to be deactivating.

Chambers et al have clearly shown that relative to hydrogen ortho and meta fluorine are strongly activating. For instance for methoxydefluorination of polyfluorobenzenes the activating effects fluorine versus hydrogen are ortho 57:1, meta 106:1 para 0.43:1. Obviously any explanation of the orientation of substitution must also be able to explain activating effects.

2.5.1 The Extrapolation Approach.

Some authors have attempted to explain nucleophilic aromatic substitution by a method which involves extrapolating data obtained for electrophilic substitution; they suggest that since in halogenobenzenes (PhX) electrophilic substitution takes place mainly para but also ortho to the halogen. The orientation may be explained either by an attenuation of the -I effect in transmission around the ring, or a preferential relaying of the -I effect to the para- position. The relative activation of these sites in the electrophilic attack of

fluorobenzene were designated α and mα with the meta position being taken as substantially unaffected by the process which determines orientation.



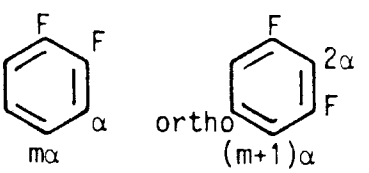
(2.36)

They defined α and mα as:

$$\alpha = -RT \ln k_o/k_m = -2.3RT(\sigma_o - \sigma_m)_p$$

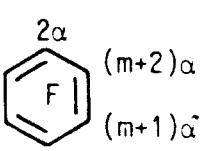
$$m\alpha = -RT \ln k_p/k_m = -2.3RT(\sigma_p - \sigma_m)_p$$

By extension of this argument they were then able to give equations for disubstitution benzenes.



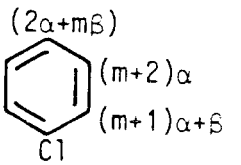
(2.37)

And finally:



(2.38)

They extended this approach to include chloro-, bromo- and iodo benzenes, using the corresponding parameters β,γ and δ respectively. Hence for chloro benzene they get:



(2.39)

This approach was apparently used successfully in predicting the ^{19}F chemical shifts for a series of 35 compounds using the values of m=0.28, α=22.3ppm and β=-2.2ppm.

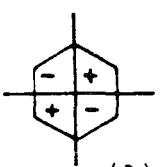
This approach was less successful at predicting relative rate constants however, this is not unexpected since during the whole procedure the effect of a meta-fluorine is ignored, We have already mentioned that the meta-fluorine was found to be by far the most important by Chambers et al. for reactions with methoxide and the polyfluorobenzenes.

2.5.2 The Frontier Orbital Approach.

An attempt at applying Frontier Orbital Theory to Nucleophilic Aromatic Substitution Reactions has been made by Epiotis and Cherry.[121,122] The essence of their approach is a consideration of the initial state rather than the Wheland intermediates. The dominant orbital interactions leading to the transition state within the context of the FO approximation, involve the Highest Occupied Molecular Orbital

(HOMO) approximation of the electron donor - the Nucleophile - and the Lowest Unoccupied Molecular Orbital (LUMO) of the electron acceptor - the substrate.

For simple nucleophiles like methoxide and ammonia the HOMO may be considered to be of at least cylindrical symmetry and thus control of the position of substitution must rest with the LUMO of the substrate. The Molecular Orbital analysis for pentafluorobenzene results in two degenerate LUMO's (A) and (S).



(A)

(S) (2.40)

Where the substituent induced energy difference between (A) and (S) is large (i.e. X is a strong donor or strong acceptor of electrons) then either (1) substitution should be nearly all <u>para</u> to X (if (S) is lowest lying) or (2) equal amounts of substitution are expected <u>meta</u> and <u>ortho</u> to X (if (A) is lowest lying). This latter prediction is modified by Epiotis and Cherry to include steric effects of the <u>ortho</u>-fluorines and hence the final predictions regarding orientation of nucleophile attack on C_6F_5X are:

X	Preferred Orientation
weak donor	<u>para</u>>><u>meta</u>><u>ortho</u>
strong donor	<u>meta</u>><u>ortho</u>>><u>para</u>

This explanation is supported by consideration of the series $X=CH_3<OMe<O^-$ in which X is order of increasing donor strength. For the powerful donor O^-, substitution is entirely para; for the weak donor CH_3,entirely meta whilst for the intermediate donor MeO^-both para and meta products are observed. However, it fails to predict the orientation of substitution in more complicated molecules such as perfluoronaphthalene [22] and where the prediction for substitution by FO theory requires that the LUMO and the next highest energy level be reversed. This situation may merely reflect the simplicity of the approach, rather than its lack of usefulness.

2.5.3 Hard-Soft Acid-Base Theory

The Hard-Soft,Acid-Base Concept of chemical reactivity was introduced some years ago by Pearson, at first in inorganic chemistry and later into organic chemistry as well. Pearson pointed out that Lewis acids and bases (including H^+ and OH^-)could be classified (empirically) as belonging to one of two classes. One class he called Hard, the other Soft. The striking observation was, and this was the basis of the empirical classification, that on the whole hard acids reacted faster and formed stronger bonds with hard bases, while soft acids reacted faster and formed stronger bonds with soft bases. The characteristics which were found empirically to be related to this representation of Hardness/ Softness are:

Hardness. Bonds with a high degree of ionic character.

Softness. Bonds with a high degree of covalent character.

The proton is a typical hard acid and is a stronger acid than the silver cation, Ag^+, when a hard base like hydroxide is used as the

reference point; but if a softer base like ammonia, NH_3, had been used we would have come to the opposite conclusion. This situation is summarised in the rule Hard-likes-Hard, Soft-likes-Soft. Nowadays, it is usual to describe HSAB theory in Molecular Orbital terms. If we consider the thermodynamic acidity/basicity expressed in the equilibrium.

$$\text{acid} + \text{base} \rightleftharpoons \text{salt} \qquad (2.41)$$

The equilibrium is affected by orbital interactions. In outline, it seems that hard acids bond strongly to hard bases because the energy difference between the reacting orbitals is large, hence an ionic bond is formed as for example that between Na^+ and F^-. On the other hand a soft acid reacts with a soft base because the orbitals involved are close in energy.

The principle of hard soft acids and bases has also been applied to kinetic phenomena. In this connection it is more directly applicable to organic chemistry, in particular to the reactions of electrophiles and nucleophiles.

Briefly in HSAB theory:

Hard nucleophiles have low energy HOMO and usually have a negative charge.

Soft nucleophiles have a high energy HOMO and do not necessarily have a negative charge.

Hard electrophiles have a high-energy LUMO and usually have a positive charge.

Soft electrophiles have a low-energy LUMO and do not necessarily have a negative charge.

To take a simple example, a nucleophile like hydroxide is hard at least partly because it has a charge and because it is based on a small electronegative element. Accordingly it reacts faster with a hard electrophile like a proton than with a soft electrophile like bromine.

$$HO^- \quad H\text{-}\overset{+}{O}H_2 \text{ faster than } HO^- \quad Br\text{--}Br \qquad (2.42)$$

The order of reactivities for 2,4 dinitrohalobenzenes with methoxide and thiophenoxide ion may be explained by the HSAB principle, in that the order of hardness is F>>Cl>Br>I whilst the order of softness is I>Br>Cl>>F. The order of reactivity with methoxide (hard base) is F>>Cl>Br>I while that for thiophenoxide (soft base) is F>I-Br>Cl. When considering the reactions of mixed chloro-fluorocompounds, we would expect that for a hard base e.g.methoxide that the hard fluorine will always be displaced in preference to the soft chlorine and this generally seems to be the case; However, for reactions in which more than one fluorine can be displaced, it becomes more difficult to apply HSAB theory, largely because of the problem in deciding which fluorine is the hardest, We must conclude therefore that the HSAB theory is of limited usefulness in deciding on the orientation of Nucleophilic Aromatic Substitution , However, it is probably useful as an adjunct to the Frontier Orbital Model giving a guide to the relative energies of the nucleophile/substrate HOMO/LUMO's.

DISCUSSION

CHAPTER 3

NUCLEOPHILIC AROMATIC SUBSTITUTION

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3.1 Introduction

The discussion of Chapter 2. showed that some progress has been made in explaining the orientation patterns in the nucleophilic substitution reactions of a variety of mono- and poly-halogenated aromatic systems, the rationalisations used however, are limited in scope and fail to take into account the activating effects of halogen. The aim of the work described here has been to relate the rates of reaction to the substituents on the aromatic ring, the structure of the substrate, and the mechanism of nucleophilic aromatic substitution. The results of these investigations have important industrial applications in the dyestuffs industry, assisting in the design and development of new fibre reactive dye systems.

3.2 The Use of Polyhalogenated Nitrogen Heterocycles in Fibre Reactive Dyes

3.2.1 Introduction.

It is very important that a dyed textile should be washable without the risk of 'bleeding' or loss of the dye during the wash. To achieve such washablility or 'colour fastness' it is necessary for there to be some interaction which will retain the dye on the fibre during the washing process. Several mechanisms exist by which a dye can be retained on different types of fibres. Nylon, polyester and cellulose acetates can be dyed using water insoluble dyes which form a solid solution of the dye 'dissolved' in the fibre. Wool, nylon and polyacrylonitriles which contain basic or acidic groups can be coloured with dyes which form an ionic bond between an acidic group in the dye

and a basic centre in the fibre or vice versa.

Dyes using either of these retention mechanisms cannot be applied to the cellulose based fibres which include the most popular textile fibre, cotton. Cellulose fibres are amorphous, very hydrophilic and the only functional groups they contain are alcoholic or hydroxy groups. Prior to the introduction of modern fibre reactive dyes in 1956, cotton dyes were one of two types.

i) Azoic and vat dyes which form an insoluble dye within the fibre from water soluble precursors, the dye then being caused to aggregate, physically trapping the dye within the fibre pores.

ii) Direct dyes which use hydrogen bonds formed between long planar dye molecules and the fibre to hold a water soluble dye on the substrate.

The Azo dyes gave good colour fastness but required complex application procedures whilst the direct dyes were easy to apply but gave poor colour fastness.

3.2.2 Fibre Reactive Dyes.

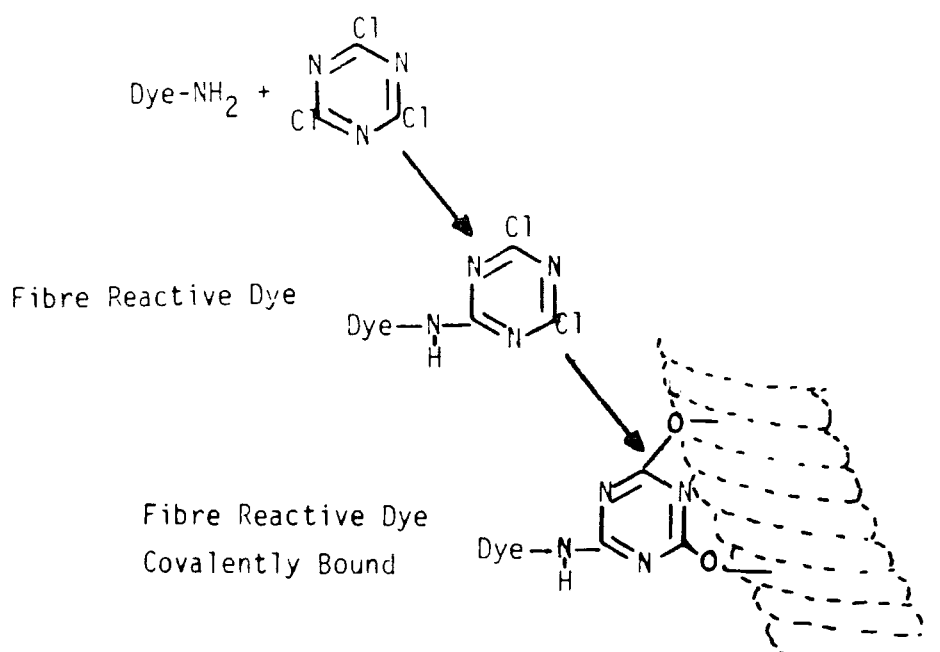
It had long be perceived that the best colour fastness would be achieved if a covalent link could be formed between the dye and the fibre. The difficulty lay in devising a simple method of doing this and it was this problem that was overcome with introduction of the fibre reactive dyes the first of which were patented by ICI in 1956.

Fibre reactive dyes consist of a chromophore (dye) attached to a small reactive system (SRS) which is susceptible to attack by fibres containing 'mobile' hydrogen (cellulosic materials, in particular, and natural or synthetic polyamides) to form a covalent fibre/dyestuff bond. The chromophore contributes the colour and so long as it contains a group, invariably amino, to which the small reactive

system (SRS) can be attached, little else is required of it. This freedom of choice removes the need to use large dye molecules which had previously been a characteristic of of all water soluble cotton dyes.

Very simple dye structures can now be chosen almost entirely on the basis of shade and light fastness. In practice chromophores which contain sulphonic acid groups to confer water solubility are preferred.

The vast majority of SRS's are small aromatic systems of nucleophilic character and the first fibre reactive dyes were based on 1,3,5-trichloro-s-triazine (cyanuric chloride) - (3.1). Since then, many hundreds of heterocycles have been patented for use in fibre reactive dyes, but with comparatively little understanding of the properties of the SRS's that govern their susceptibility to nucleophilic attack by both dye and fibre.

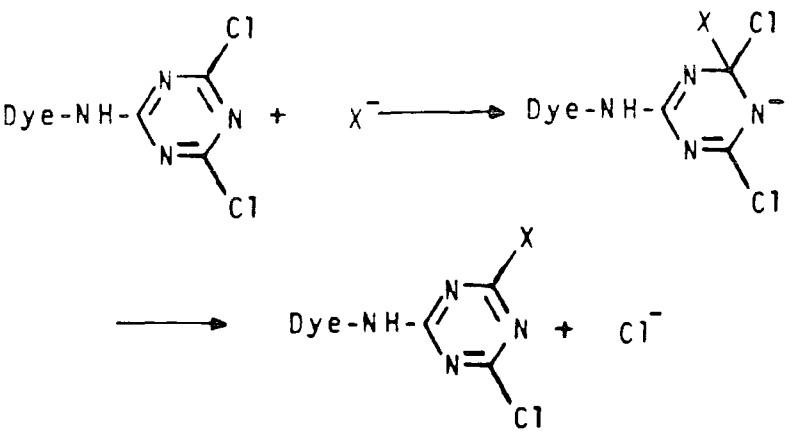


(3.1)

Since the initial use of 1,3,5-trichloro-s-triazine as the SRS by ICI many other companies have produced fibre reactive dyes, perhaps the most significant of which are the series of fluoropyrimidine based reactive dyes first discovered by Bayer in 1966 and marketed in 1970 as the first reactive dyes based on fluorine as the leaving group.

3.2.3 Method and Mechanism of Fibre Reactive Dying.

A typical method of application of a fibre reactive dye is to dissolve the dye in water and, since nucleophiles are not present to any great extent at neutral pH, the solution is quite stable. The cloth is immersed in the solution and salt (about 6% w/v) is then added causing the sulphonated dye to be driven out of the solution and adsorbed by the fibre. After these purely physical processes have taken place (taking about 30 min to complete), alkali, usually sodium carbonate, is added to raise the pH to about 10.5. Now the nucleophiles necessary for reaction are present and attack on the dye takes place thus:



(3.2)

The attacking species, X^-, can be either cellulose-O^- leading to fixation of the dye on the fibre or HO^- resulting in hydrolysis to give unfixed dye which is washed out of the cloth at the end of the dyeing process. These two reactions will be governed by the rate equations :

$$\text{Rate of Fixation} = k_1[\text{Dye}][\text{Cellulose-O}^-]$$

$$\text{Rate of Hydrolysis} = k_2[\text{Dye}][HO^-]$$

These two reactions have similar rate constants and thus give no inherent preference for fixation. If all other things are equal, the large excess of water present should lead to hydrolysis being the

overwhelming reaction. Two effects swing the reaction in favour of fixation in this heterogeneous process. First, the adsorption of the dye on to the fibre causes the concentration of dye in the fibre phase to be up to 500 times greater than the concentration of dye in solution and, second, the ready ionization of the C_6 primary hydroxyl group in cellulose leads to about a 25-fold excess of cellulose $-O^-$ ions over HO^- ions inside the fibre. These two effects completely outweigh the vast excess of water and ensures that fixation predominates.

3.2.4 Substantivity versus Reactivity.

The preference of the dye for being adsorbed on the fibre rather than remaining in solution is termed the substantivity of the dye and it is clear from the above that whilst a highly reactive dye may react at lower temperatures (with potentially enormous savings in energy costs), it will be of little practical use if it also has a low substantivity which consequently results in most of the dye being hydrolysed by alkali in solution. A dye with low reactivity but high substantivity may prove to be more practical than a dye which has such a high reactivity that it is all hydrolysed before it can become attached to the fibre.

A reactive dye for practical applications must fulfil the following requirements:

i) display good reactivity towards 'fibre nucleophiles',

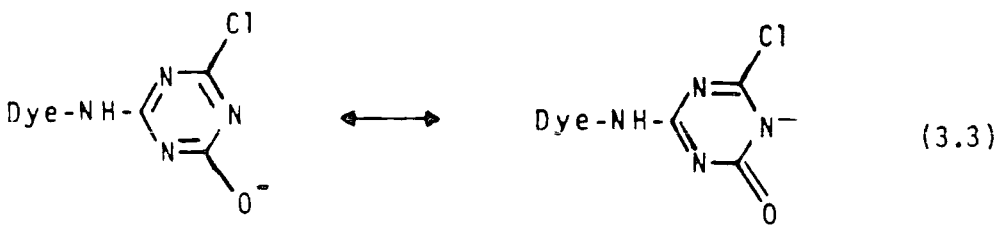
ii) give a stable fibre/dyestuff bond,

iii) undergo as little hydrolysis as possible in the aqueous alkaline dyeing solution, and

iv) allow efficient 'washing-out' of the unfixed (hydrolysed) dyestuff from the fibre, to give wet-fast dyeings.

3.2.5 The Effect of Reaction at Two Sites in the SRS.

The dichloro-s-triazinyl dyes have two equally reactive chlorine atoms but if hydrolysis occurs, the resulting chlorohydroxy-s-triazine is ionized in the alkaline medium employed, imparting a full negative charge to the system. Feedback of this into the triazine ring eliminates the positive charge on the ring carbon atoms and stops nucleophilic attack, thus denying this species a further chance to achieve fixation. In the fixed dye molecule [1] the remaining chlorine is still labile although the level of reactivity is decreased by the presence of the cellulose-O^- grouping.



(3.3)

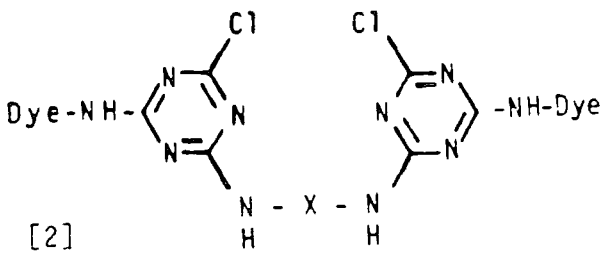
[1]

Under severe or prolonged dyeing conditions this chlorine can be hydrolysed or replaced by a further cellulose $-O^-$ leading to crosslinking of the fibre.

3.2.6 Mono Halogenated Dyes.

Replacement of one chlorine atom of a dichloro-s-triazinyl dye by a non-labile, electron repelling substituent such as an amino or alkoxy group leads to the monochloro-s-triazinyl species. The dyes form the backbone of the ICI Procion ranges of reactive dyes. The introduction of this second amino group on to the ring causes the level of reactivity to be markedly depressed. In practical terms the temperature necessary to cause fixation on to cellulose rises from about the 30-40°C range to about 80°C and generally, slightly more alkaline conditions (about pH 11) are required. In the case of small,

simple reactive dye molecules there is no economic advantage to using the monochloro-s-triazinyl dyes and the dichloro-s-trazinyl dyes are generally preferred. The higher temperature does, however allow larger dye molecules to penetrate more satisfactorily and be better adsorbed by the fibre during the exhaustion stage. This fact is exploited in dyes such as [2] which have been further enhanced by having two distinct reactive systems.



[2] (3.4)

These dyes thus have two chances of achieving fixation and, consequently, a higher proportion of the dye is fixed and less wasted.

3.2.7 The Use of Fluorine as Leaving Group.

A number of dyes have been developed with SRS'S which use fluorine as a leaving group such as the monofluoro-s-triazines produced by Ciba-Geigy. Unlike their mono chloro counterparts they can be applied to cellulose at about 50°C. Many other SRS's have been developed using fluorine but a complication arises from the preference of the soft amino containing nucleophile to displace the softer chlorine rather than the hard fluorine atoms. This preference is reversed during the fixation process when the hard alkoxide ion prefers to displace the fluorine atom thus leading to the lower fixation temperature. A consequence of the difficulties experienced in the initial condensation of amine with fluoroheterocycles has been the emergence of a number of new dyestuff intermediates carrying $-CH_2NH_2$

groups, which are more readily reacted than simple aromatic amino groups.

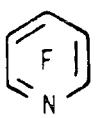
3.2.8 The Raison D'Etre For the Current Investigation

From the previous description of the fibre reactive dyes the importance of an understanding of the mechanism for Nucleophilic Aromatic Substitution to the Dyestuffs industry will be clear. Of particular importance is the mechanism of reaction with the small halogenated compounds used as SRS's and in particular those of the heterocyclic rings containing nitrogen. Much of the previous literature on these mechanisms investigated reactions with small hard nucleophiles such as methoxide and ammonia. Where softer nucleophiles such as aniline were used, then the ring under attack usually contained other substituents such as the nitro group which, when in positions ortho to the site of attack alters the course of the reaction through the formation of hydrogen bonds with the attacking nucleophile. Also, if a two step mechanism is accepted then a change from a hard to soft nucleophile could have a profound influence upon which step is rate determining. If a change in the rate determining step can be induced, then much information about the relative importance of effects acting through sigma versus pi bonds can be obtained, in particular those effects which influence the orientation of attack should be elucidated. Furthermore the reactions of a larger aromatic nucleophile such as aniline might be expected to more closely mimic the behaviour of the large dye molecules in common use, giving the results increased relevance to the dyestuff industry.

This chapter and chapter 5 describe the results of reactions between aniline, various substituted anilines and a series of polyhalogenated nitrogen heterocycles.

Table 3.1

The Orientation Of Nucleophilic Substitution in Polyaromatic Compounds.

	Nucleophile	Substrate	Position of Substitution	Conditions	
(1)	NH_3		4- (100%)	25°	a ref.96
(2)	Et_2NH	〃	4- (100%)	25°	a ref.96
(3)	$PhNH_2$	〃	4- (100%)	25°	a
			4- (100%)	80°	b,c
(4)	Ph.NH.Me	〃	4- (100%)	80°	b,c
(5)	$PhCH_2NH_2$	〃	4- (100%)	25°	b
			2,4- (65%); 4(35%)	80°	b,c

a= Dioxan/H_2O, 60:40 (v/v)

b= Dioxan

c= Sealed tube

Table 3.1 continued

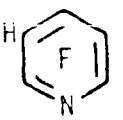
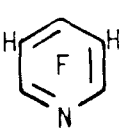
	Nucleophile	Substrate	Position of Substitution	Conditions	
(6)	NH_3		4- (79%) 2- (21%)	25°	a ref.96
(7)	$PhNH_2$	〃	4- (75%) 2- (25%)	25°	b
(8)	Ph.NH.Me	〃	4- (59%) 2- (41%)	80°	b,c
(9)	$PhCH_2NH_2$	〃	4- (60%) 2- (40%)	80°	b,c
(10)	NH_3		4- (78%) 2- (22%)	25°	a ref.96
(11)	$PhNH_2$	〃	4- (80%) 2- (20%)	25°	b,c

Table 3.1 continued

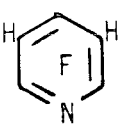
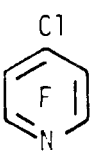
	Nucleophile	Substrate	Position of Substitution	Conditions	
(12)	PhNH.Me		4- (61%) 2- (33%) 2,6- (6%)	80°	b,c
(13)	$PhCH_2NH_2$	〃	4- (77%) 2- (23%)	80°	b,c
(14)	NH_3		2- (100%)	25°	a ref.96
(15)	Et_2NH	〃	2- (100%)	25°	a ref.96
(16)	$PhNH_2$	〃	2- (100%)	80°	b,c
(17)	$PhCH_2NH_2$	〃	2- (100%)	80°	b,c

Table 3.1 continued

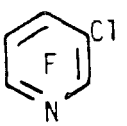
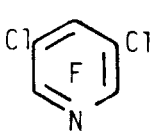
	Nucleophile	Substrate	Position of Substitution	Conditions	
(18)	NH_3		4- (100%)	25°	a ref.96
(19)	Et_2NH	〃	4- (36%) 6- (64%)	25°	a ref.96
(20)	$PhNH_2$	〃	4- (100%)	80°	b,c
(21)	NH_3		4- (100%)	25°	a ref.96
(22)	Et_2NH	〃	2- (100%)	25°	a ref.96
(23)	$PhNH_2$	〃	4- (92%) 2- (8%)	25°	a

Table 3.1 continued

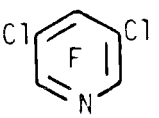
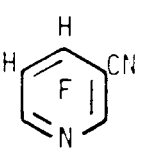
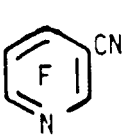
	Nucleophile	Substrate	Position of Substitution	Conditions	
(24)	PhNH.Me		2- (100%)	80°	b,c
(25)	$PhCH_2NH_2$	〃	4- (77%) 2- (23%)	80°	b,c
(26)	NH_3		2- (50%) 6- (50%)	25°	a
(27)	$PhNH_2$	〃	2- (50%) 6- (50%)	25°	a
(28)	$Ph.CH_2.NH_2$	〃	2- (63%) 6- (27%)	25°	a
(29)	NH_3		4- (67%) 6- (23%)	25°	a

Table 3.1 continued

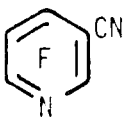
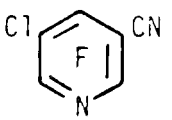
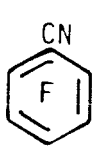
	Nucleophile	Substrate	Position of Substitution	Conditions	
(30)	$PhNH_2$		4- (70%) 6- (30%)	25°	a
(31)	NH_3		4- (75%) 2- (25%)	25°	a
(32)	$PhNH_2$	〃	4- (75%) 2- (25%)	25°	a
(33)	PhNH.Me	〃	2- (75%) 6- (25%)	80°	b,c
(34)	$Ph.CH_2.NH_2$	〃	4- (55%) 2- (45%)	25°	a
(35)	NH_3		4- (100%)	25°	a

Table 3.1 continued

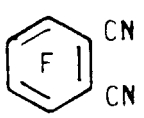
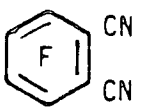
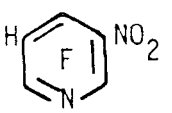
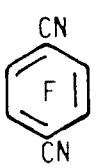
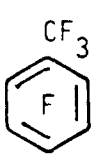
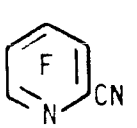
	Nucleophile	Substrate	Position of Substitution	Conditions	
(36)	$PhNH_2$		4- (100%)	25°	a
(37)	PhNH.Me	〃	2- (100%)	25°	b
(38)	$Ph.CH_2.NH_2$	〃	4- (100%)	25°	b
			4- (95%);2- (5%)	80°	b,c
(39)	NH_3		4- (50%)	80°	a
			6- (50%)		
(40)	$PhNH_2$	〃	4,6- (50%)	80°	a
			6- (50%)		
(41)	PhNH.Me	〃	4- (100%)	80°	b

Table 3.1 continued

	Nucleophile	Substrate	Position of Substitution	Conditions	
(42)	$Ph.CH_2.NH_2$		4- (7%) 6- (56%) 4,6- (37%)	80^o	b
(43)	NH_3		4- (100%)	25^o	a
(44)	$PhNH_2$	〃	2- (20%) 4- (20%) 2,4- (60%)	80^o	b
(45)	NH_3		2- (100%)	80^o	a
(46)	$Ph.NH_2$		4- (100%)	80^o	b
(47)	NH_3		4- (100%)	25^o	a
(48)	$PhNH_2$	〃	4- (100%)	25^o	b

3.3 The Orientation Patterns with Amines

The results of a series of reactions between various amines and halogenopyridines are shown in Table 3.1

3.3.1 Reactions with Primary Amines

The data of Table 3.1 show a remarkable similarity in the orientations of substitution obtained for the aliphatic and aromatic primary amines, ammonia and aniline. With pentafluoropyridine, (1) and (3), substitution is exclusively in the 4-position, whilst for 2,3,4,6-tetrafluoropyridine substitution is 4-(79%) and 2-(21%) with ammonia (6); 4-(75%) and 2-(25%) with aniline (7). Similarly both amines give exclusively 4-substitution with 3,5-dichlorotrifluoropyridine, (21) and (23), and 2-(50%) and 6-(50%) substitution with 3-cyano-2,6,-difluoropyridine (26) and (27). Thus, the benzene ring of aniline shows little effect upon the orientation of substitution with the halogenated pyridines.

3.3.2 Reactions with Secondary Amines

Reaction of both the aliphatic secondary amine diethylamine and the aromatic secondary amine N-methylaniline with pentafluoropyridine gives exclusively 4-substitution (4) and (2). Reaction of diethylamine with 3-chlorotetrafluoropyridine (19) gives a substantial amount of 2-(64%) substitution, whilst reaction of both diethylamine and N-methylaniline with 3,5-dichlorotrifluoropyridine (22) and (24) give exclusively 2-substitution. These results can be accounted for in terms of the large steric requirements of N-methylaniline and diethylamine as compared to aniline and ammonia. The effect of replacing the 3-fluorine in pentafluoropyridine by chlorine increases the steric crowding at that position for reaction with diethylamine,

which then reacts preferentially in the 5-position. This position is less sterically crowded and is activated by the para-chlorine. Addition of a second chlorine, giving 3,5-dichlorotrifluoropyridine, increases the crowding at the 4-position still further, to the point where no product resulting from attack by secondary amines at this position is given.

3.4 Unusual Orientations

3.4.1 Benzylamine

Benzylamine reacts with pentafluoropyridine (5), 2,3,4,5-tetrafluoropyridine (9) and 2,3,6-trifluoropyridine (13) to give product ratios which are close to those for aniline and ammonia. With 3,5-dichlorotrifluoropyridine (25) however, benzylamine reacts at the 4-(77%) and 2-(23%) positions whereas aniline and ammonia react with this substrate, (23) and (21) almost exclusively at the 4-position. The reaction of benzylamine and 3-chloro-5-cyanotrifluoropyridine (34) gives substitution at the 2-(45%) position as compared to aniline with this substrate which gives 2-(25%). These results are not consistent with any steric effect as a steric argument would lead to aniline having the more crowded transition state.

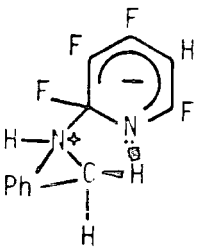
As Table 3.2 shows, benzylamine is much more basic than even diethylamine in water. Since nucleophilicity tends to follow basicity in series in which the same heteroatom is involved, we might expect benzylamine to be the faster nucleophile. Therefore, if we accept that steric crowding by the 3,5-chlorines is still significant even with benzylamine, then we may be seeing increasing formation of the (less crowded) kinetically favoured 2-isomers, as opposed to the thermodynamically favoured 4-isomer.

Table 3.2

Amine	pKb
$PhCH_2NH_2$	0.64
$(CH_3)_2NH$	3.27
NH_3	4.27
PhNH.Me	9.19
$Ph.NH_2$	9.27

3.4.2 N-Methylaniline

We have shown in section 3.3.2 that the orientation patterns with N-methylaniline are affected sterically by large halogen substituents such as chlorine. Table 3.1 demonstrates however that for reaction with 3-chloro-5-cyanotrifluoropyridine (33) substitution is exclusively 2- and for reactions with both 2,4,5,6-tetrafluoropyridine (8) and 2,4,6-trifluoropyridine (12), N-methylaniline shows significantly more (41% and 33% respectively) 2-substitution than either aniline (25% and 20%) or ammonia (21% and 22%). Since, in these substrates only fluorine or the smaller hydrogen are present in the 3- and 5-positions, this cannot be a steric effect. Table 3.2 shows N-methylaniline to be only slightly more basic than aniline and much less basic than ammonia, thus the effect on orientation cannot be due to differing basicities. This result can be explained by considering the 2-isomer to be more stable when N-methylaniline is the nucleophile because of hydrogen bonding between the N-methyl hydrogens and the lone pair of the ring nitrogen in the transition state.



(3.5)

When benzylamine is the nucleophile, structures analogous to (3.5) may be drawn, and used as an alternative to the previous explanation (Section 3.4.1) of the enhanced 2- reactivity of benzylamine.

3.4.3 Effects of Changing Aniline Basicity

Substitution of electron donating/withdrawing groups meta- and para- to the amino- group of aniline will affect its basicity without changing the steric requirements of nucleophilic aromatic substitution; thus it should be possible to determine the effect of changing basicity independently of steric effects. Tables 3.3a and 3.3b show the results for the reactions of a series of ortho and meta substituted anilines with various polyfluoropyridines and benzenes. The basicity was found to have no consistent effect upon the orientation of substitution.

3.5 An Alternative Rationalisation for the Rate Data and Orientation of Substitution

3.5.1 The Effect of Halogen upon Carbanion Stabilities

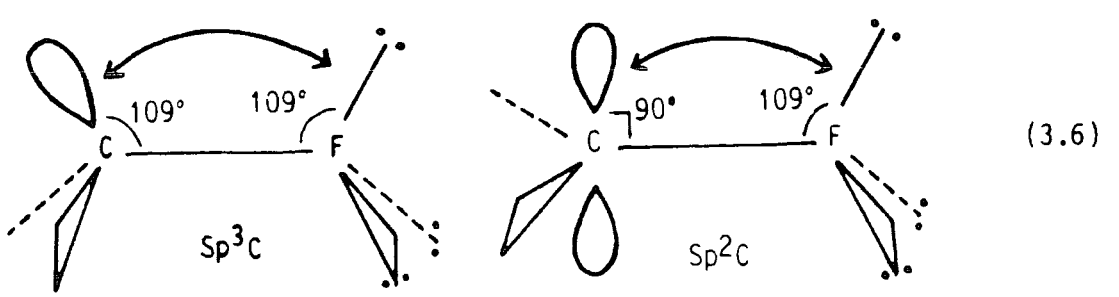
It is now well established that a fluorine atom in the situation [3] is strongly carbanion - stabilizing, whereas in the situation [4], electron withdrawal is offset by electron pair repulsion and the

Table 3.3a

Results of Reactions of Ortho-, Meta- and Para-Substituted Anilines with Pentafluoropyridine (A) and 3-Cyanotetrafluoropyridine (B) 3-Chloro-5-cyanotrifluoropyridine (C) in Dioxan at 25°C

Substituent	pKb	Position of Substitution		
		A	B	C
p-NO_2	13.00	no reaction	-	no reaction
m-NO_2	11.50	4-	4-	-
m-Cl	10.52	4-	4-(71%);4,6-(29%)	-
p-Br	10.00	4-	-	-
p-Cl	9.82	4-	4-(63%) 2,4-(25%);2,4,6-(12%)	4-(90%),2-(19%)
m-MeO	9.67	4-	4-	-
m-Me	9.31	4-	-	-
H-(aniline)	9.27	4-	4-(70%);2-(30%)	4-(75%),2-(25%)
p-Me	8.92	4-	-	-
p-MeO	8.82	4-	-	4-(90%),2-(10%)
NH_3	4.27	4-	4-(70%);2-(30%)	4-(75%),2-(25%)
m-Br	-	4-	-	-

resultant effect can be that fluorine is slightly destabilizing, with respect to hydrogen at the same position.



(3.6)

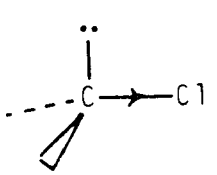
[3] [4]

Table 3.3b

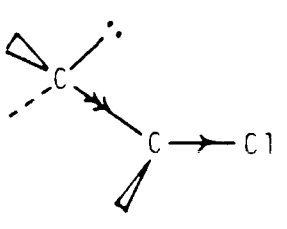
Results of Reactions of Ortho-, Meta- and Para-Substituted Anilines with Pentafluoropyridine (A) and Pentafluorobenzonitrile (D) Pentafluoro- nitrobenzene (E) in Dioxan at 25°C

Substituent	pKb	Position of Substitution		
		A	D	E
p-NO_2	13.00	no reaction	-	-
m-NO_2	11.50	4-	4-	2-
m-Cl	10.52	4-	-	2-(70%);2,6-(30%)
p-Br	10.00	4-	4-	-
p-Cl	9.82	4-	4-	-
m-MeO	9.67	4-	-	-
m-Me	9.31	4-	-	-
H-(aniline)	9.27	4-	-	2-
p-Me	8.92	4-	-	2-
p-MeO	8.82	4-	-	2-(60%);2-,6-(40%)
NH_3	4.27	4-	-	2-
m-Br	-	-	4-	2-(70%);2-,6-(30%)

For chlorine however, unlike [3], [5] is known to be a stabilizing situation, whilst the effect of chlorine on a beta-carbanion [6] is not known (Beta elimination rapidly occurs), it seems likely that it will be stabilizing compared to hydrogen.



[5]

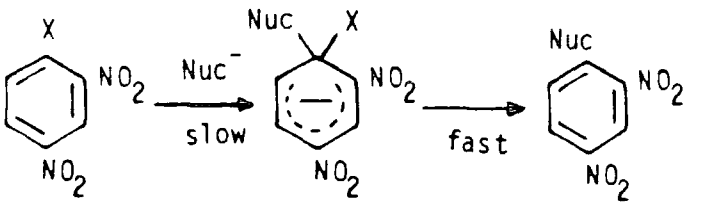


[6]

(3.7)

3.5.2 Effect of Chlorine versus Fluorine in Aromatic Nucleophilic Substitution

In the classic work on the 2,4-dinitrohalobenzenes with many nucleophiles, the ease of replacement of aromatic halogen is in the order F>>Cl>Br>I[79], consistent with a two step mechanism in which very little bond breaking is involved in the rate-limiting transition state.



(3.8)

(X=F,Cl etc.)

This apparently simple situation can become more complex with base catalysis, where the rate of the second stage becomes important; under these conditions an order of replacement Br>Cl>F has been observed[32]. However it appears that in most reactions it is the polarity of the C-F bond that leads to special reactivity, arising from a slow first step.[32]

3.6 Results of Reactions with Methoxide and Ammonia

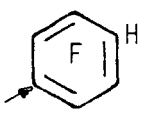
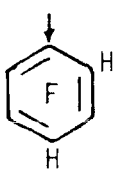
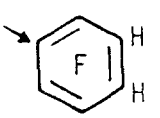
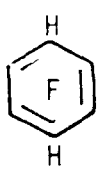
The rates of reaction for a variety of polyfluorobenzenes with sodium methoxide in methanol at 58°C are shown in Table 3.4. Comparison of the rate constants for pentafluorobenzene (50) and 1,2,3,5-tetrafluorobenzene (51) gives a relative rate constant, or substituent rate factor (srf), for fluorine versus hydrogen when they are ortho to the position of attack e.g.

$$k(50)/k(51) = k(F)/k(H)\ \underline{ortho}$$

$$k(F)/k(H)\ \underline{ortho} = \frac{3.02 \times 10^{-4}}{5.28 \times 10^{-6}} = 57$$

Table 3.4

Rate Constants for Reactions of Polyfluorobenzenes with Sodium Methoxide in Methanol at 58.0°C [101]

	Substrate	k/(l mol^{-1}s^{-1})
(49)		1.29×10^{-4} a
(50)		3.02×10^{-4}
(51)		5.28×10^{-6} a
(52)		2.85×10^{-6} a
(53)		2.57×10^{-8} a

a= corrected for statistical factors.

$k(50)/k(52) = k(F)/k(H)$ meta = 106

$k(49)/k(50) = K(F)/k(H)$ para = 0.43

Therefore the order of the activating influences of fluorine,

relative to the position of nucleophilic attack in the methoxy-defluorination of benzenes is:

F	ortho	meta	para
	57	106	0.43
	133	246	1

Table 3.5 gives the kinetic data for the methoxydefluorination reaction of various chlorobenzenes in methanol at -7.60°C.

The relative activating influences of chlorine versus fluorine at different positions may be derived.

$k(57)/k(55) = k(Cl)/k(F)$ ortho = 32

$k(56)/k(55) = k(Cl)/k(F)$ meta = 0.69

$k(55)/k(54) = K(Cl)/k(F)$ para = 35

Although the results for fluorine versus hydrogen and chlorine versus fluorine were obtained at different temperatures, if we assume that the influence of temperature on the relative results is small, then we can derive the appropriate srf's for chlorine versus hydrogen e.g.

$$[k(Cl)/k(F)] \times [k(F)/k(H)] = k(Cl)/k(H) \quad (\text{ortho})$$

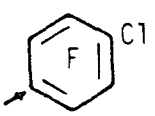
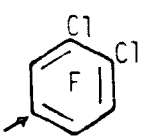
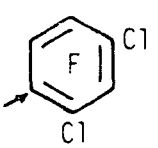
$$k(Cl)/k(H)\ (\text{ortho}) = 3.2 \times 57 = 182$$

similarly: $k(Cl)/k(H)\ (\text{meta}) = 0.69 \times 106 = 73$

$$k(Cl)/k(H)\ (\text{para}) = 35 \times 0.43 = 15$$

Table 3.5

Rate Constants for Reactions of Chlorobenzenes with Sodium Methoxide in Methanol at -7.60°C [101]

	Substrate	$k/(l\ mol^{-1}s^{-1})$	
(54)		8.94×10^{-8}	a
(55)		3.12×10^{-6}	
(56)		2.14×10^{-6}	a
(57)		1.00×10^{-5}	a

a= corrected for statistical factors.

Therefore the activating influences of chlorine relative to the position of nucleophilic attack in the methoxydefluorination of benzenes are:

Cl	ortho	meta	para	
	182	73	15	relative to hydrogen
	12	4.9	1	relative to the para position

Table 3.6 gives the kinetic data for reaction of various

halogeno-pyridines with sodium methoxide in methanol. A comparison of the rate constants for different pairs of compounds allows the activating influence of fluorine atoms ortho and para to the reaction centre to be deduced. Similarly, comparison of the rate constants for attack at the 2-position in compounds (62) and (63) allows the effect of a para fluorine to be deduced.

Attack at the 4- position:

$$k(58)/k(59) = k(F)/k(H) \quad \underline{ortho} = 79$$

$$k(58)/k(60) = k(F)/k(H) \quad \underline{meta} = 30$$

Attack at the 2-position:

$$k(62)/(63) = k(F)/k(H) \quad \underline{para} = 0.33$$

Therefore the order of the activating influences of fluorine, relative to the position of nucleophilic attack in methoxy-defluorination of pyridines is:

F	ortho	meta	para
	79	30	0.33 (relative to hydrogen)
	239	91	1 (relative to the para position)

Table 3.6

Rate Constants for Reactions of Halogeno-pyridines with Sodium Methoxide in Methanol at -7.60°C [101]

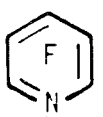
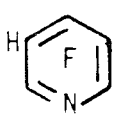
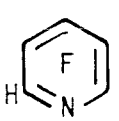
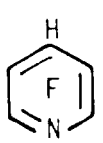
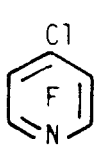
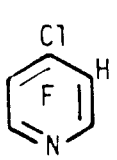
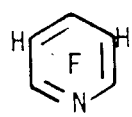
	Substrate	Position of Attack	k/l mol^{-1}s^{-1}	
(58)		4-	1.90	
(59)		4-	2.42×10^{-2}	a
		2-	0.03×10^{-2}	a
(60)		4-	6.42×10^{-2}	
(61)		2-	3.47×10^{-5}	b
(62)		2-	2.09×10^{-3}	b
(63)		6-	6.37×10^{-3}	

Table 3.6 continued.

Rate Constants for Reactions of Halogeno-pyridines with Sodium Methoxide in Methanol at -7.60°C

	Substrate	Position of Attack	$k/l\ mol^{-1}s^{-1}$	
(64)		4-	6.28×10^{-4}	
		2,6-	5×10^{-5}	b

a= separate k values calculated from nmr and glc integrations

b= corrected for statistical factors

3.7 Activating Influences in Aminodefluorination

The results of Table 3.7 for the reactions of ammonia and various halogeno-pyridines enable us to derive in a similar manner to the above, the activating influences of fluorine and chlorine relative to hydrogen.

3.7.1 For Fluorine

Comparing the rate constants for attack at the 4-position in compounds (65) and (66) gives the srf for an ortho fluorine.

$$k(65)/k(66) = k(F)/k(H) \qquad \text{ortho} = 31$$

similarly:

$$k(67)/k(65) = k(F)/k(H) \qquad \text{meta} = 23$$

And for attack at the 6-position:

$$k(66)/k(65) = k(F)/k(H) \qquad \text{para} = 0.26$$

Therefore the order of the activating influences of fluorine, relative to the position of nucleophilic attack in aminodefluorination of pyridines is:

F	ortho	meta	para	
	31	23	0.26	(relative to hydrogen)
	119	88	1	(relative to the para position)

Table 3.7

Rate Constants for Attack by Ammonia in Dioxan-Water (60:40,v/v)a[100]

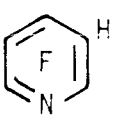
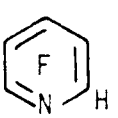
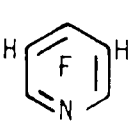
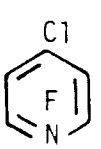
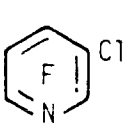
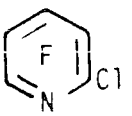
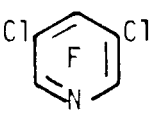
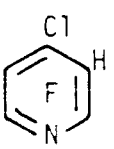
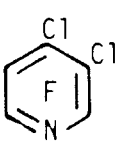
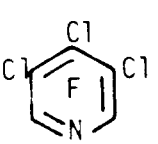
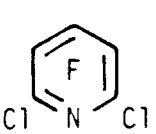
	Substrate	Position of Attack	k/(l mol^{-1}s^{-1})	
(65)		4-	6.80×10^{-4}	
(66)		4-	2.22×10^{-5}	
		6-	5.87×10^{-6}	
(67)		4-	2.93×10^{-5}	
(68)		4-	ca. 0.7×10^{-6}	b
		6-	ca. 0.2×10^{-6}	b
(69)		6-	1.55×10^{-6}	
(70)		4-	1.92×10^{-3}	

Table 3.7 continued

	Substrate	Position of Attack	k/(l $mol^{-1}s^{-1}$)
(71)		4-	7.12×10^{-4}
(72)		4-	4.75×10^{-3}
(73)		6-	5.92×10^{-6}
(74)		2- 6-	4.87×10^{-6} 4.10×10^{-5}
(75)		2-	1.30×10^{-4}
(76)		4-	6.47×10^{-4}

a= all k values have been corrected for statistical factors where appropriate

b= separate k values calculated from nmr and glc integrations

3.7.2 For Chlorine

Attack at the 4-position:

$k(70)/k(66) = k(Cl)/k(H)$ ortho

$= 86$ per ortho chlorine atom

$k(72)/k(68) = k(Cl)/k(H)$ ortho

$= 6.79 \times 10^3$,i.e. 82 per ortho chlorine atom

$k(71)/k(67) = k(Cl)/k(H)$ meta

$= 24$ per chlorine atom

Attack at the 6-position:

$k(74)/k(73) = k(Cl)/k(H)$ para

$= 6.9$ per para chlorine atom

Therefore the order of the activating influence of chlorine, relative to the position of nucleophilic attack in the methoxy-defluorination of pyridines is:

Cl	ortho	meta	para	
	86 :	24 :	6.9	relative to hydrogen
	12.5 :	3.5 :	1	relative to the para position

Values for the relative activation by fluorine and chlorine in nucleophilic aminodefluorination at different positions may be obtained directly from the following comparisons:

Attack at the 4-position:

$$k(72)/k(65) = k(Cl)/k(F) \text{ ortho}$$
$$= 7.0 \text{ i.e. } 2.6 \text{ per ortho chlorine atom}$$

$$k(70)/k(65) = k(Cl)/k(F) \text{ ortho}$$
$$= 2.8 \text{ per ortho chlorine atom}$$

$$k(71)/k(65) = k(Cl)/k(F) \text{ meta}$$
$$= 1.05 \text{ per meta chlorine atom}$$

$$k(76)/k(71) = k(Cl)/k(F) \text{ meta}$$
$$= 0.91 \text{ per meta chlorine atom}$$

$$k(76)/k(65) = k(Cl)/k(F) \text{ meta}$$
$$= 0.95 \text{ i.e } 0.98 \text{ per meta chlorine atom}$$

For attack at the 6- (or 2-) position:

$$k(74),(6-)/k(69) = k(Cl)/k(F) \text{ para}$$
$$= 26.5 \text{ per para chlorine atom}$$

$$k(75)/k(74),(2-) = k(Cl)/k(F) \text{ para}$$
$$= 26.7 \text{ per para chlorine atom}$$

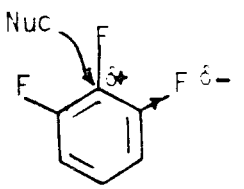
$$k(75)/k(74),(6-) = k(Cl)/k(F) \text{ ortho}$$
$$= 3.2 \text{ per ortho chlorine atom}$$

$$k(74),(2-)/k(69) = k(Cl)/k(F) \text{ ortho}$$
$$= 3.1 \text{ per ortho chlorine atom}$$

3.8 A Rationalisation of Results for Hydrofluorobenzenes

3.8.1 Effect of Fluorine Ortho to the Position of Substitution

The activating effect of fluorine relative to hydrogen in the ortho position results from ground state polarization of the sigma electrons by fluorine, leading to a build up of positive charge at the point of substitution.

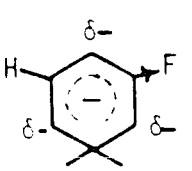


(3.9)

If an ortho hydrogen is replaced by fluorine, the resulting increase in positive charge at the point of substitution ought to increase the rate of nucleophilic attack and vice versa.

3.8.2 Effect of Fluorine Meta to the Position of Substitution

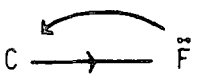
The activating effect of fluorine relative to hydrogen at the position of substitution results from inductive stabilization of the negative charge in the transition state by fluorine, which is impossible in the case of hydrogen. This is shown below:



(3.10)

3.8.3 Effect of Fluorine Para to the Position of Substitution

The fact that fluorine and hydrogen are virtually equivalent at the position para to the point of substitution can be explained by the destabilization caused by electron pair repulsion of fluorine virtually cancelling out the stabilizing effect of electron withdrawal.

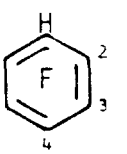


(3.11)

The result of the above effects is that nucleophilic attack occurs so as to maximize the number of ortho and meta fluorines, largely ignoring the para fluorine.

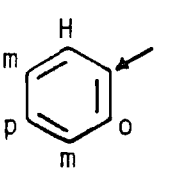
This can be illustrated by the following calculation for pentafluorobenzene (values are for the reaction with methoxide ion).

There are three possible positions of attack; the 2-, 3- and 4-positions



(3.12)

3.8.3.1 The 2-position



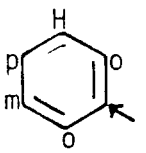
(3.13)

Attack at the 2-position is activated by the 1- ortho, 2- meta and 1- para fluorines. Therefore, the 2-position is activated relative to displacement of fluorine in monofluorobenzene by a factor of:

$$\text{Activation} = \underline{\text{ortho}} \times \underline{\text{meta}} \times \underline{\text{meta}} \times \underline{\text{para}}$$

$$= 57 \times 106 \times 106 \times 0.43 = \underline{2.75 \times 10^5}$$

3.8.3.2 The 3-position



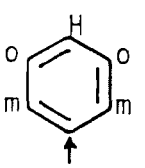
(3.14)

Attack at the 3-position is activated by the 2- ortho,1- meta and 1- para fluorines. Therefore, the 3-position is activated relative to displacement of fluorine in monofluorobenzene by a factor of:

$$\text{Activation} = \underline{\text{ortho}} \times \underline{\text{ortho}} \times \underline{\text{meta}} \times \underline{\text{para}}$$

$$= 57 \times 57 \times 106 \times 0.43 = \underline{1.48 \times 10^5}$$

3.8.3.3 The 4-position



(3.15)

Attack at the 4-position is activated by the 2- ortho and 2- meta fluorines. Therefore, the 4-position is activated relative to displacement of fluorine in monofluorobenzene by a factor of:

$$\text{Activation} = \underline{\text{ortho}} \times \underline{\text{ortho}} \times \underline{\text{meta}} \times \underline{\text{meta}}$$

$$= 57 \times 57 \times 0.43 \times 0.43 = \underline{3.65 \times 10^7}$$

Therefore the relative activation of the three positions is:

$$2\text{-} : 3\text{-} : 4\text{-} = 2.75 \times 10^5 : 1.48 \times 10^5 : 3.65 \times 10^7$$
$$= 1.9 : 1 : 250$$

Hence it is not surprising that in pentafluorobenzene nucleophilic attack occurs exclusively at the 4-position.

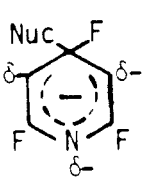
3.8.4 Rates of Attack in Hydrofluorobenzenes

Rate constants for the methoxydefluorination in a series of hydrofluorobenzenes in methanol at 58°C are shown in Table 3.4.

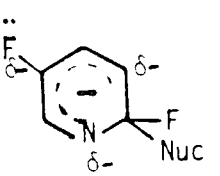
Taking these results at their face value, an ortho fluorine activates the system by a factor of 57 [compare rate constants for pentafluorobenzene (50) and 1,2,3,5,-tetrafluorobenzene (51)]; a meta fluorine activates the system by a factor of 106 [compare rate constants for pentafluorobenzene (50) and 1,2,3,4-tetrafluorobenzene (52)]; and a para hydrogen has little effect [compare hexafluorobenzene (49) and pentafluorobenzene (50)]. The theories discussed in Chapter 2 to explain orientation of substitution in pentafluorobenzenes emphasize the role of a fluorine para to the position of attack i.e. nucleophilic attack occurs so as to avoid a position which is para to a fluorine atom. It appears possible, however, that this may be grossly exaggerating the role of the para fluorine.

3.8.5 Polyfluoropyridines

Following our arguments on the effects of fluorine on carbanion stabilities we would expect that for a transition state like [7], the fluorine atom at the 2- and 6-positions, i.e. meta to the point of attack, to be activating. We can also understand the fact that a para fluorine atom is slightly deactivating i.e. as in [8] but then we might anticipate that the effect of fluorine would be the same at the ortho position. This is clearly not the case since ortho fluorine is more activating than meta for the halogeno-pyridines. Therefore there must be some non-conjugative effect arising from fluorine at the ortho position.



[7]



[8]

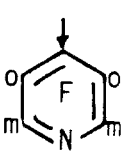
(3.16)

This effect may be considered to be an initial state effect (as with the hydrofluorobenzenes).

The order of activating influence of substituent fluorine atoms, relative to the point of nucleophilic attack, ortho > meta > para, leads to a simple explanation of the controlling influence of fluoro-substituents on the orientation of nucleophilic substitution in pentafluoropyridine. Activation of the system by ring nitrogen is substantial, and there is some discrimination, by nitrogen, between the 2- and 4-positions. This is clear from the fact that 4-chloropyridine is more reactive than 2-chloropyridine towards attack by methoxide ion , and , in (7) Table 3.6 k4-/k6- is ca.4.

The orientation of substitution in polyfluorinated pyridines is therefore governed by the effects of both nitrogen atom and the fluoro-substituents. Thus nucleophilic substitution in pentafluoropyridine gives mono-substitution exclusively at the 4-position, where the number of activating ortho and meta fluorine atoms is at a maximum. This is illustrated below using the empirical values for aminodefluorination.

3.8.5.1 4-Substitution



(3.17)

4- Activation = ortho x ortho x meta x meta fluorines

2- Activation = ortho x meta x meta x para fluorines

therefore on fluorine influences alone:-

$$\text{Ratio of 4 : 2 substitution} = \frac{\text{ortho} \times \text{ortho} \times \text{meta} \times \text{meta}}{\text{ortho} \times \text{meta} \times \text{meta} \times \text{para}}$$

$$= \frac{\text{ortho}}{\text{para}} = \frac{31}{0.69}$$

$$= 45 : 1$$

And including the effect of ring - N (ca 4:1)gives:-

Ratio of 4 : 2 substitution = 180 : 1 in pentafluoropyridine

On a similar basis we can also explain attack at both the 4- and 6-positions in 2,3,4,6-tetrafluoropyridine (66); in contrast to pentafluoropyridine, attack at both positions is associated with the same numbers of activating fluorines and thus the ratio of 4- to 6-substitution is due to the effect of ring nitrogen. In general, we must conclude that the activating effect of ring nitrogen is not dominating the orientation in pentafluoropyridines and that it is only an additional influence to the fluorines.

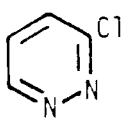
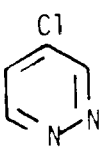
(3.18)

3.9 Other Heterocyclic Systems

The results of rate measurements for the reactions of the chlorodiazines with p-nitrophenoxide in methanol at 50°C were discussed briefly in Chapter 2. The results for 2- and 3-chloropyridine, (82) and (83), are reproduced below.

Table 3.9

Rate Constant for Reactions with p-Nitrophenoxide/Methanol at 50°C.[74]

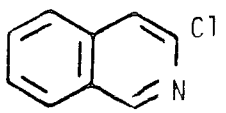
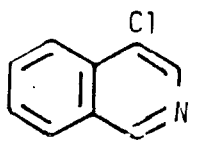
	Substrate	$k/(l\ mol^{-1}s^{-1})$
(82)		1.3×10^{-6}
(83)		2.1×10^{-6}

Since both compounds have a ring nitrogen meta to the chlorine being displaced and hydrogen has little or no effect upon the orientation of substitution, the difference between the two compounds, in terms of activating groups, is that between an ortho and para ring nitrogen. The remarkable similarity in the rate constants suggests that in pyridazine systems also, the ring nitrogen has little effect upon the orientation of substitution.

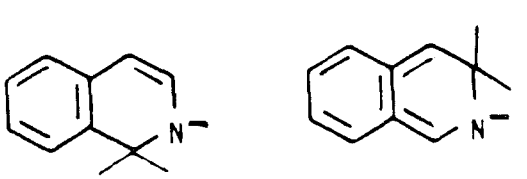
Similarly for the reaction of the 2- and 4-chloroquinolines (84) and (85) with ethoxide in ethanol at 20°C, the rate constants are virtually the same, resulting in the same conclusion that ring nitrogen has no effect upon the orientation of substitution.

Table 3.10

Rate Constants for Reactions with Ethoxide/Ethanol at 20°C.[31]

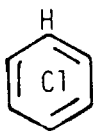
	Substrate	$k/(1\ mol^{-1}s^{-1})$
(84)		1.2×10^{-11}
(85)		6.9×10^{-7}

By analogy with the quinoline system, the rate constants for the 1- and 3-chloroisoquinolines ought to be similar; however, the values are very different, 6.90×10^{-7} and 1.20×10^{-11} $l\ mol^{-1}\ s^{-1}$, respectively, the ring nitrogen obviously having a large effect in these compounds. It may be deceptive to attribute this effect to the nitrogen alone and these results can be explained by considering the transition states formed. Molecular orbital calculations have shown that for nitrogen heterocycles, the highest electron density in the ground state tends to reside on the nitrogen. Extrapolating this to the transition states, for attack at the 1-position, negative charge can be localized on the nitrogen without loss of aromaticity in the benzene ring, whereas localization of the negative charge on nitrogen for attack at the 3-position destroys the aromaticity.

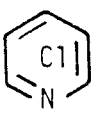
 (3.19)

3.9.1 Polychloro- compounds

Monosubstitution in pentachlorobenzene occurs preferentially para to the hydrogen atom, and reaction of pentachloropyridine with different nucleophiles leads to preferential, but not exclusive, 4-substitution. Attack para to hydrogen in [9] obviously leads to the maximum activating influence by the chlorine atoms,



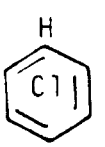
[9]



[10]

(3.20)

i.e. two meta and two ortho to the point of nucleophilic attack and, in an analogous way, attack at the position in pentachloropyridine [10] maximizes the activating influence of the chlorine atoms. However, from the foregoing results, this orientating influence of chlorine atoms in pentachloropyridine is markedly less than that of the fluorine atoms in pentafluoropyridine. Multiplying the activating influences of the appropriate halogens in aminodefluorination leads to the calculated ratios of rate constants for 4- and 2- attack in pentachloropyridine of 180 : 1 whereas for pentachlorobenzene :-



(3.21)

4-attack Activation = ortho x ortho x meta x meta

= 86 x 86 x 24 x 24 $= 4.3 \times 10^6$

2-attack Activation = ortho x meta x meta x para

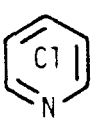
$$= \quad 86 \times 24 \times 246 \times 6.9 \quad = 3.4 \times 10^5$$

Thus the ratio of 4 : 2 attack = $4.3 \times 10^6 / 3.4 \times 10^5 = 12.6 : 1$

If we include a factor of ~ 0.27 for the effect of ring nitrogen we obtain a calculated ratio of 4- : 2- attack of 50: 1. The fact that a noticeable amount of 2- attack has been found experimentally is probably due entirely to the additional steric requirements of chlorine as discussed earlier (Section 3.3.2).

3.9.2 Rationalisation of Results in Terms of the I-pi Effect

As has been mentioned previously (Chapter 2.), the orientating effects in nucleophilic aromatic substitution can be explained in a limited way by an I-pi effect. In this approach , it may be argued that the observed difference in reactivity between the 2- and 4-positions in pentafluoropyridine arises mainly from the discussion of Chapter 2. Substitution at the 2-position would lead to a transition state in which the charge is on a carbon atom bearing a fluorine [11] and this would be far less favourable than a transition state resulting from attack at the 4-position in which charge is accommodated on the nitrogen.



(3.22)

[11]

3.9.3 Effect of Chlorine and the Nitrile Group as Substituents

On the basis of the I-pi effects, replacement of the 3- and 5-fluorines by chlorine or the cyano-group will increase the degree

(rate) of attack at the 4- and the 2- and 6-positions as chlorine will produce less lone pair destabilization than fluorine, and the nitrile group should produce no lone pair destabilization. This activation is observed.

3.9.4 Problems with this Rationalisation

If the I-pi effect of fluorine were dominant in determining rate and orientation of attack, hydrogen would be expected to be activating relative to fluorine at positions ortho and para to the position of substitution, as hydrogen has no I-pi effect. However, hydrogen is so non-activating compared to fluorine that at room temperature 2,4,6-trifluoropyridine does not react with aniline, whereas pentafluoropyridine reacts quite readily; thus, the rate reduction by a 3- or 5-hydrogen, relative to fluorine, is substantial. Similar effects have been found when comparing rate constants for reactions with aniline, ammonia and methoxide - these will be discussed later.

3.10 Orientating Effects of Non-Halogenated Substituents

3.10.1 Orientating Effects of Nitrile.

3.10.1.1 In Pyridines

Nucleophilic attack by both aniline and ammonia in 3-cyano-2,6-difluoropyridine, results in equal 2- and 4- substitution, this would suggest that the nitrile group is equally ortho/para directing. Using a similar analysis to that of section 3.7, we can

demonstrate that for 3-cyano-tetrafluoropyridine:-

in 4-substitution activation is: o-CN x o-F x m-F x m-F x 4-N

in 2-substitution activation is: p-CN x o-F x m-F x m-F x 4-N

where -N is ring nitrogen and 4-N/2-N =4.

therefore the ratio of 4-/2- substitution is:

$$4\text{-}/2\text{-} = \text{o-CN/p-CN} \times \text{4-N/2-N}$$

$$\text{p-CN/o-CN} = 2\text{-}/4\text{-} \times 4 = 1.7:1$$

similarly for 3-chloro-5-cyanotrifluoropyridine:

$$\text{p-CN/o-CN} = 1.25:1$$

The reactions of ammonia and aniline with 2-cyanotetrafluoropyridine in which only 4- substitution is found are consistent with the above ratios and show in addition that the nitrile is not as strongly activating in pyridine systems as the ring nitrogen.

3.10.1.2 In Benzenes

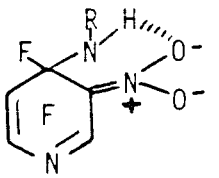
In pentafluorobenzonitrile attack by ammonia and aniline is entirely 4- as would be expected from our previous discussions on the orientating effects of Fluorine. In 1,2 dicyanotetrafluorobenzenes, attack was found to be 4-(50%) and 6(50%) for ammonia and for aniline the 6-(50%) and 4,6-disubstituted (50%) products were found. These results conflict with those of the literature for the reactions of ammonia and aniline in aqueous ethanol.[93] It would be unwise with the

limited data to draw any conclusions from this as the reactions were performed at elevated temperatures and direct comparisons are not therefore valid.

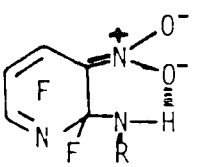
3.10.2 Effect of the Nitro Group

3.10.2.1 In pyridines

Only two reactions were investigated with 3-nitro--2,4,6-trifluoropyridine. With ammonia attack was entirely 4- whilst with aniline attack was 4- and 2- resulting also in the disubstituted 4,2- product. The transition states [12] and [13] are probably involved.



[12]



[13] (3.23)

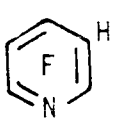
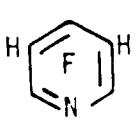
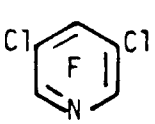
This being so it is difficult to explain why with ammonia only 4-substitution occurs unless we assume that the attack is so fast that the inductive effects of the fluorines (as discussed earlier) are dominating, i.e. the kinetic isomer is favoured over the thermodynamic isomer.

3.10.2.2 In Benzenes

For nitropentafluorobenzene attack is seen primarily at the 2 position for 3-nitroaniline and at the 2- and 6- positions for most other anilines. However, for ammonia and aniline attack is 4-, again this may be due to the speed of attack meaning that the kinetic isomer is favoured over the thermodynamic isomer.

Table 3.11

Results of Reactions of Various Nucleophiles with Halogenopyridines in the Presence and Absence of Sodium Metal.

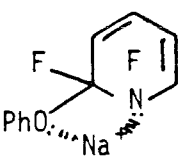
Substrate	$PhNH_2$a /dioxan	$PhNH_2$ + Na /dioxan	Na+MeO- /dioxan	Na+MeO- + Na /dioxan	Na+PhO- /dioxan
	4-(100%)	-	4-(100%)	-	4-(100%)
	4-(80%) 2-(20%)	-	4-(50%) 2-(50%)	-	4-(20%) 2-(80%)
	4-(80%) 2-(20%)	2-(100%)	4-(36%) 2-(64%)	4-(8%) 2-(92%)	2-(100%)
	2-(100%)	-	-	-	2-(100%)

3.11 Unusual Effects in Nucleophilic Substitution

3.11.1 Salt Effects in the Reactions of Methoxide and Phenoxide

Table 3.11 shows the results for a series of reactions in dioxan of the hard nucleophile sodium methoxide. It can be seen from the

results that the orientation of substitution is broadly similar to that for aniline except that for 2,3,4,6-tetrafluoropyridine and 2,4,6-trifluoropyridine, methoxide shows a marked tendency towards 2- as opposed to 4- substitution. Comparison of the results for the larger nucleophile phenoxide, show that the tendency towards 2- substitution is even stronger. This could be explained by the salt effect.[95]



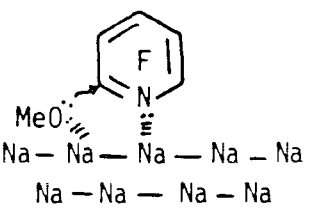
(3.24)

The coordination of the sodium to the nitrogen as in [14] should enhance the stability of the transition state for 2- substitution over that for the transition state for 4- substitution, increasing the amount of the 2- adduct formed. Since the concentration of the sodium phenoxide solutions used was not accurately determined we are unable to make a direct comparison between the result for phenoxide and methoxide as we would expect any salt effect to be highly concentration dependent, as the coordination with solvent increases at lower concentrations.

3.11.2 Catalytic Effect of Sodium Metal

An alternative explanation of the effects in phenoxide is that the phenoxide solutions (unlike those for methoxide) were not filtered and thus probably contained some sodium metal. The addition of freshly prepared molecular sodium to the reaction of (filtered) sodium methoxide and 2,4,6-trifluoropyridine resulted in substantially increased 2- substitution (92% vs. 64%). For the reaction of aniline and 2,4,6-trifluoropyridine, we also find that addition of molecular

sodium gives 100% 2- substitution and the reaction is catalysed to such an extent that the solution in dioxan becomes hot to the touch and the excess aniline chars. Clearly then sodium <u>metal</u> is having a catalytic effect in the reaction possibly by coordination of both the nucleophile and substrate to its surface (3.22) in which case we would expect enhanced 2- substitution.



(3.25)

CHAPTER 4

DEVELOPMENT OF THE KINETIC METHOD

CHAPTER 4

THE DEVELOPMENT OF KINETIC METHODS

4.1 Introduction

For a kinetic method to be generally useful it should be:

a) suitable for use with a large number of substrates.

b) simple to execute.

c) capable of following the reaction continously, or quickly enough to allow several readings to be taken;

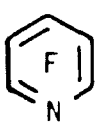
and:

d) have no effect upon the reaction to be studied.

In this chapter we will discuss the various methods, together with their advantages and disadvantages, that we have used to try and follow the kinetics of nucleophilic aromatic substitution when aniline is the nucleophile.

4.2 Direct Spectroscopic Determination

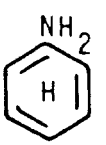
Frequently the method of choice in kinetic analysis, direct spectroscopic determination, was found to be unsuitable for following the reactions of aniline and fluorinated pyridines. For a typical reaction, that between pentafluoropyridine and aniline, we find that the reactants [1],[2] and products [3] all have absorbance peaks in the 250 - 350nm region, as shown overleaf:



[1]

λ_{max} = 256

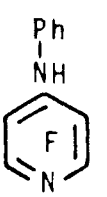
ε 3.5 x 10^6



[2]

λ_{max} = 235,288

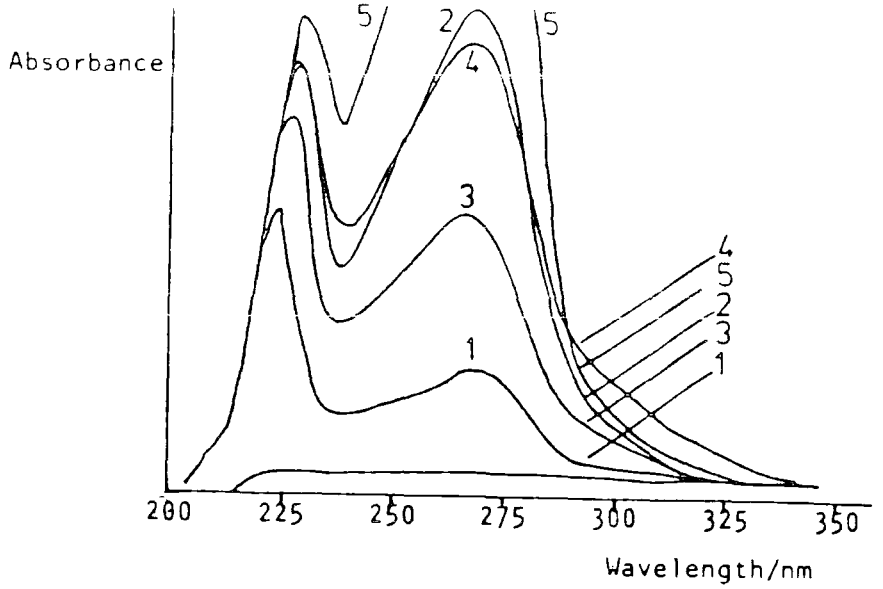
8.8,1.0 x 10^3



[3]

λ_{max} = 272

1.7 x 10^6



(4.1)

Under the reaction conditions of dioxan/water,60:40,(v/v) solvent, the UV cut off comes at 225nm. The major peak for aniline is at 235nm and thus not observable while the minor peak at 288nm is buried under those for pentafluoropyridine [1] and 4-anilinotetrafluoropyridine [3]. A typical reaction of aniline [2] and pentafluoropyridine [1] under first order conditions is shown in Fig. 4.1. Note the order of the scans in the 300 - 350nm region where the least amount of overlap between reactant and product peaks occurs; the obvious complications in this region mean that the reaction cannot be easily followed spectophotometrically.

4.3 Attempted Determination of Aniline by Bromination and Back Titration

Activated aromatic compounds such as aniline will undergo an electrophilic bromination in the presence of excess bromate - bromide solution and dilute hydrochloric acid. The equations for the reaction are:

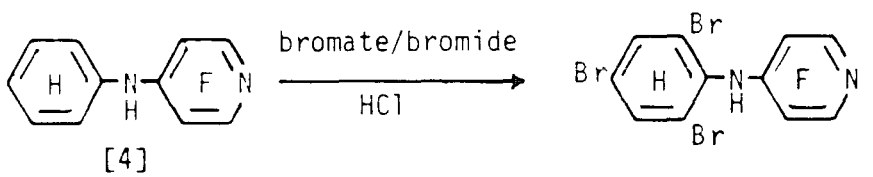
$$KBrO_3 + 5KBr + 6HCl \longrightarrow 3Br_2 + 6KCl + 3H_2O \qquad (4.2)$$

$$C_6H_5NH_2 + 3Br_2 \longrightarrow 2,4,6\text{-}Br_3\text{-}C_6H_2NH_2 \; 3HBr$$

The amount of aniline present is thus determined by back titration of the excess bromine using an iodometric method. Addition of excess potassium iodide, resulting in the liberation of free iodine, is determined by titration with standard sodium thiosulphate solution.

$$Br_2 + 2KI \longrightarrow I_2 + 2KBr \qquad (4.3)$$

It was thought that the products found from the reactions of aniline with electron withdrawing polyhalopyridines, would not be sufficiently activated to undergo bromination. However, a final reaction with 4-anilinotetrafluoropyridine [3], showed that it underwent bromination in the same way as aniline, hence this technique did not prove suitable for following the kinetics of reactions with aniline.



[4] (4.4)

4.4 Determination of Substrate Concentrations by Gas Chromatography

Introduction

The volatile halopyridine substrates and aniline nucleophiles readily pass through gas chromatography (gc) columns at moderate (100°C) temperatures whereas the solid products formed in nucleophilic aromatic substitution reactions will not go through gc columns even at elevated (400°C) temperatures. Sampling and chromatography of the reaction mixtures should enable us to determine the concentration of reactants with time, by comparing the ratio of peak areas obtained for

reactants, and a suitable non-reactive standard, with a previously prepared calibration chart. The following criteria must be met if this method is to give good results for the rate constants to be studied.

We need:

1) Good separation of reactants, products and solvent peaks on the chromatogram.

2) Sharp peaks which give good integrations.

3) Retention times which are significantly shorter than the time interval between sampling (30mins) to ensure that a sufficient number of readings are obtained.

4) Good reproducibility between injections so that the error in determining the rate constant is as small as possible.

5) A standard which will not interfere in anyway with the reaction under study, yet will run on the gc near to the peak being studied but without overlap between the two peaks so that integrations remain good.

4.4.1 Preliminary Investigations

Preliminary investigations of the reaction between aniline and pentafluoropyridine showed that the best gas chromatographic separations of the reaction mixture components were obtained with a 3 metre, 17% di-n-decylphthalate on celite column, at 90°C. The retention times however, were greater than 30 mins, the maximum sampling interval compatible with obtaining good rate constants.

The optimum conditions - balancing peak separation against peak width - were found at 125°C with a 30% silicone elastomer on celite column packing the longest retention time being 15 minutes. Under these conditions the peaks in order of increasing retention time were: pentafluoropyridine, aniline and dioxan. The aniline peak was too

broad to give good integrations and on repeated gas chromatograms it showed a tendency to broaden and cover the pentafluoropyridine peak. To overcome this problem it was necessary to remove the aniline prior to injection of the reaction mixture onto the gc column, and two precipitation reagents were considered as suitable for this:

i) HCl in dioxan.

ii) BF_3 etherate.

Of these (i) was initially considered the reagent of choice because it is in a solvent which is already part of the reaction mixture.

4.4.2 Problems Associated with using Acidic Reagents in the GC

Flame ionisation detector filaments are delicate and corroded by acidic reagents, as are celite based column packings. It was therefore necessary to remove all traces of HCl or BF_3 before they could come into contact with either the column packing or the detector. This was achieved by using a 10cm pre-column of anhydrous sodium carbonate to remove the acids. The pre-column had to be repacked with fresh material before each kinetic run, and its length was limited by its tendency to absorb pentafluoropyridine as well as the acid reagents.

4.4.3 Use of HCl to Precipitate Aniline

Precipitation of aniline as the hydrochloride proved to be unsatisfactory, the precipitate formed being fine and flocculent making it difficult to remove the supernatant liquid, even after centrifugation. Injection of aniline hydrochloride onto the pre-column resulted in its slow breakdown - releasing aniline onto the main column - and producing a wandering baseline and spurious peaks.

4.4.4 Use of BF_3 Etherate to Precipitate Aniline

Precipitation of aniline as the boron trifluoride adduct gave a heavier precipitate than the hydrochloride and after centrifugation it proved comparatively easy to remove the supernatant liquid with a gas chromatography syringe.

The use of BF_3 etherate as a precipitant meant that the diethyl ether, eliminated during aniline adduct formation, was also present in the gas chromatogram. This did not present any problems as the ether had a very short retention time and ran clear of the other peaks.

4.4.5 Choice of Standard

In order to determine the variation of substrate concentration with time it is necessary to have present in the reaction mixture a standard compound whose concentration remains constant and with which the substrate concentration may be directly compared on the gc To do this the standard must be:

1) non-reactive.
2) soluble in dioxan/water and ether.
3) able to give a sharp peak near the substrate peak and which will not overlap with other peaks.

After testing about twenty compounds it was found that, for the reaction of aniline and pentafluoropyridine, 1,3-dimethylpentane was the most suitable standard. The gc was calibrated with ten solutions of known pentafluoropyridine/standard ratios, the standard concentration being held constant. The calibration graph obtained gave a straight line over the concentration range 10^{-2} to 10^{-3}M pentafluoropyridine.

4.4.6 Results of Attempted Kinetic Runs

Initial attempts to follow the kinetics of the reaction between aniline and pentafluoropyridine by this method showed excessive scattering of the points obtained. This resulted in poor reproducibility and consequent inaccuracies in the measured rate constants. Much of this trouble seemed to be due to poor integration and after trying several electronic integrators, the best results were obtained when peak areas were determined by triangulation.

Subsequent attempts at deterimining rate constants also failed to give consistent results, several problems being encountered as outlined below, and it was decided to abandon this technique.

4.4.7 Problems with the Gas Chromatographic Technique

1) The precipitated aniline/boron trifluoride adduct was not fully removed from solution even though the solutions appeared clear to the naked eye. It was found that after four or five injections on the gc column that a wandering baseline and spurious broad peaks were obtained, this being traced to the aniline/boron trifluoride adduct breaking down on the pre-column and releasing aniline onto the main column.

2) The sodium carbonate pre-column quickly became ineffective at absorbing all the BF_3 resulting in BF_3 peaks appearing on the chromatogram and subsequent damage to the detector system. It was not practical to increase the length of the pre-column without destroying overall resolution and it was not possible to change the pre-column quickly enough while a kinetic run was in progress.

3) The results obtained for runs in which the above problems were minimised gave poor rate constants. This was traced to absorption of

the pentafluoropyridine by the aniline/boron trifluoride precipitate in varying amounts. Recalibration of the gc with solutions to which the precipitate had been added and then removed again, showed much larger scatter than was considered desirable.

4) The use of substrates other than pentafluoropyridine, would mean that, because of the different retention times, a new standard would have to be found for each substrate; this has been found to be too difficult to be considered routine.

In conclusion, this gas chromatographic method for following the kinetics of reaction with aniline and polyhalogenopyridine substrates, although initially promising, was found to be too problematical to be used as a general method.

4.5 Determination of Substrate Concentration by High Performance Liquid Chromatography

The principles and requirements for the use of high performance liquid chromatography (hplc) in following reaction kinetics are essentially the same as those for gas chromatography described in section 4.4. There are however, several important differences; these were found to be:

i) Because of the better separations obtained with hplc it was not necessary to remove any of the reaction mixture components prior to separation on the hplc

ii) The reaction could be stopped by simply diluting the sample with solvent.

iii) The solvents used do not show up on the hplc when a UV detector is used.

iv) The standard used must be UV active for it to be detected on the hplc.

4.5.1 The General Method

The general method of use is similar to, though simpler than that used for g.l.c. An aliquot (1ml) of the reaction mixture (in dioxan/water,60:40,v/v) was diluted ten-fold and run on the hplc. The amount of substrate at any one time was determined by comparing the ratio of peak areas for the substrate and a standard.

4.5.2 Results and Conclusions

When this method was used to follow the reaction of aniline and pentafluoropyridine, under first-order conditions, it gave good agreement with the fluoride ion-electrode method to be described later. However, as with the gc method, finding a suitable standard was difficult and the choice limited by the necessity for it to be UV active also. As with the gc method, it would be necessary to find a new standard and thus recalibrate for almost every substrate used, limiting the usefulness of this method when a series of substrates are to be examined. Finally, it was found that over a period of time, the hplc column suffered from physical damage, presumably caused by the small amounts of HF present in the reaction mixture attacking and erroding the silica column packing. Whilst this hplc method did give good results, it was not considered suitable for the series of substrates we wished to examine and its long-term cost in terms of column damage would have been prohibitive.

4.6 Direct Fluoride Ion Analysis

Previous attempts to follow the kinetics of Nucleophilic

substitution in fluorinated compounds, by colourimetric or gravimetric determination of evolved fluoride ion, have proved unsuccessful, the methods used being too cumbersome or inaccurate in the presence of organic solvents. The recent use of a fluoride ion selective electrode, for the direct determination of fluoride ion in water, prompted us to investigate its use as a means of following the kinetics of amino-defluorination reactions.

4.6.1 Principle of measurement

The electrochemical behaviour of the electrode is similar to that of the glass electrode, down to a lower concentration limit of about 1×10^5 g ion l^{-1}. The electrode potential (E) can be described by the Nernst equation.

$$E=E_0 - \frac{RT}{zF} \ln a_{F^-}$$

where:

E_0 is a constant (V);

R is the universal gas constant (8.314 J K^{-1} mol^{-1});

T is the tempererature in K;

z is the number of electrons transferred (in this case one);

F is the Faraday number (96 487 C mol^{-1});

a_{F^-} is the activity of the F^- ions

In a similar manner to that for H^+ we may write:

$$pF = -\lg a_{F^-}$$

$$\text{hence} \quad E=E_0 + 2.3 \frac{RT}{F} pF$$

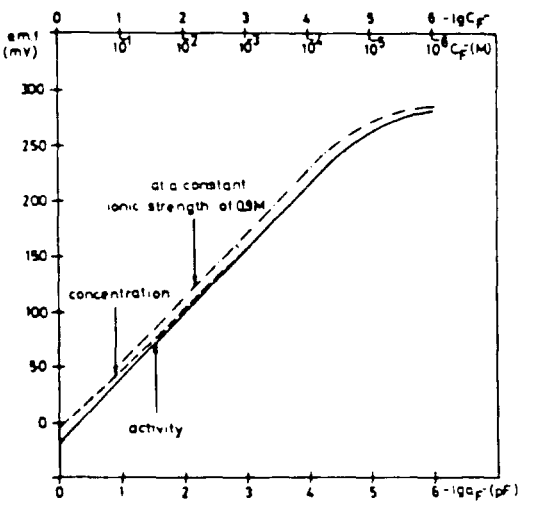
The value of $2.3\ ^{RT}/_{F}$ varies with temperature and at 25°C is

59.1mV; at $10^{o}C$, 56.1mV and at $45^{o}C$, 63.1mV.

It is apparent from eq. (3) that the correlation of E vs pF is, at room temperature, a linear one. This linearity breaks down at concentrations below 10^{-5} g ion l^{-1}. However, using a calibration curve, in water, it is possible to determine the F^{-} ion concentration down to 5×10^{-7} g ion l^{-1}.

The electrochemical cell used for these measurements comprises a silver/silver chloride reference electrode and the fluoride ion selective electrode.

The electromotive force of this cell (which differs from E only by an additive constant), plotted against the activity or concentration of F^{-} ions is shown in Fig. 4.5.



(4.5)

The plot of activity is a straight line. The plot of concentration may be determined (from such calibration curves) more accurately if a constant ionic strength is maintained, in which case the activity coefficient is constant and the concentration graph follows a straight line. The constant ionic background is usually provided by a buffer solution or sodium chloride.

4.6.2 Electrode Selectivity

The fluoride ion electrode is amazingly selective. It is essentially unaffected by the presence of other ions except hydroxide, and then only when the fluoride/hydroxide ratio is less than 10 to 1. ($K_{sel}F^-/HO^- = 10^{-1}$). For concentration ratios above this, the eletrode responds to fluoride ions only. The electrode responds only to free fluoride ion and the measured concentration will thus be lower than the true concentration if there are any ions present which can form a complex (e.g. Al^{3+},Fe^{3+},H^+) or a precipitate (e.g. Ca^{2+}) with fluoride ion.

4.6.3 Effect of pH on Measured EMF

The variation of measured EMF with pH is shown by the plots of Fig. 4.6. (See overleaf) It can be seen that the best linearity of fluoride ion concentration versus EMF is obtained at pH 5.5.

At lower pH, complexation with H^+ removes free fluoride ion from solution, and at higher pH hydroxide ion is formed in sufficient amounts to be measured as well.

4.6.4 Use of Buffer Solutions

The most widely accepted buffer solution for use with fluoride ion sensitive electrodes is the 'Total Ionic Strength Adjustment Buffer' (TISAB) of the following compostion:

Sodium chloride	1.0	mole l^{-1}
Acetic acid	0.25	mole l^{-1}
Sodium acetate	0.75	mole l^{-1}
Sodium citrate	0.001	mole l^{-1}

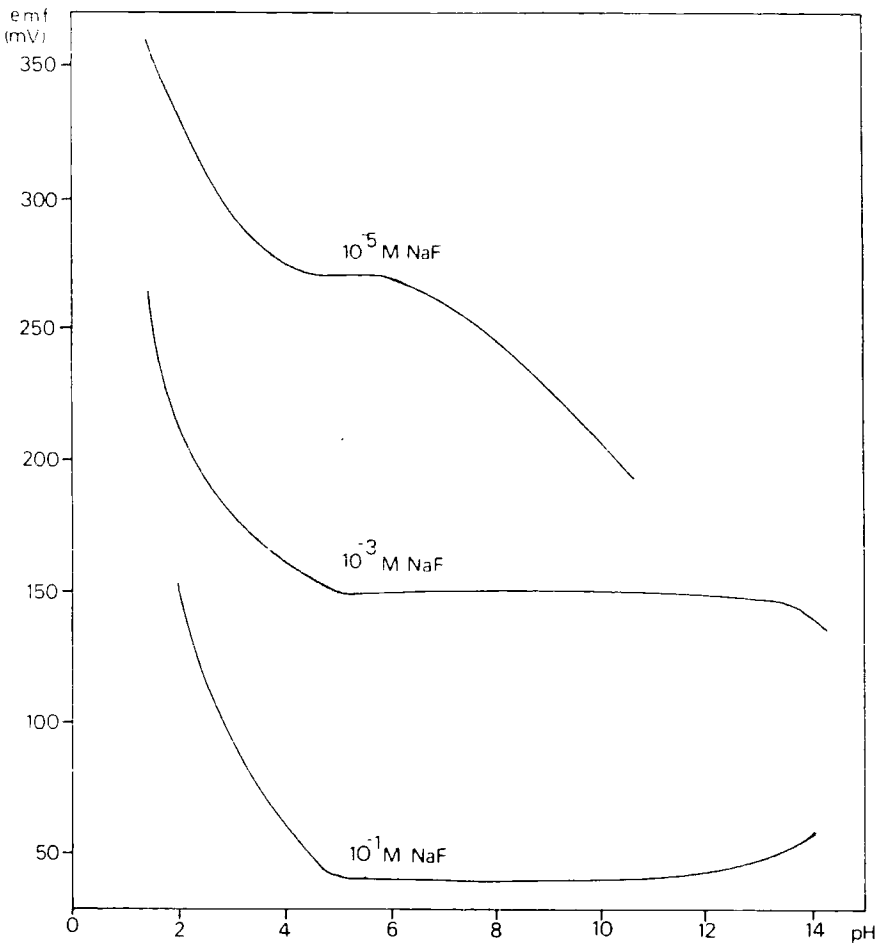


Fig. 4.6 Effect of pH on Measured EMF for the Activion Fluoride Ion Electrode

The buffer has a pH of 5.0 - 5.5 and is 1.75 M. It is used by diluting with the solution whose fluoride ion strength is to be determined in the ratio of 1:1 with the buffer.

4.6.5 Effect of Solvent on Measured E.M.F

Measurement of the EMF produced by sodium fluoride solutions in various dioxan/water solvent systems - ranging from 50 to 100% water - showed that the overall shape of the EMF versus concentration curve remained the same while the electrode constant changed so that the EMF measured was dependent upon solvent composition.

4.6.6 Practical Considerations in the Use of the Fluoride Ion Selective Electrode

The lanthanum fluoride sensing element of the electrode is generally fairly rugged but it should not be touched with the hand or allowed to come into contact with metal parts during storage. To prevent loss of sensitivity the electrode should be stored dry.

The response time of the electrode varies with concentration being less than 30 sec for concentrations down to 10^{-3} M and longer (a few minutes) in more dilute solutions. The response time becomes shorter with increasing background ionic strength. When using the fluoride ion electrode to follow reaction kinetics, the response time is the principal factor limiting the rate at which reaction can be followed.

4.6.7 The Use of the Fluoride Ion Electrode in Measuring Rate Constants

The main reason for adopting the fluoride ion electode as a means of following kinetics was its potential for continuous monitoring,

hopefully giving us the ability to detect changes in the overall rate constant and thus detect features such as base catalysis. Nucleophilic substitution of fluoropyridine substrates by ammonia and aniline under second-order conditions results in a continuously varying pH. To enable the fluoride ion concentration to be determined under these conditions we would have to continuously and accurately monitor pH; this was not possible with the equipment available. Alternatively we could buffer the solution to achieve constant pH. The standard TISAB buffer however, would give pH 5.5, unsuitable for following reactions with ammonia and aniline as at this pH they are in their protonated forms. A review of other buffer solutions available revealed that they would all contain either an unacceptably high hydroxide ion concentration, or other species such as acetate, which are known to act as nucleophiles. The finally adopted solution was to perform the reactions under first-order conditions with a large (20-fold) excess of the nucleophile, the pH remaining constant by virtue of the effectively constant base (nucleophile) concentration.

4.6.8 Reactions with Ammonia

The use of ammonia as nucleophile in 20-fold excess, means that a concentration of 10^{-2}M ammonia is necessary in dioxan/water,60:40,(v/v) solutions if reaction rates amenable to measurement are to be obtained. The fluoride ion calibration curves obtained at this ammonia concentration are too non-linear for fluoride ion concentrations to be determined accurately; this is because the pH (11.0) of these solutions is well beyond the limit of linearity for the fluoride ion selective electrode. Thus it was not possible to follow the reactions of ammonia continuously and a sampling method was employed instead.

4.6.9 Reactions with Aniline

Unlike ammonia, it was possible to obtain a useful fluoride ion calibration curve for solutions with 0.2M aniline in dioxan-water,60:40,(v/v). The calibration curve was reproducible, though non-linear, and spanned only 150 millivolts compared with the 300 millivolts obtained for sodium fluoride solutions at pH5.5 in water.

Attempts to calibrate the fluoride ion electrode in 0.2M aniline solutions using sodium fluoride as the ion source, were unsuccessful, the solubility of sodium fluoride being too low to cover all the required curve. Standardised hydrofluoric acid solutions were used instead, and since hydrogen fluoride is actually produced during the reactions to be studied, the use of hydrofluoric acid as a calibrant has the additional advantage of more closely imitating the actual reaction conditions.

4.6.10 Calibration Method

Plastic apparatus was used throughout to minimise side reactions between the hydrofluoric acid and the glass, and to reduce absorption of fluoride ion by glass.

To half a litre of aniline (0.2M) in dioxan/water,60:40,(v/v), were added 1ml portions of hydrofluoric acid (1M) using an automatic pipette with a plastic tip. The solution was stirred after each addition and the EMF produced by the fluoride ion electrode recorded. This procedure was repeated using fresh aniline solutions and 10^{-1}, 10^{-2}, 10^{-3} and 10^{-4} M solutions of hydrofluoric acid. Calculation of the fluoride ion concentrations (allowing for dilution) enabled a calibration curve to be established for concentration versus EMF

produced, the slight change in solvent composition being ignored.

4.6.11 Method for Measuring Rate Constants

To measure a rate constant, the fluoride ion and reference electrodes were immersed in a dioxan/water,60:40,(v/v) solution of aniline in a teflon container, The substrate was then added and the EMF produced recorded against time by a chart recorder. The fluoride ion concentration was determined by use of the calibration curve and the rate constant calculated as below.

4.6.12 Calculation of Rate Constants for Reactions with Aniline

The first order rate constants were calculated from the equation.

$$k_1 t = \ln ([S]_o/([S]_o - [F]_t)) \qquad (4.6)$$

where: $[S]_o$=conc. of substrate at time zero.

$[F]_t$=conc. of fluoride ion at time t.

Second order rate constants k_2 were determined by dividing k_1 by the aniline concentration.

In cases where two products arose, from attack at positions m and n in the nucleus, the rate constants for attack at these positons k_m and k_n were calculated from the observed rate constant k_{obs}, by the expressions.

$$k_{obs} = k_m + k_n$$

$$\frac{k_m}{k_n} = \frac{\%\text{ of product arising from attack at position m}}{\%\text{ of product arising from attack at position n}} \qquad (4.7)$$

Equation 4.8 implies that aniline is extensively protonated in dioxan/water,60:40,(v/v) i.e. that two molecules of aniline are used for the reaction of one molecule of substrate; i.e. the equilibrium

constant of the reaction.

$$H^+ + PhNH_2 \rightleftharpoons PhNH_3^+ \qquad (4.8)$$

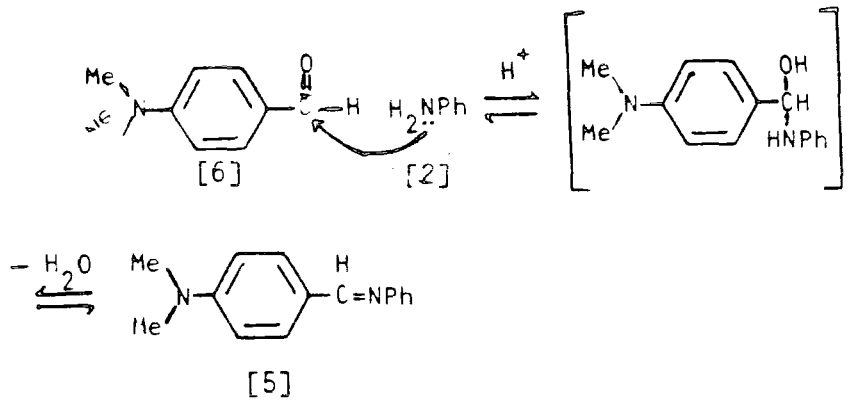
lies far to the right, leading to the formation of the aniline hydrofluoride salt.

4.6.13 Problems with the Fluoride Ion Electrode Technique

The main problem encountered using this technique was that of observing accurate and reproducible infinity values for the reaction. It was found that initial rate constants, calculated by using the known concentrations of reactants, were reproducible to within acceptable limits. However, it was rarely possible to obtain a measured infinity value (by fluoride ion electrode) that agreed with the known infinity value, although these were usually within 10% of each other and comparison of the rate constants obtained by this technique and the hplc technique showed good agreement.

4.7 A Schiff's Base Method of Following Aniline Concentration

Primary amines react with aldehydes to give stable imines of Schiff's bases which usually absorb in or near the visible region of the spectrum. The Schiff's base [5] formed by the reaction of aniline [2] and p-dimethylaminobenzaldehyde [6] has an absorption maximum at ~435nm in acidic methanol - well clear of the maxima for the other components in our nucleophilic substitution reactions. Thus it should be possible to follow second-order kinetics using a sampling technique, determining the aniline concentration by Schiff's base formation.



(4.9)

The Schiff's base of aniline was formed by taking an aliquot of the reaction mixture (in dioxan/water,60:40,(v/v)) and pipetting it into a volumetric flask (10ml), this was then made up to volume with an acidic solution of p-dimethylaminobenzaldehyde in methanol. The acid prevents reaction between the fluoropyridine substrate and methanol. The absorbance of the solution was then measured at the maxima for the Schiff's base (λ=436nm, ε=1.517 x10^4 l $M^{-1}cm^{-1}$) and the aniline concentration thus determined from the Beer-Lambert law. The absorption maxima of the Schiff's base is dependent upon the acidity of the solution which must therefore be kept constant. The validity of the Beer-Lambert law under the experimental conditions was determined by the construction of a calibration graph.

4.7.1 Calculation of Rate Constants

The second order-rate constants were determined from the expression:

$$k_2 t = \frac{1}{a - 2b} \ln \frac{b(a - 2x)}{a(b - x)}$$

where a=initial concentration of nucleophile.

b=initial concentration of substrate.

x=concentration of substrate reacted at time t.

This technique seems to be a simple reliable method for following second-order kinetics by determining aniline concentration with time. Its development was too late however, to be of any use for the investigations reported here.

CHAPTER 5

REACTIONS WITH ANILINE

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5.1 Reactions of Aniline with Polyfluoro and Polychloro-pyridines

Rate constants were obtained for a series of polyfluoro and chloro-substituted pyridines by monitoring fluoride ion concentration during the course of the reaction as described previously in Chapter 4. All the reactions were carried out in 60:40 dioxan/water at 25°C.

Table 5.1 shows the rate constants obtained, together with the position of attack. Where a mixture of products resulted, the rate constant for substitution at each position is quoted. Also shown are the rate constants relative to pentafluoropyridine and where attack occurs ortho to the ring nitrogen, i.e. in the 2 or 6 position, rate constants are given relative to the rate constant for 4-chloro-tetrafluoropyridine.

5.2 Activating Influences in Anilinodefluorination

The results of Table 5.1 for the reactions of aniline and various halogeno-pyridines enable us to derive, in a similar manner to that of Chapter 3, the activating influences of fluorine and chlorine relative to hydrogen.

5.2.1 Fluorine

Comparison of the rate constants for attack at the 4-position in pentafluoropyridine (1) and 2,4,5,6-tetrafluoropyridine (2) gives a relative rate constant, or substituent rate factor (srf), for fluorine versus hydrogen when they are ortho to the position of attack.

Table 5.1

Rate constants for reactions of halogeno-pyridines with aniline in dioxan/water 60:40, v/v at 25°C

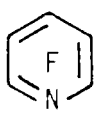
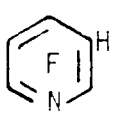
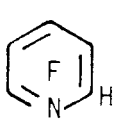
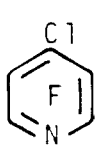
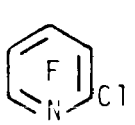
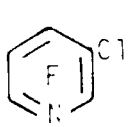
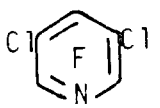
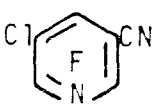
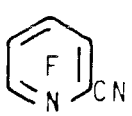
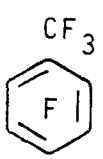
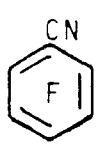
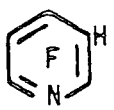
	Substrate	Position of Attack	$k/l\ mol^{-1}s^{-1}$	krel relative to (1)
(1)		4-	3.33×10^{-4}	1
(2)		4-	1.82×10^{-4}	0.55
		6-	6.05×10^{-5}	3×10^{3} a
(3)		4-	9.71×10^{-6}	0.03
(4)		2-	2×10^{-8}	1 a
(5)		4-	6×10^{-4}	1.67
(6)		4-	4.72×10^{-4}	1.42

Table 5.1 continued

	Substrate	Position of Attack	k/l $mol^{-1}s^{-1}$	krel relative to (1)
(7)		4-	4.04×10^{-4}	1.21
		2-	2.77×10^{-5}	1×10^{3}
(8)		4-	6.83×10^{-2}	205
		6-	1.71×10^{-2}	9×10^{5} a
(9)		4-	6.83×10^{-3}	20.5
(10)		4-	7×10^{-9}	2×10^{-4}
(11)		4-	2.12×10^{-2}	63.7
(12)		4-	1.12×10^{-4}	0.36

a = Relative to (4)

e.g.  vs.  $k(1)/k(2) = k(F)/k(H)$ ortho

$$k(F)/k(H) \text{ ortho} = \frac{3.33 \times 10^{-4}}{1.82 \times 10^{-4}} = 1.8$$

similarly:

$$k(1)/k(3) = k(F)/k(H) \text{ meta} = 34$$

Therefore the order of the activating influences of fluorine, relative to the position of nucleophilic attack in anilino-defluorination of pyridines is:

F	ortho	meta	para	
	1.8	: 34	: -	(relative to hydrogen)

5.2.2 Chlorine

Attack at the 4-position:

$k(6)/k(2) = k(Cl)/k(H)$ ortho

$= 2.6$ per ortho chlorine atom

$k(5)/k(3) = k(Cl)/k(H)$ meta

$= 57$ per chlorine atom

Therefore the order of the activating influence of chlorine, relative to the position of nucleophilic attack in the methoxy-defluorination of pyridines is:

Cl	ortho	meta	para	
	2.6	: 57	: -	relative to hydrogen

5.2.3 Chlorine versus Fluorine

Values for the relative activation by fluorine and chlorine in nucleophilic anilinodefluorination at different positions may be obtained directly from the following comparisons.

Attack at the 4-position:

$k(7)/k(1)$ = $k(Cl)/k(F)$ ortho

= 1.21 i.e. /1.2 = 1.1 per ortho chlorine atom

$k(6)/k(1)$ = $k(Cl)/k(F)$ ortho

= 1.4 per ortho chlorine atom

$k(5)/k(1)$ = $k(Cl)/k(F)$ meta

= 1.7 per meta chlorine atom

5.2.4 Nitrile

For the nitrile group in similar way as before:

$k(9)/k(1)$ = $k(CN)/k(F)$ meta

= 21 per meta cyano group

$k(9)/k(3)$ = $k(CN)/k(H)$ meta

= 700 per meta cyano group

$k(9)/k(5)$ = $k(CN)/k(Cl)$ meta

= 12 per meta cyano group

$k(8)/k(6)$ = $k(CN)/k(F)$ ortho

= 145 per ortho cyano group

$k(8)/k(7)$ = $k(CN)/k(Cl)$ ortho

= 169 per ortho cyano group

Using the value for k(F)/k(H) ortho we get k(CN)/k(H) ortho = 1.83

= 42.3 x 1.8

= 78 per ortho cyano group

CN	ortho		meta		para	
	78	:	70	:	-	relative to hydrogen

5.2.5 Ring Nitrogen

For the ring nitrogen in similar way as before:

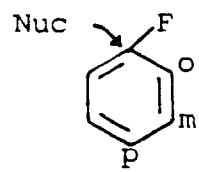
$$k(1)/k(12) = k(N)/k(CN) \text{ para}$$
$$= 3.0$$

$$k(1)/k(10) = k(N)/k(CCF3) \text{ para}$$
$$= \ddot{5}.1 \times 10^4$$

$$k(11)/k(9) = k(N)/k(CN) \text{ meta}$$
$$= 3.1$$

$$k(11)/k(1) = k(N)/k(CF) \text{ meta}$$
$$= 64$$

The relationship between the ortho , meta and para fluorines and the position of substitution is shown diagrammatically in Fig. 5.1.



(5.1)

5.3 Interpretation of the Activating Effects

The relative activating influences of fluorine and chlorine in nucleophilic anilinodefluorination reactions of polyhalogeno-pyridines are shown in Tables 5.2 and 5.3 together with the activating influences observed when methoxide and ammonia are the nucleophiles.

Table 5.2

Substituent Rate Factors for Chlorine and Fluorine in Polyhalopyridines for Fluoride Ion Displacement

Ratio	Position relative to site of substitution	NaMeO in MeOH[a]	NH_3 in dioxan/water[b]	$PhNH_2$ in dioxan/water[b]
Cl/F	ortho	-	2.8	1.4
	meta	-	1	1.7
	para	-	26.7	-
F/H	ortho	79	31	1.8
	meta	30	23	34
	para	0.33	0.26	-
Cl/H	ortho	-	86	2.6
	meta	-	24	57.4
	para	-	6.9	-

Table 5.3

Substituent Rate Factors for Chlorine and Fluorine in Polyhalobenzenes for Fluoride Ion Displacement

Ratio	Position relative to site of substitution	NaMeO in MeOH
Cl/F	ortho	3.2
	meta	0.69
	para	35
F/H	ortho	57 c
	meta	106 c
	para	0.43 c
Cl/H	ortho	182 d
	meta	73 d
	para	15 d

a= at -7.60°C
b= 60:40 v/v at 25°C
c= at 58°C
d= calculated using the Cl/F from 58°C.

Several features stand out from the tables.

1) Despite expectations to the contrary nucleophilic reactions of ammonia and aniline proceed at comparable rates.

2) The ortho activating effects of fluorine and chlorine have become less than the meta activating effects when aniline is the nucleophile, in contrast to the situation with methoxide and ammonia, where the ortho effect is significantly stronger than the meta effect.

3) The ortho activating influences of fluorine and chlorine are not very much greater than those for hydrogen when aniline is the nucleophile (o-F/H 1.8, o-Cl/H 2.6) unlike the situation for reactions with ammonia where significant differences are found (o-F/H 31, o-Cl/H 86)

These conclusions present us with three problems.

1) Why for aniline are the ortho and meta activating influences so reversed?

Is this evidence for a later transition state?

2) Why are the ortho halogen activating influences so similar to those for hydrogen in reactions with aniline?

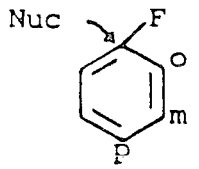
3) Why in view of the smaller ortho activating influences of the ring halogens are the observed rate constants for ammonia and aniline so similar?

We will discuss these problems in the light of the theories proposed earlier i.e. Early/late transition state and frontier orbital control.

5.4 Early/Late Transition State Theory

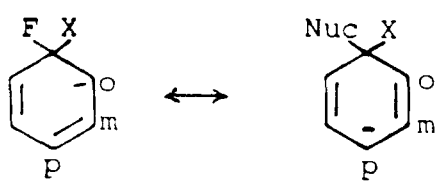
We have seen from our previous discussion on transition state theory (Chapter 3) that in an early transition state, we would expect the

initial state inductive effects to be in the order o>m>>p.



(5.2)

Similarly if we had a late transition state, then we would expect that the effects which go to stabilize the intermediate will be dominant. Considering the resonance forms:



(5.3)

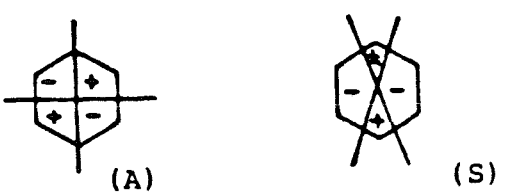
Where fluorine is the substituent it will be stabilizing in the meta position because of its inductive effects, but where it is ortho and para , because of the fluorine electron pair - ring negative charge repulsion effects it will be destabilizing. Thus in a late transition state we should have the order of effects m>o>>p.

For methoxide and ammonia, we find that the activating influences are of the order o>m>>p which is in line with transition state theory where the initial state effects predominate. In fact, para fluorine in these cases is slightly deactivating and thus we can see the effects of the localized charge resonance forms coming into play. For aniline,

however, we find that the meta activating effects are much greater than the ortho activating effects. This could only be explained by the early/late transition state theory by assuming we had a late transition state, as we move towards a later transition state, we reach a point where the decreasing ortho effects and increasing meta effects cross over. If this were so however, we would still expect that halogen will be significantly more activating than hydrogen. Since in both the early and late transition state forms it will still have a stabilizing effect, only the position of greatest stabilization changes. This is inconsistent with an explanation of the results for aniline by a transition state theory, although this theory may still hold true for the results with methoxide and ammonia. Furthermore, if we consider the rates for ammonia and aniline, we would expect under transition state theory, that nucleophiles that react at similar rates would have similar transition states, and thus must have (under this theory) similar activating effects. Since this is not true we must either abandon the early/late transition state theory or consider that something unusual has happened within the reactions with aniline.

5.5 Molecular Orbital Theory

From our earlier discussion of molecular orbital theory we have seen that for these systems there are two degenerate LUMO's.



(5.4)

The symmetrical form (S) would lead us to expect substitution para

to the nitrogen and lead to ortho and meta activating effects being the same. The antisymmetrical (A) form, should lead to attack ortho and meta to the nitrogen and the ortho /meta activating effects being the same. In either case if the frontier orbitals are the controlling factor then the ortho and meta activating influences should be the same.

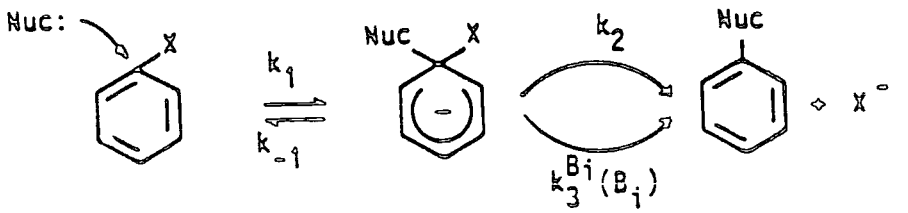
An alternative explanation under molecular orbital theory is to consider that the reaction is under coulombic control and that in this case the same factors operate as have been discussed for an early transition state and we expect the activating order o>m>p.

Under molecular orbital theory, the faster a reaction (nucleophile) the more important the frontier orbital theory becomes. Thus if this explanation was applicable to our results we would expect that if attack by aniline were to be frontier orbital controlled - which it might seem to be since the ortho effect is approximately the same as the meta effect - then the faster reactions for methoxide and ammonia should also be frontier orbital controlled which they are clearly not.

Thus we must conclude that neither the early/late transition state or frontier orbital theory is capable of explaining fully the results for aniline and something more complicated must be occurring.

5.6 Effect of a Change in the Rate Determining Step

We have discussed previously (Chapter 3.) the effects generally observed on proceeding from the first stage being rate determining to the second stage being rate determining using the mechanism shown overleaf.



(5.5)

Now it has been found for some reactions of aniline and various halogeno-nitrobenzenes that base catalysis occurs, both by the aniline itself and by added bases such as triethylamine. This is indicative of a change in the rate determining step. Since our reactions with aniline were of necessity performed under second-order conditions with an excess of aniline, it is possible for base catalysis to occur. Since the base, which might be either solvent or aniline, is in excess and thus at an effectively constant concentration no changes in the observed rate constant would occur.

We will now examine what such changes in the rate determining step mean in terms of the observed rate constant.

5.7 Effect of Rate Determining Step.

$$S + N \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow[k_2]{B} C$$

$$\text{rate} = \frac{k_1[S][N] * k_2[B]}{k_{-1} + k_2[B]}$$

Limits :-

$k_2[B] >> k_{-1}$

$$\text{rate} = k_1[S][N]$$

$k_{-1} >> k_2[B]$

$$\text{rate} = \frac{k_1[S][N]\ k_2[B]}{k_{-1}} = k_o[S][N]$$

k_o = observed rate constant

$$\text{but } k_o = \frac{k_1 k_2[B]}{k_{-1}}$$

From the above it follows that for the limit $k_{-1} >> k_2[B]$ the observed rate constant is dependent on k_1, k_2 and k_{-1} as well as solvent concentration which is constant. Now, since k_2 is part of the rate determining step, we might expect that the leaving group bond strength should be involved in determining the rate -as discussed earlier (Chapter 3.). However, since k_1 and k_{-1} are also involved it is possible that the contribution of k_1 to the rate constant is still just large enough to keep the leaving group order for aniline F>Cl.

It need only be F > 10 x Cl for no detection of Cl as a leaving group to occur since in the 1-halogeno-2,4-dinitrobenzenes, with ammonia kF/kCl is 480:1; this does not seem unreasonable.

Thus if we have the borderline situation where k_2 is becoming involved in k_{obs} then we must accept that the observed rate constant, being composed of three separately variable parameters is too complex to be analysed. Therefore our attempts at assigning values to the activating effects of fluorine and chlorine become meaningless, since they will not be sufficiently constant between different substituted pyridines.

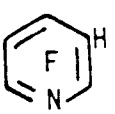
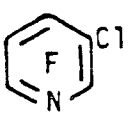
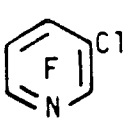
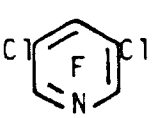
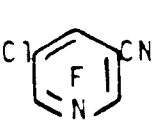
5.8 Effects of Solvent on Rates of Nucleophilic attack with Aniline

In order to examine the effect of solvent on the relative rates of nucleophilic attack with aniline as the nucleophile and to demonstrate

the relevance of these results to the reactions of dyestuffs, a series of competition reactions were performed in which 1 mole of each of two different substrates were reacted with one mole of aniline. The proportion of each of the substrates which reacted with the aniline is representative of the relative rates of reaction. The reactions were carried out in 10% acetone/water in an open beaker at room temperature ($20^{o}C$). Since these reactions were carried out in open beakers they became effectively two phase reactions, because the acetone quickly evaporates leaving only the reactants and water. The results are shown in Table 3.4 and are broadly similar for the two solvent systems used. We can conclude therefore that the results obtained for aniline in dioxan/water are also generally applicable (with the usual caution) to the reactions in acetone/water.

Table 5.4

Competition Reactions of Aniline with Various Polyhalogenopyridines in 10% Acetone/Water (Two Phase Reactions) at 20°C.

Substrates		% of A or B in Anilino Adducts formed	
A	B	Acetone/Water (10:90)	Dioxan/Water (60:40)
		A (100%)	A (88%) B (12%)
		A (60%) B (40%)	A (62%) B (38%)
		A (40%) B (30%) (+ 30% disubstituted A)	A (60%) B (40%)
		A (50%) B (50%)	A (48%) B (52%)
		A (100%)	A (98%) B (2%)

CHAPTER 6

EFFECTS OF OTHER SUBSTITUENTS

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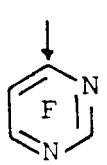
EFFECTS OF OTHER SUBSTITUENTS

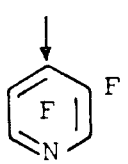
6.1 Introduction

Previously we have been able to establish the activating influences of fluorine, relative to hydrogen, at different positions with respect to the site of nucleophilic attack (NH_3, aq. dioxan, 25°C) as ortho:meta:para = 31:23:0.26. In this chapter we describe for comparison the separation of activating influences of ring nitrogen and of the trifluoromethyl and cyano groups at different sites.

6.2 Ring-Nitrogen

Comparing the rate constants for substitution in (1), (3) and (4) there is an increase of 10^2 or more in reactivity associated with the introduction of each ring nitrogen. More precisely, we can obtain an estimate of the effects of introducing nitrogen at the ortho position as follows.





$$k(3)/k(1) = k(N)/k(CF)\ \underline{ortho} = 2.0 \times 10^3$$

$$k(N)/k(CH)\ \underline{ortho} = 2.0 \times 10^3 \times 31 = 6.2 \times 10^4$$

Similarly, comparing (5) with (1) we obtain a meta effect.

$$k(5)/k(1) = k(N)/k(CF)\ \underline{meta} = 37$$

$$k(N)/k(CH)\ \underline{meta} = 37 \times 23 = 851$$

We are able to obtain the para effect if we compare (3) and (2), assuming that the value of (2) is very close to the value for attack

Table 6.1

Rate constants for attack by ammonia in dioxan/water 60:40, v/v at 25°C and at 80°C (where indicated)

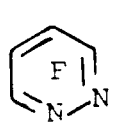
	Substrate	Position of Attack	$k/l\ mol^{-1}s^{-1}$	
(1)		4-	6.80×10^{-4}	ref.99
		(80°C)4-	3.09×10^{-2}	
(2)		2-	1.55×10^{-6}	ref.99
(3)		4-	1.35	ref.102
(4)		2-	70	
(5)		4-	2.52×10^{-2}	ref.102
(6)		2-	5.07×10^{-5}	ref.102

Table 6.1 continued

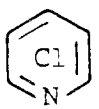
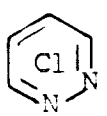
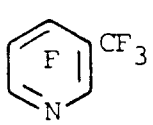
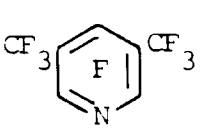
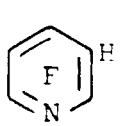
	Substrate	Position of Attack	k/l $mol^{-1}s^{-1}$	
(7)		4-	1.67×10^{-7}	ref.96
(8)		4-	1.08×10^{-5}	ref.96
(9)		4-	3.08×10^{-3}	ref.96
(10)		4- 6-	5.31×10^{-2} 2.66×10^{-2}	ref.96
(11)		4- 2-	3.25 0.63	
(12)		4- 2-	2.22×10^{-5} 5.87×10^{-6}	ref.99

Table 6.1 continued

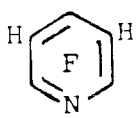
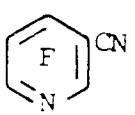
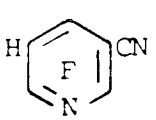
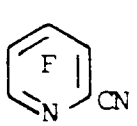
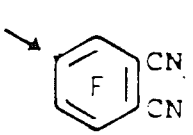
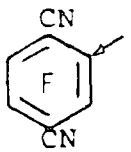
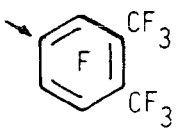
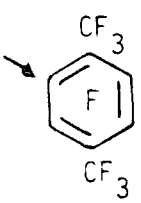
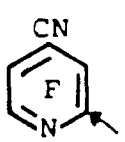
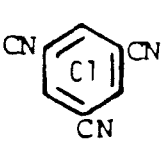
	Substrate	Position of Attack	$k/l\ mol^{-1}s^{-1}$	
(13)		4-	7.0×10^{-7}	ref.100
		2-	2.0×10^{-7}	
(14)		4-	1.11×10^{-1}	
		6-	5.71×10^{-2}	
(15)		2-	3.13×10^{-3}	
		4-	4.62×10^{-3}	
		6-	4.15×10^{-3}	
(16)		4-	6.83×10^{-2}	
(17)		4-	2.50×10^{-4}	
		(80°C)4-	1.71×10^{-2}	
(18)		4-	1.35×10^{-3}	a

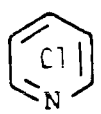
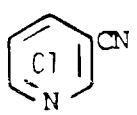
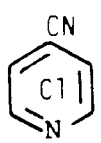
Table 6.1 continued

	Substrate	Position of Attack	k/l $mol^{-1}s^{-1}$
(19)		2-	7.54×10^{-5} a
(20)		4-	4.4×10^{-6}
		(80°C)4-	7.15×10^{-4}
(21)		4-	1.19×10^{-4} a
(22)		2-	1.23×10^{-5} a
(23)		2-	2.11×10^{-4} a
(24)		2-	3.3×10^{-3} a

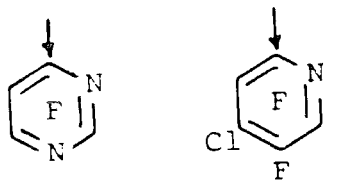
a = statistically corrected

Table 6.2

Rate constants for attack by ammonia in dioxan/water 60:40, v/v at 80°C

	Substrate	Position of Attack	k/l $mol^{-1}s^{-1}$	krel relative to (1)
(25)		4-	6.78×10^{-5}	
(26)		4-	3.48×10^{-2}	
(27)		2-	8.58×10^{-5} a	

at the 2-position in pentafluoropyridine (1), if this could be measured. This is justified because we have established earlier that the effects of chlorine and of fluorine meta- to the site of nucleophilic attack are very similar. Therefore para effects are obtained as follows.



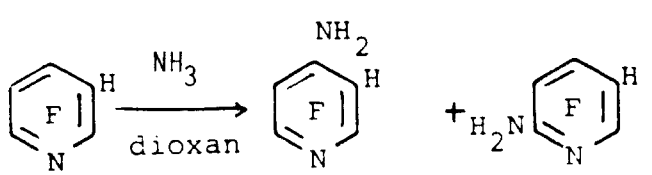
$$k(3)/k(2) = k(N)/k(CF) \quad \underline{para}$$
$$= 8.7 \times 10^5$$

$$k(N)/k(CH) \quad \underline{para} = 8.7 \times 10^5 \times 0.26$$
$$= 2.3 \times 10^5$$

Overall, therefore, the influence of ring-nitrogen, may be compared for different sites:

ortho	:	meta	:	para	
6.2×10^4	:	8.5×10^2	:	2.3×10^5	(rel. to H)
[72	:	1	:	266]	(rel. to the meta position)

As we can see, even at the meta position, nitrogen has a substantial activating influence and the ratio ortho:para = 1:3.7 fits surprisingly well with the observed distribution of isomers for nucleophilic attack in compound [1]. Here, the activating effects of fluorine are closely similar for attack at both the 4- and 6-positions in [1] (one ortho F, two meta F) and, therefore, the composition [2]:[3] = 3.8:1 reflects the para:ortho influence of ring nitrogen.



(6.1)

[1] [2] [3]

A comparison of the chloro compounds (7)-(9) allows us to determine the influence of ring nitrogen in ortho and meta positions, from the point of displacement of chlorine.

$$k(8)/k(7) = k(N)/k(C\text{-}Cl)\ \underline{meta} = 65$$

We are unable, however, to obtain reliable values for k(N)/k(CH) in these systems since we have not obtained activating effects for chlorine vs. hydrogen at positions ortho and meta to the site of displacement of chlorine. If, however, we use the values of the activating effects of a chlorine for displacement of fluorine which have already been established (see Chapter 3.), i.e. ortho:meta:para = 86:24:6.9, then it is possible to obtain an estimate of k(N)/k(CH) for displacement of chlorine.

$$k(N)/k(CH)\ \underline{meta} = 65 \times 24 = 1.6 \times 10^3 \text{ (Cl displacement)}$$

$$k(9)/k(7) = k(N)/k(C\text{-}Cl)\ \underline{ortho} = 1.84 \times 10^4$$

$$k(N)/k(CH)\ \underline{ortho} = 1.84 \times 10^4 \times 86 = 1.6 \times 10^6 \text{ (Cl displacement)}$$

It appears therefore, that the activating influence of ring-nitrogen is more pronounced for displacement of chlorine than for fluorine, and this would be consistent with the later transition state which would be undoubtly associated with the slower displacement of chlorine, than fluorine.

6.3 Trifluoromethyl

6.3.1 In Azines

Using the same approach as described above, we may obtain corresponding values for the activating influence of trifluoromethyl

groups ortho and para to the site of displacement of fluorine.

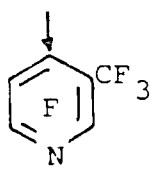
$$k(10)/k(1) = k(CF_3)/k(F) = 78$$

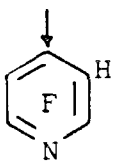
$$k(CF_3)/k(H) \text{ ortho} = 78 \times 31 = 2.4 \times 10^3$$

$$k(11)/k(1) = 4.8 \times 10^3$$

$$k(CF_3)/k(F) \text{ ortho} = \sqrt{4.8 \times 10^3} = 69$$

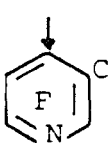
$$k(CF_3)/k(H) \text{ ortho} = 69 \times 31 = 2.1 \times 10^3$$





$$k(10)/k(12) = k(CF_3)/k(H) \text{ para} = 4.5 \times 10^3$$

The ortho values may be obtained from different sources and good agreement is observed. It is clear that trifluoromethyl has an even smaller preference for ortho over para activation, than ring nitrogen and we can now make direct comparisons of the activating influences of ring-nitrogen and trifluoromethyl.



$$k(3)/k(10)(6\text{-position}) = k(N)/k(CCF_3) \text{ para} = 51$$

$$k(3)/k(10)(4\text{-position}) = k(N)/k(CCF_3) \text{ ortho} = 25$$

$$k(1)/k(20) = k(N)/k(CCF_3) \text{ para} = 43 \ (80^\circ C)$$

A comparison of (1) and (20) was only possible at 80°C but this gives $k(N)/k(CCF_3)$ para of roughly the same order as the value

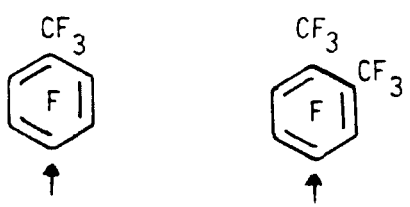
determined by comparison of (3) and (10) at 25°C. It should be possible to obtain the corresponding meta effects from further studies. Overall, therefore, the influence of trifluoromethyl may be compared for different sites:

ortho	:	meta	:	para	
2.3×10^3	:	-	:	4.5×10^3	(rel. to H)
[1	:		:	2]	(rel. to the ortho-position)

Clearly the effect of trifluoromethyl is substantial but is significantly less activating than that of ring nitrogen.

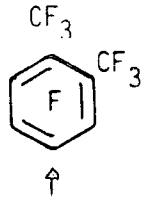
6.3.2 In Polyfluorobenzenes

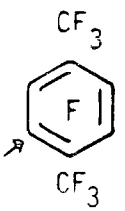
Because data for the effects of fluorine vs. hydrogen are not available for ammonia and the perfluorobenzenes, we are unable to extract all the information otherwise available from the rate constants for fluorine displacement in the polyfluorinated benzonitriles. It is possible to obtain a $k(CF_3)/k(F)$meta by comparing (21) and (20):



$$k(21)/k(20) = k(CF_3)/k(F) \text{ meta} = 27$$

Attempts to obtain $k(CF_3)/k(F)$ values for the ortho and para positions for the fluorine substituent rate factors in the polyfluoropyridine systems or for methoxide in polyfluorobenzenes have proved to give very inconsistent results. We are, however, able to make a direct comparison of the ortho and para activating effects of trifluoromethyl:





k(21)/k(22)=

$k(CF_3)$para/$k(CF_3)$ortho = 10:1

This compares with the $k(CF_3)$para /$k(CF_3)$ortho ratio of 2:1 in the pyridine systems. Thus we are able to see a change in the relative activating effects on proceeding from pyridine to benzene. This is not explainable at the present time, further investigation being required.

6.4 Nitrile

6.4.1 In Polyhalogenopyridines

Again using the same approach as before, we may obtain corresponding values for the activating influence of nitrile groups ortho meta and para to the site of displacement of fluorine.

for 4-attack in compounds (15) and (14):

$$k(15)/k(13) = k(CN)/k(H)\ \text{ortho} = 6.6 \times 10^3$$

$$k(14)/k(12) = k(CN)/k(H)\ \text{ortho} = 5.0 \times 10^3$$

for 2-attack in compound (15):

$$k(15)/k(13) = k(CN)/k(H)\ \text{ortho} = 1.6 \times 10^4$$

Taking an average of the figures for 4-attack we have.

$$k(CN)/k(H)\ \text{ortho} = 5.8 \times 10^3$$

Similarly:

for 6-attack in compound (14) and (15):

$$k(14)/k(12) = k(CN)/k(H)\ \text{para} = 9.7 \times 10^3$$

$$k(15)/k(13) = k(CN)/k(H)\ \text{para} = 2.1 \times 10^4$$

Taking an average of the figures for 6-attack we have.

$$k(CN)/k(H)\ \text{para} = 1.5 \times 10^4$$

for 4-attack:

$$k(16)/k(1) = k(CN)/k(F)\ \underline{meta} = 100$$

$$k(CN)/k(H)\ \underline{meta} = 100 \times 23 = 2.3 \times 10^3$$

$$k(23)/k(2) = k(CN)/k(Cl)\ \underline{meta} = 1.36 \times 10^2$$

$$k(CN)/k(H)\ \underline{meta} = 1.36 \times 10^2 \times 24 = 3.26 \times 10^3$$

Overall, therefore, the influence of nitrile may be compared for different sites:

<u>ortho</u>	:	<u>meta</u>	:	<u>para</u>	
5.81×10^3	:	2.36×10^3	:	1.6×10^4	(rel. to H)
[2.5	:	1	:	6.8]	(rel. to the <u>ortho</u>-position)

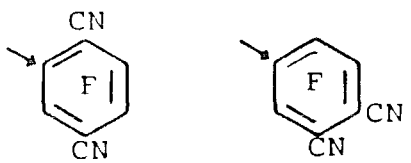
We can now make comparisons of the activating influences of ring-nitrogen, trifluoromethyl and nitrile.

	ring-N	:	CF_3	:	-CN	
<u>ortho</u>	6.2×10^4		2.3×10^3		5.8×10^3	(rel. to H)
	10.5		0.39		1	
<u>meta</u>	8.5×10^2		-		2.4×10^3	(rel. to H)
	10.5		-		1	
<u>para</u>	2.3×10^5		4.5×10^3		1.6×10^4	(rel. to H)
	14		0.28		1	

6.4.2 <u>In Polyfluorobenzenes</u>

Because data for the effects of fluorine vs. hydrogen are not available for ammonia and the perfluorobenzenes, we are unable to extract all the information otherwise available from the rate

constants for fluorine displacement in polyfluorinated benzonitriles. Attempts to do so using values for fluorine in polyfluoropyridine systems or for methoxide in polyfluorobenzenes have proved to give very inconsistent results. We are, however, able to make a direct comparison of the ortho and para activating effects of nitrile.

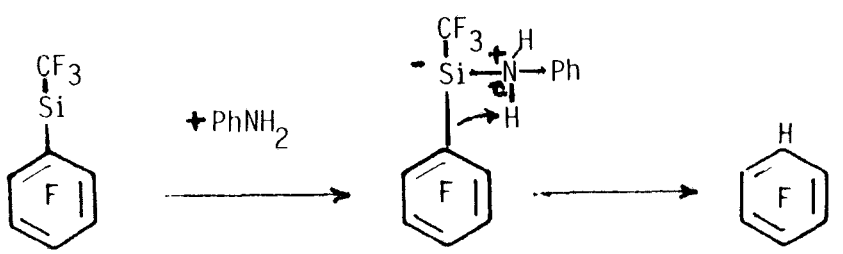


k(CN)ortho/k(CN)para = 5.1:1

This compares with the k(CN)ortho/k(CN)para ratio 1:1.9 in the pyridine systems. Thus we are able to see a change in the relative activating effects on proceeding from pyridine to benzene. This is not explainable at the present time, further investigation being required.

6.5 Trifluoromethylsilyl

It has been suggested[97] that the trifluoromethylsilyl group would be strongly ortho directing in nucleophilic aromatic substitution, in order to test this theory trifluoromethylsilylpentafluorobenzene was reacted with ammonia and aniline the products being examined by nmr. It was found that substitution occurred so as to displace the silyl group possibly by the following mechanism.



(6.2)

$+CF_3SiNH.Ph$

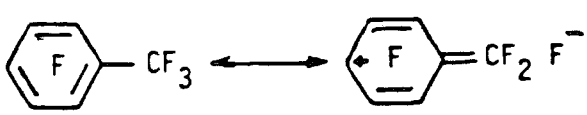
6.6 Rate Measurements For Reactions of Fluoromethylpentafluorobenzene With Ammonia.

6.6.1 Background.

Octafluorotoluene[102,103] is known to react with nucleophiles exclusively in the position para to the trifluoromethyl group. Rate measurements for the reactions of octafluorotoluene with nucleophiles have shown the CF_3 group to increase the rate of reaction with fluorine by a factor of 10^4 to 10^5.[96] The aim of the present investigation was to observe the effects of the CF_3, CF_2H and CFH_2 groups on the reactivities of the methylpentafluorobenzene series, and to determine whether there was any evidence for the occurrence of the process of fluoride ion hyperconjugation.

6.6.2 Consequences of Hyperconjugation in Nucleophilic Substitution Reactions of Fluoromethylpentafluorbenzenes

For octafluorotoluene, ground state canonicals [1] and [2] could be written if fluoride ion hyperconjugation were appreciable.

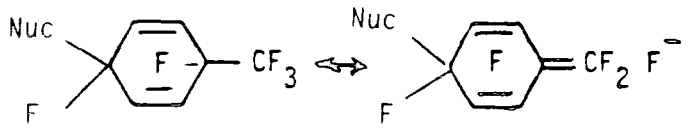


(6.3)

[1] [2]

The exsistence of canonical [2] will increase the electrophilicity of the point of substitution and hence will activate the system towards nucleophilic attack.

In the transition state, occurrence of fluoride ion hyperconjugation would lead to the formation of canonical [3].

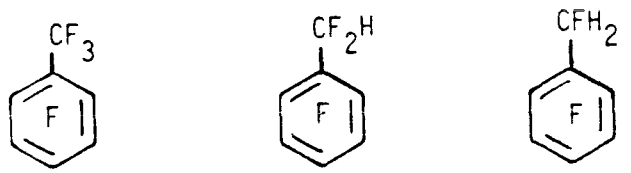


(6.4)

[3]

Such a process would stablise the transition state. Hence if fluoride ion hyperconjugation were significant in this system, appreciable activation towards nucleophilic attack ought to result.

Alternatively, if negative hyperconjugation does not occur, then the fluoromethyl group effects must be inductive in nature.



(6.5)

[4] [5] [6]

Determination of the rate constants for the nucleophilic substitution reactions of octafluorotoluene [4], 1,1-difluoromethyl-pentafluorobenzene [5] and 1-fluoromethylpentafluorobenzene [6] under the same conditions ought to reveal which situation is occurring.

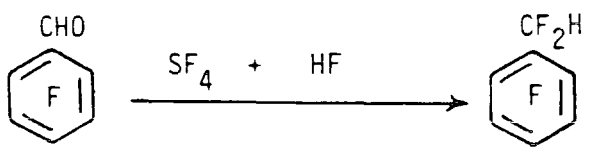
6.6.3 Choice of System in Present Study

In an attempt to relate the reactions of the fluoromethylbenzenes with those of the substrates discussed previously, ammonia was chosen as the nucleophile. Preliminary investigation of the reaction of octafluorotoluene with ammonia in 60:40 dioxan/water at 25°C showed the reaction to be too slow for accurate determinations: the most suitable temperature was found to be 80°C (accurate value: 80.05°C). This temperatures was used in all rate measurements.

6.6.4 Preparation of Substrates

It was necessary to prepare 1,1-difluoromethylpentafluorobenzene

[6] and 1-fluoromethylpentafluorobenzene [6], octafluorotoluene [4] being available commercially. The same general method was used for both compounds, commercially available pentafluorobenzaldehyde and pentafluorobenzylalcohol were reacted with sulphur tetrafluoride in 80% hydrofluoric acid. The reaction vessels were steel cylinders of capacity 100ml, the reactions being carried out under pressure. Before releasing the intial pressure, the cylinder was cooled to a temperature of -5 to $-10^{o}C$ and the reaction mass treated with water. The organic layer was separated, dried over magnesium sulphate and distilled.



(6.6)

6.6.5 Discussion of Results

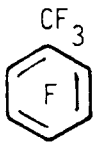
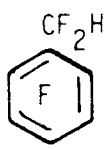
Rate constants for the reaction of fl oromethylpentafluorobenzenes with ammonia in dioxan/water,60:40 (v/v) at $80^{o}C$ are shown in Table 6.3 Attack occured exclusively para to the substituent in all cases. An attempt to obtain the rate constant for the reaction with pentafluorobenzene under the same conditions failed: the reaction did not noticeably proceed over a period of one week. Previous estimates[96] lead us to expect a rate constant of -2×10^{-7} l $mol^{-1}s^{-1}$ for the reaction of pentafluorobenzene.

6.6.6 Interpretation of Rate Data

It can be seen from Table 6.3 that all three substrates are of low reactivity. As expected octafluorotoluene (20) is the most reactive of the three with rate constants decreasing down the series to 1,1-difluoromethylpentafluorobenzene (28) and 1-fluoromethyl-pentafluorobenzene (29).

Table 6.3

Rate Constants for Reactions of Halogeno-benzenes with Ammonia in Dioxan/Water 60:40, v/v at 80°C

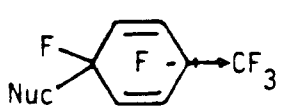
	Substrate	Position of Attack	k/l $mol^{-1}s^{-1}$
(20)		4-	7.1×10^{-4}
(28)		4-	5.0×10^{-5}
(29)		4-	1.1×10^{-5}

It is possible to account for these differences in rate solely in terms of inductive effects. If the effect is a pi-inductive one, as was used to explain certain properties of the trifluoromethylbenzene compounds, such as enhanced dipole moments, then application of this effect to the ground state of octafluorotoluene would lead to the structures [7] and [8].

[7] [8] (6.7)

Formation of structure [8] would activate the system towards nucleophilic attack. Such activation in hexafluorobenzene is not possible owing to the lone pair repulsions between the p electrons of fluorine and the pi-electrons. Exchange of the CF_3 group for H, i.e. in moving along the series CF_3, CF_2H, CFH_2 will alter this inductive activation and the effect on the rates of reaction may not be simple.

In the transition state, stabilisation of the negative charge by CF_3 is achieved by a simple -I effect [9].



[9] (6.8)

Such stabilisation is impossible in the case of hexafluorobenzene, owing to the destabilisation caused by the lone pairs of fluorine which offsets the -I stablisation of fluorine.

The result of the above effects is that the fluoromethylpentafluorobenzenes are progressively activated towards nucleophilic attack as compared to pentafluorobenzene.

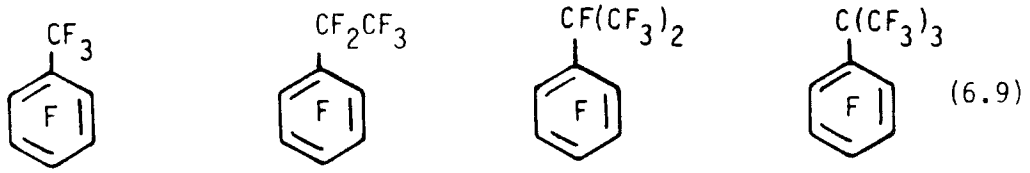
6.6.7 Rationalisation of the Orientation of Substitution

The orientation of substitution in fluoromethylpentafluorobenzenes,

i.e. exclusively para to the substituent, can be accounted for in terms of the ideas developed in Chapter 3. The nucleophile attacks at such a position as to maximise the number of ortho and meta fluorines.

6.6.8 Other Evidence against Negative Hyperconjugation in Nucleophilic Aromatic Substitution Reactions.

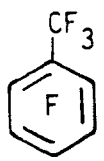
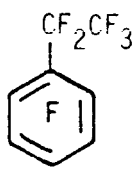
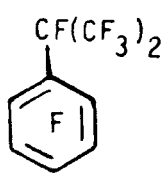
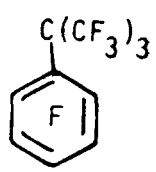
Investigation of the related series of compounds,[96] octafluorotoluene, perfluoroethylbenzene, perfluoroisopropylbenzene and perfluoro-t-butylbenzene gaves rate constants for reaction with ammonia as shown in Table 6.4 Attack occurred exclusively para to the substituent in all cases. It was found that all four substrates were of similar reactivity. As expected octafluorotoluene is the least reactive of the four, if negative hyperconjugation had any role to play we would have expected the converse to be true



(6.9)

Table 6.4

Rate Constants for Reactions of Halogeno-benzenes with Ammonia in Dioxan/Water 77:23,v/v at 92°C[96]

	Substrate	Position of Attack	k/l $mol^{-1}s^{-1}$
(30)		4-	6.7 x 10-4
(31)		4-	1.4 x 10-3
(32)		4-	1.0 x 10-3
(33)		4-	1.7 x 10-3

CHAPTER 7

CARBON NMR

CHAPTER 7

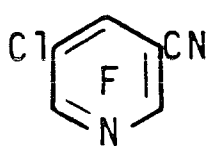
CARBON NMR

7.1 Analysis of Key NMR Spectra

There follows a detailed nmr analysis of the reaction products of the 3-chloro-5-cyanotrifluoropyridine with aniline, N-methylaniline and benzylamine upon which the subsequent nmr analysis of the reaction products of other compounds was based.

7.2 Substrate Pyridines

7.2.1 3-Chloro-5-cyano-tetrafluoropyridine



(7.1)

The following ^{19}F nmr chemical shifts were obtained for this compound.

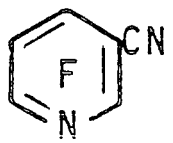
Carbon to Which Fluorine Atom is Attached	Chemical Shift (ppm from $CFCl_3$)
6	-61.1
4	-87.7
2	-59.5

The ^{19}F-^{19}F coupling constants are as follows:

$^4J(F_2F_6) = {}^4J(F_6F_4) = 10.6$ Hz.

$^4J(F_4F_6) = 20.0$ Hz.

7.2.2 3-Cyano-tetrafluoropyridine



(7.2)

[1]

The ^{19}F chemical shifts in ppm from $CFCl_3$ are written on the structure.

The following is the analysis of the ^{13}C chemical shifts from TMS.

Compound [1]

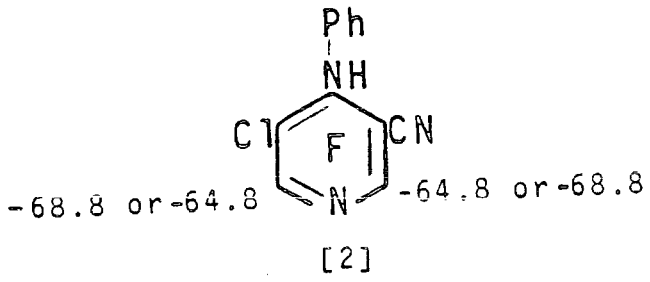
Carbon	Peak Position	Coupling
2	153.0	$^3J(C\text{-}C\text{-}C\text{-}F_4)$ = 7.4Hz $^1J(C\text{-}F)$ = 251Hz.
		$^3J(C\text{-}N\text{-}C\text{-}F_6)$ = 17.2Hz $^4J(C\text{-}C\text{-}C\text{-}C\text{-}F_5)$ = 4.4Hz
3	88.0	$^2J(C\text{-}C\text{-}F_3)$ = 36.8Hz $^4J(C\text{-}C\text{-}C\text{-}C\text{-}F_6)$ = 7.4Hz
		$^2J(C\text{-}C\text{-}F_4)$ = 17.7Hz.
4	161.0	2 x $^3J(C\text{-}C\text{-}C\text{-}F)$ = 5.9Hz $^1J(C\text{-}F)$ = 276.5Hz.
		$^2J(C\text{-}C\text{-}F)$ = 11.8Hz.
5	133.7	$^4J(C_5\ F_2)$ = 8.8Hz $^2J(C\text{-}C\text{-}F_6)$ = 29.4Hz.
		$^2J(C\text{-}C\text{-}F_4)$ = 13.2Hz $^1J(C\text{-}F)$ = 250Hz.
6	156.0	$^3J(C\text{-}C\text{-}C\text{-}F_4)$ = 7.4Hz $^1J(C\text{-}F)$ = 251.0Hz.
		$^3J(C\text{-}N\text{-}C\text{-}F_2)$ = 17.7Hz $^2J(C\text{-}C\text{-}F_5)$ = 13.2Hz.
CN	106.6	$^5J(CN\ F_6)$ = 5.9Hz.

7.3 Aminopyridines

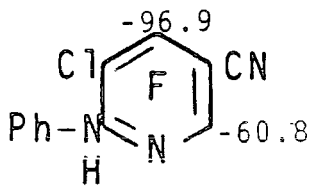
7.3.1 2- and 4-anilino-3-Chloro-5-cyano-tetrafluoropyridine

The product of a reaction between aniline and 3-chloro-5-cyano-tetrafluoropyridine at 25°C were shown by ^{19}F and ^{13}C nmr to be a

mixture of compounds [2] and [3].



[2]



[3]

(7.3)

The ^{19}F chemical shifts in ppm from $CFCl_3$ are written on the structures , the ratio of [2] to [3] was found to be 3.3 :1.0. The ^{13}C nmr spectrum agrees well with structures [2] and [3] However, some of the peaks from the minor component [3] are not resolved.

Compound [2]

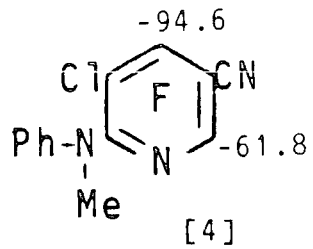
Carbon	Peak Position	Coupling
2 & 6	162.2	$^1J(C\text{-}F) = 242.7Hz$, $^3J(C\text{-}N\text{-}C\text{-}F) = 22.1Hz$.
3	79.5	$^2J(C\text{-}C\text{-}F_6) = 36.8Hz$, $^4J = 4.4Hz$.
4	155.3	$2 \times {}^3J(C\text{-}C\text{-}C\text{-}F) = 5.9Hz$.
6 & 2	158.6	$^1J(C\text{-}F) = 239.7Hz$, $^3J(C\text{-}N\text{-}C\text{-}F) = 22.1Hz$.
5	99.1	$^2J(C\text{-}C\text{-}F_6) = 35.3Hz$, $^4J = 5.9Hz$.
CN	109.8	$^3J(C\text{-}C\text{-}C\text{-}F_2) = 4.4Hz$.

Compound [3]

Carbon	Peak Position	Coupling
2	154.1	$^3J(C\text{-}N\text{-}C\text{-}F_6) = 22.1Hz$ $^3J(C\text{-}C\text{-}C\text{-}F_4) = 5.9Hz$.
3	98.6	$^2J(C\text{-}C\text{-}F_4) = 17.7Hz$ $^4J = 7.4Hz$
4	165.0	$^3J(C\text{-}C\text{-}C\text{-}F) = 7.4Hz$ $^1J(C\text{-}F) = 261.8Hz$.
5	75.6	$^2J(C\text{-}C\text{-}F_2) = 38.2Hz$ $^2J(C\text{-}C\text{-}F_4) = 19.1Hz$.
6	obscured	$^3J(C\text{-}C\text{-}C\text{-}F) = 8.8Hz$ $^1J(C\text{-}F)$ obscured.
CN	109.4	$^3J(C\text{-}C\text{-}C\text{-}F_2) = 5.9Hz$,

7.3.2 4-N-(N-methylanilino)-3-Chloro-5-cyano-tetrafluoropyridine

The product of a reaction between N-methylaniline and 3-chloro-5-cyanotetrafluoropyridine.



[4] (7.4)

The ^{19}F chemical shifts in ppm from $CFCl_3$ are written on the structure.

The ^{13}C nmr spectrum agrees well with structure [4]

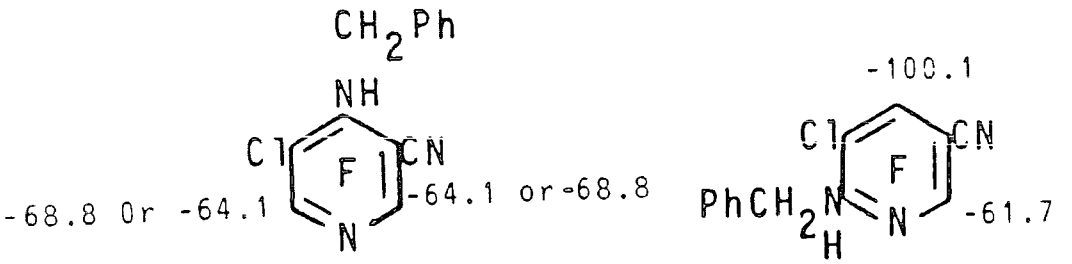
Compound [4]

Carbon	Peak Position	Coupling
2	155.9	$^3J(C\text{-}N\text{-}C\text{-}F_6)$ = 20.6Hz $^3J(C\text{-}C\text{-}C\text{-}F_4)$ = 7.4Hz.
3	101.7	$^2J(C\text{-}C\text{-}F_4)$ = 17.6Hz ^4J = 7.4Hz
4	166.5	$^3J(C\text{-}C\text{-}C\text{-}F)$ = 7.4Hz $^1J(C\text{-}F)$ = 261.8Hz.
5	76.8	$^2J(C\text{-}C\text{-}F_2)$ = 38.2Hz $^2J(C\text{-}C\text{-}F_4)$ = 19.1Hz.
6	159.7	$^3J(C\text{-}C\text{-}C\text{-}F)$ = 7.4Hz $^1J(C\text{-}F)$ = 261.8Hz.
CN	112.1	$^3J(C\text{-}C\text{-}C\text{-}F_2)$ = 5.9Hz,
1'	144.8	
2'	125.4	
3'	129.5	
4'	127.1	

7.3.3 4-Benzylamino-3-Chloro-5-cyano-tetrafluoropyridine

The product of a reaction between benzylamine and

3-chloro-5-cyanotetrafluoropyridine at 25°C were shown by ^{19}F and ^{13}C nmr to be a mixture of compounds [5] and [6].



(7.5)

[5] [6]

The ^{19}F chemical shifts in ppm from $CFCl_3$ are written on the structures , the ratio of [5] to [6] was found to be 1.2:1.0. The ^{13}C nmr spectrum agrees well with structures [5] and [6].

Compound [5]

Carbon	Peak Position	Coupling
2	158.6	$^3J(C\text{-}N\text{-}C\text{-}F_6)$ = 22.1Hz. $^1J(C\text{-}F)$ = 239.7Hz.
3	98.1	$^2J(C\text{-}C\text{-}F_2)$ = 33.8Hz ^4J = 4.4Hz
4	155.7	2 x $^3J(C\text{-}C\text{-}C\text{-}F)$ = 5.9Hz.
5	76.3	$^2J(C\text{-}C\text{-}F_2)$ = 36.8Hz ^4J = 2.9Hz.
6	163.5	$^3J(C\text{-}N\text{-}C\text{-}F)$ = 20.7Hz $^1J(C\text{-}F)$ = 242.7Hz.
CN	112.6	$^3J(C\text{-}C\text{-}C\text{-}F_6)$ = 2.9Hz.
CH_2	46.6	

Compound [6]

Carbon	Peak Position	Coupling
2	156.4	$^3J(C\text{-}N\text{-}C\text{-}F)$ = 22.1Hz. $^3J(C\text{-}C\text{-}C\text{-}F_4)$ = 7.4H_3
3	97.5	$^2J(C\text{-}C\text{-}F_6)$ = 16.2Hz, ^4J = 7.4Hz.
4	164.4	$^1J(C\text{-}F)$ = 261.8Hz, $^3J(C\text{-}C\text{-}C\text{-}F)$ = 8.8Hz.

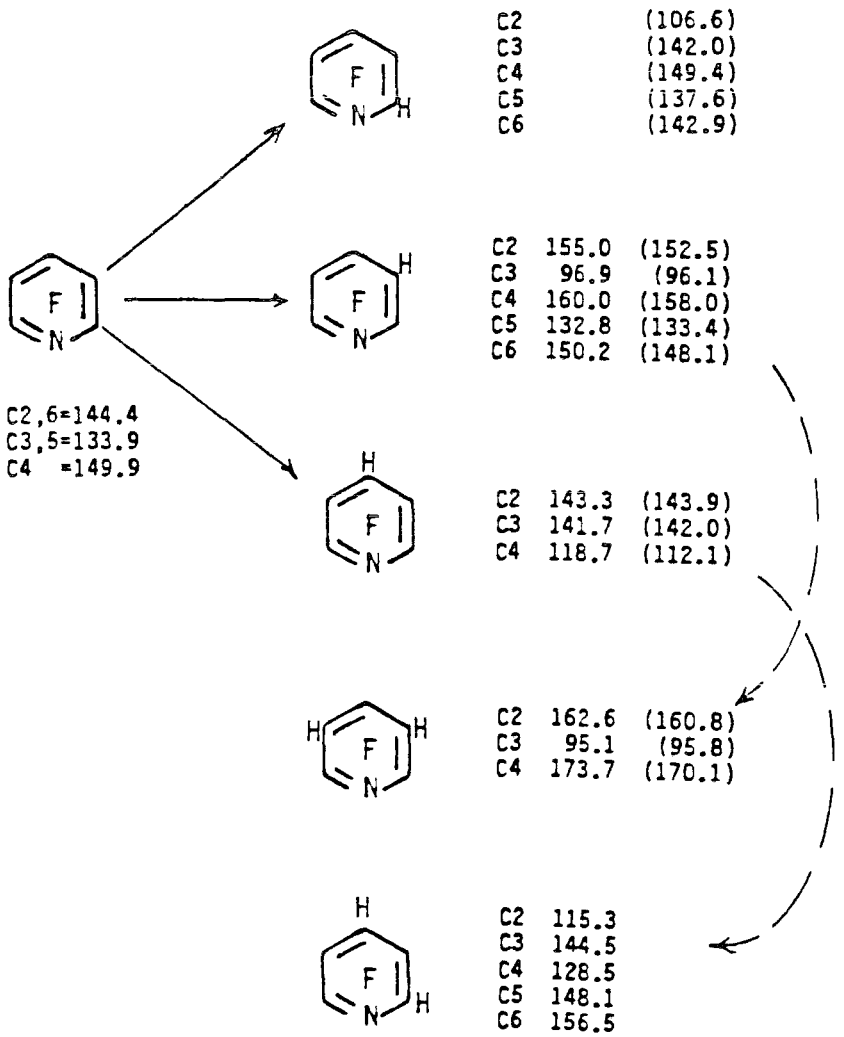
5	73.3	$^{2}J(C\text{-}C\text{-}F_6)$ = 39.7Hz, $^{2}J(C\text{-}C\text{-}F_4)$ = 19.1Hz.
6	161.6	$^{1}J(C\text{-}F)$ = 239.7Hz, $^{3}J(C\text{-}C\text{-}C\text{-}F)$ = 8.8Hz.
CN	109.8	$^{3}J(C\text{-}C\text{-}C\text{-}F_2)$ = 5.9Hz.
CH_2	45.1	

7.4 Substituent Chemical Shifts in Polyhalogeno-pyridines

The tables below show the analysis of the carbon-13 spectra for the simple chloro and cyano-polyfluorpyridines, these have not been previously analysed in this systematic manner, using the substituent chemical shifts (scs), and the use of such analysis was very important in assigning the position of substitution in the compounds studied in this thesis.

Table 7.1

^{13}C Chemical Shifts of the Polyfluoropyridines



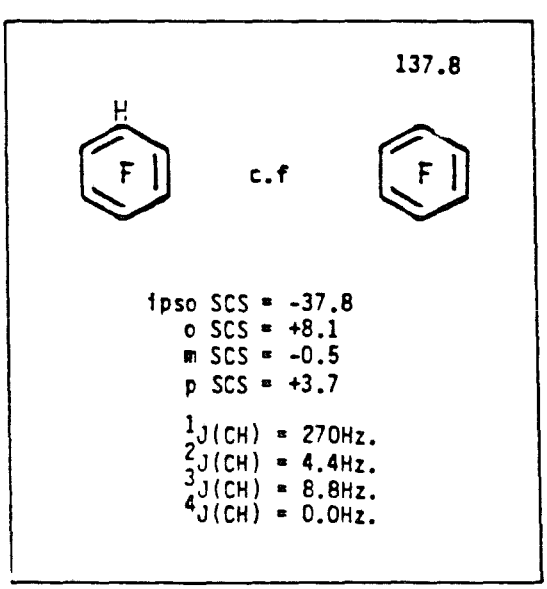
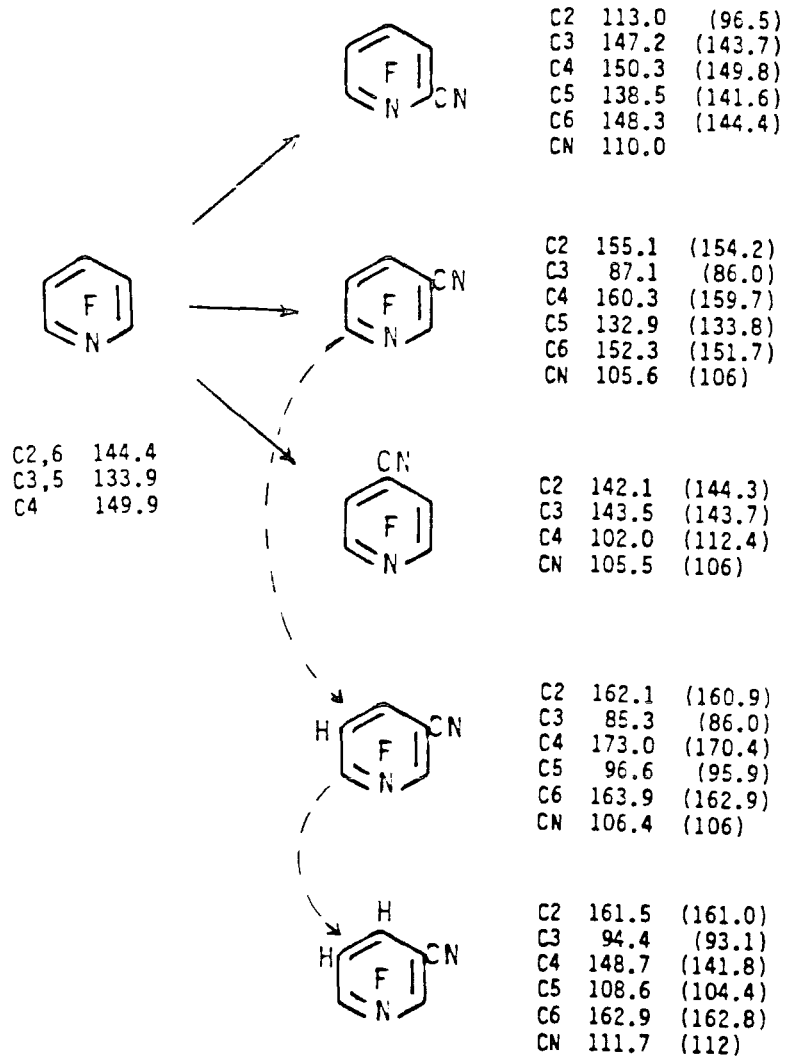


Table 7.2

^{13}C Chemical Shifts of the Cyanopolyfluoropyridines



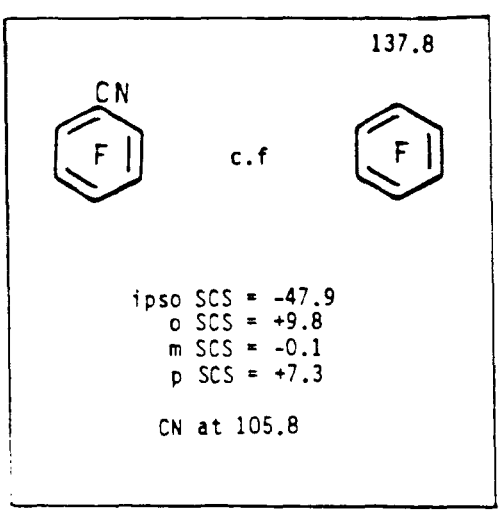
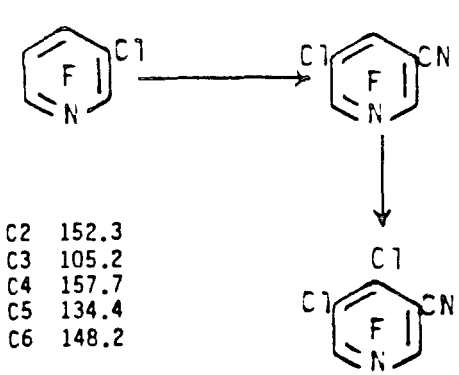


Table 7.3

^{13}C Chemical Shifts of the Cyanopolyhalogeno-pyridines



C2	152.3	
C3	105.2	
C4	157.7	
C5	134.4	
C6	148.2	

C2	159.5	(158.5)
C3	86.8	(87.1)
C4	168.6	(167.7)
C5	104.5	(103.8)
C6	159.8	(159.8)
CN	106.1	

C2	159.7	(159.7)
C3	111.5	(111.5)
C4	151.5	(145.3)
C5	97.5	(94.9)
C6	159.1	(159.4)
CN	108.9	

Table 7.4

^{13}C Chemical Shifts of the Cyanopolyfluorobenzenes

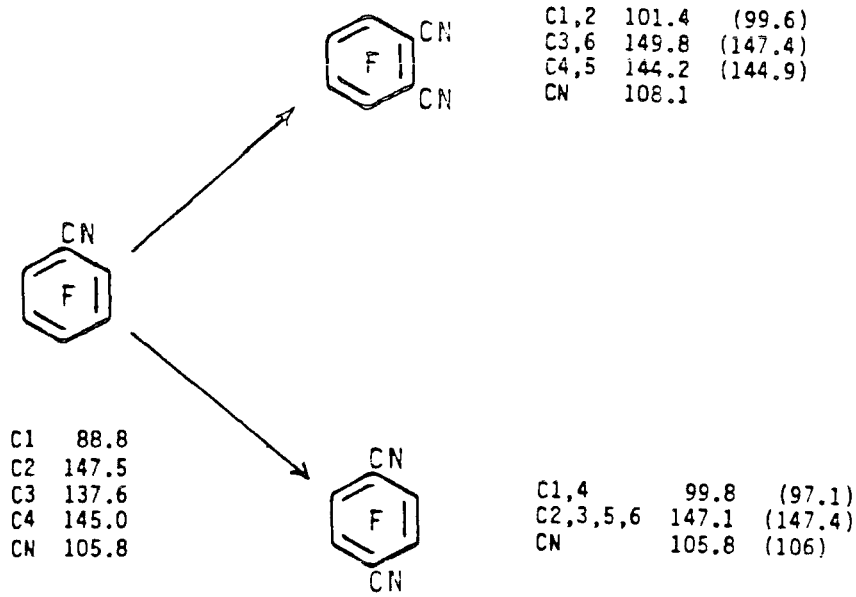
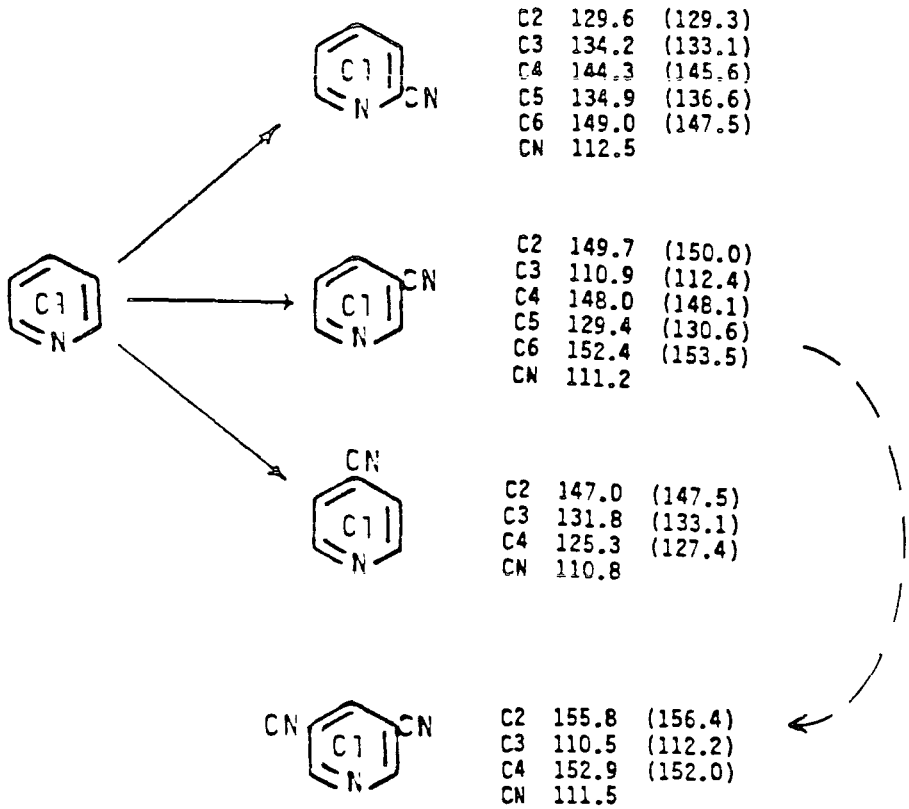
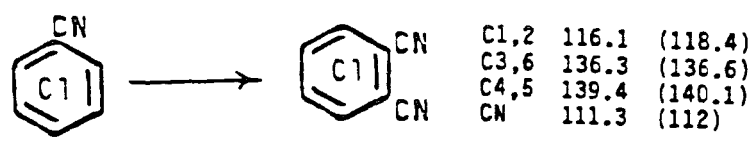


Table 7.5

^{13}C Chemical Shifts of the Cyanopolychloropyridines





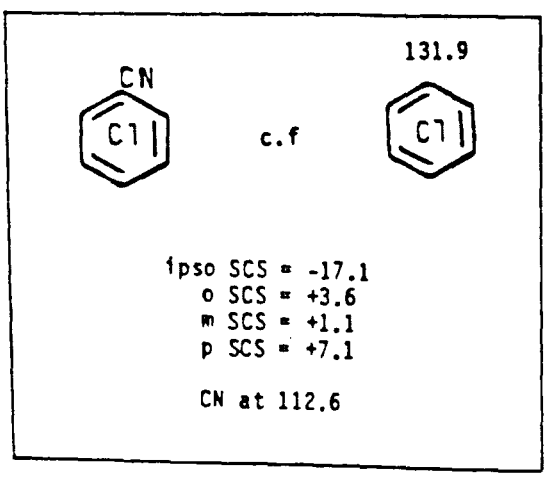
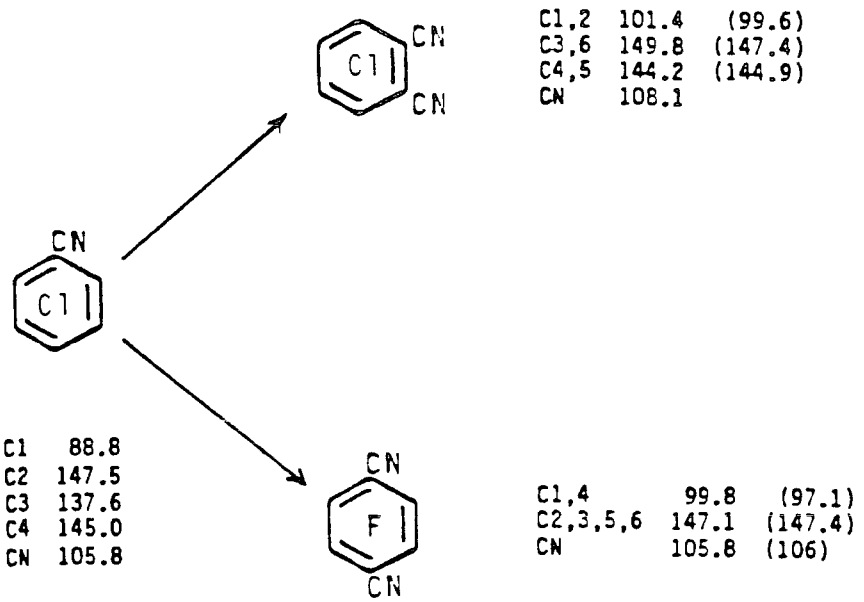


Table 7.6

^{13}C Chemical Shifts of the Cyanopolychlorobenzenes



C1,2	101.4	(99.6)
C3,6	149.8	(147.4)
C4,5	144.2	(144.9)
CN	108.1	

C1	88.8
C2	147.5
C3	137.6
C4	145.0
CN	105.8

C1,4	99.8	(97.1)
C2,3,5,6	147.1	(147.4)
CN	105.8	(106)

EXPERIMENTAL

CHAPTER 8

EXPERIMENTAL FOR CHAPTER 3

CHAPTER 8

EXPERIMENTAL FOR CHAPTER 3

8.1 Instrumentation

Infra red spectra were recorded on a Perkin Elmer 320 or 340 Spectrometer. Liquid samples in the form of thin contact films between potassium bromide plates, and solid samples were pressed into homogeneous thin discs with potassium bromide.

Proton(^{1}H) and fluorine(^{19}F) nuclear magnetic resonance spectra were recorded on either a Varian A56/60D spectrometer operating at 60 and 56.4 MHz respectively, or on a Bruker FT-90 at 90 and 84.7 MHz, the standard temperature of the probes was 40°C.

Ultraviolet spectrometry was carried out on either a Pye Unicam SP.600, SP.800 or SP.8000.

Preparative scale vapour phase chromatography was achieved using a Varian 'Aerograph'. Analytical vapour phase chromatography was carried out either on the 'Aerograph' equipped with a mass density balance detector or on a Pye 104 Chromatograph equipped with a flame ionisation detector.

High performance liquid chromatography (hplc) was carried out using a Waters associates RP8 reverse phase column and acetonitrile/water 50:50 solvent. The chromatographs used were a Hewlett Packard 240 and a Perkin Elmer Model 1. both with UV detectors.

Carbon, hydrogen and nitrogen analyses were obtained using a Perkin Elmer 240 Elemental Analyser and analysis for halogens was as in the literature.[97]

Mass Spectra and molecular weights were obtained using an A.E.I.

M.S.9 spectrometer.

8.2 Solvents

8.2.1 Dioxan

The method adopted was that of Vogel. Commercial dioxan (2.1 l) was refluxed for 8 hours with concentrated hydrochloric acid ($30cm^3$) and water ($168cm^3$), with a steady stream of nitogen bubbling through the solution to remove acetaldehyde as it was formed. Sodium hydroxide pellets were then added, with vigorous shaking, until no more dissolved, and the aqueous layer was separated off. The dioxan was left standing over fresh potassium hydroxide pellets for a further 20 hrs. The dioxan was refluxed with excess sodium for about 24 hours, until the surface of the sodium was bright. A small sample was tested for peroxide by adding potassium iodide solution, acidified with dilute hydrochloric acid. If no iodine was detected, i.e. peroxide was not present. The dioxan was distilled into an oven dried flask under dry nitrogen. The fraction boiling between 101 - 102°C was collected. The residue was destroyed by the addition of methylated spirit under nitrogen. When not in use, the dioxan was stored under nitrogen in a refrigerator at -5°C.

8.2.2 Water

Distilled water was used as a solvent, and its neutrality was checked prior to use, by the addition of methyl red indicator.

8.2.3 Methanol

Dry Methanol was prepared by refluxing 'analar' methanol with magnesium and iodine for 3 hours. The methanol was then distilled through a Frenske column and the median fraction collected. Storage

was under dry nitogen.

8.3 Reagents

8.3.1 Ammonia

Analytical grade ammonia was used without further treatment.

8.3.2 Ammonia in Dioxan

Ammonia gas was bubbled through dioxan at 5-10°C until a saturated solution was obtained. This was used within 3 hours of preparation.

8.3.3 Aniline

Commercial aniline was distilled off zinc dust under reduced pressure (5mmHg). Storage was over No. 8 molecular sieves at 5°C until needed for use.

8.3.4 Substituted Anilines

The commercial anilines were distilled off zinc dust under reduced pressure (5mmHg) and columned through alumina. Storage was over No. 8 molecular sieves at 5°C until needed for use.

8.3.5 Sodium Methoxide

Fresh lumps of Na were transfered rapidly into dry methanol, the resulting solution was filtered under slight suction through a sintered glass funnel, in an all glass system protected from moisture by maintenance of a CO_2 blanket over the apparatus. The solution of sodium methoxide was titrated with HCl (0.1M) using methyl red indicator to determine its strength. Storage was under a dry nitrogen

8.3.6 Sodium Phenoxide

Fresh lumps of Na were transfered rapidly into a dry solution of phenol (20g) in dioxan (100ml), the resulting solution was filtered through glass wool. Apparatus was an all glass system protected from moisture by maintenance of a CO_2 blanket over the apparatus. The solution of sodium phenoxide was used immediately.

8.3.7 Molecular Sodium

Fresh lumps of sodium were heated in a strong walled flask to 100°C. The vessel was stoppered and shaken vigorously for about five minutes until all the sodium had formed small balls. The flask was allowed to cool and the toluene decanted off. The molecular sodium was washed several times with dioxan. Storage was under dry dioxan. The sodium was used within 2 days of preparation and the excess material destroyed in propanol.

8.3.8 Anhydrous Potassium Fluoride

The commercial material was heated under vacuum at approximately 200°C for 24hrs. in a strong walled flask. The material was shaken vigorously at frequent intervals to prevent a hard mass forming. The resulting anhydrous KF was stored under dry nitrogen.

8.4 Preparation and Purification of Substrates

The substrates used were obtained from a variety of sources. Where the substrates were supplied by the departmental technicians only a description of the purification carried out by the author is given, and a reference is cited for the method of preparation. Commercial

materials were generally used 'as is' after checking their purity by glc and hplc. Full characterisation is given for compounds not previously synthesised.

8.4.1 Pentafluoropyridine[98]

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',140°C).

8.4.2 3-Chlorotetrafluoropyridine[98]

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',140°C).

8.4.3 3,5-Dichlorotrifluoropyridine[98]

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',140°C).

8.4.4 4-Chlorotetrafluoropyridine[96]

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',140°C).

8.4.5 3-(Trifluoromethyl)-2,4,5,6- tetrafluoropyridine[96]

This was purified by repeated use of preparative scale glc. ('Aerograph, column 'A',120°C). The main impurity was 3,5-Bis(Trifluoromethyl)-2,4,6-trifluoropyridine which was isolated and further purified.

8.4.6 Tetrafluoropyrimidine[96]

This was purified prior to use by molecular distillation (Room

temperature vessel to liquid nitrogen cold trap -196°C).

8.4.7 2,4,5,6-Tetrafluoropyridine[96]

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',80°C).

8.4.8 2,4,6-Trifluoropyridine

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',80°C).

8.4.9 3-Nitro-2,4,6-trifluoropyridine

This was purified by repeated use of preparative scale glc. ('Aerograph, column 'A',120°C).

8.4.10 Pentafluorobenzonitrile

The commercial product was used as supplied after checking the purity on the glc ('Aerograph, column 'A',80°C).

8.4.11 Pentafluoronitrobenzene

This was purified prior to use by preparative scale glc. ('Aerograph, column 'A',140°C).

8.4.12 1,4 Dicyanotetrafluorobenzene

The commercial product was used as supplied after checking the purity on the glc ('Aerograph, column 'A',80°C).

8.4.13 1,2 Dicyanotetrafluorobenzene

The commercial product was used as supplied after checking the

purity on the glc ('Aerograph, column 'A',80°C).

8.4.14 Octafluororbenzene

The commercial product was used as supplied after checking the purity on the glc ('Aerograph, column 'A',80°C).

8.4.15 3-cyanopentafluoropyridine

Method 1

To sulpholane (250ml) was added anhydrous potassium fluoride (242g) and the mixture heated at 220°C without a condensor for 1/2 hr. Cooled to 90°C and 3-cyanotetrachloropyridine (64g) added, a condenser and drying tube were fitted and the reaction mixture was heated at 220°C for 16hrs. Glc showed little reaction had taken place. A further portion (51g) of KF was added and the reaction stirred at 220°C for a further 22hrs. The reaction mixture was worked up by pouring it into water (2l) and extracting with carbon tetrachloride (2x 250ml). After drying (magnesium sulphate) and removal of the carbon tetrachloride a yellow oil was obtained (8g) which was fractionated under reduced pressure (20mmHg) the fraction boiling at 60-62°C was collected and found by glc to be pure 3-cyano-tetrafluoropyridine. (5g,10%).

Method 2

Commercial 3-cyanopentachloropyridine (35g) and anhydrous potassium fluoride (45g),(1:5.6 moles) were heated in a 100ml stainless steel autoclave at 350°C for 20 hrs. The Autoclave removed from the furnace while still hot and opened to a vacuum line (0.1mmHg), the product distilled out under the remaining heat of the autoclave and

collected in a vessel at -196°C. The product was further purified by distillation. (10g,39%).

8.4.16 2-cyanopentafluoropyridine

Commercial 2-cyanopentachloropyridine (35g) and anhydrous potassium fluoride (45g),(1:5.6 moles) were heated in a 100ml stainless steel autoclave at 350°C for 20 hrs. The Autoclave removed from the furnace while still hot and opened to a vacuum line (0.1mmHg), the product distilled out under the remaining heat of the autoclave and collected in a vessel at -196°C. The product was further purified by distillation. (14g,55%).

8.5 Reactions with Aromatic Amines

Aniline and pentafluorobenzonitrile

Aniline (0.93g.) and pentafluorobenzonitrile (1.03g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a pink solid. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product. Solid was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the adduct 4-anilinotetrafluorobenzonitrile. (1.2g.,90%) m.p.120°C. (Found: C, 58.60; H, 2.25; N, 10.43%; M, 266. $C_{13}H_6F_4N_2$ requires: C, 58.65; H, 2.28; N, 10.52; F, 28.55%; M, 266). Ir spectrum no.25, Nmr Table no. 23.

Aniline and pentafluoropyridine

Aniline (1.03g.) and pentafluoropyridine (0.57g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 22 hrs. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the adduct 4-anilino-2,3,5,6-tetrafluoropyridine. (0.77g.,88%) m.p.87°C. (Found: C 54.85,; H, 2.41; N, 11.91%; M, 242. $C_{11}H_6F_4N_2$ requires: C, 54.55; H, 2.46; N, 11.57; F, 31.40%; M, 242). Ir spectrum no. 3, Nmr Table no. 1.

The reaction was repeated at 25°C to give the 4-adduct (100%).

Aniline and 2,3,4,6-tetrafluoropyridine

Aniline (0.93g.) and 2,3,4,6-tetrafluoropyridine (0.76g.) (2:1 moles) in dioxan (6ml) were stirred at 25°C for 3 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown solid (1.3g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the solid showed the presence of two isomers. From nmr these were the 2-adduct 2-anilino-3,4,6-trifluoropyridine (25%), and the 4-adduct 4-anilino-2,3,6-trifluoropyridine (75%). Nmr Table no. 6.

Aniline and 2,4,6-trifluoropyridine

Aniline (0.93g.) and 2,4,6-trifluoropyridine (0.67g.) (2:1 moles)

in dioxan (6ml) were heated in a sealed tube at 25°C for 8 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.26g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil only showed the presence of starting materials.

Aniline and 4-chloro-2,3,5,6-tetrafluoropyridine

Aniline (0.93g.) and 4-chloro-2,3,5,6-tetrafluoropyridine (0.93g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 3 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product the 2-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be 2-anilino-4-chlorotrifluoropyridine (1.02g.,78%). (Found: C, 50.98; H, 2.26; N, 10.78%; M, 258. $C_{11}H_6ClF_3N_2$ requires: C, 50.98; H, 2.34; N, 10.83; Cl, 13.71; F, 22.04%; M, 258). Ir spectrum no.26, Nmr Table no. 8.

Aniline and 3,5-dichloro-2,4,6-trifluoropyridine

Aniline (0.93g.) and 3,5-dichloro-2,4,6-trifluoropyridine (1.1g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 8 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown solid. Nmr, hplc and tlc (silica, dichloromethane/hexane,

60:40) of the solid showed the presence of two isomers. From nmr these were the 4-adduct (98%), 4-anilino-3,5-dichlorodifluoropyridine and the 2-adduct (8%), 2-anilino-3,5-dichlorodifluoropyridine. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be the 4-adduct, 4-anilino-3,5-dichlorodifluoropyridine (1.3g.,86%) m.p.73°C. (Found: C, 48.33; H, 2.18; N, 10.26%. $C_{11}H_6Cl_2F_2N_2$ requires: C, 48.03; H, 2.20; N, 10.18; Cl, 25.78; F, 13.82%). Ir spectrum no.45, Nmr Table no. 16.

Aniline and 3-chlorotetrafluoropyridine

Aniline (0.93g.) and 3-chlorotrifluoropyridine (0.93g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 hrs. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.1g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product the 4-adduct, 4-anilino-3-chlorotrifluoropyridine. Nmr Table no. 9.

Aniline and 3-cyano-2,6-difluoropyridine

Aniline (0.93g.) and 3-cyano-2,6-difluoropyridine (0.70g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 8 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40)

of the oil showed the presence of two isomers, the 2-adduct (50%), 2-anilino-3-cyano-2-fluoropyridine and the 6-adduct (50%), 6-anilino-3-cyano-2-fluoropyridine. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be the 6-adduct, 6-anilino-3-cyano-2-fluoropyridine. (0.4g.,37%) m.p.85°C. (Found: C, 67.89; H, 3.76; N, 19.68%. $C_{12}H_8FN_3$ requires: C, 67.76; H, 3.78; N, 19.71; F, 8.91%). Ir spectrum no.6 , Nmr Table no. 19. The 2-adduct was not obtained in pure form.

Aniline and 3-chloro-5-cyano-2,4,6-trifluoropyridine

Aniline (32.0g.) and 3-chloro-5-cyano-2,4,6-trifluoropyridine (8.0g.) (2:1 moles) in dioxan (160ml) were stirred in a conical flask at 25°C for 3 days. The solution was The solution was poured into diethyl ether and washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-adduct (75%), 4-anilino-3-chloro-5-cyanodifluoropyridine and the 2-adduct (25%), 2-anilino-3-chloro-5-cyanodifluoropyridine. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be a mixture of the 2- and 4-adducts. ies. (12g.,66%). (Found for mixed isomers: C, 53.94; H, 2.41; N, 15.74%; M, 265. $C_{12}H_6ClF_2N_3$ requires: C, 54.24; H, 2.26; N, 15.82;Cl, 13.37; F, 15.82%; M, 265). The mixed product was seperated by by repeated analytical scale hplc to give the 2- and 4-adducts in small quantities. The nmr's were run and the 4-adduct characterised, 4-anilino-3-chloro-5-cyanodifluoropyridine (0.2g). (Found: C, 53.94; H, 2.41; N, 15.74%; M, 265. $C_{12}H_6ClF_2N_3$ requires: C, 54.24; H, 2.26;

N, 15.82;Cl, 13.37; F, 15.82%; M, 265). Ir spectrum no.2 , Nmr Table no. 20.

Aniline and 3-cyanotetrafluoropyridine

Aniline (0.93g.) and 3-cyanotetrafluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 8 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.2g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-adduct (70%), and the 6-adduct (30%). Nmr Table no. 12 and 14.

Aniline and 1,2-dicyanotetrafluorobenzene

Aniline (0.93g.) and 1,2-dicyanotetrafluorobenzene (1.06g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 25°C for 9 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.4g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two products, the 4-adduct (50%), and the 4,6 disubstituted adduct (50%). The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be 4-anilino-1,2-dicyanotrifluorobenzene (1.3g.,89%) m.p.159°C. (Found: C, 61.57; H, 2.02; N, 15.42%; M, 273. $C_{14}H_6F_3N_3$ requires: C, 61.54; H, 2.22; N, 15.37; F, 20.89%; M, 273). Ir spectrum no.9, Nmr Table no. 26.

The 4,6-adduct was not isolated as a pure compound.

Aniline and 2-cyanotetrafluoropyridine

Aniline (0.31g.) and 2-cyanotetrafluoropyridine (0.29g.) (2:1 moles) in dioxan (20ml) were stirred in a conical flask at 25°C for 3 days. The solution was poured into diethyl ether and washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 4-adduct, 4-anilino-2-cyano-trifluoropyridine (0.35g.,88%) m.p.83°C. Ir spectrum no.4, Nmr Table no. 18.

N-methylaniline and pentafluorobenzonitrile

N-methylaniline (1.03g.) and pentafluorobenzonitrile (1.17g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 3 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one isomer. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 2-adduct 2-N(N-methylanilino)-tetrafluorobenzonitrile (1.4g.,82%) (Found: C, 59.95; H, 2.83; N, 9.92%. $C_{14}H_8F_4N_2$ requires: C, 60.01; H, 2.88; N, 10.00; F, 27.12%). Ir spectrum no.20, Nmr Table no. 24.

N-methylaniline and pentafluoropyridine

N-methylaniline (4.7g.) and pentafluoropyridine (2.4g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 7 hrs. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one isomer. The crude product was columned on silica with hexane/dichloromethane (10/90), to give a white solid which proved to be the 4-adduct, 4-N(N-methylanilino)-tetrafluoropyridine (3.0g.,63%). Nmr Table no. 1.

N-methylaniline and 2,3,4,6-tetrafluoropyridine

N-methylaniline (1.07g.) and 2,3,4,6-tetrafluoropyridine (0.76g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 6 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-adduct (59%) and the 2-adduct (41%). The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be a mixture of the 2 and 4-adducts (1.1g.,84%). Nmr Table no. 3 and 4.

N-methylaniline and 2,4,6-trifluoropyridine

N-methylaniline (1.07g.) and 2,4,6-trifluoropyridine (0.67g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 6 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried

with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of three products, the two isomers, the 2-(33%) and 4-(61%) adducts and the 2,6-disubstituted adduct (6%). Nmr Table no. 3,4 and 5.

N-methylaniline and 3,5-dichloro-2,4,6-trifluoropyridine

N-methylaniline (5.0g.) and 3,5-dichloro-2,4,6-trifluoropyridine (3.0g.) (3:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 2 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one isomer. The crude product was columned on silica with dichloromethane to give a white solid which proved to be the 2-adduct (2.5g.,53%). (Found: C, 50.10; H, 2.97; N, 10.19%. $C_{12}H_8Cl_2F_2N_2$ requires: C, 49.85; H, 2.79; N, 9.69; Cl, 24.53; F, 13.14,%). Nmr Table no. 16.

N-methylaniline and 3-chloro-5-cyano-2,4,6-trifluoropyridine

N-methylaniline (5.0g.) and 3-chloro-5-cyano-2,4,6-trifluoropyridine (3.0g.)(2:1 moles) in dioxan (30ml) were heated in a sealed tube at 80°C for 36 hrs. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two

isomers, the 2-(75%) and 6-(25%) adducts. The crude product was columned on silica with hexane/dichloromethane (50:50), to give two fractions the first proved to be the pure 2-adduct 2-N(N-methyl anilino)-3-chloro-5-cyanodifluoropyridine. (0.5g.,9%). (Found: M, 279. $C_{13}H_8ClF_2N_3$ requires: M, 279). Ir spectrum no.2, Nmr Table no. 21. The second fraction proved to be a mixture of the 6 and 2-adducts (Found for mixed isomers: C, 55.78; H, 2.92; N, 14.96%. $C_{13}H_8ClF_2N_3$ requires: C, 55.83; H, 2.88; N, 15.02; Cl, 12.68; F, 13.59%).

N-methylaniline and 1,2-dicyanotetrafluorobenzene

N-methylaniline (1.07g.) and 1,2-dicyanotetrafluorobenzene (1.06g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 2 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give a yellow solid which proved to be a mixture of the 2 and 4-adducts (1.2g.,76%) m.p.128°C. (Found: C, 62.81; H, 2.80; N, 14.68%. $C_{15}H_8F_3N_3$ requires: C, 62.72; H, 2.81; N, 14.63; F 19.84,%). Nmr Table no. 26 and 27.

Benzylamine and pentafluoropyridine

Benzylamine (1.07g.) and pentafluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 9 days. The tube was cooled, opened to the air and washed out with diethyl ether.

The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.3g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two products, the 4-adduct (35%), and the 2,4-disubstituted adduct (65%). The reaction was repeated at 25°C to give the 4-adduct (100%). Nmr Table no. 1.

Benzylamine and pentafluorobenzonitrile

Benzylamine (1.07g.) and pentafluorobenzonitrile (0.55g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 1 day. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-adduct (95%), and the 2-adduct (5%). The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be a mixture of the 2 and 4-adducts (0.79g.,75%). The reaction was repeated at 25°C to give the 4-adduct (100%). Nmr Table no. 23 and 24.

Benzylamine and 2,4,6-trifluoropyridine

Benzylamine (1.07g.) and 2,4,6-trifluoropyridine (0.76g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 9 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.08g.90%). Nmr, hplc and tlc (silica,

dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 2-adduct (23%), and the 4-adduct (77%). Nmr Table no. 3 and 4.

Benzylamine and 2,3,4,6-tetrafluoropyridine

Benzylamine (1.76g.) and 2,3,4,6-tetrafluoropyridine (1.07g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 9 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (1.76g.95%). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 2-adduct (20%) and the 4-adduct (70%). Nmr Table no. 6 and 7.

Benzylamine and 4-chloro-2,3,5,6-tetrafluoropyridine

Benzylamine (1.07g.) and 4-chloro-2,3,5,6-tetrafluoropyridine (0.93g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80 °C for 9 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a red oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed it to be exclusively the 2-adduct, plus some unreacted starting material. Nmr Table no. 8.

Benzylamine and 3,5-dichloro-2,4,6-trifluoropyridine

Benzylamine (1.07g.) and 3,5-dichloro-2,4,6-trifluoropyridine (1.1g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at

80°C for 10 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a red oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed it to be exclusively the 4-adduct. Nmr Table no. 16.

Benzylamine and 3-cyano-2,6-difluoropyridine

Benzylamine (1.07g.) and 3-cyano-2,6-difluoropyridine (0.70g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 10 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a yellow oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed it to be a mixture of the 2-(63%) and 4-(27%) adducts. Nmr Table no. 19.

Benzylamine and 3-chloro-5-cyano-2,4,6-trifluoropyridine

Benzylamine (1.07g.) and 3-chloro-5-cyano-2,4,6-trifluoropyridine (0.8g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-adduct (55%)and the 2-adduct (45%). The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be a mixture of the 2 and 4-adducts (0.4g.,35%). (Found: C, 55.71; H, 2.85; N, 14.98%. $C_{13}H_8ClF_2N_3$ requires: C, 55.83; H, 2.88; N, 15.02;

F, 13.59%). Ir spectrum no.27, Nmr Table no. 20 and 21.

Benzylamine and 1,2-dicyanotetrafluorobenzene

Benzylamine (1.07g.) and 1,2-dicyanotetrafluorobenzene (1.06g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a yellow oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-(7%) and 6-(65%) adducts and the 4,6-disubstituted adduct (37%). Nmr Table no. 26 and 27.

8.6 Reactions with Ammonia

Ammonia and 3-cyanotetrafluoropyridine

Saturated ammonia solution (1ml) and 3-cyanotetrafluoropyridine (0.88g.) in dioxan (6ml) were stirred at 25°C for 2 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers, the 4-adduct (67%) and the 6-adduct (3%). The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid. (0.37g.,50%) which nmr showed to be the 4-amino-3-cyanotetrafluoropyridine. Ir spectrum no.21, Nmr Table no. 12. The 6-adduct was not obtained as a pure compound.

Ammonia and 3-chloro-5-cyano-2,4,6-trifluoropyridine

Saturated ammonia solution (1ml) and 3-chloro-5-cyano-2,4,6-trifluoropyridine (0.70g.) in dioxan (6ml) were heated in a sealed tube at 80°C for 2 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be a mixture of the 2-(50%) and 4-(50%) adducts (0.6g.,85%) Nmr Table no. 20 and 21. The reaction was repeated at 25°C to give the 4-adduct (100%)

Ammonia and 3-cyano-2,6-difluoropyridine

Saturated ammonia solution (1ml) and 3-cyano-2,6-difluoropyridine (0.7g.) (:1moles) in dioxan (6ml) were sitrred at 25°C for 3 days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers, the 2-(50%) and 6-(50%) . The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be a mixture of the 2 and 6-adducts. Nmr Table no. 19.

Ammonia and 1,2-dicyanotetrafluorobenzene

Saturated ammonia solution (1ml) and 1,2-dicyanotetrafluorobenzene

(1.0g.) in dioxan (6ml) were heated in a sealed tube at 80°C for 16days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be a mixture of the 4-(50%) and 6-(50%) adducts (0.7g.). Nmr Table no. 26 and 27. The reaction was repeated at 25°C to give the 4-adduct (100%)

Ammonia and 3-nitro-2,4,6-trifluoropyridine

Saturated ammonia solution (1ml) and 3-nitro-2,4,6-trifluoropyridine (0.96g.) in dioxan (6ml) were heated in a sealed tube at 25°C for 16days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil (0.9g.). Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product the 4-adduct. Nmr Table no. 30.

Ammonia and 2-cyanotetrafluoropyridine

Saturated ammonia solution (1ml) and 2-cyanotetrafluoropyridine (0.29g.) in dioxan (6ml) were heated in a sealed tube at 25°C for 16days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product

4-amino-2-cyanotetrafluoropyridine. Nmr Table no. 18.

Ammonia and 1,4-dicyanotetrafluorobenzene

Saturated ammonia solution (1ml) and 1,2-dicyanotetrafluorobenzene (1.0g.) in dioxan (6ml) were heated in a sealed tube at 80°C for 16days. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product the 2-adduct. Nmr Table no. 35.

Aniline and octafluorotoluene

Aniline (0.93g.) and octafluorotoluene (1.18g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 1 day. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a white solid. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product. Solid was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the adduct 4-anilinoheptafluorotoluene. (1.2g.,90%) m.p.120°C. (Found: C, 58.60; H, 2.25; N, 10.43%; M, 266. $C_{13}H_6F_4N_2$ requires: C, 58.65; H, 2.28; N, 10.52; F, 28.55%; M, 266). Ir spectrum no.8, Nmr Table no. 29.

8.7 Reactions with Substituted Anilines

4-Nitroaniline and Pentafluoropyridine

4-Nitroaniline (0.69g.) and pentafluoropyridine (1.25g.) (1:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed it to be starting material.

3-Nitroaniline and Pentafluoropyridine

3-Nitroaniline (1.38g.) and pentafluoropyridine (0.89g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give a yellow solid which proved to be 4-(3'-nitro)-tetrafluoropyridine (1.4g.,93%) m.p.104°C. Nmr Table no. 1.

3-Chloroaniline and Pentafluoropyridine

3-Chloroaniline (1.21g.) and pentafluoropyridine (0.85g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica,

dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be 4-(3'-chloro)-tetrafluoropyridine (1.2g.,90%). Nmr Table no. 1.

3-Bromoaniline and Pentafluoropyridine

3-Bromoaniline (1.58g.) and pentafluoropyridine (0.86g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be 4-(3'-bromoanilino)tetrafluoropyridine (1.5g.,81%) m.p.87°C. (Found: C, 41.36; H, 1.58; N, 8.66%. $C_{11}H_5BrF_4N_2$ requires: C, 41.15; H, 1.57; N, 8.72; F, 23.67%;). Ir spectrum no. 40, Nmr Table no. 1.

4-Chloroaniline and Pentafluoropyridine

4-Chloroaniline (1.28g.) and pentafluoropyridine (0.85g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be 4-(4'-chloroanilino)-tetrafluoropyridine (1.2g.,87%) m.p.81°C. Ir

spectrum no. 19 , Nmr Table no. 1.

3-Methylaniline and Pentafluoropyridine

3-Methylaniline (1.0g.) and pentafluoropyridine (0.85g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be 4-(3'methylanilino)tetrafluoropyridine (1.2g.,83%) m.p.120°C. Nmr Table no. 1.

4-Methylaniline and Pentafluoropyridine

4-Methylaniline (1.07g.) and pentafluoropyridine (0.85g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct, 4-(4'-methylanilino)-tetrafluoropyridine (1.3g.,89%). Nmr Table no. 1.

4-Methoxyaniline and Pentafluoropyridine

4-Methoxyaniline (1.23g.) and pentafluoropyridine (0.85g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 7 days. The tube was cooled and opened to air, washed out with acetone and

filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of two isomers, the 4-(90%) and the 2-(10%) adducts. The crude product was columned on silica with pentane/chloroform (50:50), to give two fractions, the first fraction were white needles which were shown by nmr to be 4-(4'-methoxyanilino)-tetrafluoropyridine (0.5g.,31%) m.p.82^{o}C.; the second fraction were white needles which were shown by nmr to be 2-(4'-methoxyanilino)-tetrafluoropyridine (0.3g.,14%) m.p.76^{o}C. Nmr Table no. 1.

4-Bromoaniline and Pentafluoropyridine

4-Bromoaniline (1.58g.) and pentafluoropyridine (0.86g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80^{o}C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one product, the 4-adduct, 4-(4'bromoanilino)-tetrafluoropyridine (1.4g.,75%). Nmr Table no. 1.

3-Methoxyaniline and Pentafluoropyridine

3-Methoxyaniline (1.1g.) and pentafluoropyridine (0.85g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80^{o}C for 19 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed the presence of one

product, the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give white needles which proved to be 4-(3'methoxyanilino)tetrafluoropyridine (1.1g.,76%) m.p.184-187°C. (Found: C, 56.31; H, 3.10; N, 10.86%. $C_{12}H_8F_4N_2$ requires: C, 56.26; H, 3.15; N, 10.93; F, 29.66%). Ir spectrum no. 28 , Nmr Table no. 1.

3-Nitroaniline and 3-cyanotetrafluoropyridine

3-Nitroaniline (1.38g.) and 3-cyanotetrafluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product the 4-adduct. Product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 4- adduct, 4-(3'-nitroanilino)-3-cyanotrifluoropyridine. (g., %) m.p.147°C. (Found: C, 48.86; H, 1.69; N, 18.98%. $C_{13}H_5F_3N_4O_2$ requires: C, 48.99; H, 1.72; N, 19.04; O, 10.88; F, 19.38%; M ,294). Ir spectrum no. 12. NMR Table no.12.

3-Chloroaniline and 3-cyanotetrafluoropyridine

3-Chloroaniline (1.21g.) and 3-cyanotetrafluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two products the 4-adduct 4-(3'-chloroanilino)-

-3-cyanotrifluoropyridine and the 4,6 disubstituted pyridine 2,4-di-(3'-chloroanilino)-5-cyanodifluoropyridine.The crude product was columned on silica with pentane/chloroform (50:50), to give two fractions ,fraction 1 a white solid which proved to be the 4- adduct (0.5g.,35%) m.p.110°C. Ir spectrum no.17, Nmr Table no. 12 ; and fraction 2 a white solid which proved to be the 2,6-disubstituted pyridine (0.45g.,23%) m.p.202°C. Ir spectrum no. 18, Nmr Table no. 13.

4-Chloroaniline and 3-cyanotetrafluoropyridine

4-Chloroaniline (1.20g.) and 3-cyanotetrafluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two disubstituted isomers, the 2,4-(75%) and 4,6-(25%) adducts. Product was columned on silica with pentane/chloroform (50:50), to give an orange solid which proved to be the 2,4-di-(4'-chloroanilino)--3-cyanodifluoropyridine (0.4g.,26%) m.p. 170°C. (Found: C, 50.85; H, 1.76; N, 14.65%. $C_{12}H_5ClF_3N_3$ requires: C, 50.81; H, 1.78; N, 14.81; Cl, 12.50; F, 20.10%; M, 283). Ir spectrum no.16, Nmr Table no. 12.

4-Methoxyaniline and 3-cyanotetrafluoropyridine

4-Methoxyaniline (1.23g.) and 3-cyanotetrafluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 14 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica,

dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers which by nmr were the 4,6-(86%)and 2,4-(14%)disubstituted adducts. Nmr Table no. 14 and 15.

3-Methoxyaniline and 3-cyanotetrafluoropyridine

3-Methoxyaniline (1.1g.) and 3-cyanotetrafluoropyridine (0.88g.) (1.9:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 7 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product the 4-adduct. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be 4-(3'-methoxyanilino)-3-cyanotrifluoropyridine (0.95g.,84%) m.p.105°C. (Found: C, 56.10; H, 3.15; N, 14.66%; F, 19.50; M ,279. $C_{13}H_7F_3N_3O$ requires: C, 55.92; H, 2.89; N, 15.04; O, 5.73; F, 20.41%; M,). Ir spectrum no. 46, Nmr Table no. 12.

4-Nitroaniline and 3-chloro-5-cyano-2,4,6-trifluoropyridine

4-Nitroaniline (0.69g.) and 3-chloro-5-cyano-2,4,6-trifluoropyridine (0.69g.) (1:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed it to be starting material.

4-Chloroaniline and 3-chloro-5-cyano-2,4,6-trifluoropyridine

4-Chloroaniline (1.1g.) and 3-chloro-5-cyano--2,4,6-trifluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers, the 4-adduct (90%) and the 2-adduct (10%). Product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 4- adduct (1.0g.,87%) . Nmr Table no. 20.

4-Methoxyaniline and 3-chloro-5-cyano-2,4,6-trifluoropyridine

4-Methoxyaniline (1.2g.) and 3-chloro-5-cyano--2,4,6-trifluoropyridine (0.88g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers, the 4-adduct (90%) and the 2-adduct(10%). Product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 4- adduct (1.1g.,70%). Nmr Table no. 20.

4-Nitroaniline and Pentafluorobenzonitrile

4-Nitroaniline (0.69g.) and pentafluorobenzonitrile (0.69g.) (1:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18

days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the oil showed it to be starting material.

3-Nitroaniline and Pentafluorobenzonitrile

3-Nitroaniline (1.38g.) and pentafluorobenzonitrile (1.03g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 14 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a yellow solid which proved to be 4-(3'-nitroanilino)cyanotetrafluorobenzene (0.8g.,48%) m.p.104°C. Ir spectrum no. 13. Nmr Table no. 23.

3-Chloroaniline and Pentafluorobenzonitrile

3-Chloroaniline (1.21g.) and pentafluorobenzonitrile (1.03g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 14 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 4- adduct (1.2g.,75%) m.p.122°C. (Found: C, 51.97; H, 1.50;

N, 9.40%. $C_{13}H_5ClF_4N_2$ requires: C ,51.93; H, 1.68; N, 9.31; Cl, N, 11.79; F, 25.28%;). Ir spectrum no. 7, Nmr Table no. 23.

4-Bromoaniline and Pentafluorobenzonitrile

4-Bromoaniline (0.86g.) and pentafluorobenzonitrile (1.03g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be the 4- adduct (1.5g.,82%) Ir spectrum no. 38, Nmr Table no. 23.

4-Chloroaniline and Pentafluorobenzonitrile

4-Chloroaniline (1.28g.) and pentafluorobenzonitrile (1.03g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 19 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be 4-(4'-chloranilino)cyanotetrafluoropyridinethe (1.1g.,68%) . (Found: C, 51.79; H, 1.36; N, 9.32; Cl, 11.94; F, 24.70%. $C_{13}H_5ClF_4N_2$ requires: C, 51.93; H, 1.68; N, 9.31; Cl, 11.79; F, 25.28%; M,). Ir spectrum no. 32, Nmr Table no. 23.

3-Bromoaniline and Pentafluorobenzonitrile

4-Methoxyaniline (1.58g.) and pentafluorobenzonitrile (1.03g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of one product. The crude product was columned on silica with pentane/chloroform (50:50), to give a white solid which proved to be 4-(3'-bromoanilino)cyanotetrafluorobenzene (1.2g.,66%) m.p.116°C. Ir spectrum no. 11 , Nmr Table no. 23.

3-Nitroaniline and Pentafluoronitrobenzene

3-Nitroaniline (1.38g.) and pentafluoronitrobenzene (1.3g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers. Product was columned on silica with pentane/chloroform (50:50), to give a yellow solid which proved to be the 2- adduct, 2-(3'-methoxyanilino)nitrotetrafluorobenzene (1.1g.,66%) . (Found: C, 43.37; H, 1.50; N, 12.90; %;M, . $C_{12}H_5O_4F_4N_3$ requires: C, 43.52; H, 1.53; N, 12.68; O, 19.33; F, 22.94%;M,). Ir spectrum no. 29, Nmr Table no. 33.

3-Chloroaniline and Pentafluoronitrobenzene

3-Chloroaniline (1.21g.) and pentafluoronitrobenzene (1.13g.) (2:1

moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 15 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers. Product was columned on silica with pentane/chloroform (50:50), to give the first fraction, a yellow solid which proved to be 2-(3'-chloroanilino)nitrotetrafluorobenzene (0.5g.,30%) . (Found: C, 44.67; H, 1.23; N, 8.58%;M, . $C_{12}H_5ClF_4N_2O_2$ requires: C, 44.95; H, 1.58; N, 8.73; O, 9.98; Cl, 11.06; F, 23.70%;M,). Ir spectrum no. 30, Nmr Table no. 33; and a second fraction, an orange solid which proved to be 2,6-di-(3'-chloroanilino)nitrotrifluorobenzene (0.6g.,28%) m.p.146°C. M,. Ir spectrum no. 34, Nmr Table no. 34.

4-Methoxyaniline and Pentafluoronitrobenzene

4-Methoxyaniline (1.23g.) and pentafluoronitrobenzene (1.13g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 16 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers. Product was columned on silica with pentane/chloroform (50:50), to give a first fraction, a white solid which proved to be 2-(3'-methoxyanilino)nitrotrifluorobenzene. Ir spectrum no. 37, Nmr Table no. 33; and a second fraction, a white solid which proved to be 2,6-di-(4'-methoxyanilino)nitrotrifluorobenzene. Ir spectrum no. 36, Nmr Table no. 34.

3-Bromoaniline and Pentafluoronitrobenzene

4-Bromoaniline (1.58g.) and pentafluoronitrobenzene (1.13g.) (2:1 moles) in dioxan (6ml) were heated in a sealed tube at 80°C for 18 days. The tube was cooled and opened to air, washed out with acetone and filtered to remove the insoluble hydrofluoride. Removal of the acetone gave a brown oil. Nmr, hplc and tlc (silica, dichloromethane/hexane, 60:40) of the crude product showed the presence of two isomers. Product was columned on silica with pentane/chloroform (50:50), to give a first fraction a white solid which proved to be 2-(3'-bromoanilino)nitrotetrafluorobenzene. Ir spectrum no. 10, Nmr Table no. 33; and a second fraction a white solid which proved to be 2,6-di-(3'-bromoanilino)nitrotrifluorobenzene. Ir spectrum no. 33, Nmr Table no. 34.

8.8 Reactions With Sodium Methoxide

To the substrate (0.5g) in dioxan (20ml) were added 5ml of sodium methoxide in dioxan (1M),(1:1 moles) and stirred at 25°C for 1 day.

As the products with sodium methoxide have been previously synthesised and characterised the reaction mixtures were analysed by nmr. The results are shown in Table 3.11.

8.9 Reactions With Sodium Methoxide and Molecular Sodium

The reaction was carried out as above, with the addition of molecular sodium (0.3g) at the start of the reaction. Products were analysed by nmr and the results are given in Table 3.11.

8.10 Reactions With Aniline and Molecular Sodium

To the substrate (0.5g) in dioxan (20ml) were added aniline (1.0g) and molecular sodium (0.3g) in dioxan and stirred at 25°C for 1 day. The reaction was very exothermic and became very hot to the touch.

As the products with aniline have been previously synthesised and characterised the reaction mixtures were analysed by nmr. The results are shown in Table 3.11.

8.11 Reactions With Sodium Phenoxide

To the substrate (0.5g) in dioxan (20ml) were added 5ml of sodium phenoxidein dioxan and stirred at 25°C for 1 day.

The reaction mixtures were analysed by nmr. The results are shown in Table 3.11.

The reaction product with 2,4,6-trifluoropyridine was purified by crystallisation from methanol and the IR spectrum no.31 showed the presence of an ether peak at 1245cm^{-1} demonstrating that the reactions with phenoxide were forming adducts via the oxygen atom.

CHAPTER 9

EXPERIMENTAL FOR CHAPTER 5

CHAPTER 9

EXPERIMENTAL FOR CHAPTER 5

9.1 Instrumentation

9.1.1 For Preparative work

See Chapter 8 .

9.1.2 Rate Measurements

All runs were carried out in thermostatted baths, which were heated electrically by filament-type heaters, the temperature being controlled to + 0.01^{o}C by contact thermometer. Water (with a few drops of acetic acid to prevent scale formation) was used as the liquid in baths at temperatures around 25^{o}C, and lissapol was used for the baths at temperatures up to 80^{o}C. The accurate temperature of each bath was measured by thermometers standardised to + 0.02^{o}C by the National Physics Laboratory.

Rates were followed using an Activion fluoride ion sensitive electrode and a silver/silver chloride reference electrode.

When reactions were determined by hplc a Perkin Elmer model 1 was used. The column was a Waters Associates silicia column with a 10 micron packing. The solvent was dichloromethane/hexane 60/40,(v/v).

9.2 Solvents

9.2.1 Dioxan

See Chapter 8.

9.2.2 Acetone

Analar acetone was used with out further treatment.

9.2.3 Water

See Chapter 8.

9.3 Reagents

9.3.1 Aniline

See Chapter 8.

9.4 Preparation and Purification of Substrates

The substrates used for the determination of rates constants were obtained from a variety of sources. Commercial materials were generally used 'as is' after checking their purity by glc and hplc. The methods of purification etc. are given in chapter 9.

9.5 Identification of Products

The reactions of these systems have been extensively studied see Chapters 3,9 and reference 96. The product analysis was therefore carried out by nmr and hplc. Because of the unknown extinction coefficients of many of the compounds, where more than one product was formed, the ratio of products was determined exclusively by nmr.

9.5.1 Work-up for Reaction Products

After the kinetic run was complete the reaction mixture was evaporated downto an oil. The hplc of a little of the oil dissolved in acetone was run. The oil was poured into water ($50cm^3$) and then extracted with ether ($2 \times 50cm^3$). The ether was removed, the product dissolved in acetone and the nmr run to determine the product ratios.

Reaction of Aniline and Pentafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilinotetrafluoropyridine.

Reaction of Aniline and 2,4,6-trifluoropyridine

Hplc showed starting materials and two products. Nmr showed the

4-adduct, 4-anilino-2,6-difluoropyridine (75%) and the 6-adduct, 6-anilino-2,4-difluoropyridine(25%).

Reaction of Aniline and 2,3,4,5-tetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-2,3,5-trifluoropyridine.

Reaction of Aniline and 4-chlorotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 2-adduct, 2-anilino-4-chlorotrifluoropyridine.

Reaction of Aniline and 2-chlorotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-2-chlorotrifluoropyridine.

Reaction of Aniline and 3-chlorotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-3-chlorotrifluoropyridine.

Reaction of Aniline and 3,5-dichlorotrifluoropyridine

Hplc showed starting materials and two products. Nmr showed the 4-adduct, 4-anilino-3,5-dichlorodifluoropyridine(75%) and the 2-adduct, 2-anilino-3,5-dichlorodifluoropyridine(25%).

Reaction of Aniline and 3-chloro-5-cyano-trifluoropyridine

Hplc showed starting materials and two products. Nmr showed the 4-adduct, 4-anilino-3-chloro-5-cyano-difluoropyridine(80%) and the 2-adduct, 2--anilino-3-chloro-5-cyano-difluoropyridine(20%).

Reaction of Aniline and 2-cyanotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-2-cyanotrifluoropyridine.

Reaction of Aniline and 3-trifluoromethyltetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-3-trifluoromethyltrifluoropyridine.

Reaction of Aniline and Tetrafluoropyrimidine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilinotetrafluoropyrimidine.

Reaction of Aniline and Pentafluorobenzonitrile

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilinotetrafluorobenzonitrile.

9.6 Methods of Rate Measurements

9.6.1 Calibration of the Fluoride Ion Electrode

The fluoride ion electrode was calibrated with a series of standard solutions made up from a standardized 1M solution of hydrofluoric acid. The calibration series contained 0.21M aniline in dioxan/water 60:40,(v/v). i.e. The same conditions as the reaction mixtures to be used. A graph was constructed of the measured EMF versus fluoride ion concentration and this was used to determine the fluoride ion concentration during the kinetic runs.

9.6.2 Calibration of the Hplc

The hplc was calibrated with a series of standard solutions made up from a stock solutions of pentafluoropyridine and ethyl benzene in dioxan/water 60 :40,(v/v). i.e. The same conditions as the reaction mixtures to be used. A graph was constructed of the ratio of pentafluoropyridine to ethyl benzene and this was used to determine the pentafluoropyridine concentration during the kinetic runs.

9.6.3 Fluoride Ion Sensitive Electrode Method

Stock solutions of aniline and substrate in dioxan were prepared, usually being approximately 1.1 mol l^{-1} and 0.05 mol l^{-1} respectively.

Dioxan ($20cm^3$), water ($40cm^3$) and stock aniline solution (20mls) were pipetted into a stoppered teflon flask and immersed in the thermostat bath (25.02°C).

The reaction was initiated by the addition of $10cm^3$ substrate solution, having been thermostated at 25.02°C, to the reaction vessel (resulting solution was a dioxan/water, 60:40,(v/v) mixture), and the reaction followed, up to at least 75% of total reaction, by a fluoride ion electrode connected via the appropriate circuitry to a chart recorder. The concentration of fluoride ion was determined from a calibration graph of the measured electrode potential versus concentration. An infinity reading was taken after at least 10 half lives.

Second order rate constants were calculated as in section 9.7.1

9.6.4 Hplc Method

For pentafluoropyridine one run was carried out in which the reaction was followed by Hplc. Ethyl benzene was used as a suitable

standard which would be inert under the reaction conditions and which gave a clearly defined peak close to pentafluoropyridine on the hplc trace.

Stock solutions of aniline, ethyl benzene and substrate in dioxan were prepared, usually being approximately 1.1 mol l^{-1}, 2.0 mol l^{-1} and 0.05 mol l^{-1} respectively.

Dioxan ($10cm^3$), water ($40cm^3$), stock aniline solution ($20cm^3$) and ethyl benzene ($20cm^3$) were pipetted into a stoppered teflon flask and immersed in the thermostat bath (25.02°C).

The reaction was initiated by the addition of $10cm^3$ substrate solution, having been thermostated at 25.02°C, to the reaction vessel (resulting solution was a dioxan/water, 60:40,(v/v) mixture), and the reaction followed, up to at least 75% of total reaction, by removing aliquots of the reaction mixture ($1cm^3$) at appropriate intervals, quenching in dioxan ($10cm^3$) and running the hplc. The amount of pentafluoropyridine present at any one time was deterined by cutting out the substrate and standard peaks and determining the ratio by weighing.

Second order rate constants were calculated as in section 9.7.2

9.7 Calculation of Rate Constants for 1st Order Reactions of Aniline

For the reaction :

$$\text{Substrate} + \text{Nucleophile} \longrightarrow \text{Product}$$

Then:

If concentration of Substrate is $[S]_t$ at time t

The rate of reaction is $-\frac{d[S]_t}{dt} \propto [S]_t$

$$-\frac{d[S]_t}{dt} = k_1[S]_t$$

$$-\ln [S] = k_1 t + \text{constant}$$

(constant = $-\ln [S]_0$ where $[S]_0$ = concentration of substrate at time zero)

$$-\ln [S] = k_1 t + \ln [S]_0$$

which has the form of $y = mx + \text{constant}$

Therefore a plot of $\ln [S]_t$ versus time is a staight line of slope $-k_1$ with the y intercept at $\ln [S]_0$.

9.7.1 Rate constants from Fluoride Ion Determinations

Kinetic runs were carried out under conditions of $\sim$ 20 fold excess of nucleophile (aniline) to substrate. The amount of fluoride ion liberated was measured by the use of a fluoride ion selective electrode. The calibration of the electrode was carried out with the same concentration of aniline in HF solutions therefore the measured EMF was directly related to the fluoride ion concentration.

Now for each mole of substrate used up one fluoride ion is produced, thus [S] at time t is:

$$[S]_t = [S]_0 - [F^-]_t$$

where:

$[F^-]_t$ = concentration of fluoride ion liberated at time t.

Thus a plot of $\ln([S]_0 - [F^-]_t)$ versus t gives a line of slope $-k_1$

9.7.2 Rate constants from Hplc Determinations

Kinetic runs were carried out under conditions of $\sim$ 20 fold excess

of nucleophile (aniline) to substrate. The amount of substrate remaining at time t was measured by hplc. The calibration of the hplc was carried out with the same concentration of standard.

Thus a plot of $\ln [S]_t$ versus t gives a line of slope $-k_1$

9.7.3 Calculation of Rate Constants for 2nd Order Reactions of Aniline

First order rate constants were calculated from the expression:

$$-\ln [S] = k_1 t + \ln [S]_0$$

Since k_1 the first order rate constant is related to k_2 the second order rate constant by the expression:

$$k_1 = [N] k_2$$

where [N] = the concentration of the nucleophile.

The aniline was present in a large excess and thus the concentration could thus be considered to be constant, Second order rate constants were obtained by dividing the observed rate constant by the concentration of aniline.

9.7.4 Errors

Errors quoted are the 'standard errors from the mean' (r), and are calculated from the standard deviation (σ) by the expression:

$$r = \frac{\sigma}{n^t}$$

where n= number of readings.

σ is obtained from the expression

$$\sigma = \left[\frac{\Sigma(k_i - \bar{k})^2}{n-1}\right]^{\frac{1}{2}}$$

where k_i = i^{th} value of the rate constant for the run

where $\bar{k}$ = the mean rate constant for the run

Values of k_i for which $(k_i - \bar{k}) > 2.5\sigma$ were rejected and new values for $\bar{k}$ and σ calculated.

9.8 Competition Reactions

Aniline (0.01 mole) was added to water (50cm^3) in a conical flask, conc. hydorchloric acid was added dropwise with stirring until a pH of 4 was attained (pH meter). The two pyridines (0.01 mole of each) were dissolved in acetone (15cm^3) in acetone and this was added to the acetone solution. The solution was stirred at room temperature (20^{o}C) for 2 days. The pH was adjusted as necessary with HCl/NaOH to maintain a pH of 4. The solid products were then filterd off and washed with water followed by cold petroleum ether (60/40), to remove any remaining aniline and unreacted pyridines. ^{19}F nmr was used to determine the product ratios.

CHAPTER 10

EXPERIMENTAL FOR CHAPTER 6

CHAPTER 10

EXPERIMENTAL FOR CHAPTER 6

10.1 Instrumentation

10.1.1 For Preparative work

See Chapter 8.

10.1.2 Rate Measurements

All runs were carried out in thermostatted baths, which were heated electrically by filament-type heaters, the temperature being controlled to $\pm 0.01^{o}C$ by contact thermometer. Water (with a few drops of acetic acid to prevent scale formation), was used as the liquid in baths at temperatures around $25^{o}C$, and lissapol was used for the baths at temperatures up to 80^{o}. The accurate temperature of each bath was measured by thermometers standardised to $\pm 0.02^{o}C$ by the National Physics Laboratory.

Rates were followed using an Activion fluoride ion sensitive electrode and a silver/silver chloride reference electrode.

When reactions were determined by hplc a Perkin Elmer model 1 was used. The column was a Waters Associates silicia column with a 10 micron packing. The solvent was dichloromethane/hexane 60/40, (v/v).

10.2 Solvents

See Chapter 8.

10.3 Reagents

See Chapter 8.

10.4 Preparation and Purification of Substrates

The substrates used for the determination of rate constants were obtained from a variety of sources. Commercial materials were generally used 'as is' after checking their purity by glc and hplc.

The methods of purification etc. are given in chapter 8.

Trimethylsilylpentafluorobenzene

Magnesium (30g) together with a complete reflux set-up was dried in an oven at 220°C for 2 hrs. The apparatus then set up in a fume cupboard and diethyl ether (200cm^3) added, followed by the dropwise addition over 1 1/2 hrs of bromopentafluorobenzene. Trimethylsilylchloride (10g) was then added over 1/2 hr and refluxed for 18 hrs. Product was poured into water (300cm^3) and extracted with ether (2 x 100ml) the extract dried, magnesium sulphate, and the ether removed. The black liquid obtained was distilled under reduced pressure and the colourless fraction boiling at 60°C, 30 mmHg collected. This was then redistilled at atomospheric and the fraction boiling at 165-170°C collected (25g,75%). literature value bp. 170°C.[98] Nmr showed this to be the desired product. Ir spectrum no.15.

1-fluoromethylpentafluorobenzene

Commercially available pentafluorobenzylalcohol (4.5g) was heated with sulphur tetrafluoride (4.0g) in 80% hydrofluoric acid (0.6g) at 80°C for 24 hrs.. in a stainless steel autoclave of capacity 100ml, the reactions being carried out under pressure. Before releasing the intial pressure, the cylinder was cooled to a temperature of -5 to -10°C and the excess pressure slowly released the gases being allowed to bubble through a sodium dioxide trap before being vented through a flue. The reaction mass was then treated with water. The organic layer seperated, dried over magnesium sulphate and distilled. The fraction boiling at 128-134°C being collected. literature value bp 132°C. (3.5g 80%) Nmr showed this to be the desired product.

1,1-difluoromethylpentafluorobenzene

Commercially available pentafluorobenzaldehyde (7.0g) was heated with sulphur tetrafluoride (5.8g) in 80% hydrofluoric acid (0.7g) at 100°C for 20 hrs. in a stainless steel autoclave of capacity 100ml, the reactions being carried out under pressure. Before releasing the intial pressure, the cylinder was cooled to a temperature of -5 to -10°C and the excess pressure slowly released the gases being allowed to bubble through a sodium dioxide trap before being vented through a flue. The reaction mass was then treated with water. The organic layer separated, dried over magnesium sulphate and distilled. The fraction boiling at 122-124°C being collected. (4.8g 70%). literature value bp 122°C. Nmr showed this to be the desired product.

10.5 Identification of Products

The reactions of these systems have been extensively studied see Chapters 3,8 and reference 96. The product analysis was therefore carried out by nmr and hplc. Because of the unknown extinction coefficients of many of the compounds, where more than one product was formed, the ratio of products was determined exclusively by nmr.

10.5.1 Work-up for Reaction Products

After the kinetic run was complete the reaction mixture was poured into water (500cm^3) and then extracted with ether (2 x 100cm^3). The ether was removed, the product dissolved in acetone and the nmr run to determine the product ratios.

Reaction of Ammonia and Pentafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilinotetrafluoropyridine.

Reaction of Ammonia and 4-chlorotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 2-adduct, 2-anilino-4-chlorotrifluoropyridine.

Reaction of Ammonia and Tetrafluoropyrimidine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilinotetrafluoropyrimidine.

Reaction of Ammonia and Trifluoro-1,3,5-triazine

Hplc showed starting materials and one product. Nmr showed exclusively the 2-adduct, 2-anilinotrifluoro-1,3,5-triazine.

Reaction of Ammonia and Tetrafluoropyridazine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilinotetrafluoropyridazine.

Reaction of Ammonia and Tetrafluoropyrazine

Hplc showed starting materials and one product. Nmr showed exclusively the 2-adduct, 2-anilinotetrafluoropyrazine.

Reaction of Ammonia and Pentachloropyridine

Hplc showed starting materials and one product. Reference 96 suggests this is the 4-adduct, 4-anilinotetrachloropyridine.

Reaction of Ammonia and Tetrachloropyridazine

Hplc showed starting materials and one product. Reference 96 suggests this is the 4-adduct, 4-anilinotetrachloropyridazine.

Reaction of Ammonia and Tetrachloropyrazine

Hplc showed starting materials and one product. Reference 96 suggests this is the 2-adduct, 2-anilinotetrachloropyrazine.

Reaction of Ammonia and 3-trifluoromethyltetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-3-trifluoromethyltrifluoropyridine.

Reaction of Ammonia and 3,5-bis(trifluoromethyl)-tetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-3,5-bis(trifluoromethyl)--trifluoropyridine.

Reaction of Ammonia and 2,4,6-trifluoropyridine

Hplc showed starting materials and two products. Nmr showed the 4-adduct, 4-anilino-2,6-difluoropyridine (75%) and the 6-adduct, 6-anilino-2,4-difluoropyridine(25%).

Reaction of Ammonia and 2,3,4,5-tetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-2,3,5-trifluoropyridine.

Reaction of Ammonia and 3-cyanotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-3-cyanotrifluoropyridine.

Reaction of Ammonia and 3-cyano-2,4,6-trifluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-3-cyano-2,6-difluoropyridine.

Reaction of Ammonia and 2-cyanotetrafluoropyridine

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-2-cyanotrifluoropyridine.

Reaction of Ammonia and Octafluorotoluene

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-heptafluorotoluene.

Reaction of Ammonia and 3-cyanotetrachloropyridine

Hplc showed starting materials and one product. Comparison with the results for the pentachloropyridine and 3-cyanotetrafluoropyridine suggests that this is the 4-adduct, 4-anilino-3-cyanotrichloropyridine.

Reaction of Ammonia and 4-cyanotetrachloropyridine

Hplc showed starting materials and one product. IR showed the presence of the cyano group and comparison with the result for 4-chlorotetrafluoropyridine suggests this is the 2-adduct, 2-anilino-4-cyanotrichloropyridine.

Reaction of Ammonia and 1,2-dicyano-tetrafluorobenzene

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-1,2-dicyano-trifluorobenzene.

Reaction of Ammonia and 1,4-dicyano-tetrafluorobenzene

Hplc showed starting materials and one product. Nmr showed exclusively the 2-adduct, 2-anilino-1,4-dicyano-trifluorobenzene.

Reaction of Ammonia and 1,2-bis(trifluoromethyl)-tetrafluorobenzene

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-1,2-bis(trifluoromethyl)-trifluorobenzene.

Reaction of Ammonia and 1,4-bis(trifluoromethyl)-tetrafluorobenzene

Hplc showed starting materials and one product. Nmr showed exclusively the 2-adduct, 2-anilino-1,4-bis(trifluoromethyl)-trifluorobenzene.

Reaction of Aniline and Trimethylsilylpentafluorobenzene

Aniline (0.20g.) and trimethylsilylpentafluorobenzene (0.24g.) (2:1 moles) in dioxan (2ml) were heated in a sealed tube at 80°C for 30 hrs. The tube was cooled, opened to the air and washed out with diethyl ether. The combined extracts were washed with dilute HCl (1M), dried with magnesium sulphate and filtered. Removal of the ether gave a colourless liquid. ^{19}F nmr suggested that this was a mixture of the trimethylsilylpentafluorobenzene and pentafluorobenzene. Addition of pentafluorobenzene to some of the starting material reproduced the nmr profile confirming this result.

Reaction of Ammonia and 1-fluoromethylpentafluorobenzene

Hplc showed starting materials and one product. Nmr showed exclusively

the 4-adduct, 4-anilino-(1'-fluoromethyl)tetrafluorobenzene

Reaction of Ammonia and 1,1-difluoromethylpentafluorobenzene

Hplc showed starting materials and one product. Nmr showed exclusively the 4-adduct, 4-anilino-(1',1'-difluoromethyl)tetrafluorobenzene

10.6 Methods of Rate Measurement

10.6.1 Titrimetric methods

10.6.1.1 Reactions of Ammonia with Halopyridine /Benzene Substrates in Dioxan/Water (60/40,v:v) at 25°C

Stock solutions of ammonia in water and substrate in dioxan were prepared, usually being approximately 1.5 mol l^{-1} and 0.5 mol l^{-1} respectively.

To dioxan ($60cm^3$) and water ($40cm^3$) was added stock ammonia solution ($5cm^3$) and the initial concentration of ammonia found by removing two aliquots ($5cm^3$) and titrating them against standardised hydrochloric acid(~0.02M) using methly red indicator. Stock solution of substrate in dioxan was added to the reaction mixture, this addition representing time zero for the reaction. Aliquots were removed at appropriate time intervals, quenched in water ($100cm^3$) and titrated against standardised hydrochloric acid (~0.02M) with methyl red indicator. Two aliquots were kept in the bath for at least 10 half lives to give the infinity titre.

10.6.1.2 Reactions of Ammonia with Halopyridine /Benzene Substrates in Dioxan/Water (60/40,v:v) at 80°C

Stock solutions of ammonia in water and substrate in dioxan were prepared, usually being approximately 1.5 mol l^{-1} and 0.5 mol l^{-1} respectively.

To dioxan ($60cm^3$) and water ($40cm^3$) was added stock ammonia solution ($5cm^3$) and the initial concentration of ammonia found by removing two aliquots ($5cm^3$) and titrating them against standardised hydrochloric acid(0.02M) using methly red indicator. Stock solution of substrate in dioxan was added to the reaction mixture and aliquots taken (~18 x $5cm^3$) and sealed in glass ampoules; these were simultaneously immersed in thermostatted oil bath (80^oC),the time of immersion being taken as zero time for the reaction. The ampoules were removed at appropriate time intervals and frozen in liquid air to stop the reaction; the ampoules were cleaned with acetone followed by distilled water and then broken under water (~$100cm^3$) in a stout glass jar. The contents were then titrated against standardised hydrochloric acid (~0.02M) with methyl red indicator. Two ampoules were kept in the oil bath for at least 10 half lives to give the infinity titre.

10.6.2 Spectrophotometric methods

Stock solutions of ammonia in water and substrate in dioxan were prepared, usually being approximately 0.5 x 10^{-3} mol l^{-1} and 10^{-4} mol l^{-1} respectively.

The stock solutions were immersed in a 25^oC thermostat bath, water from which passed through the cell compartment of the spectrometer (Unicam SP8000) which was used for the absorbance measurements. 1.2ml of the stock ammonia solution and 1.80ml of the stock substrate solution were pipetted into a 1cm silica UV cell, giving a solvent

composition of 60:40 (v/v) dioxan/water. The cell was immediately stoppered, shaken and placed in the spectrometer. The instrument was standardised at the wavelength used with a blank solution of 1.20ml of 60:40,(v/v) dioxan/water.

Values of optical density were recorded and each reaction followed for about three half-lives. Zero time for each reaction was taken to be that of the first reading, and an infinity reading taken after at least 10 half-lives.

The exact concentrations of the stock ammonia solutions were determined against standard hydrochloric acid, and the ammonia concentration in the cell calculated from this allowing for the dilution by the substrate solution.

First and second order rate constants were calculated as described in Section 10.7.2

10.7 Calculation of Rate Constants for 2nd Order Reactions of Ammonia

10.7.1 Titrimetric Method

The rate constants for reactions with ammonia were determined under second order conditions by titrating aliquots of the reaction mixture with dilute acid hence determining the concentration of nucleophile remaining.

For reactions with ammonia, secomd order rate constants (k_2) were obtained from the equation:

$$k_2 t = \frac{1}{a - 2b} \ln \frac{b(a - 2x)}{a(b - x)}$$

Where a=initial concentration of nucleophile

b=initial concentration of substrate

x=concentration of substrate reacted at time t.

This equation implies that ammonia is extensively protonated in 60/40 dioxan/water, i.e. that two molecules of ammonia are used for the reaction of one molecule of substrate; i.e. that the equilibrium constant of the reaction:-

$$H^+ + NH_3 \rightleftharpoons NH_4^+$$

lies far to the right, leading to the formation of the ammonium halide salt.

10.7.2 Spectrophotometric Method

Reactions which were too fast to be followed by titration methods were (conveniently) those which were suitable to follow by Ultra Violet spectrophotometric methods. A large excess of Ammonia was used for each run and first order rate constants k_1 calculated from the equation.

$$k_1 t = \ln \frac{OD_\infty - OD_0}{OD_\infty - OD_t}$$

OD_∞ = Optical density at infinity

OD_0 = Optical density at time zero.

OD_t = Optical density at time t.

Dividing by the ammonia concentration (assumed to be constant throughout the run), gives the second order rate constant, k_2.

In cases where two products arose, from attack at positions m and n in the ring, the rate constants for attack at these positions k^m and

k_n were calculated from the observed rate constant, k, from the expressions:

$$k_m + k_n = k$$

$$\frac{k_m}{k_n} = \frac{\%\text{ of product arising from attack at the position m}}{\%\text{ of product arising from attack at the position n}}$$

For the reactions of ammonia at 80°C it was not possible to determine time zero with any great accuracy due to the mixing of the reactants taking place at room temperature prior to being sealed in glass ampoules and rapidly heated to the reaction of 80°C. k_1 was calculated by plotting $\ln(OD_\infty - OD_t)$ against time t, k_1 being derived from the slope. This procedure gave plots which were excellent straight lines and gave consistent values for rate constants in duplicate runs.

10.7.3 Errors

Errors quoted are the 'standard errors from the mean' (r), and are calculated from the standard deviation (σ) by the expression:

$$\sigma = \left[\frac{\Sigma(k_i - \bar{k})^2}{n-1}\right]^{\frac{1}{2}}$$

$$r = \frac{\sigma}{n^{\frac{1}{2}}}$$

where n= number of readings.

σ is obtained from the expression

where k_i = i^{th} value of the rate constant for the run

where $\bar{k}$ = the mean rate constant for the run

Values of k_i for which $(k_i - \bar{k}) > 2.5\sigma_{-}$ were rejected and new values for $\bar{k}$ and σ_{-} calculated.

APPENDIX 1

RATE DATA

Rate Data For Table 5.1

Reactions with Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Rate Data For Table 6.1

Reactions with Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Reactions with Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Pentafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.1.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	1.0	55.5	8.26	4.6409
2	2.0	59.0	8.10	4.6456
3	3.0	62.0	7.96	4.6503
4	4.0	64.0	7.78	4.6576
5	5.0	66.5	7.69	4.6617
6	6.0	68.0	7.64	4.6642
7	7.0	69.5	7.54	4.6696
8	8.0	71.0	7.45	4.6749
9	9.0	72.5	7.38	4.6795
10	10.0	73.5	7.31	4.6843
11	11.0	74.5	7.29	4.6858
12	12.0	75.5	7.22	4.6912
13	13.0	76.0	7.20	4.6928
14	14.0	76.5	7.15	4.6970
15	15.0	77.5	7.13	4.6987
16	16.0	78.0	7.08	4.7032
17	17.0	78.5	7.04	4.7070
18	18.0	79.0	7.02	4.7090
19	19.0	80.0	6.97	4.7141
20	20.0	80.5	6.95	4.7162
21	25.0	84.0	6.79	4.7350
22	30.0	86.0	6.65	4.7544
23	35.0	88.5	6.49	4.7808
24	40.0	90.0	6.39	4.8000

Pentafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.1.

continued.

25	45.0	91.5	6.30	4.8194
26	50.0	93.0	6.21	4.8411
27	55.0	94.0	6.12	4.8653
28	60.0	95.5	6.00	4.9024
29	65.0	96.0	5.90	4.9381

Initial [substrate] =0.00991 [PhNH2] =0.21390

$k_1 = 4.27 \times 10^{-3}(+/- 7.2 \times 10^{-5})\ min^{-1}$

$k_2 = 2.00 \times 10^{-2}(+/- 3.4 \times 10^{-4})\ l\ mol^{-1}min^{-1}$

$k_2 = 3.33 \times 10^{-4}(+/- 5.6 \times 10^{-6})\ l\ mol^{-1}sec^{-1}$

duplicate $k_2 = 3.33 \times 10^{-4}(+/- 5.5 \times 10^{-6})\ l\ mol^{-1}sec^{-1}$

Average $k_2 = 3.33 \times 10^{-4}(+/- 1.1 \times 10^{-5})\ l\ mol^{-1}sec^{-1}$

2,3,4,6-Tetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.2.

i	time/sec	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	15.0	0.0	10.65	4.6153
2	30.0	9.0	10.28	4.6164
3	45.0	15.0	10.03	4.6174
4	60.0	20.0	9.80	4.6186
5	75.0	24.0	9.64	4.6195
6	90.0	27.0	9.50	4.6205
7	105.0	30.0	9.41	4.6212
8	120.0	33.0	9.22	4.6230
9	135.0	35.0	9.18	4.6234
10	150.0	37.0	9.11	4.6242
11	165.0	39.0	9.02	4.6252
12	180.0	40.5	8.95	4.6261
13	195.0	43.0	8.83	4.6278
14	210.0	44.0	8.79	4.6284
15	225.0	45.5	8.74	4.6292
16	240.0	46.5	8.69	4.6301
17	255.0	47.0	8.65	4.6308
18	270.0	48.5	8.60	4.6317
19	285.0	50.0	8.53	4.6331
20	300.0	51.0	8.51	4.6335
21	315.0	51.5	8.46	4.6345
22	300.0	52.5	8.42	4.6354
23	345.0	53.0	8.37	4.6366
24	360.0	54.0	8.33	4.6376
25	375.0	54.5	8.30	4.6383

2,3,4,6-Tetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.2.

continued.

26	390.0	55.0	8.28	4.6388
27	405.0	56.0	8.23	4.6402
28	420.0	56.0	8.23	4.6402
29	450.0	58.0	8.14	4.6428
30	465.0	58.0	8.14	4.6428
31	480.0	58.5	8.12	4.6434
32	495.0	59.0	8.10	4.6440
33	510.0	59.5	8.07	4.6450
34	525.0	60.0	8.05	4.6456
35	540.0	60.5	8.03	4.6463
36	555.0	61.0	8.00	4.6473
37	571.0	62.0	7.94	4.6495
38	600.0	62.0	7.94	4.6495
39	660.0	64.0	7.84	4.6534
40	720.0	65.0	7.80	4.6551
41	780.0	66.0	7.73	4.6582
42	840.0	67.0	7.68	4.6606
43	900.0	68.0	7.64	4.6626
44	960.0	68.5	7.59	4.6652
45	1020.0	70.0	7.52	4.6691
46	1140.0	72.0	7.41	4.6759

Initial [substrate] =0.00992 [PhNH2] =0.21390

$k_1 = 5.31 \times 10^{-5} (+/- 7.2 \times 10^{-7})$ sec^{-1}

$k_2 = 2.48 \times 10^{-4} (+/- 3.4 \times 10^{-6})$ $l\ mol^{-1} sec^{-1}$

duplicate $k_2 = 2.35 \times 10^{-4} (+/- 3.2 \times 10^{-6})$ $l\ mol^{-1} sec^{-1}$

Average $k_2 = 2.42 \times 10^{-4} (+/- 6.6 \times 10^{-6})$ $l\ mol^{-1} sec^{-1}$

2,3,4,5-Tetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.3.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	10.0	-33.5	10.15	4.6486
2	20.0	-28.0	9.85	4.6500
3	30.0	-23.0	9.63	4.6513
4	40.0	-19.0	9.50	4.6523
5	50.0	-16.0	9.35	4.6536
6	60.0	-13.0	9.15	4.6556
7	70.0	-10.5	9.00	4.6574
8	80.0	-9.0	8.95	4.6581
9	90.0	-7.0	8.80	4.6603
10	100.0	-5.0	8.80	4.6603
11	110.0	-4.0	8.65	4.6629
12	120.0	-2.0	8.60	4.6638
13	130.0	-1.0	8.55	4.6648
14	140.0	1.0	8.45	4.6670
15	150.0	2.0	8.40	4.6681
16	190.0	6.0	8.30	4.6707
17	200.0	7.0	8.15	4.6750
18	240.0	10.0	8.00	4.6800
19	280.0	13.0	7.95	4.6819
20	300.0	14.0	7.90	4.6838

Initial [substrate] =0.00961 [PhNH2] =0.21000

$k_1 = 1.26 \times 10^{-4} (+/- 3.0 \times 10^{-6})\ min^{-1}$

$k_2 = 5.99 \times 10^{-4} (+/- 1.4 \times 10^{-5})\ l\ mol^{-1} min^{-1}$

$k_2 = 9.98 \times 10^{-6} (+/- 2.4 \times 10^{-7})\ l\ mol^{-1} sec^{-1}$

duplicate $k_2 = 9.44 \times 10^{-6} (+/- 2.5 \times 10^{-7})\ l\ mol^{-1} sec^{-1}$

Average $k_2 = 9.71 \times 10^{-6} (+/- 4.9 \times 10^{-7})\ l\ mol^{-1} sec^{-1}$

4-Chlorotetrafluoropyridine + Aniline in 60/40,v:v Dioxan/Water at 25°C.

Table 5.1 compound no.4.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	240.0	-93	14.88	4.6043
2	360.0	-67	13.67	4.6044
3	480.0	-74.5	14.03	4.6044
4	600.0	-51	13.45	4.6044
5	720.0	-33	13.44	4.6044
6	1440.0	-57	13.26	4.6044
7	1920.0	-34	12.20	4.6048
8	2160.0	-26	11.82	4.6050
9	2890.0	-22	11.66	4.6051
10	4340.0	-29	11.51	4.6053

Initial [substrate] =0.01001 [PhNH2] =0.21939

$k_1 = 2.61 \times 10^{-7} (+/- 2.8 \times 10^{-8})$ min^{-1}

$k_2 = 1.19 \times 10^{-6} (+/- 1.3 \times 10^{-7})$ $l\ mol^{-1} min^{-1}$

$k_2 = 1.97 \times 10^{-8} (+/- 2.2 \times 10^{-9})$ $l\ mol^{-1} sec^{-1}$

2-Chlorotetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.5.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	1.0	23	9.68	4.6352
2	2.0	48.5	8.68	4.6464
3	3.0	50	8.54	4.6490
4	4.0	58.5	8.12	4.6597
5	5.0	61.5	7.97	4.6647
6	6.0	61.5	7.96	4.6653
7	7.0	69.5	7.54	4.6848
8	8.0	74	7.29	4.7014
9	9.0	75.5	7.24	4.7052
10	10.0	75	7.25	4.7044
11	11.0	75.5	7.24	4.7052
12	12.0	77.5	7.11	4.7160
13	13.0	78	7.10	4.7168
14	14.0	82	6.86	4.7429
15	16.0	82	6.86	4.7425
16	17.0	83.5	6.83	4.7465
17	19.0	85.5	6.67	4.7682
18	21.0	84.5	6.71	4.7624
19	23.0	88	6.51	4.7950
20	24.0	88.5	6.46	4.8031
21	26.0	89	6.43	4.8097
22	27.0	89.5	6.42	4.8108
23	28.0	92	6.29	4.8400

2-Chlorotetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.5.

continued.

Initial [substrate] =0.00977 [PhNH2] =0.21390

$k_1 = 6.96 \times 10^{-3}(+/- 1.9 \times 10^{-4})$ min^{-1}

$k_2 = 3.26 \times 10^{-2}(+/- 8.9 \times 10^{-4})$ $l\ mol^{-1}min^{-1}$

$k_2 = 5.43 \times 10^{-5}(+/- 1.5 \times 10^{-5})$ $l\ mol^{-1}sec^{-1}$

duplicate $k_2 = 5.72 \times 10^{-4}(+/- 2.0 \times 10^{-5})$ $l\ mol^{-1}sec^{-1}$

Average $k_2 = 5.57 \times 10^{-4}(+/- 4.0 \times 10^{-5})$ $l\ mol^{-1}sec^{-1}$

3-Chlorotetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.6.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	0.5	-2.0	10.74	4.6091
2	1.0	17.5	9.91	4.6119
3	2.0	35.5	9.15	4.6176
4	3.0	45.5	8.74	4.6231
5	4.0	53.0	8.40	4.6297
6	5.0	58.0	8.17	4.6357
7	6.0	62.0	7.94	4.6433
8	7.0	65.5	7.75	4.6510
9	8.0	68.5	7.59	4.6589
10	9.0	70.5	7.52	4.6628
11	10.0	72.5	7.38	4.6714
12	11.0	74.5	7.29	4.6777
13	12.0	76.0	7.20	4.6847
14	13.0	77.4	7.11	4.6923
15	14.0	78.5	7.04	4.6988
16	15.0	80.0	6.95	4.7079
17	16.0	81.0	6.90	4.7134
18	17.0	82.0	6.85	4.7191
19	18.0	82.5	6.81	4.7240
20	19.0	83.5	6.79	4.7265
21	20.0	84.0	6.76	4.7304
22	25.0	88.0	6.51	4.7684
23	30.0	91.5	6.30	4.8102
24	35.0	92.5	6.23	4.8267

3-Chlorotetrafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.6.

continued.

25	40.0	94.5	6.10	4.8614
26	45.0	96.0	5.98	4.8991
27	50.0	97.5	5.87	4.9393
28	55.0	98.5	5.82	4.9597
29	60.0	100.0	5.73	5.0004
30	65.0	100.5	5.68	5.0254
31	70.0	101.5	5.64	5.0469
32	75.0	102.0	5.61	5.0638
33	80.0	102.5	5.54	5.1067
34	90.0	103.0	5.52	5.1199

Initial [substrate] =0.00998 [PhNH2] =0.21390

$k_1 = 6.17 \times 10^{-3}(+/- 7.5 \times 10^{-5})$ min^{-1}

$k_2 = 2.88 \times 10^{-2}(+/- 3.5 \times 10^{-4})$ $l\ mol^{-1} min^{-1}$

$k_2 = 4.81 \times 10^{-4}(+/- 5.8 \times 10^{-6})$ $l\ mol^{-1} sec^{-1}$

duplicate $k_2 = 4.62 \times 10^{-4}(+/- 5.9 \times 10^{-6})$ $l\ mol^{-1} sec^{-1}$

Average $k_2 = 4.72 \times 10^{-4}(+/- 8.3 \times 10^{-6})$ $l\ mol^{-1} sec^{-1}$

3,5-Dichlorotrifluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.7.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	1.0	28.0	9.45	4.6132
2	2.0	42.0	8.88	4.6193
3	3.0	50.0	8.53	4.6252
4	4.0	56.0	8.46	4.6267
5	5.0	60.0	8.05	4.6377
6	6.0	63.0	7.89	4.6434
7	7.0	66.0	7.73	4.6502
8	8.0	68.5	7.59	4.6571
9	9.0	70.5	7.48	4.6633
10	10.0	71.5	7.43	4.6664
11	11.0	73.5	7.31	4.6745
12	12.0	75.0	7.25	4.6789
13	13.0	76.5	7.15	4.6870
14	14.0	77.5	7.08	4.6932
15	15.0	78.5	7.04	4.6969
16	16.0	79.5	6.97	4.7039
17	17.0	81.0	6.90	4.7115
18	18.0	81.5	6.88	4.7138
19	19.0	82.5	6.83	4.7196
20	20.0	83.5	6.79	4.7246
21	21.0	84.0	6.76	4.7285
22	22.0	85.0	6.72	4.7338
23	23.0	85.5	6.67	4.7409
24	24.0	86.0	6.65	4.7438

3,5-Dichlorotrifluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.7.

continued.

25	25.0	87.0	6.58	4.7547
26	30.0	89.5	6.42	4.7830
27	35.0	92.0	6.26	4.8174
28	40.0	93.5	6.16	4.8425
29	45.0	95.0	6.05	4.8742

Initial [substrate] =0.01000 [PhNH2] =0.21390

$k_1 = 5.88 \times 10^{-3}(+/- 3.9 \times 10^{-5})$ min^{-1}

$k_2 = 2.75 \times 10^{-2}(+/- 1.8 \times 10^{-4})$ $l\ mol^{-1}min^{-1}$

$k_2 = 4.58 \times 10^{-4}(+/- 3.0 \times 10^{-6})$ $l\ mol^{-1}sec^{-1}$

duplicate $k_2 = 4.39 \times 10^{-4}(+/- 3.5 \times 10^{-6})$ $l\ mol^{-1}sec^{-1}$

Average $k_2 = 4.49 \times 10^{-4}(+/- 6.5 \times 10^{-6})$ $l\ mol^{-1}sec^{-1}$

2-Cyanopentafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.9.

i	time/sec	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	10.0	31.0	9.34	4.7160
2	20.0	50.0	8.53	4.7284
3	30.0	59.5	8.07	4.7415
4	40.0	66.0	7.96	4.7457
5	50.0	71.0	7.52	4.7681
6	60.0	74.5	7.27	4.7864
7	70.0	75.5	7.08	4.8040
8	80.0	79.5	6.99	4.8137
9	90.0	81.5	6.88	4.8270
10	100.0	83.5	6.79	4.8392
11	120.0	86.0	6.65	4.8608
12	130.0	87.5	6.56	4.8766
13	140.0	88.5	6.49	4.8902
14	150.0	89.5	6.42	4.9049
15	160.0	90.5	6.35	4.9210
16	170.0	91.0	6.33	4.9259
17	180.0	92.0	6.26	4.9438
18	190.0	92.5	6.21	4.9577
19	200.0	93.5	6.16	4.9724
20	210.0	94.0	6.12	4.9850
21	220.0	94.5	6.11	4.9882
22	230.0	95.0	6.05	5.0085
23	240.0	96.0	5.98	5.0345
24	250.0	96.0	5.98	5.0345

2-Cyanopentafluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.9.

continued.

25	260.0	96.5	5.96	5.0423
26	270.0	97.5	5.89	5.0717
27	280.0	98.0	5.84	5.0946
28	290.0	98.0	5.84	5.0946
29	300.0	98.5	5.82	5.1042
30	310.0	99.0	5.80	5.1142
31	320.0	99.5	5.75	5.1403
32	330.0	100.0	5.73	5.1514
33	340.0	100.0	5.73	5.1514
34	350.0	100.5	5.68	5.1805
35	410.0	102.0	5.59	5.2394
36	480.0	103.5	5.50	5.3080
37	500.0	104.0	5.43	5.3697

Initial [substrate] =0.00904 [PhNH2] =0.21390

$k_1 = 1.32 \times 10^{-3} (+/- 1.1 \times 10^{-5})\ sec^{-1}$

$k_2 = 6.18 \times 10^{-3} (+/- 5.3 \times 10^{-5})\ l\ mol^{-1} sec^{-1}$

duplicate $k_2 = 7.48 \times 10^{-3} (+/- 5.0 \times 10^{-5})\ l\ mol^{-1} sec^{-1}$

Average $k_2 = 6.83 \times 10^{-3} (+/- 1.0 \times 10^{-4})\ l\ mol^{-1} sec^{-1}$

Octafluorotoluene + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.10.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	600.0	-90	14.72	4.6043
2	1440.0	-60	13.42	4.6044
3	1920.0	-63	13.49	4.6044
4	2160.0	-55	13.19	4.6045
5	2880.0	-51	12.99	4.6045
6	4320.0	-47	12.82	4.6045
7	7200.0	-28	11.94	4.6049

Initial [substrate] =0.01001 [PhNH2] =0.21939

$k_1 = 8.69 \times 10^{-8}(+/- 8.9 \times 10^{-9})\ min^{-1}$

$k_2 = 3.96 \times 10^{-7}(+/- 4.1 \times 10^{-8})\ l\ mol^{-1}min^{-1}$

$k_2 = 6.61 \times 10^{-9}(+/- 6.8 \times 10^{-10})\ l\ mol^{-1}sec^{-1}$

Pentafluoropyridazine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.11.

i	time/sec	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	1.0	51.0	8.50	4.5957
2	2.0	62.0	7.97	4.6098
3	3.0	67.0	7.69	4.6211
4	4.0	72.0	7.41	4.6363
5	5.0	74.5	7.30	4.6436
6	6.0	77.0	7.14	4.6558
7	7.0	79.0	7.02	4.6665
8	8.0	81.0	6.91	4.6776
9	9.0	82.0	6.86	4.6831
10	10.0	84.0	6.77	4.6939
11	11.0	85.0	6.70	4.7030
12	12.0	86.0	6.65	4.7100
13	13.0	87.0	6.59	4.7189
14	14.0	88.0	6.52	4.7301
15	15.0	88.5	6.49	4.7352
16	16.0	84.5	6.42	4.7478
17	17.0	90.0	6.38	4.7555
18	18.0	91.0	6.33	4.7657
19	19.0	92.5	6.29	4.7743
20	20.0	92.0	6.24	4.7856
21	21.0	92.5	6.24	4.7856
22	22.0	93.0	6.19	4.7976
23	23.0	94.0	6.12	4.8158
24	24.0	94.0	6.12	4.8158
25	25.0	95.0	6.06	4.8327

Pentafluoropyridazine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.11.

continued.

Initial [substrate] =0.01030 [PhNH2] =0.21390

k_1 = $9.37 \times 10^{-3}(+/- 1.2 \times 10^{-4})$ sec^{-1}

k_2 = $4.38 \times 10^{-2}(+/- 5.4 \times 10^{-4})$ $l\ mol^{-1}sec^{-1}$

duplicate k_2 = $4.10 \times 10^{-2}(+/- 9.4 \times 10^{-5})$ $l\ mol^{-1}sec^{-1}$

Average k_2 = $4.24 \times 10^{-2}(+/- 6.3 \times 10^{-4})$ $l\ mol^{-1}sec^{-1}$

Cyanopentafluorobenzene + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 compound no.12.

i	time/min	EMF/mV	- ln[F]	$-\ln([S]_o-[F]_t)$
1	10.0	46.0	8.72	4.6205
2	20.0	59.0	8.10	4.6349
3	30.0	67.0	7.68	4.6513
4	40.0	72.0	7.41	4.6664
5	50.0	75.0	7.25	4.6777
6	60.0	79.0	6.94	4.7058
7	70.0	81.0	6.90	4.7102
8	80.0	83.0	6.81	4.7208
9	90.0	85.0	6.69	4.7367
10	100.0	87.0	6.58	4.7533
11	110.0	89.0	6.44	4.7778
12	120.0	90.0	6.37	4.7916
13	130.0	90.0	6.37	4.7916
14	140.0	91.5	6.30	4.8067
15	150.0	92.5	6.23	4.8231
16	160.0	94.0	6.12	4.8520
17	170.0	94.0	6.12	4.8520
18	180.0	95.0	6.05	4.8726
19	190.0	96.0	6.00	4.8886
20	200.0	96.0	6.00	4.8886

Initial [substrate] =0.01001 [PhNH2] =0.21390

$k_1 = 1.45 \times 10^{-3} (+/- 2.3 \times 10^{-5})$ min^{-1}

$k_2 = 6.80 \times 10^{-3} (+/- 1.1 \times 10^{-4})$ l mol^{-1}min^{-1}

$k_2 = 1.13 \times 10^{-4} (+/- 1.8 \times 10^{-6})$ l mol^{-1}sec^{-1}

duplicate $k_2 = 1.11 \times 10^{-4} (+/- 2.0 \times 10^{-6})$ l mol^{-1}sec^{-1}

Average $k_2 = 1.12 \times 10^{-4} (+/- 3.8 \times 10^{-6})$ l mol^{-1}sec^{-1}

3-Cyano-5-chloro-2,4,6-trifluoropyridine + Aniline in 60/40,(v:v) Dioxan/Water at 25°C.

Table 5.1 Compound No.8

i	time/sec	ODt	$-\ln[OD_\infty - ODt]$
1	2.0	0.40	-0.476
2	10.0	0.44	-0.548
3	20.0	0.50	-0.646
4	30.0	0.54	-0.736
5	40.0	0.54	-0.736
6	50.0	0.62	-0.924
7	60.0	0.66	-1.016
8	70.0	0.69	-1.115
9	80.0	0.72	-1.207
10	90.0	0.75	-1.298
11	100.0	0.77	-1.394
12	110.0	0.79	-1.487
13	120.0	0.81	-1.580
14	130.0	0.83	-1.677
15	140.0	0.85	-1.772

Initial Optical Density = 0.38 Optical Density at Infinity = 1.02

Initial $[PhNh_2] = 1.1 \times 10^{-2}$

$k_1 = 9.49 \times 10^{-3}(+/- 1.5 \times 10^{-4})$ sec $^{-1}$

$k_2 = 8.62 \times 10^{-2}(+/- 1.4 \times 10^{-2})$ 1 mol^{-1} sec $^{-1}$ (15 readings)

duplicate $k_2 = 8.46 \times 10^{-2}(+/- 1.5 \times 10^{-2})$ 1 mol^{-1} sec^{-1} (15 readings)

average $k_2 = 8.54 \times 10^{-2}(+/- 2.05 \times 10^{-2})$ 1 mol^{-1} sec^{-1}

3,5-Bis-trifluoromethyltrifluoropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 11.

i	time/sec	ODt	$-\ln[OD_\infty - ODt]$
1	0.0	0.323	0.770
2	15.0	0.373	0.884
3	30.0	0.375	0.889
4	45.0	0.420	1.005
5	60.0	0.420	1.005
6	75.0	0.444	1.073
7	90.0	0.491	1.221
8	120.0	0.504	1.266
9	150.0	0.537	1.390
10	180.0	0.563	1.501
11	210.0	0.584	1.599
12	240.0	0.605	1.709
13	270.0	0.625	1.826
14	300.0	0.644	1.952
15	600.0	0.741	3.101

Initial Optical Density = 0.323 Optical Density at Infinity= 0.786

Initial $[NH_3]$ = 8.4×10^{-4}

k_1 = 3.83×10^{-3} (+/- 4.9×10^{-5}) sec^{-1}

k_2 = 4.55 (+/- 5.8×10^{-2}) 1 mol^{-1} sec^{-1} (15 readings)

duplicate k_2 = 4.47 (+/- 1.8×10^{-2}) 1 mol^{-1} sec^{-1} (14 readings)

average k_2 = 4.51 (+/- 1.5×10^{-1}) 1 mol^{-1} sec^{-1}

3-Cyanotetrafluoropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 14.

i	time/sec	ODt	$-1n[OD_\infty - ODt]$
1	0.0	0.140	0.236
2	5.0	0.200	0.315
3	10.0	0.250	0.386
4	15.0	0.290	0.446
5	20.0	0.340	0.528
6	25.0	0.370	0.580
7	35.0	0.440	0.713
8	45.0	0.520	0.892
9	50.0	0.550	0.968
10	55.0	0.570	1.022
11	60.0	0.600	1.109
12	65.0	0.620	1.171
13	70.0	0.640	1.238
14	75.0	0.650	1.273

Initial Optical Density = 0.140 Optical Density at Infinity= 0.930

Initial $[NH_3] = 8.4 \times 10^{-2}$

$k_1 = 1.42 \times 10^{-2}(+/- 1.6 \times 10^{-4})$ sec^{-1}

$k_2 = 1.69 \times 10^{-1}(+/- 2.0 \times 10^{-3})$ $l\ mol^{-1}\ sec^{-1}$ (14 readings)

duplicate $k_2 = 1.67 \times 10^{-1}(+/- 2.0 \times 10^{-3})$ $l\ mol^{-1}\ sec^{-1}$ (14 readings)

average $k_2 = 1.68 \times 10^{-1}(+/- 4.0 \times 10^{-3})$ $l\ mol^{-1}\ sec^{-1}$

3-Cyano-2,4,6-trifluoropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 15.

i	time/sec	ODt	$-\ln[OD_\infty - ODt]$
1	0.0	0.014	2.590
2	1.0	0.022	2.703
3	2.0	0.028	2.797
4	3.0	0.033	2.882
5	5.0	0.043	3.079
6	6.0	0.047	3.170
7	7.0	0.051	3.270
8	8.0	0.055	3.381
9	10.0	0.061	3.576
10	11.0	0.064	3.689
11	12.0	0.066	3.772
12	13.0	0.068	3.863
13	14.0	0.070	3.963

Initial Optical Density = 0.014 Optical Density at Infinity= 0.089

Initial $[NH_3] = 8.4 \times 10^{-2}$

$k_1 = 9.80 \times 10^{-4}(+/- 5.3 \times 10^{-6})$ sec^{-1}

$k_2 = 1.17 \times 10^{-2}(+/- 6.3 \times 10^{-5})$ $l\ mol^{-1}\ sec^{-1}$ (13 readings)

duplicate $k_2 = 1.19 \times 10^{-2}(+/- 5.0 \times 10^{-6})$ $l\ mol^{-1}\ sec^{-1}$ (13 readings)

average $k_2 = 1.20 \times 10^{-2}(+/- 6.8 \times 10^{-5})$ $l\ mol^{-1}\ sec^{-1}$

2-Cyanotetrafluoropyridine + Ammonia in 60/40.(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 16.

i	time/sec	ODt	$-\ln[OD_\infty - ODt]$
1	0.0	0.100	0.315
2	3.0	0.200	0.462
3	4.0	0.250	0.545
4	5.0	0.290	0.616
5	6.0	0.320	0.673
6	7.0	0.340	0.713
7	8.0	0.370	0.777
8	9.0	0.400	0.844
9	10.0	0.420	0.892
10	11.0	0.440	0.942
11	12.0	0.460	0.994
12	13.0	0.480	1.050
13	14.0	0.490	1.079
14	15.0	0.510	1.139

Initial Optical Density = 0.100 Optical Density at Infinity= 0.830

Initial $[NH_3] = 8.4 \times 10^{-2}$

$k_1 = 5.54 \times 10^{-3}(+/- 9.7 \times 10^{-5})$ sec^{-1}

$k_2 = 6.60 \times 10^{-2}(+/- 1.2 \times 10^{-3})$ $l\ mol^{-1}\ sec^{-1}$ (14 readings)

duplicate $k_2 = 7.05 \times 10^{-2}(+/- 1.9 \times 10^{-5})$ $l\ mol^{-1}\ sec^{-1}$ (14 readings)

average $k_2 = 6.83 \times 10^{-2}(+/- 1.2 \times 10^{-3})$ $l\ mol^{-1}\ sec^{-1}$

Pentafluoropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 1.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	0.0	18.75	1.125
2	25.0	17.85	1.153
3	45.0	17.18	1.176
4	65.0	16.58	1.199
5	85.0	16.02	1.222
6	100.0	15.64	1.239
7	125.0	15.11	1.265
8	175.0	14.04	1.326
9	200.0	13.67	1.350
10	250.0	12.88	1.408
11	350.0	11.67	1.523

Initial titres = 19.74 and 19.74 mls

Average initial titre = 19.74 mls

Equivalent initial titre after dilution = 18.80 mls

Infinity titre = 6.58 mls

Initial $[NH_3]$ = 0.07407 M

initial [substrate] = 0.02407 M

Titrating [HCl]= 0.0197 M

$k_2 = 4.377 \times 10^{-2}$ (+/-1.6×10^{-4}) l $mole^{-1}min^{-1}$ (11 readings)

$k_2 = 7.295 \times 10^{-4}$ (+/-2.7×10^{-6}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 7.310 \times 10^{-4}$(+/-$5.6 \times 10^{-6}$) l $mole^{-1}sec^{-1}$ (11 readings)

average $k_2 = 7.31 \times 10^{-4}$ (+/-8.3×10^{-6}) l $mole^{-1}sec^{-1}$

Octafluorotoluene + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 20.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	15.0	18.10	1.297
2	20.0	17.80	1.311
3	45.0	17.50	1.325
4	75.0	17.00	1.352
5	135.0	16.04	1.409
6	205.0	14.74	1.506
7	275.0	14.06	1.568
8	395.0	12.80	1.717
9	475.0	11.20	2.010
10	830.0	10.00	2.408

Initial titres = 20.00 and 20.00 mls

Average initial titre = 20.00 mls

Equivalent initial titre after dilution = 19.05 mls

Infinity titre = 8.20 mls

Initial $[NH_3]$ = 0.07505 M

initial [substrate] = 0.02137 M

Titrating [HCl]= 0.0197 M

$k_2 = 4.304 \times 10^{-2} (+/- 2.2 \times 10^{-3})$ l $mole^{-1} min^{-1}$ (10 readings)

$k_2 = 7.173 \times 10^{-4} (+/- 3.7 \times 10^{-5})$ l $mole^{-1} sec^{-1}$

dup. $k_2 = 7.129 \times 10^{-4} (+/- 2.8 \times 10^{-5})$ l $mole^{-1} sec^{-1}$ (9 readings)

average $k_2 = 7.15 \times 10^{-4} (+/- 6.5 \times 10^{-5})$ l $mole^{-1} sec^{-1}$

Pentafluorobenzonitrile + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 17.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	40.0	18.36	1.285
2	80.0	17.93	1.304
3	100.0	17.70	1.315
4	120.0	17.55	1.323
5	180.0	17.03	1.350
6	210.0	16.74	1.366
7	270.0	16.22	1.397
8	330.0	15.79	1.426
9	450.0	15.04	1.481
10	570.0	14.45	1.531
11	810.0	13.33	1.648
12	1350.0	11.59	1.922

Initial titres = 19.80 and 19.80 mls

Average initial titre = 19.80 mls

Equivalent initial titre after dilution = 18.86 mls

Infinity titre = 8.20 mls

Initial $[NH_3]$ = 0.07430 M

initial [substrate] = 0.02099 M

Titrating [HCl]= 0.0197 M

$k_2 = 1.493 \times 10^{-2}$ (+/-1.1×10^{-4}) l $mole^{-1}min^{-1}$ (12 readings)

$k_2 = 2.489 \times 10^{-4}$ (+/-1.8×10^{-6}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 2.498 \times 10^{-4}$ (+/-1.8×10^{-6}) l $mole^{-1}sec^{-1}$ (12 readings)

average $k_2 = 2.50 \times 10^{-4}$ (+/-3.6×10^{-6}) l $mole^{-1}sec^{-1}$

Pentafluorobenzonitrile + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 17.

i	time/min	titre/mls	ln[a-2x)/(b-x)]
1	5.0	17.00	1.318
2	10.0	15.40	1.413
3	15.0	13.60	1.563
4	20.0	12.50	1.693
5	25.0	11.50	1.855
6	30.0	11.00	1.960
7	35.0	10.50	2.089
8	40.0	9.60	2.424
9	60.0	8.70	3.080

Initial titres = 19.80 and 19.80 mls

Average initial titre = 19.80 mls

Equivalent initial titre after dilution = 18.86 mls

Infinity titre = 7.90 mls

Initial $[NH_3]$ = 0.07430 M

initial [substrate] = 0.02159 M

Titrating [HCl]= 0.0197 M

k_2 = 1.037 (+/-4.9 x 10^{-2}) l $mole^{-1}min^{-1}$ (9 readings)

k_2 = 1.728 x 10^{-2} (+/-8.1 x 10^{-4}) l $mole^{-1}sec^{-1}$

dup. k_2 = 1.688 x 10^{-2} (+/-1.9 x 10^{-4}) l $mole^{-1}sec^{-1}$ (8 readings)

average k_2 = 1.71 x 10^{-2} (+/-1.0 x 10^{-3}) l $mole^{-1}sec^{-1}$

1,2-Dicyanotetrafluorobenzene + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 18.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	5.0	18.50	1.250
2	10.0	19.37	1.217
3	33.0	15.40	1.413
4	41.0	15.47	1.408
5	60.0	13.73	1.550
6	85.0	11.73	1.812
7	115.0	11.93	1.778
8	160.0	10.35	1.841
9	215.0	10.35	2.134
10	424.0	8.46	3.408

Initial titres = 21.00 and 21.00 mls

Average initial titre = 21.00 mls

Equivalent initial titre after dilution = 20.00 mls

Infinity titre = 7.90 mls

Initial $[NH_3]$ = 0.07880 M

initial [substrate] = 0.02384 M

Titrating [HCl]= 0.0197 M

$k_2 = 1.593 \times 10^{-1}$ (+/-9.1×10^{-3}) l $mole^{-1}min^{-1}$ (10 readings)

$k_2 = 2.655 \times 10^{-3}$(+/-$1.5 \times 10^{-4}$) l $mole^{-1}sec^{-1}$

dup. $k_2 = 2.75 \times 10^{-3}$(+/-$7.7 \times 10^{-5}$) l $mole^{-1}sec^{-1}$ (10 readings)

average $k_2 = 2.70 \times 10^{-3}$ (+/-2.3×10^{-4}) l $mole^{-1}sec^{-1}$

1,4-Dicyanotetrafluorobenzene + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 19.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	15.0	19.00	0.982
2	30.0	18.86	0.984
3	75.0	17.90	1.002
4	100.0	17.70	1.006
5	180.0	16.38	1.036
6	260.0	15.35	1.064
7	420.0	13.30	1.136
8	580.0	12.20	1.188
9	1360.0	9.18	1.424

Initial titres = 20.54 and 20.54 mls

Average initial titre = 20.54 mls

Equivalent initial titre after dilution = 19.56 mls

Infinity titre = 4.76 mls

Initial $[NH_3]$ = 0.07707 M

initial [substrate] = 0.02916 M

Titrating [HCl]= 0.0197 M

$k_2 = 1.782 \times 10^{-2}$ (+/-4.3×10^{-4}) l $mole^{-1}min^{-1}$ (9 readings)

$k_2 = 2.971 \times 10^{-4}$ (+/-7.2×10^{-6}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 3.058 \times 10^{-4}$ (+/-1.0×10^{-6}) l $mole^{-1}sec^{-1}$ (9 readings)

average $k_2 = 3.02 \times 10^{-4}$ (+/-8.2×10^{-6}) l $mole^{-1}sec^{-1}$

Octafluorotoluene + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 20.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	360.0	18.88	0.984
2	4600.0	17.88	1.003
3	11400.0	16.34	1.037
4	14280.0	15.80	1.052

Initial titres = 20.00 and 20.00 mls

Average initial titre = 20.00 mls

Equivalent initial titre after dilution = 19.05 mls

Infinity titre = 4.76 mls

Initial $[NH_3]$ = 0.07505 M

initial [substrate] = 0.02815 M

Titrating [HCl]= 0.0197 M

$k_2 = 2.625 \times 10^{-4}$ (+/-4.7×10^{-6}) l $mole^{-1}min^{-1}$ (4 readings)

$k_2 = 4.375 \times 10^{-6}$ (+/-7.8×10^{-8}) l $mole^{-1}sec^{-1}$

1,2-Bis-(trifluoromethyl)benzene + Ammonia 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 21.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	5.0	18.88	1.091
2	20.0	18.70	1.096
3	40.0	18.44	1.103
4	85.0	17.87	1.119
5	145.0	17.27	1.138
6	225.0	16.37	1.169
7	295.0	15.76	1.193
8	520.0	14.28	1.263
9	1355.0	10.76	1.552
10	1802.0	9.58	1.735
11	2770.0	8.34	2.053
12	4136.0	7.30	2.586

Initial titres = 20.00 and 19.80 mls

Average initial titre = 19.90 mls

Equivalent initial titre after dilution = 18.95 mls

Infinity titre = 6.20 mls

Initial $[NH_3]$ = 0.07467 M

initial [substrate] = 0.02512 M

Titrating [HCl]= 0.0197 M

$k_2 = 1.466 \times 10^{-2}$ (+/-1.1×10^{-4}) l $mole^{-1}min^{-1}$ (12 readings)

$k_2 = 2.443 \times 10^{-4}$ (+/-1.9×10^{-6}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 2.327 \times 10^{-4}$ (+/-1.8×10^{-6}) l $mole^{-1}sec^{-1}$ (10 readings)

average $k_2 = 2.38 \times 10^{-4}$ (+/-3.7×10^{-6}) l $mole^{-1}sec^{-1}$

1,4-Bis-(trifluoromethyl)benzene + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 22.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	5.0	18.98	1.120
2	12.0	18.96	1.121
3	30.0	18.92	1.122
4	75.0	18.76	1.127
5	155.0	18.68	1.129
6	275.0	18.20	1.144
7	607.0	17.50	1.167
8	1425.0	15.90	1.229
9	1869.0	15.24	1.261
10	2839.0	14.12	1.323

Initial titres = 20.00 and 19.80 mls

Average initial titre = 19.90 mls

Equivalent initial titre after dilution = 18.95 mls

Infinity titre = 6.60 mls

Initial $[NH_3]$ = 0.07467 M

initial [substrate] = 0.02433 M

Titrating [HCl]= 0.0197 M

$k_2 = 2.801 \times 10^3$ (+/-4.1×10^{-5}) l $mole^{-1}min^{-1}$ (10 readings)

$k_2 = 4.668 \times 10^{-5}$ (+/-6.8×10^{-7}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 5.151 \times 10^{-5}$ (+/-3.9×10^{-7}) l $mole^{-1}sec^{-1}$ (10 readings)

average $k_2 = 4.91 \times 10^{-5}$ (+/-1.1×10^{-6}) l $mole^{-1}sec^{-1}$

Pentachloropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 25 .

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	15.0	38.00	1.889
2	30.0	38.20	1.877
3	45.5	38.00	1.889
4	75.0	37.60	1.914
5	135.0	37.50	1.921
6	225.0	36.90	1.961
7	375.0	36.20	2.011
8	615.0	34.40	2.166
9	840.0	33.70	2.238
10	1415.0	32.00	2.456

Initial titres = 41.80 and 41.80 mls

Average initial titre = 41.80 mls

Equivalent initial titre after dilution = 39.81 mls

Infinity titre = 26.51 mls

Initial $[NH_3]$ = 0.15685 M

initial [substrate] = 0.02620 M

Titrating [HCl]= 0.0197 M

$k_2 = 4.035 \times 10^{-3}$ (+/-1.2×10^{-4}) l $mole^{-1}min^{-1}$ (10 readings)

$k_2 = 6.725 \times 10^{-5}$ (+/-2.0×10^{-6}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 6.413 \times 10^{-5}$ (+/-6.5×10^{-7}) l $mole^{-1}sec^{-1}$ (10 readings)

average $k_2 = 6.78 \times 10^{-5}$ (+/-2.7×10^{-6}) l $mole^{-1}sec^{-1}$

3-Cyanotetrachloropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 26.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	10.0	14.90	1.340
2	15.0	11.60	1.640
3	20.0	10.50	1.821
4	26.0	9.60	2.039
5	30.0	9.10	2.208
6	35.0	8.00	2.878
7	40.0	7.90	2.983
8	45.0	7.70	3.245
9	50.0	7.50	3.624
10	65.0	7.20	4.970

Initial titres = 19.30 and 19.30 mls

Average initial titre = 19.30 mls

Equivalent initial titre after dilution = 18.38 mls

Infinity titre = 7.10 mls

Initial $[NH_3]$ = 0.07242 M

initial [substrate] = 0.02222 M

Titrating [HCl]= 0.0197 M

k_2 = 2.284 (+/-1.3 x 10^{-1}) l $mole^{-1}min^{-1}$ (10 readings)

k_2 = 3.807 x 10^{-2}(+/-2.2 x 10^{-3}) l $mole^{-1}sec^{-1}$

dup. k_2 = 3.150 x 10^{-2}(+/-2.2 x 10^{-3}) l $mole^{-1}sec^{-1}$ (10 readings)

average k_2 = 3.48 x 10^{-2} (+/-4.4 x 10^{-3}) $mole^{-1}sec^{-1}$

4-Cyanotetrachloropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 27.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	15.0	14.30	1.061
2	30.0	13.90	1.074
3	100.0	13.50	1.088
4	170.0	13.10	1.102
5	240.0	12.90	1.110
6	380.0	12.20	1.140
7	540.0	11.20	1.192
8	1320.0	9.70	1.298

Initial titres = 15.70 and 15.70 mls

Average initial titre = 15.70 mls

Equivalent initial titre after dilution = 14.95 mls

Infinity titre = 4.40 mls

Initial $[NH_3]$ = 0.05891 M

initial [substrate] = 0.02079 M

Titrating [HCl]= 0.0197 M

$k_2 = 1.037 \times 10^{-2}$ (+/-6.1×10^{-4}) l $mole^{-1}min^{-1}$ (8 readings)

$k_2 = 1.728 \times 10^{-4}$ (+/-1.0×10^{-5}) l $mole^{-1}sec^{-1}$

dup. $k_2 = 1.702 \times 10^{-4}$ (+/-8.1×10^{-7}) l $mole^{-1}sec^{-1}$ (8 readings)

average $k_2 = 1.72 \times 10^{-4}$ (+/-1.1×10^{-5}) l $mole^{-1}sec^{-1}$

4-Cyanotetrafluoropyridine + Ammonia in 60/40,(v:v) Dioxan/Water at 25°C.

Table 6.1 Compound No. 23.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	2.0	18.50	1.008
2	5.0	18.40	1.010
3	10.0	18.00	1.019
4	20.0	17.60	1.027
5	36.0	17.30	1.034
6	55.0	16.70	1.049
7	142.0	16.00	1.068
8	262.0	13.50	1.156

Initial titres = 19.00 and 19.00 mls

Average initial titre = 19.00 mls

Equivalent initial titre after dilution = 18.10 mls

Infinity titre = 5.00 mls

Initial $[NH_3]$ = 0.07130 M

initial [substrate] = 0.02580 M

Titrating [HCl]= 0.0197 M

$k_2 = 2.65 \times 10^{-2}$ (+/-2.0×10^{-3}) l $mole^{-1}min^{-1}$ (8 readings)

$k_2 = 4.42 \times 10^{-4}$ (+/-3.3×10^{-5}) l $mole^{-1}sec^{-1}$

2,4,6-Tricyanochlorobenzene + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 24.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	10.0	11.00	1.386
2	35.0	9.40	1.573
3	55.0	8.40	1.757
4	60.0	8.20	1.804
5	75.0	7.70	1.946
6	100.0	7.10	2.183
7	175.0	5.70	4.043

Initial titres = 16.84 and 16.84 mls

Average initial titre = 16.84 mls

Equivalent initial titre after dilution = 16.04 mls

Infinity titre = 5.50 mls

Initial $[NH_3]$ = 0.08019 M

initial [substrate] = 0.02635 M

Titrating [HCl]= 0.0250 M

$k_2 = 5.871 \times 10^{-1}$ (+/-7.4×10^{-2}) 1 $mole^{-1}min^{-1}$ (7 readings)

$k_2 = 9.785 \times 10^{-3}$ (+/-1.2×10^{-3}) 1 $mole^{-1}sec^{-1}$

Pentafluoropyridine + Ammonia in 60/40.(v:v) Dioxan/Water at 80°C.

Table 6.1 Compound No. 1.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	5.0	15.75	1.166
2	10.0	13.10	1.296
3	15.0	9.95	1.599
4	20.0	9.20	1.728
5	26.0	8.35	1.932
6	30.0	7.80	2.121
7	35.0	7.42	2.299
8	45.0	6.86	2.691
9	55.0	6.56	3.036
10	70.0	6.28	3.580
11	90.0	6.10	4.273
12	120.0	5.98	5.477

Initial titres = 19.70 and 19.70 mls

Average initial titre = 19.70 mls

Equivalent initial titre after dilution = 18.76 mls

Infinity titre = 5.93 mls

Initial $[NH_3]$ = 0.07392 M

initial [substrate] = 0.02528 M

Titrating [HCl]= 0.0197 M

k_2 = 1.592 (+/-1.4 x 10^{-2}) l $mole^{-1}min^{-1}$ (12 readings)

k_2 = 2.653 x 10^{-2} (+/-2.3 x 10^{-4}) l $mole^{-1}sec^{-1}$

dup. k_2 = 3.532 x 10^{-2} (+/-7.4 x 10^{-4}) l $mole^{-1}sec^{-1}$ (12 readings)

average k_2 = 3.09 x 10^{-2} (+/- 9.7 x 10^{-4}) l $mole^{-1}sec^{-1}$

1',1'-Difluoromethylpentafluorobenzene + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.3 Compound No. 29.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	15.0	10.05	1.282
2	42.0	10.00	1.286
3	130.0	9.90	1.294
4	288.0	9.74	1.307
5	492.0	9.66	1.314
6	1360.0	8.70	1.414
7	1727.0	8.30	1.467
8	2845.0	7.50	1.599

Initial titres = 10.85 and 10.85 mls

Average initial titre = 10.85 mls

Equivalent initial titre after dilution = 10.33 mls

Infinity titre = 4.47 mls

Initial $[NH_3]$ = 0.08597 M

initial [substrate] = 0.02439 M

Titrating [HCl]= 0.0416 M

$k_2 = 3.001 \times 10^{-3} (+/- 9.2 \times 10^{-5})$ l $mole^{-1} min^{-1}$ (8 readings)

$k_2 = 5.002 \times 10^{-5} (+/- 1.5 \times 10^{-6})$ l $mole^{-1} sec^{-1}$

1'-Fluoromethylpentafluorobenzene + Ammonia in 60/40,(v:v) Dioxan/Water at 80°C.

Table 6.3 Compound No. 30.

i	time/min	titre/mls	ln[(a-2x)/(b-x)]
1	15.0	19.00	1.231
2	37.0	19.00	1.231
3	120.0	18.80	1.238
4	210.0	17.90	1.275
5	340.0	18.80	1.238
6	1610.0	17.40	1.298
7	2937.0	17.40	1.298
8	4505.0	16.90	1.323
9	5675.0	16.10	1.368
10	7200.0	15.70	1.393
11	11370.0	14.80	1.456

Initial titres = 20.20 and 21.30 mls

Average initial titre = 20.75 mls

Equivalent initial titre after dilution = 19.76 mls

Infinity titre = 7.90 mls

Initial $[NH_3]$ = 0.07786 M

initial [substrate] = 0.02337 M

Titrating [HCl]= 0.0197 M

$k_2 = 6.285 \times 10^{-4}$ (+/- 4.3×10^{-5}) l $mole^{-1}min^{-1}$ (11 readings)

$k_2 = 1.047 \times 10^{-5}$ (+/- 7.2×10^{-7}) l $mole^{-1}sec^{-1}$

APPENDIX 2

NMR DATA

NMR SPECTRA

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Solvent is acetone unless otherwise stated.

Table 1

Fluorine Chemical Shifts for 4-X-Tetrafluoropyridines

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	2,6	3,5
PhNH	95.28	155.75
PhNH.Me	101.25	151.4
$PhCH_2NH$	98.40	165.2
EtNH	96.6	158.0
4'-MeO-PhNH	96.36	158.12
4'-Me-PhNH	95.80	151.76
3'-Me-PhNH	95.45	151.61
4'-Cl-PhNH	95.0	155.8
3'-Cl-PhNH	95.98	155.00
3'-NO_2-PhNH	96.8	164.2
3'-Br-PhNH	95.55	150.26
3'-MeO-PhNH	95.28	155.75

Table 2

Fluorine Chemical Shifts for 2-X-Tetrafluoropyridines

	Chemical shift/ppm from $CFCl_3$			
Substituent-X	3	4	5	6
$PhCH_2NH$	166.9	132.8	177.1	99.06

Table 3

Fluorine Chemical Shifts for 4-X-2,6-Difluoropyridine

	Chemical shift/ppm from $CFCl_3$
Substituent-X	2,6
NH_3	68.7
PhNH	67.5
PhNH.Me	65.3
$PhCH_2NH$	74.8

Table 4

Fluorine Chemical Shifts for 2-X-2,6-Difluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	4	6
PhNH.Me	93.0	71.9
$PhCH_2NH$	103.0	68.7

Table 5

Fluorine Chemical Shifts for 2,6-X-4-Fluoropyridine

	Chemical shift/ppm from $CFCl_3$
Substituent-X	4
PhNH.Me	69.5

Table 6

Fluorine Chemical Shifts for 4-X-2,5,6-Trifluoropyridine

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	2	5	6
NH_3	76.4	173.7	95.0
PhNH	75.5	171.6	96.0
PhNH.Me	74.9	159.0	93.5
$PhCH_2NH$	76.12	176.4	98.24

Table 7

Fluorine Chemical Shifts for 6-X-2,4,5-Trifluoropyridine

	Chemical shift/ppm from $CFCl_3$		
Sustituent-X	2	4	5
NH_3	70.9	124.6	172.6
PhNH	71.6	126.3	170.9
PhNH.Me	69.0	123.0	157.5
$PhCH_2NH$	72.2	128.8	167.2

Table 8

Fluorine Chemical Shifts for 2-X-4-Chlorotrifluoropyridines

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	3	4	5
PhNH	143.7	158.5	94.2
$PhCH_2NH$	166.9	163.1	94.2
EtNH	136.3	156.2	87.0
3'-MeO-PhNH	142.8	155.5	94.9

Table 9

Fluorine Chemical Shifts for 4-X-3-Chlorodifluoropyridines

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	2	5	6
PhNH	73.5	163.3	91.6
$PhCH_2NH$	77.2	165.4	92.9
EtNH	74.4	154.0	92.5

Table 10

Fluorine Chemical Shifts for 6-X-3-Chlorotrifluoropyridines

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	2	5	6
EtNH	75.5	156.0	94.5

Table 11

Fluorine Chemical Shifts for 4-X-2-Chlorotrifluoropyridines

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	3	5	6
NH_3	141.8	161.3	91.0
PhNH	152.7	163.9	92.2
$PhCH_2NH$	161.2	166.9	94.4

Table 12

Fluorine Chemical Shifts for 4-X-3-Cyanotrifluoropyridines

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	2	5	6
PhNH	67.7	170.9	65.3
PhNH.Me	66.5	157.3	65.3
$PhCH_2NH$	70.2	159.4	66.6
3'-Me-PhNH	64.73	164.27	86.54
3'-Cl-PhNH	67.9	163.5	88.7
3'-NO_2-PhNH	67.7	162.0	88.1
3'-Br-PhNH	67.2	162.5	88.1
4'-NO_2-PhNH	67.73	158.22	86.52

Table 13

Fluorine Chemical Shifts for 2-X-3-Cyanotrifluoropyridine

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	2	4	5
PhNH.Me	63.2	120.9	157.3
$PhCH_2NH$	67.7	90.9	169.0

Table 14

Fluorine Chemical Shifts for 4,6-X-3-Cyanodifluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	2	5
4'-Cl-PhNH	64.6	160.4
3'-Cl-PhNH	67.2	156.1
PhNH.Me	85.3	136.0

Table 15

Fluorine Chemical Shifts for 2,4,6-X-3-Cyanofluoropyridine

	Chemical shift/ppm from $CFCl_3$
Substituent-X	5
4'-Cl	148.6

Table 16

Fluorine Chemical Shifts for 4-X-3,5-Dichlorodifluoropyridine

	Chemical shift/ppm from $CFCl_3$
Substituent-X	2,6
PhNH	75.2
$PhCH_2NH$	76.4
4'-MeO	74.29
4'-Me	73.73
4'-Cl	73.80

Table 17

Fluorine Chemical Shifts for 2-X-3,5-Dichlorodifluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	2	4
PhNH	74.35	103.84
PhNH.Me	70.97	97.76

Table 18

Fluorine Chemical Shifts for 4-X-2-Cyanotrifluoropyridine

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	3	5	6
NH_3	156.2	139.8	91.4
PhNH	143.35	130.52	89.67

Table 19

Fluorine Chemical Shifts for 6-X-3-Cyano-2-fluoropyridine

	Chemical shift/ppm from $CFCl_3$
Substituent-X	6
PhNH	59.5
$PhCH_2NH$	60.3

Table 20

Fluorine Chemical Shifts for 4-X-3-Chloro-5-cyanodifluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	2	6
PhNH	61.24	65.85
$PhCH_2NH$	66.72	67.99
4'-MeO-PhNH	65.17	67.65
4'-Me-PhNH	65.17	67.65
4'-Cl-PhNH	56.64	64.37

Table 21

Fluorine Chemical Shifts for 2-X-3-Chloro-5-cyanodifluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	4	6
PhNH	94.5	58.7
PhNH.Me	97.8	62.7
$PhCH_2NH$	107.4	65.9
4'-MeO-PhNH	97.0	61.6
4'-Cl-PhNH	97.1	61.8

Table 22

Fluorine Chemical Shifts for 6-X-3-Chloro-5-cyanodifluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	2	4
PhNH.Me	60.31	92.36

Table 23

Fluorine Chemical Shifts for 4-X-Tetrafluorobenzonitrile

	Chemical shift/ppm from $CFCl_3$	
Sustituent-X	2,6	3,5
NH_3	140.2	162.8
PhNH	139.7	151.2
$NH.CH_2Ph$	144.1	161.6
4'-MeO-PhNH	138.5	153.8
4'-Me-PhNH	137.2	151.5
3'-Me-PhNH	136.8	149.7
4'-Br-PhNH	137.9	150.9
4'-Cl-PhNH	137.9	151.5
4'-Cl-PhNH	138.0	150.7
4'-NO_2-PhNH	137.6	149.8
4'-Br-PhNH	138.0	151.3
4'-MeO-PhNH	138.0	151.8

Table 24

Fluorine Chemical Shifts for 2-X-Tetrafluorobenzonitrile

	Chemical shift/ppm from $CFCl_3$			
Sustituent-X	3	4	5	6
$NH.CH_2Ph$	149.0	135.5	166.3	153.4
4'-MeO-PhNH	142.3	139	158.3	155.4
4'-Br-PhNH	157.0	145.0	174.8	158.2
4'-Cl-PhNH	147.6	136.0	165.5	149.3
3'-MeO-PhNH	149	135.0	166.0	149

Table 25

Fluorine Chemical Shifts for 2,4-X-Tetrafluorobenzonitrile

	Chemical shift/ppm from $CFCl_3$		
Sustituent-X	3	5	6
$NH.CH_2Ph$			

Table 26

Fluorine Chemical Shifts for 4-X-1,2-Dicyanotrifluorobenzenes

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	3	5	6
NH_3	129.35	149.05	135.85
PhNH	118.95	134.35	136.95
PhNH.Me	112.15	129.85	132.65
$PhCH_2NH$	127.00	129.10	144.00

Table 27

Fluorine Chemical Shifts for 6-X-1,2-Dicyanotrifluorobenzenes

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	3	4	5
NH_3	143.9	145.4	152.4
PhNH	118.95	134.35	136.95
$PhCH_2NH$	140.8	147.0	125.6

Table 28

Fluorine Chemical Shifts for 4,6-X-1,2-Dicyanotrifluorobenzenes

	Chemical shift/ppm from $CFCl_3$			
Substituent-X	3		5	
NH_3			119.8	133.2
PhNH	110.9	116.3		
$PhCH_2NH$			131.8	127.7

nx:NMR 7

Table 29

Fluorine Chemical Shifts for 4-X-Octafluorotoluene

	Chemical shift/ppm from $CFCl_3$		
Substituent-X	2,6	3,5	CF_3
NH_3	147.0	165.3	56.8
PhNH	147.4	163.0	56.8
$PhCH_2NH$	147.43	162.10	56.87

Table 30

Fluorine Chemical Shifts for 4-X-3-Nitro-2,6-difluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	2	6
PhNH	109.8	65.1

Table 31

Fluorine Chemical Shifts for 2-X-3-Nitro-4,6-difluoropyridine

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	4	6
PhNH	109.8	65.1

Table 32

Fluorine Chemical Shifts for 2,4-X-3-Nitro-6-fluoropyridine

	Chemical shift/ppm from $CFCl_3$
Substituent-X	6
PhNH	72.3
$PhCH_2NH$	62.0

Table 33

Fluorine Chemical Shifts for 2-X-Nitrotetrafluorobenzenes

	Chemical shift/ppm from $CFCl_3$			
Substituent-X	3	4	5	6
NH_3	150.04	160.02	175.54	146.84
3'-Me-PhNH	149.7	152.2	166.7	145.9
3'-Cl-PhNH	150.1	152.5	164.7	145.3
3'-NO_2-PhNH	149.5	1651.8	163.6	144.95
3'-Br-PhNH	148.8	151.2	163.3	144.5

Table 34

Fluorine Chemical Shifts for 2,6-X-Nitrotrifluorobenzenes

	Chemical shift/ppm from $CFCl_3$	
Substituent-X	3,5	4
NH_3	151.3	175.3
4'-MeO	151.5	154.7
3'-Me-PhNH	150.2	154.1
3'-Cl-PhNH	143.5	153.9
3'-Br	143.5	152.3

Table 35

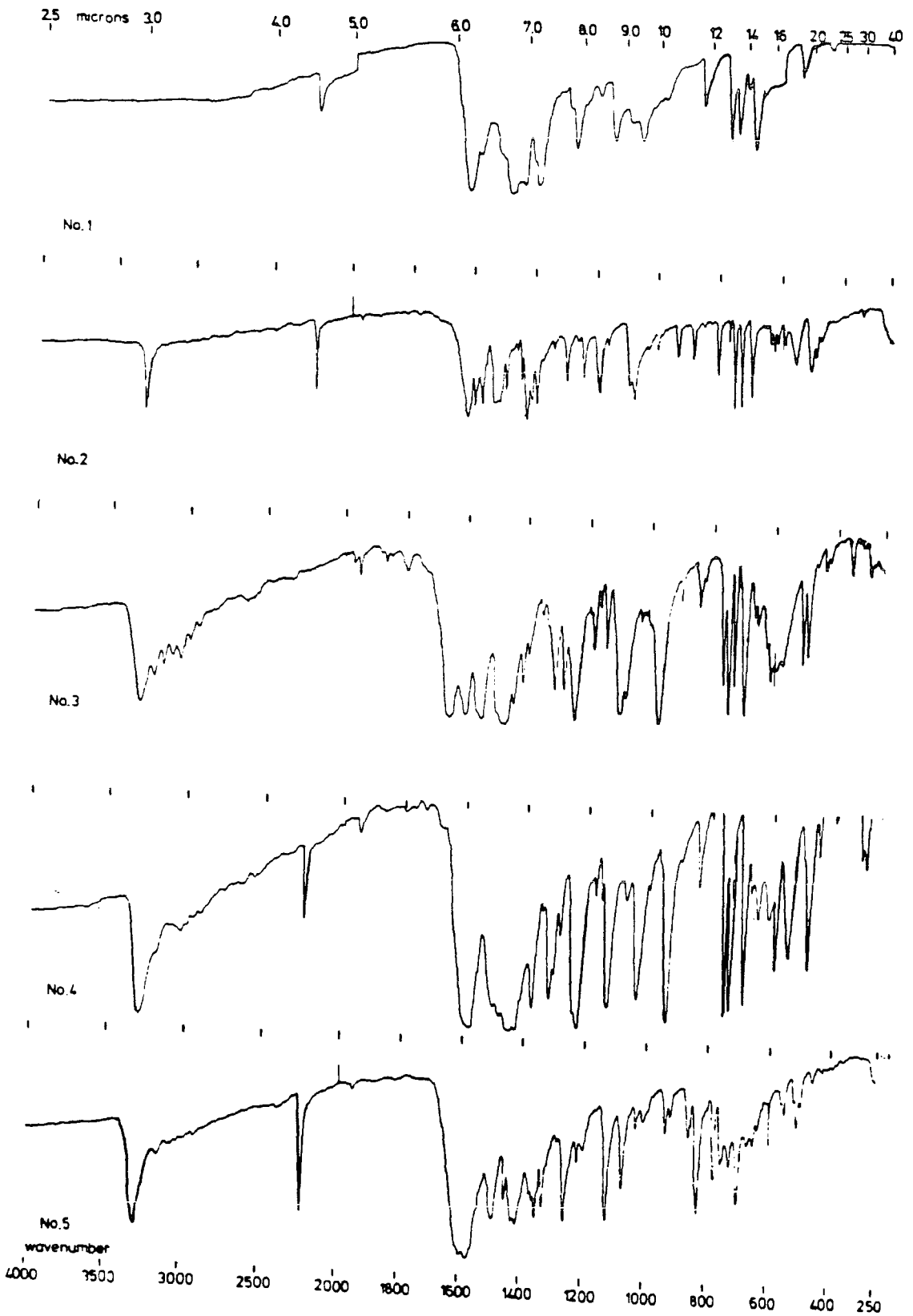
Fluorine Chemical Shifts for 4-X-Nitrotetrafluorobenzenes

	Chemical shift/ppm from $CFCl_3$	
Sustituent-X	2,6	3,5
NH_3	161.3	148.2
3'-Me-$PhNH_2$	158.5	149.4
3'-Cl-$PhNH_2$	151.1	149.9

APPENDIX 3

INFRA RED SPECTRA

INFRA RED SPECTRA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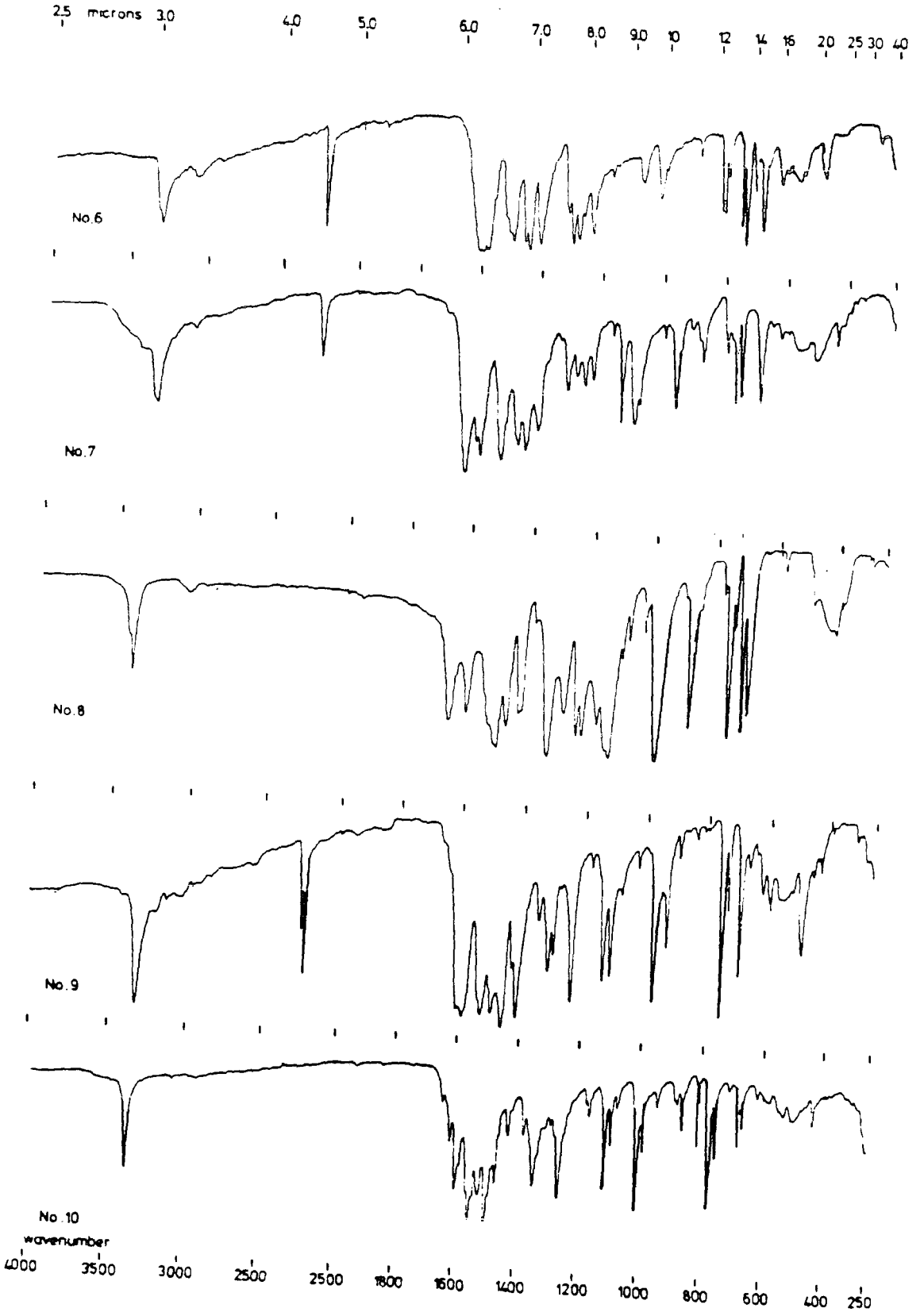
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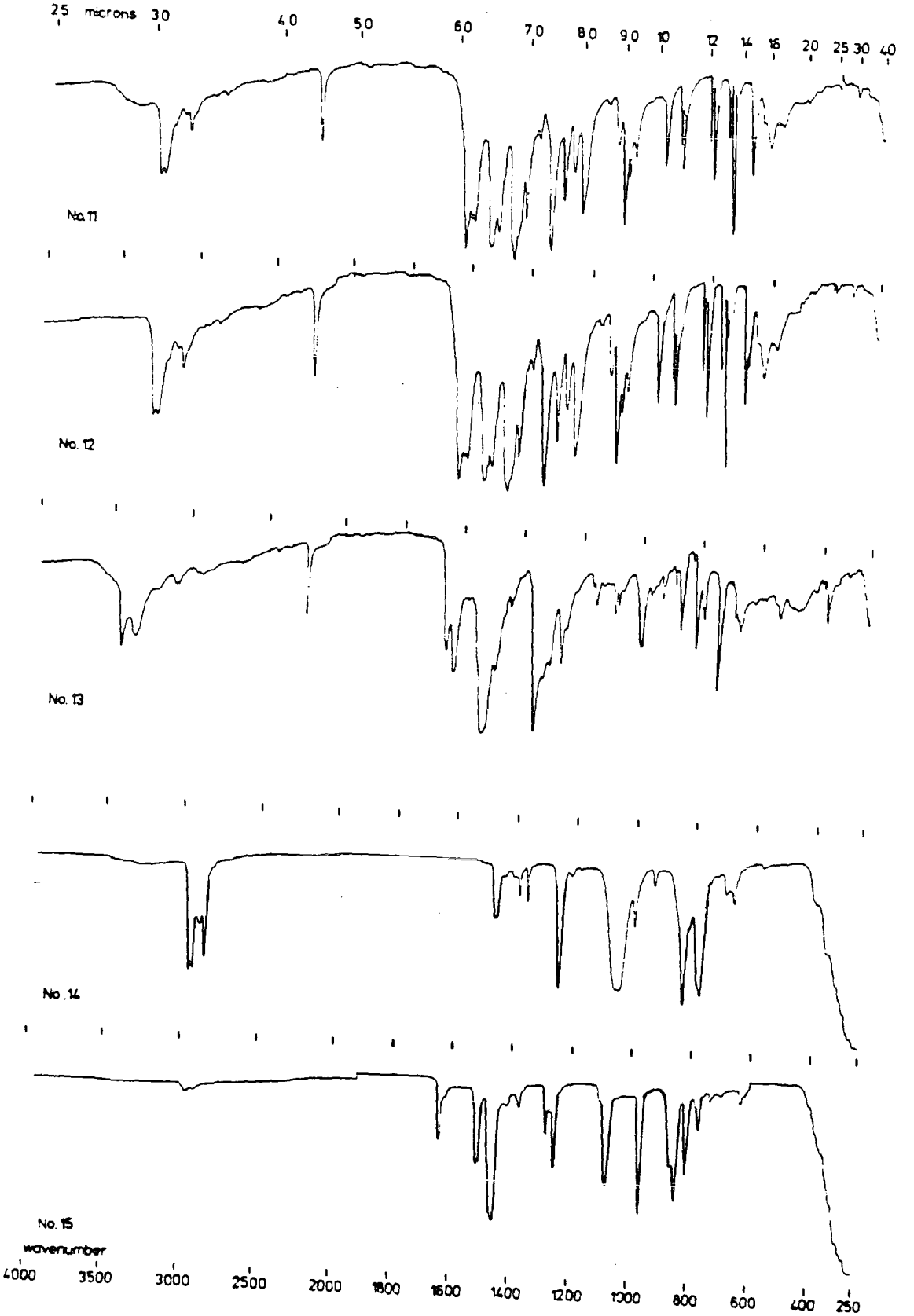
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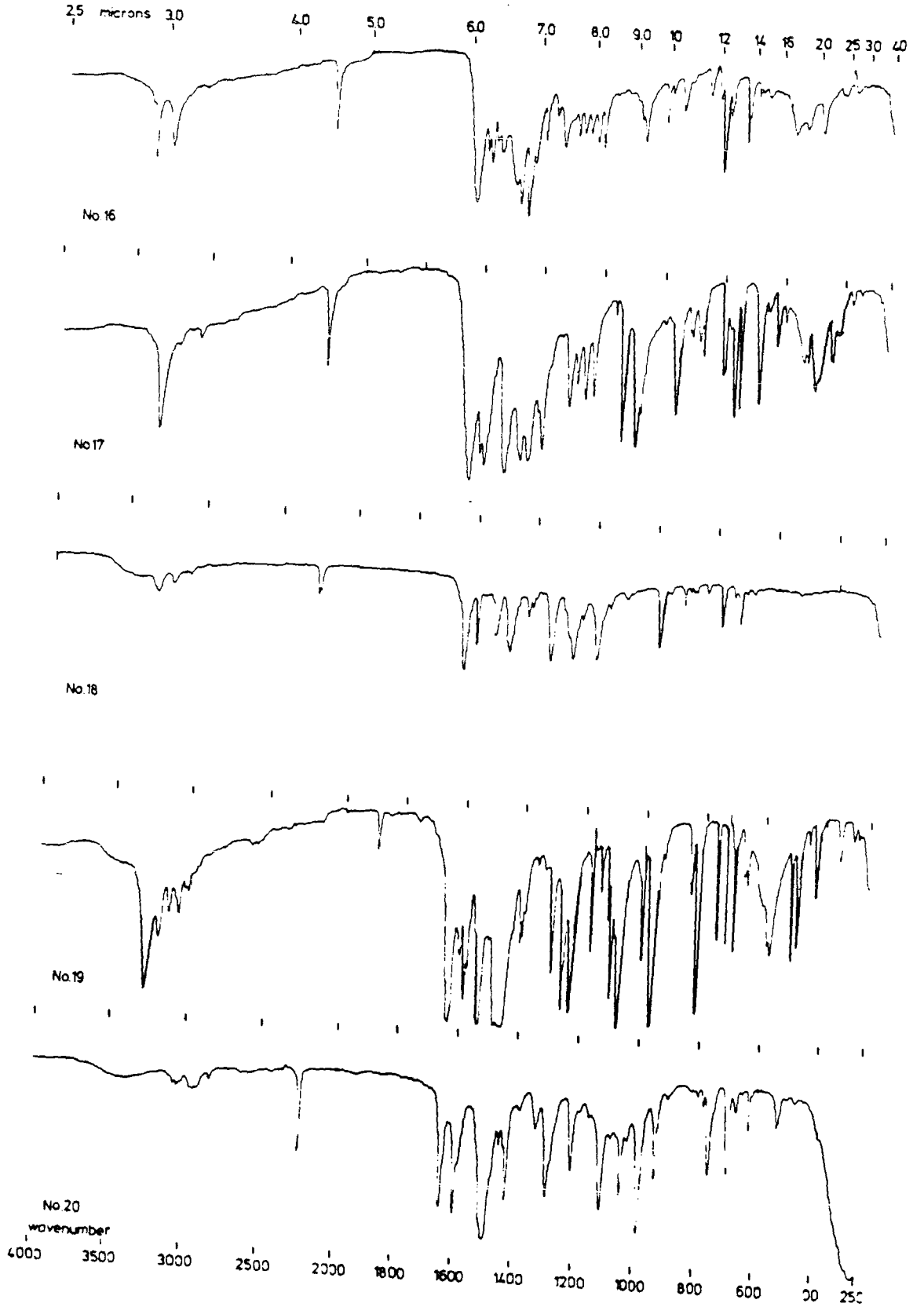
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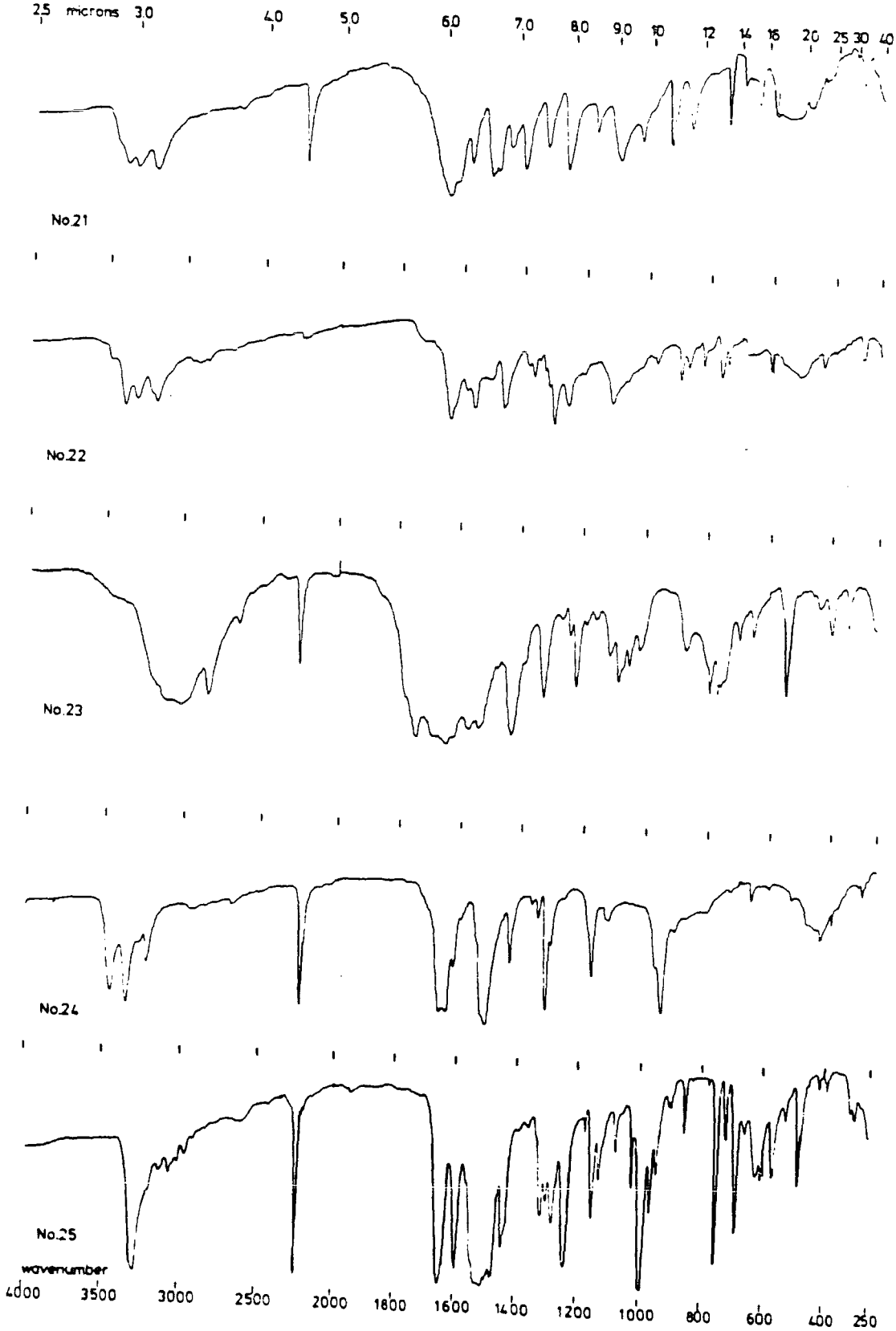
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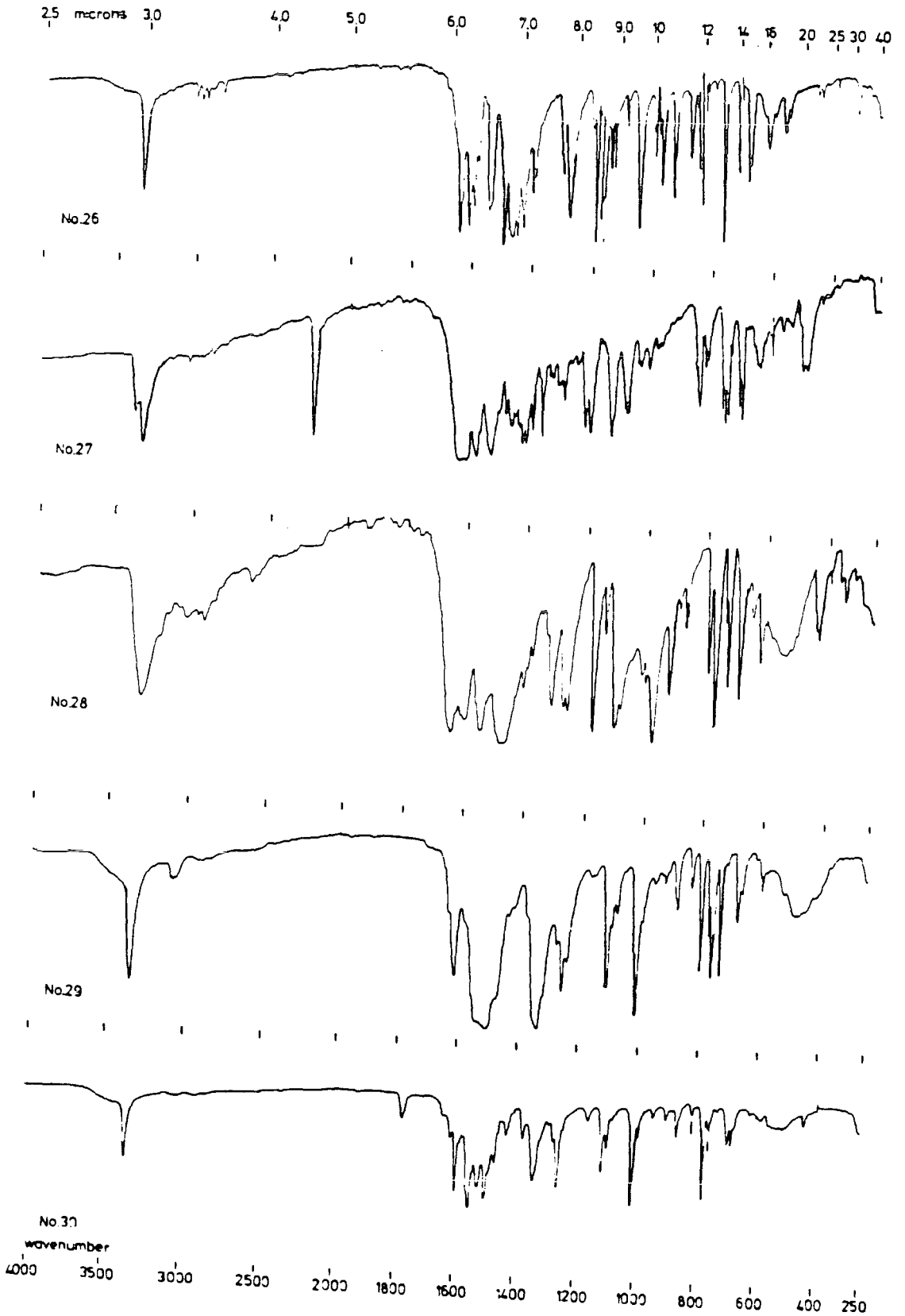
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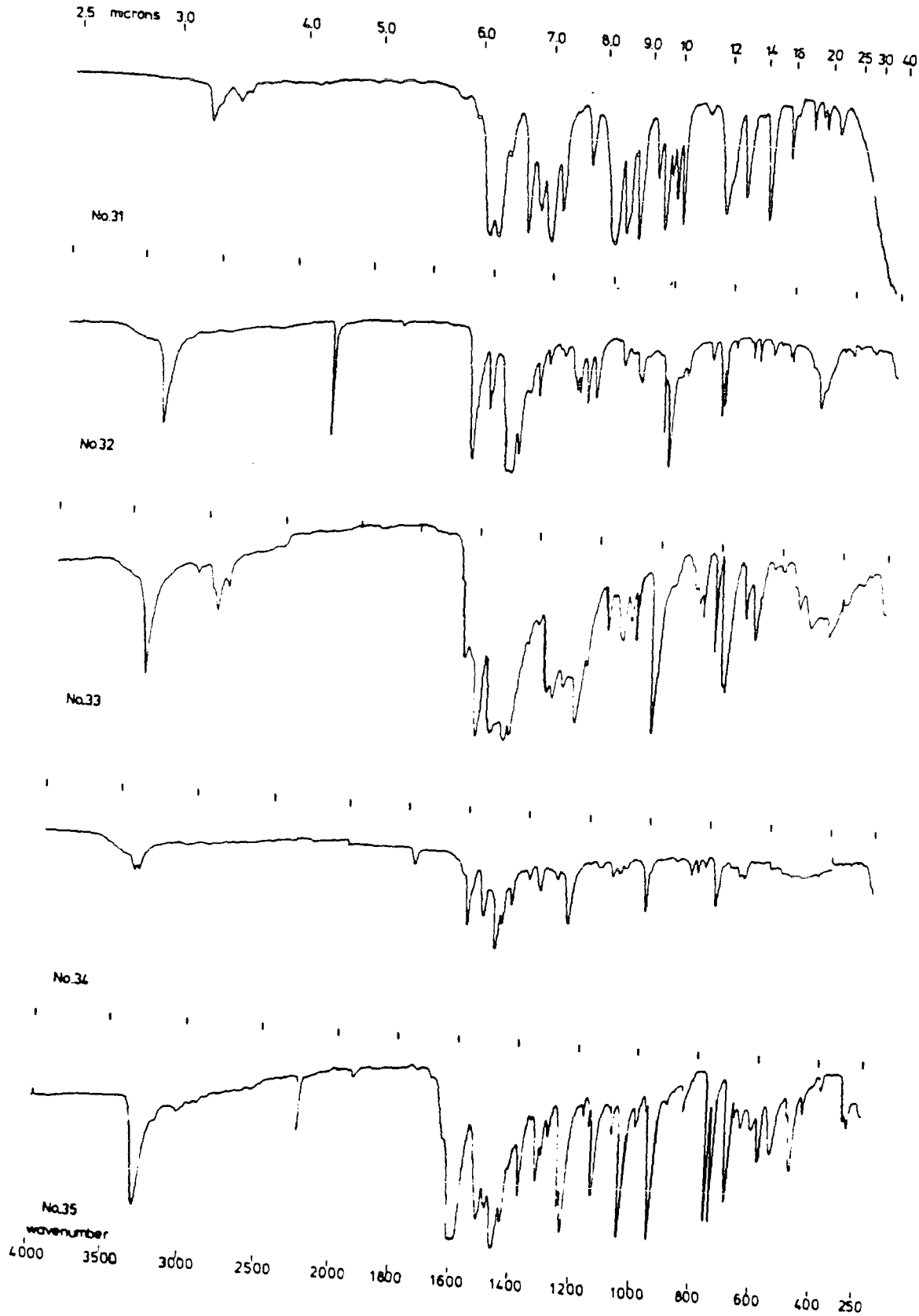
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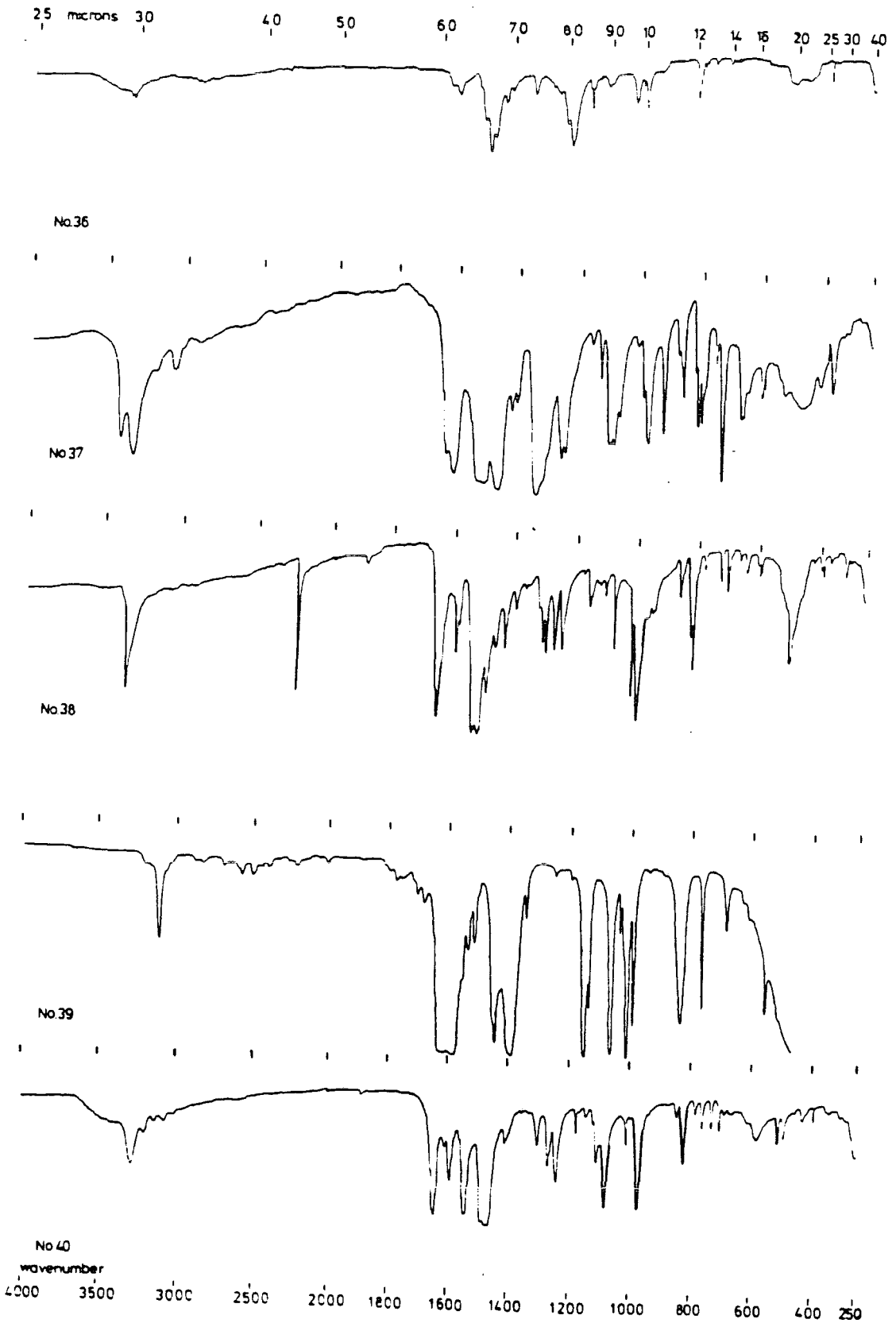
2.5 microns 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10 12 14 16 20 25 30 40
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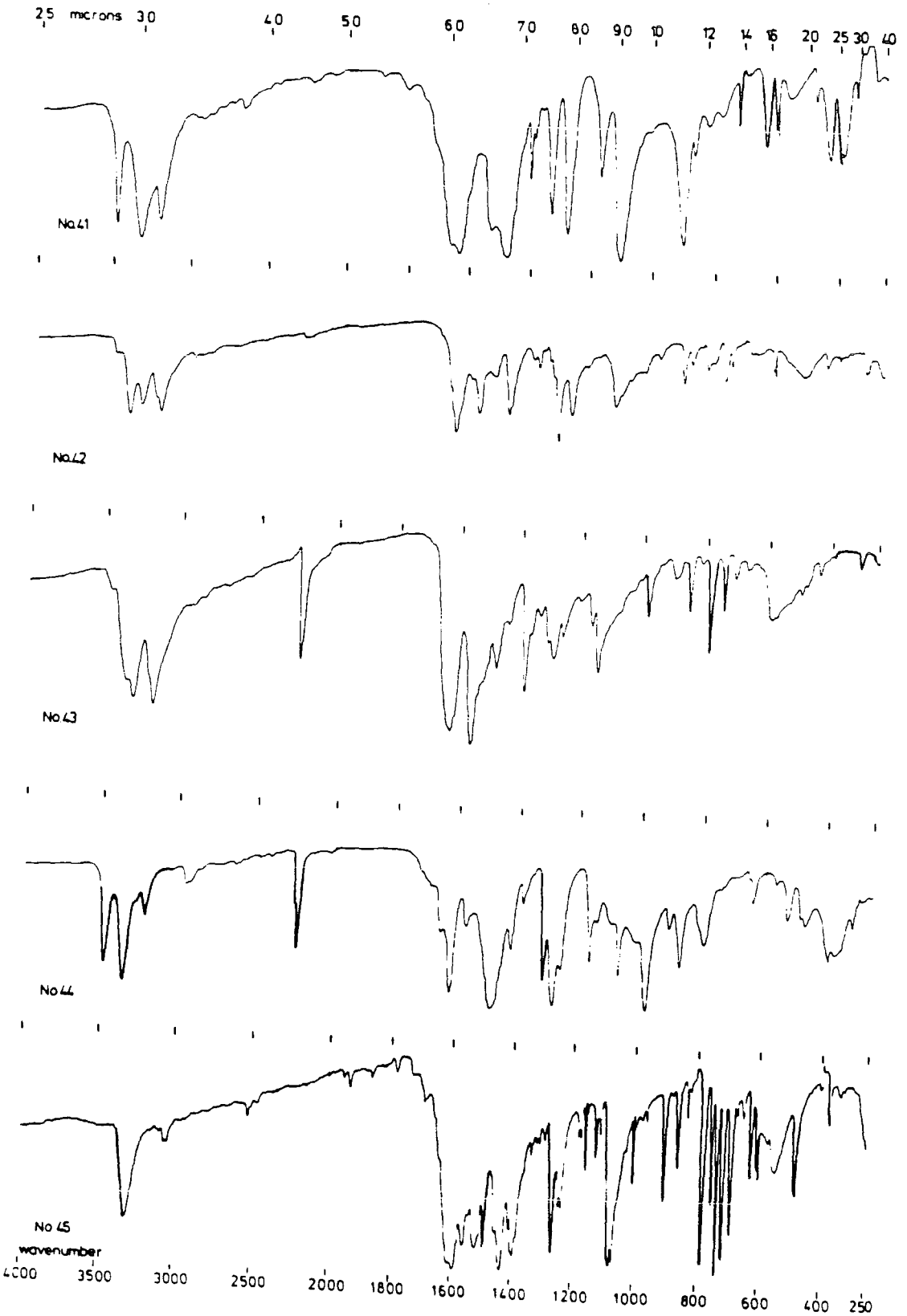
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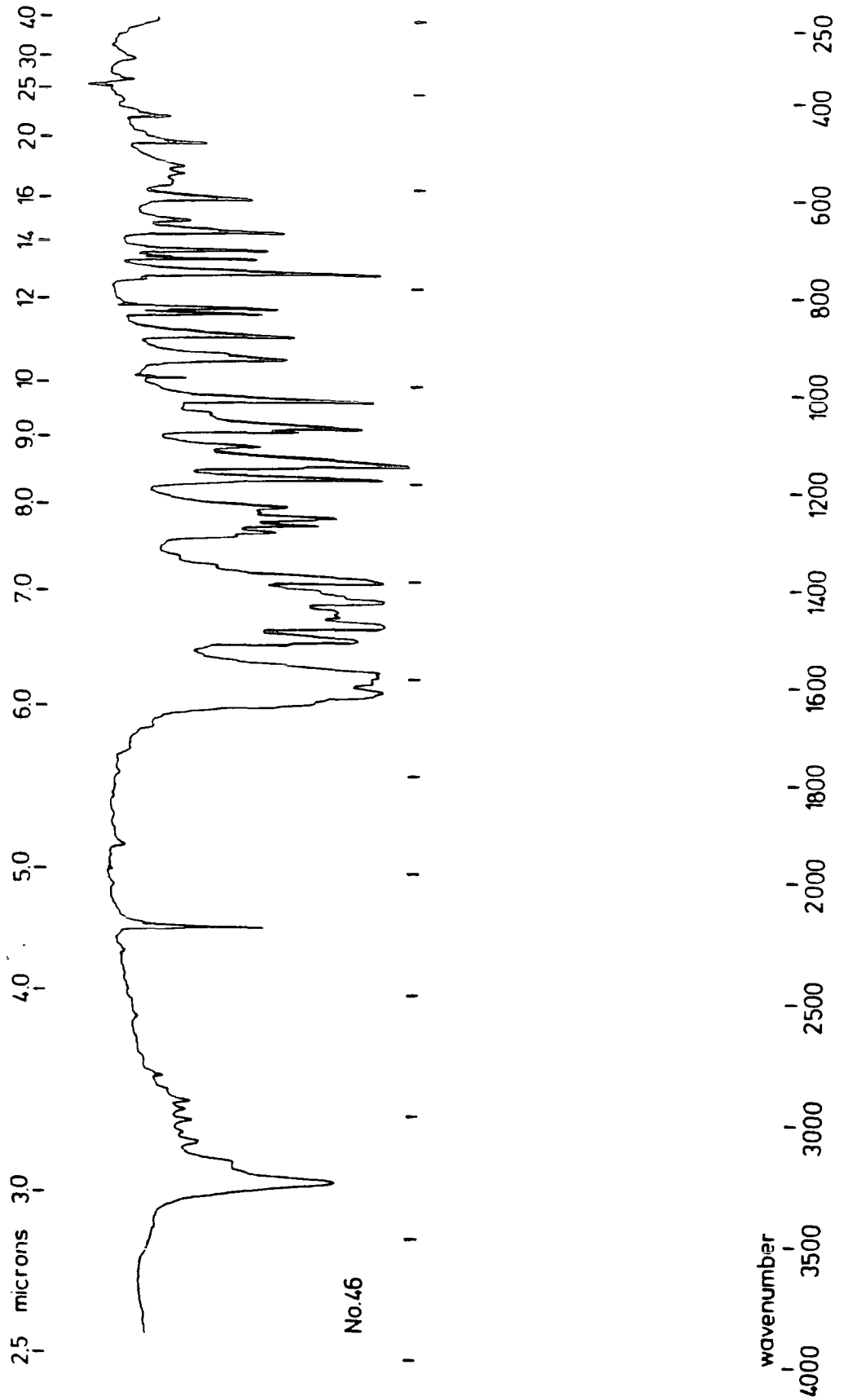
2.5 microns 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10 12 14 16 20 25 30 40
wavenumber 4000 3500 3000 2500 2000 1800 1600 1400 1200 1000 800 600 400 250
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APPENDIX 4

COLLOQUIA

DEPARTMENTAL COLLOQUIA AND INDUCTION COURSE FOR POSTGRADUATES

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing

a) all research colloquia, research seminars and lectures arranged by the department of Chemistry during the period of the writer's residence as a postgraduate student;

b) all research conferences attended and papers read out by the writer of the thesis during the period when the research for the thesis was carried out; and

c) details of the postgraduate induction course.

Events in a) which were attended are marked.*

Colloquia

Research Colloquia, Seminars and Lectures

1. University of Durham Chemistry Colloquia

Academic Year 1978-1979

12 Dec. Professor C.J.M. Stirling (U. of Bangor), "Parting is such sweet sorrow - the leaving group in organic chemistry".

31 Jan. Professor P.D.B. de la Mare (U. of Auckland, New Zealand), "Some pathways leading to electrophilic substitution".

14 Feb. Professor B. Dunnel (U. of British Columbia), "The application of n.m.r. to the study of motions of molecules in solids".

14 Mar. Dr. J.C. Walton (U. of St. Andrews), "Pentadienyl radicals".

28 Mar. Dr. A. Reiser (Kodak Ltd.), "Polymer photography and the mechanism of cross link formation in solid polymer matrices".

25 Apr. Dr. C.R. Patrick (U. of Birmingham), "Chlorofluorocarbons and stratospheric ozone: an appraisal of the environmental problem".

1 May Dr. G. Wyman (European Research Office, U.S. Army), "Excited state chemistry of indigoid dyes".

2 May Dr. J.D. Hobson (U. of Birmingham), "Nitrogen-centred reactive intermediates".

8 May Professor A. Schmidpeter (Inst. of Inorg. Chem., U. of Munich), "Five-membered phosphorus heterocycles containing dicoordinate phosphorus".

9 May Professor G. Maier (Lahn-Giessen U.), "Tetra-tert-butyltetrahedrane".

9 May Dr. A.J. Kirkby (U. of Cambridge), "Structure and reactivity in intramolecular and enzymic catalysis".

16 May Dr. J.F. Nixon (U. of Sussex), "Some recent developments in platinum metal phosphine complexes".

23 May Dr. B. Wakefield (U. of Salford), "Electron transfer in the reaction of metals and organometallic compounds with polychloropyridine derivatives".

* 13 Jun. Professor I. Ugi (U. of Munich), "Synthetic uses of super nucleophiles".

* 25 Sep. Professor R. Soulen (Southwestern U., Texas), "Applications of HSAB theory to vinylic halogen substitution reactions and a few copper coupling reactions".

Academic Year 1979-1980

* 21 Nov. Dr. J. Müller (U. of Bergen), "Photochemical reactions of ammonia".

28 Nov. Dr. B. Cox (U. of Stirling), "Macrobicyclic cryptate complexes: dynamics and selectivity".

* 5 Dec. Dr. G.C. Eastmand (U. of Liverpool), "Synthesis and properties of some multicompqnent polymers".

12 Dec. Dr. C.I. Ratcliffe, "Rotor motions in solids".

* 18 Dec. Dr. K.E. Newman (U. of Lausanne), "High pressure multinuclear n.m.r. in the elucidation of mechanism of fast simple inorganic reactions".

* 30 Jan. Dr. M.J. Barrow (U. of Edinburgh), "The structures of some simple inorganic compounds of silicon and germanium - pointers to structural trends in group IV".

* 6 Feb. Dr. J.M.E. Quirke (U. of Durham), "Degradation of chlorophyll-a in sediments".

* 23 Apr. B. Grievson B.Sc. (U. of Durham), "Halogen radio-pharmaceuticals".

* 14 May Dr. R. Hutton (Waters Associates), "Recent developments in multi-milligram and multi-gram scale preparative high performance liquid chromatography".

* 21 May Dr. T.W. Bentley (U. of Swansea), "Medium and structural effects on solvolytic reactions".

* 10 Jul. Professor D. Des Marteau (U. of Heidelberg), "New developments in organonitrogen fluorine chemistry".

Academic Year 1980-1981

* 7 Oct. Professor T. Fehlner (Notre Dame U., Indiana), "Metalloboranes - cages or co-ordination compounds".

* 15 Oct. Dr. R. Alder (U. of Bristol), "Doing chemistry inside cages - medium ring bicyclic molecules".

12 Nov. Dr. M. Gerloch (U. of Cambridge), "Magneto-chemistry is about chemistry".

* 19 Nov. Dr. T. Gilchrist (U. of Liverpool), "Nitroso-olefines as synthetic intermediates".

3 Dec. Dr. J.A. Connor (U. of Manchester), "Thermochemistry of transition metal compounds".

18 Dec. Dr. R.F. Evans (U. of Brisbane), "Some recent communications to the editor of Australian Journal of Failed Chemistry".

* 18 Feb. Professor S.F.A. Kettle (U. of East Anglia), "Variations in the molecular dance at the crystal ball".

* 25 Feb. Dr. K. Bowden (U. of Essex), "The transmission of polar substituent effects".

4 Mar. Dr. S. Cradock (U. of Edinburgh), "Pseudo-linear pseudohalides".

* 18 Mar. Dr. P.J. Smith (Int. Tin Research Institute), "Organotin compounds - a versatile class of organometallic derivatives".

* 6 May Professor M. Szwarc, F.R.S., "Ions and ion pairs".

* 8 May Professor H.F. Koch (Bathaca College, U.S.A.), "Proton-transfer during elimination reactions".

13 May Professor H. Fritzer (U. of Graz), "Simple methods to construct representations for discrete symmetry groups".

14 May Professor H. Fritzer (U. of Graz), "The interplay of permutational and geometrical symmetry of certain electronic systems".

* 10 Jun. Dr. J. Rose (I.C.I. Plastics Division), "New engineering plastics".

* 17 Jun. Dr. P. Moreau (U. of Montpellier), "Recent results in perfluoro-organometallic chemistry".

* 24 Jun. Dr. S.A.R. Knox (U. of Bristol), "Coordination and reactivity of organic species at dinuclear metal centres".

26 Jun. Professor A.P. Schaap (U.S. Office of Naval Research, London), "Mechanisms of chemiluminescence and photooxygenation".

2. Durham University Chemical Society

Academic Year 1978-1979

* 10 Oct. Professor H.C. Brown (Purdue U.), 'The tool of increasing electron demand in the study of cationic processes".

* 19 Oct. Mr. F.C. Shenton (Public Analyst, Co. Durham), "There is death in the pot".

* 26 Oct. Professor W.J. Albery (Imperial College, London), "Photogalvanic cells for solar energy conversion".

* 9 Nov. Professor A.R. Katritsky (U. of East Anglia), "Some adventures in heterocyclics".

* 16 Nov. Dr. H.C. Fielding (I.C.I. Mond Division), "Fluorochemical surfactants and textile finishes".

* 23 Nov. Dr. C. White (U. of Sheffield), "The magic of chemistry",

* 18 Jan. Professor J.C. Robb (U. of Birmingham), "The plastics revolution".

* 8 Feb. Mr. C.G. Dennis (Vaux Ltd.), "The art and science of brewing".

* 1 Mar. Professor R. Mason (Govt. Scientific Advisor), "The scientist in defence policy".

10 May Professor G. Allen (Chairman S.R.C.), "Neutron scattering for polymer structures".

Academic Year 1979-1980

* 18 Oct. Dr. G. Cameron (U. of Aberdeen), "Synthetic polymers - twentieth century polymers".

25 Oct. Professor P. Gray (U. of Leeds), "Oscillatory combustion reactions".

* 1 Nov. Dr. J. Ashby (I.C.I. Toxicological Laboratory), "Does chemically-induced cancer make chemical sense ?"

* 8 Nov. Professor J.H. Turnbull (R.M.C. Shrivenham), "Luminescence of drugs".

15 Nov. Professor E.A.V. Ebsworth (U. of Edinburgh), "Stay still you brute: the shape of the simple silyl complexes".

* 24 Jan. Professor R.J.P. Williams (U. of Oxford), "On first looking into biology's chemistry".

14 Feb. Professor G. Gamlen (U. of Salford), "A yarn with a new twist - fibres and their uses".

* 21 Feb. Dr. M.L.H. Green (U. of Oxford), "Synthesis of highly reactive organic compounds using metal vapours".

* 28 Feb. Professor S.F.A. Kettle (U. of East Anglia), "Molecular shape, structure and chemical blindness".

* 6 Mar. Professor W.D. Ollis (U. of Sheffield), "Novel molecular rearrangements".

Academic Year 1980-1981

* 16 Oct. Dr. D. Maas (U. of Salford), "Reactions a go-go".

* 23 Oct. Professor T.M. Sugden (U. of Cambridge), "Some reactions of metals in high temperature flames".

* 30 Oct. Professor N. Grassie (U. of Glasgow), "Inflammability hazards in commercial polymers".

6 Nov. Professor A.G. Sykes (U. of Newcastle), "Metallo-proteins: An inorganic chemists approach".

* 13 Nov. Professor N.N. Greenwood (U. of Leeds), "Metalloborane chemistry".

* 4 Dec. Rev. R. Lancaster, "Fireworks".

* 22 Dec. Professor E.A. Dawes (U. of Hull), "Magic and mystery through the ages".

*29 Jan. Mr. H.J.F. MacLean (I.C.I. Agricultural Division), "Managing the chemical industry in the 1980s".

*5 Feb. Professor F.G.A. Stone (U. of Bristol), "Chemistry of carbon to metal triple bonds".

*12 Feb. Dr. I. Fleming (U. of Cambridge), "Some uses of silicon compounds in organic synthesis".

17 Mar. Professor W.P. Jencks (Brandes U., Massachusetts), "When is an intermediate not an intermediate?".

7 May. Professor M. Gordon (U. of Essex), "Do scientists have to count?".

Research Conferences Attended

3rd Annual Congress of the Chemical Society, Durham, 9-11 April 1980.

9th International Symposium on Fluorine Chemistry, Avignon, France 3-7 September 1979

Postgraduate Induction Course

In each part of the course, the uses and limitations of the various services available were explained by those responsible for them.

Departmental organisation	- Dr E.J.F. Ross
Electrical appliances and infrared spectroscopy	- Mr. R.N. Brown
Chromatography and microanalysis	- Mr. T.F.H. Holmes
Atomic absorption spectrometry and inorganic analysis	- Mr. R. Coult
Mass spectrometry	- Dr. M. Jones
N.M.R. spectrometry	- Dr R.S. Mathews
Glassblowing techniques	- Mr. W.H. Fettis and Mr R. Hart
Safety matters	- Dr. D.L.H. Williams

ORGANIC CHEMISTRY SEMINARS 1979-80

Seminars will be held on Wednesdays at 1.30 p.m. in CG.125.

12th December	C.G.P. Jones "Nucleophilic Addition to Acetylenes"
19th December	M.J. Silvester "Radical Cations"
16th January	B. Grievson "Substituent Effects in Free Radical Reactions"
23rd January	J.R. Kirk "Reactions of Fluoride Ion"
30th January	D. Wallis "Thermal Reactions of Pentafluorophenylallyl-sulphides"
6th February	P.A. Martin "Catalysis Reactions on Solid Surfaces"
13th February	R.N. Barnes "Reactions of Singlet Oxygen"
20th February	Prof. R.D. Chambers "Superacids in Organic Chemistry"
27th February	Dr. C.R. Sargent. Title to be Announced
5th March	Dr. G.M. Brooke. Title to be Announced

P.A. Martin/R.N. Barnes

APPENDIX 5

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REFERENCES

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