Kinetics and mechanism for nucleophilic substitution in some polyfluoroaromatic compounds

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A THESIS

entitled

KINETICS AND MECHANISM FOR NUCLEOPHILIC SUBSTITUTION IN SOME POLYFLUOROAROMATIC COMPOUNDS

submitted by

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To my Mother and Father

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MEMORANDUM

The work described in this thesis was carried out at the University of Durham between October 1970 and October 1973. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

'There are more things in heaven and earth, Horatio,

Than are dreamt of in your philosophy.'

Hamlet, Act 1, Scene V.

SUMMARY

Rate measurements for the reactions of a series of polyfluoro- and polychloro-pyridines with ammonia in 60/40 dioxan/water at 25° 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 group was also found to be activating relative to fluorine when ortho and para to the point of substitution, but to a much greater extent than chlorine.

Under the same conditions, the reactivities of 2,4,5,6-tetrafluoro- and 2,4,6-trifluoro-pyridine were found to be much less than that of pentafluoro-pyridine, and from the product mixture obtained from the former compound (resulting from attack at the 4- and 6-positions), hydrogen was found to deactivate a position ortho to itself relative to fluorine (c. x 30) but para to the point of attack, hydrogen is slightly activating relative to fluorine (c. x 3). This appeared to be at variance with the currently accepted theories of substitution in polyfluoro-aromatic compounds, in which the proposed destabilising effect of the para fluorine is emphasised in determining orientation of substitution. These results obtained for the pyridines, together with previously measured rate constants for the reaction of hydrofluoropyridines with methoxide ion in methanol at 50°, led to the conclusion that attack occurs in such a position as to maximise the possible number of ortho and meta fluorine atoms with a para fluorine being of comparatively little significance.

Rate measurements for the reactions of the tetrafluorodiazines with ammonia in 60/40 dioxan/water at 25° showed the following reactivity sequence: tetrafluoropyrimidine > tetrafluoropyridazine > pentafluoropyridine > tetrafluoropyrazine. Both tetrachloropyrimidine and tetrachloropyridazine

were found to react at a much slower rate than the corresponding tetrafluorodiazine. Under the same conditions, the reactivities of the 2- and 4-positions of heptafluoroquinoline and the 1-position of heptafluoroisoquinoline were found to be similar with a factor of 2 or 3 and these reactivities were less than an order of magnitude greater than that of pentafluoropyridine.

Kinetic investigations into the reactions of the polychlorofluoropyridines used for the reactions with ammonia, with diethylamine in dioxan at 25°, revealed that in these reactions, chlorine is deactivating relative to fluorine when ortho to the point of attack; this is accounted for by steric effects. Relative to fluorine, however, a para chlorine was found to be activating by the same factor as for the reactions with ammonia, and a meta chlorine and fluorine were also found to have a similar effect on reactivity.

Rate measurements for the reactions of perfluorotoluene, perfluoroethylbenzene, perfluoroisopropylbenzene and perfluoro-t-butylbenzene with ammonia in 77/23 dioxan/water at 92°, showed these compounds to have similar reactivities, within a factor of 3 or 4, but their reactivities were several orders of magnitude greater than that of pentafluorobenzene. The order of reactivity was found to be perfluoro-t-butylbenzene > perfluoroethylbenzene > perfluoroisopropylbenzene > perfluorotoluene. From these results it was concluded that the process of fluoride ion hyperconjugation was unimportant in the reactions, and that the similarities in activating powers of the perfluoroalkyl groups could adequately be accounted for by their similar inductive effects.

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INTRODUCTION

CHAPTER 1

NUCLEOPHILIC AROMATIC SUBSTITUTION

It is only over the past twenty five years that intensive investigation has been carried out generally in the field of nucleophilic aromatic substitution. Prior to that time the term 'aromatic substitution' tended only to imply electrophilic reactions, such as nitration, sulphonation and halogenation of the benzene ring. Unlike electrophilic aromatic substitution reactions, hydrogen is seldom displaced in nucleophilic substitutions. In order for a group to be easily replaceable it must be able to accept an extra electron pair, and exist as a stable anion; halogen substituents are thus readily replaced in activated systems. On account of this, most of the reactions in the following discussion will be concerned with displacements of halide ions.

1.1 Mechanisms of Nucleophilic Aromatic Substitutions

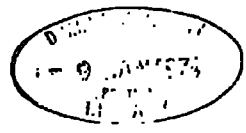
Nucleophilic aromatic substitution reactions have been found to occur by three different mechanisms: these are

(a) a two-step elimination-addition or 'benzyne' process encountered for reactions of 'unactivated' substrates with powerful nucleophiles;

(b) a S_N1 mechanism, analogous with the S_N1 mechanism in aliphatic reactions;

(c) a bimolecular process which appears to be the most common process for reactions in 'activated' systems.

Each of these mechanisms will be discussed in turn; the first two briefly, as these are least frequently encountered, while fuller discussion



will be given to the bimolecular process, as nucleophilic reactions of polyhalo-aromatic compounds, including perfluoro compounds, can be explained by this mechanism.

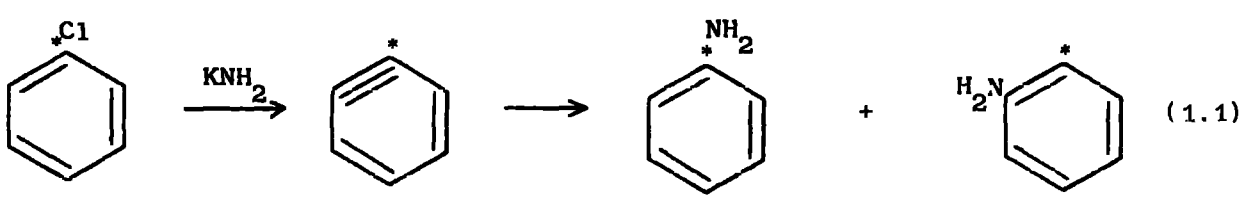
1.1.1 Elimination-Addition Mechanism

Simple aromatic compounds which do not contain an electron-withdrawing activating group such as NO_2 are unreactive towards nucleophiles.[1] Chlorobenzene reacts with aqueous sodium hydroxide to give high yields of phenol only at temperatures above 300°.[2]

This reaction, and other reactions under very basic conditions such as the reaction of phenyl lithium and fluorobenzenes to form biphenyl[3] and that of chlorobenzene and potassamide in liquid ammonia to form aniline,[4] occur by a two step elimination-addition mechanism. The first stage of the reaction is the elimination of HX from the aromatic nucleus by the strongly basic nucleophile to form the intermediate 'benzyne' (I).

(I)

Evidence for the occurrence of a benzyne intermediate has been found in reactions such as the following. the reaction of [1-^{14}C]chlorobenzene with potassamide in liquid ammonia gives [1-^{14}C]aniline and [2-^{14}C]aniline[4] in almost equal concentration. The following route involving a benzyne intermediate was proposed[4] (Equation 1.1).



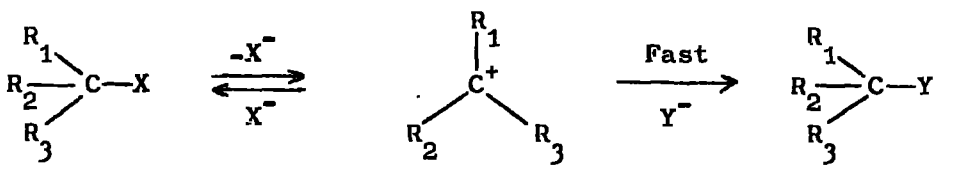
(1.1)

The initial step in the formation of the intermediate has been shown to involve proton abstraction.[5] With potassamide in liquid ammonia, 2-d-fluorobenzene exchanges deuterium for hydrogen, but is otherwise unchanged; 2-d-bromobenzene does not exchange its deuterium without losing bromine; and 2-d-chlorobenzene can both exchange its deuterium without losing chlorine, and lose chlorine as well.[5] This shows that the anion formed by initial proton (or deuteron) abstraction can either remove a proton from the solvent, or eliminate halide ion, forming a benzyne intermediate, from which the amino product is formed.

Further evidence for the postulation of a benzyne intermediate arises from the fact that halobenzenes not possessing ortho hydrogen atoms are unreactive towards strongly basic nucleophiles. 2-Bromo-3-methylanisole[6] does not react with sodamide in liquid ammonia, whereas bromobenzene does.

1.1.2 S_N1 Mechanism

S_N1 reaction occur with aliphatic compounds by the following mechanism[7] (Equation 1.2).

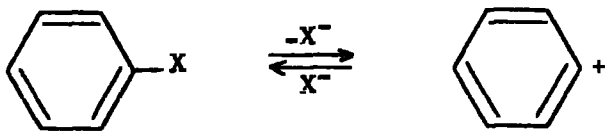


(1.2)

(II)

The intermediate carbonium ion (II) is stabilised by electron releasing substituents on the central carbon atom by an inductive effect (e.g. for methyl groups) or a mesomeric effect (e.g. for phenyl groups). The rate of formation of the carbonium ion is generally the slow, rate determing step, and reactions often have first order kinetics.

An analogous mechanism for an aromatic compound would be as follows (Equation 1.3).



(1.3)

(III)

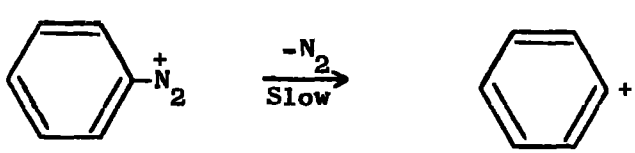
A reaction scheme of this nature would be expected to be energetically very unfavourable for several reasons.[8] Stabilisation of the intermediate cation (III) by the π electrons of the ring is impossible as the singly occupied sp^2 orbital at the reaction centre is in the plane of the ring, whereas the p electrons of carbon forming the delocalised system are perpendicular to it.[9]

The positive centre of (III) is less exposed for solvent stabilisation than its aliphatic counterpart (II),[8] and also bonds to common leaving groups are stronger in Ar-X system than in Alph-X systems.[8]

The only aromatic reactions which appear to operate by an S_N1 mechanism as in Equation 1.3 are the nucleophilic displacement reactions of the diazonium groups of aromatic diazonium salts.[8,10] The driving force behind these reactions is the stability of the elemental nitrogen displaced.

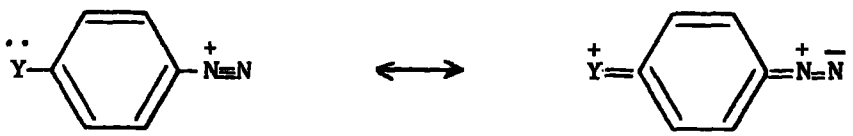
Such reactions in aqueous solution have first order kinetics.[6,11,12] Evidence for a unimolecular process is derived from the fact that the rate of reaction does not depend upon the concentration or identity of anions in solution,[11,12] even though they are incorporated into the products.[11,12]

The reactions may be represented as in Equation 1.4, in which the rate determining step is the formation of the cationic intermediates, which reacts rapidly with water, or with whatever anions are present, to form the product.



(1.4)

The effects of substituents on reaction rates are generally in accord with the proposed mechanism. In the meta position, electron-releasing groups increase the rate of reaction, while electron-attracting groups cause deceleration of rate.[12] In the para position both electron donating and attracting groups retard the reaction rate.[13] The deceleration caused by electron donating groups has been explained[9] as arising from conjugative stabilisation of the initial state leading to double bond character of the C-N bond, which is strengthened (structures IV and V).



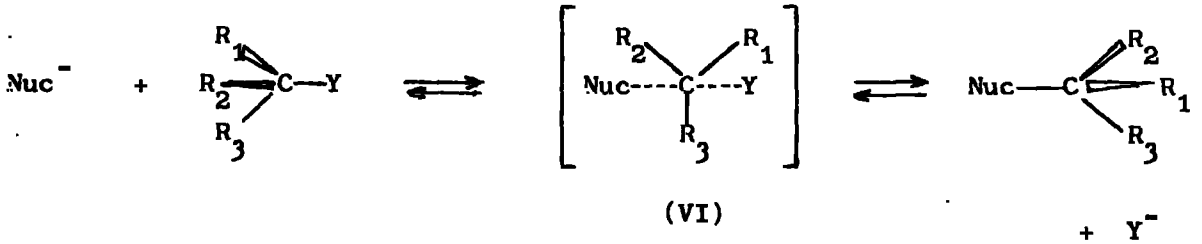
(IV) (V)

1.1.3 Bimolecular Mechanism

(a) Possible Mechanisms

When the aromatic nucleus contains electron attracting groups, nucleophilic substitution occurs fairly readily and the reactions frequently have second-order kinetics, which is indicative of a bimolecular mechanism.

S_N2 displacement reactions in aliphatic compounds pass through a transition state which can be represented as (VI).[13]



(VI)

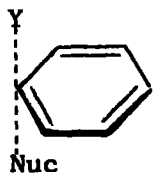
The nucleophile approaches the molecule on the opposite side to the leaving group Y, and in the transition state Nuc and Y are positioned linearly about the central carbon atom: the hybridisation of the central carbon atom changing from sp^3 to sp^2 in the transition state, with the remaining p orbital

used for forming half-bonds to Y and Nuc.

For bimolecular reactions of aromatic compounds with nucleophiles there are two obvious possibilities for the course of the reaction. These will now be discussed.

(i) <u>One Step Process</u>

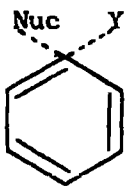
By analogy with the aliphatic S_N2 reactions, a transition state could occur in which partial bonds are formed from the carbon atom at the point of substitution to both the nucleophile and leaving group (Y), all three being co-linear, with the aromaticity of the benzene ring retained. Such a transition state is represented as (VII).



(VII)

This is highly unlikely since in (VII) the p orbital used for partial bond formation is the one used in the π-system.

A further possibility exists in which nucleophile and Y are at an angle to the central carbon atom in a plane perpendicular to that containing the benzene ring (structure VIII).



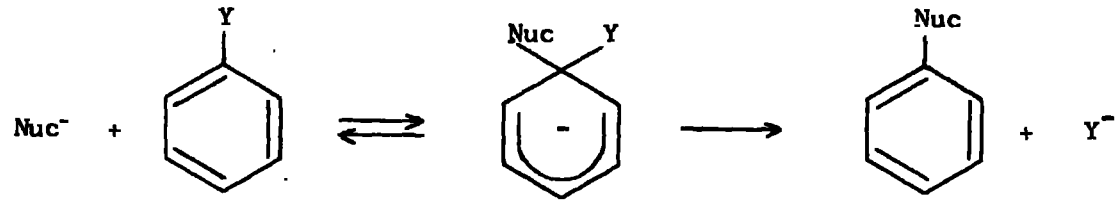
(VIII)

The sp^2 orbital used for the C-Y bond would be used to form the two half bonds: this again is highly unlikely. The sp^2 orbital is in the plane of the benzene ring and is directed at neither Nuc nor Y, and any bending of

the orbital towards Nuc or Y would cause it to adopt some of the nature of a p orbital which is used in the π-system: this would be a violation of the Pauli Principle.[1]

(ii) Two Step Process

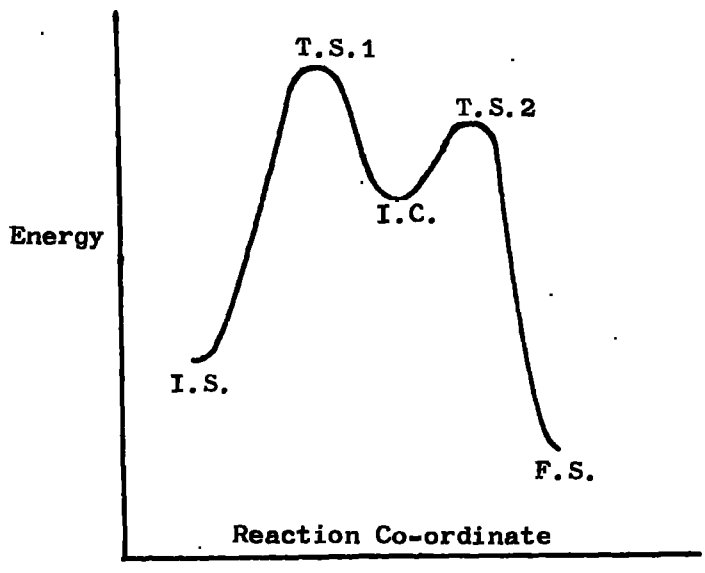
A different possibility is that the attacking nucleophile forms a fully bonded intermediate with the aromatic system, with the negative charge delocalised in the ring. This is represented as structure (IX).



(IX)

The central carbon atom would be sp^3 hybridised and such a species, by its nature, would be an intermediate, not a transition state. The mechanism would then be a two-step addition-elimination process. This process would be more favourable if electron-attracting groups are substituted in the benzene ring to stabilise the negative charge.

The reaction would have two transition states (T.S.1 and T.S.2), one on each side of the intermediate complex. This is represented on an energy profile diagram (Figure 1.1).



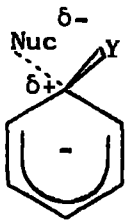
I.C. = Intermediate Complex

I.S. = Initial State

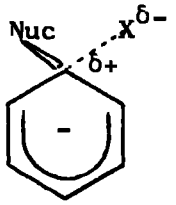
F.S. = Final State

Figure 1.1

The structures of T.S.1 and T.S.2 may be represented as (X) and (XI) respectively.



(X)



(XI)

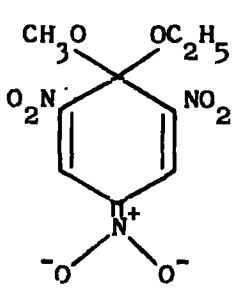
The relative energies of the two transition states will depend upon the reaction. If the energy of T.S.1 is greater than that of T.S.2, the formation of the intermediate will be rate determining. Alternatively, if the energy of T.S.2 is greater than that of T.S.1, the rate limiting step will be the dissociation of the intermediate to give the product.

Phenomena association with nucleophilic substitution in activated aromatic compounds can be most easily explained by invoking the two-step addition-elimination mechanism, and evidence for its general occurrence will now be discussed.

(b) Evidence for Intermediate Complex Formation

(i) Isolation of Intermediates

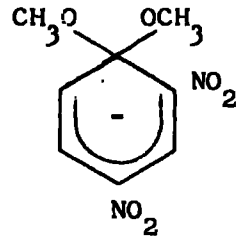
In highly activated systems complexes of similar structure to (IX) have been isolated. Meisenheimer[14] isolated a red salt on the addition of potassium ethoxide to 2,4,6-trinitroanisole, and assigned a structure to it represented by (XII).



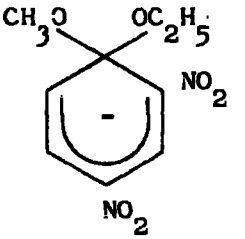
(XII)

The same salt was also obtained on adding potassium methoxide to 2,4,6-trinitrophenetole.[14]

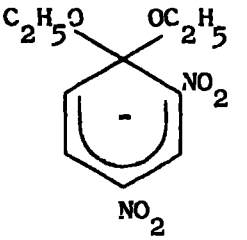
More recent work[15,16] on dinitro substituted benzenes has shown that various complexes isolated have the following structures (XIII - XV).



(XIII)



(XIV)



(XV)

(ii) Leaving Group Mobilities

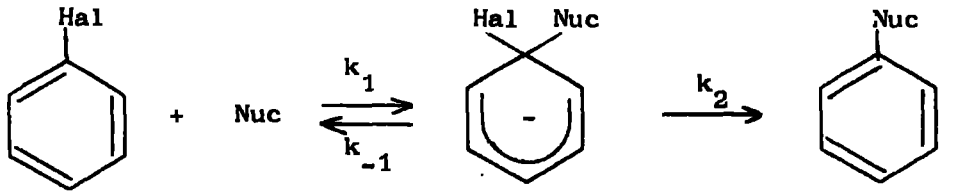
Halide ion mobilities: This term refers to the relative ease of displacement of halide ions in substitution reactions.

In nucleophilic aromatic substitution reactions the observed ease of displacement of halide is generally F >> Cl > Br > I. There are numerous reactions in which this reactivity order has been found, for example the reaction of ortho and para nitrophenylhalides with methoxide ions in methanol.[17-19] The difference in reactivity between a fluoride and 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 the reaction of 2,4-dinitrochlorobenzene.[20]

This order of mobility is the reverse order of the carbon-halogen bond strengths,[21] and hence cannot be accounted for by a concerted one-step mechanism as in aliphatic S_N2 substitution, in which bond breaking in the transition state leads to the reaction rate being proportional to the carbon-halogen bond strength i.e. the order of mobility is I > Br > Cl > F.[22]

If no carbon-halogen bond breaking is occurring in the rate determining step, the mechanism can only be explained by an addition-elimination process

in which the rate determining step is the rate of formation of the intermediate[10] (Equation 1.5). (No substituents apart from Hal are shown).



(1.5)

If the rate of formation of intermediate is rate determining the rate of reaction will depend upon the rate of formation of the carbon-nucleophile bond. This is likely to be greater for the fluoride than for the other halide compounds as the greater electronegativity of fluorine[23] will lead, in the initial state of the molecule, to a greater polarisation of the carbon-halogen bond than is the case for the other halogens. The increased positive charge on the carbon atom will increase the rate of nucleophilic attack.[19,24]

In some reactions, as in that between 1-halo-2,4-dinitrobenzenes and N-methylaniline in nitrobenzene,[25] the rate of halide ion displacements is reversed, and the order of reactivity becomes I > Br > Cl > F. Further examples showing the reactivity order I > F are the reaction of iodide ions with 1-halo-2,4-dinitrobenzenes in acetone[26] and the reaction of thiophenoxide and 1-halo-2,4-dinitrobenzenes in methanol.[27]

It has been proposed[26,28] that reactions, in which the fluorides are the least reactive of the halides, operate by a one-step concerted mechanism in which bond breaking is occurring in the rate determining step. The reactions can, however, be readily explained in terms of the addition-elimination mechanism (Equation 1.5),[29,30] in which the rate limiting step is now the dissociation of the intermediate to give the product. It has been suggested[30] that in the case where the nucleophile is iodide ion the intermediate complex of Equation 1.5 would lose iodide faster than fluoride

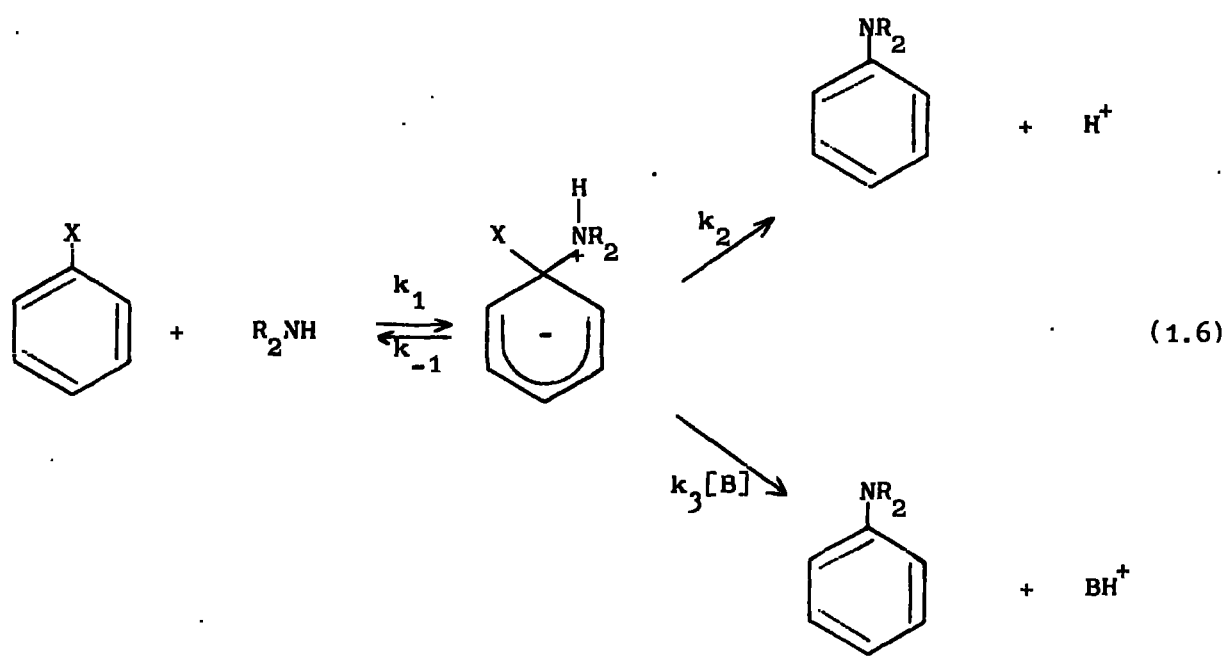
(differences in bond strength) thus lessening the value of k_2 to such an extent that the second step, in which the C-F bond is broken, becomes rate determining.

Mobilities of other groups: Studies on the reactions of 1-substituted-2,4-dinitrobenzenes with piperidine,[29] in which the substituents are Cl, Br, I, SOPh, SO_2Ph and $O\text{-}C_6H_4\cdot pNO_2$, have shown that the rate constants for the reactions are very similar; the maximum variation being less than a factor of five. There are great differences in bond strengths between carbon and each substituent, and 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.

(iii) Base Catalysis

When nucleophiles are amines reactions are sometimes found to be base catalysed. Rate enhancements can be due to the amine itself[29,30,33] or other bases apart from the nucleophile such as hydroxide ion and acetate ion.[29-32]

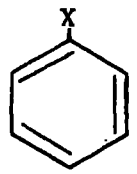
To account for base catalysis the two-step mechanism has been slightly modified in that the formation of product from the intermediate can be base-assisted[30,34] (Equation 1.6).



(1.6)

The base, B, can be either the amine itself or an extra added base.

An expression for the observed rate constant, k_A, can be obtained as follows.

S =  , I = intermediate complex

$$\text{Rate} = -\frac{d}{dt}[S] = k_1[S][R_2NH] - k_{-1}[I]$$

If the intermediate concentration, [I], is assumed constant, then

$$k_1[S][R_2NH] - k_{-1}[I] - k_2[I] - k_3[I][B] = 0$$

$$[I] = \frac{k_1[S][R_2NH]}{k_{-1} + k_2 + k_3[B]}$$

$$\therefore \quad \text{Rate} = \frac{k_1k_2 + k_1k_3[B][S][R_2NH]}{k_{-1} + k_2 + k_3[B]}$$

$$= k_A[S][R_2NH]$$

$$\therefore \quad k_A = \frac{k_1k_2 + k_1k_3[B]}{k_{-1} + k_2 + k_3[B]}$$

If $(k_2 + k_3[B] >> k_{-1}$,

$$k_A = k_1$$

In such cases, in which k_2 is comparatively very large, the rate constants should be insensitive to base concentration and normal second order kinetics would be observed.

If $k_{-1} >> (k_2 + k_3[B])$

$$k_A = \frac{k_1k_2}{k_{-1}} + \frac{k_1k_3[B]}{k_{-1}} = k' + k''[B]$$

In this instance, where the second step is comparatively slow, the observed rate constant is dependent upon base concentration, and base catalysis is observed.

The sensitivities of amino-dehalogenation reactions to base concentration vary considerably. The reactions of 2,4-dinitrofluorobenzene with n-butylamine and aniline in alcohol/ or dioxan/water solvents are not base catalysed,[35] while the reactions of 2,4-dinitrofluorobenzene with amines in benzene are so subject to base catalysis that they are virtually second order in base concentration under most conditions.[33,36,37]

A measure of the magnitude of base catalysis is obtained from the ratio k''/k'.[35] Where base catalysis does occur, the effect is much greater for fluoro-compounds than for the corresponding chloro-compounds.[34,35] A value of 150 for k''/k' has been found for the reaction of N-methylaniline with 2,4-dinitrofluorobenzene in ethanol, when catalysed by added acetate ion,[30] and an even higher value of 350 was calculated for the same reaction in 60% dioxan - 40% water.[30] For reactions of chloro-compounds which have been found to be sensitive to base concentration, values of k''/k' are normally no higher than about 4.[35]

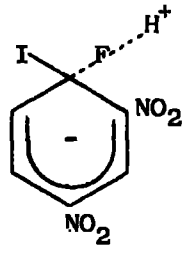
(iv) Acid Catalysis

The type of acid catalysis discussed here is that which causes rate enhancement in reactions of activated (i.e. nitro) fluorobenzenes with nucleophiles.

In order to observe such acid catalysis it is necessary to use a nucleophile which is virtually unaffected by the presence of hydrogen ions.

It has been found[38] that the rate of reaction of 2,4-dinitrofluorobenzene with iodide ion in methanol increases by a factor of 5×10^5 in using hydroiodic acid instead of potassium iodide. This is explained[38] 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 for the transition state is shown below (XVI).



(XVI)

1.2 Electronic Effects of Substituents in Bimolecular Nucleophilic Substitution Reactions

This discussion is concerned with electronic interactions between substituents in the aromatic nucleus and the electrons of the nucleus, and how these interactions affect the rate of nucleophilic aromatic substitution.

There are two methods by which electronic effects can be transmitted through a molecule. The first of these, the inductive effect, is where a substituent X causes polarisation of the electrons of the σ C-X bond due to differences in electronegativity between carbon and X. This polarisation of charge is then transmitted through the σ bonds of the molecule by displacement of the electrons of the σ bonds:

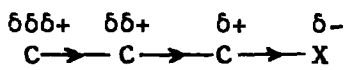
$$C \rightarrow C \rightarrow C \rightarrow X$$

The arrows represent flow of charge in the direction of the arrows.

In the case shown, X is electron attracting and causes the carbon atoms to become electron deficient: this is called the -I effect. Examples of groups having a -I effect are[39] halogens, OH, NO_2, $\overset{+}{N}H_3$ and CN.

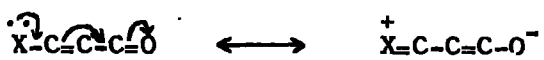
Groups which donate electronic density by the inductive effect (+I) include[39] CH_3 and CO_2^-.

The magnitude of the inductive effect decreases as the distance from the substituent increases. The charge distribution in a molecule caused by a -I group can be represented as follows:[40]



When inductive electronic interactions between parts of molecules occurs 'through space' as opposed to via sigma bonds, the process is known as a field effect.

The second method of electronic interaction is the resonance or mesomeric effect. Where a group is able to donate an electron pair to a conjugated system, it is said to have a +M effect. Examples of groups of this class are[40] NH_2, OH, O^- and halogens. The effect can be represented as follows:



Groups which are able to accept electrons from a conjugated system have a -M effect and include NO_2, C=O, CHO and C N.

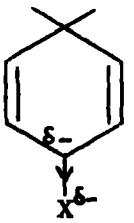
Unlike the inductive effect, the mesomeric effect in a conjugated system does not decrease with distance from the electron donating or withdrawing group.

1.2.1 Para-Substituent Effects

(a) Activating Groups

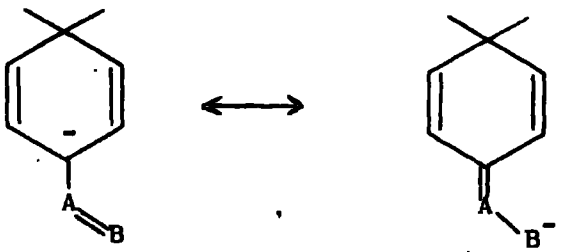
Groups in the position para to the point of substitution in nucleophilic aromatic substitution reactions can activate the system by stabilisation of the anionic transition state by either an inductive or mesomeric effect. Inductive stabilisation involves the increase in electronegativity of the carbon atom to which the substituent X is attached and on which negative charge in the transition state is located. Such a stabilised transition state

is (XVII).



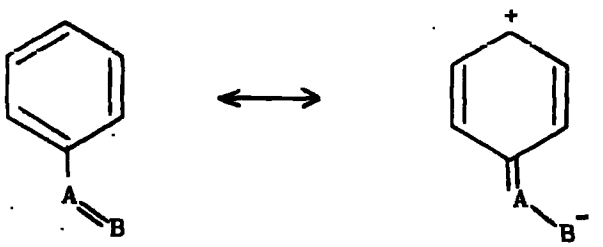
(XVII)

Mesomeric stabilisation can be achieved by a group -A=B (-M) which can delocalise the negative charge as in (XVIII)



(XVIII)

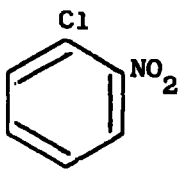
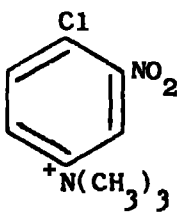
Another important activating factor is the effect of -I groups and -M groups on the initial state of the aromatic nucleus: any increase in the electrophilicity of the carbon atom as the point of substitution will increase the rate of attack of nucleophile. As the para position is the furthest point in the nucleus from the position of attack, the mesomeric effect is likely to be more important than the inductive effect. Mesomeric interaction in the ground state of the molecule is represented as (XIX).



(XIX)

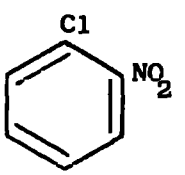
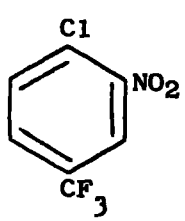
Inductive activation: A group which is able to interact with a negative charge solely by an inductive effect is $\overset{+}{N}Me_3$. A measure of its activating effect in the para position has been obtained[41] by comparison of the rate constants for the reactions of 4-trimethylammonium-2-nitrochlorobenzene and 2-nitrochlorobenzene with methoxide ions in methanol at 25°. Values are shown in Table 1.1

TABLE 1.1

Substrate	k(l.mole^{-1}sec^{-1})
	1.5×10^{-7}
	8.23×10^{-4}

The CF_3 group has also been found to be inductively activating. Table 1.2 shows the rate constants for the reactions of 2-nitrochlorobenzene and 4-(trifluoromethyl)-2-nitrochlorobenzene with methoxide ions in methanol at 50°.

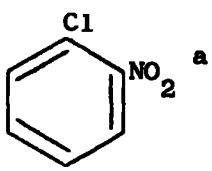
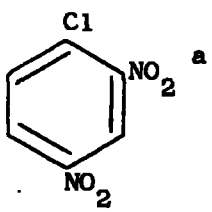
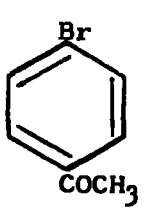
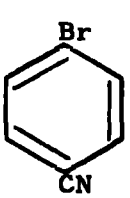
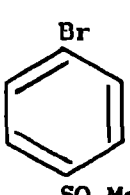
TABLE 1.2

Substrate	k(l.mole^{-1}sec^{-1})
	2.52×10^{-6}
	2.50×10^{-3}

Mesomeric activation: Examples of groups able to cause activation by the mesomeric effect are:

Table 1.3 shows the values of rate constant obtained for reactions of p-substituted systems with nucleophiles. In each case halogen is displaced.

TABLE 1.3

Substrate	k(l.mole^{-1}sec^{-1})	Ref.
 a	0.363×10^{-5}	43
 a	14.9×10^{-2}	43
 b	64.5×10^{-7}	44
 b	0.86×10^{-7}	44
 b	1.98×10^{-7}	44
 b	3.40×10^{-7}	44

a reaction with methoxide in methanol at 50°

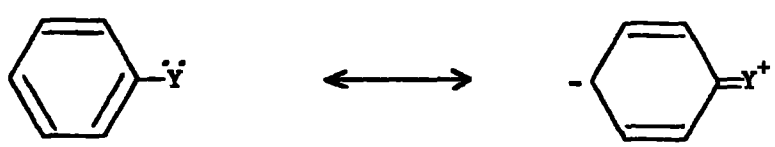
b reaction with piperidine in benzene at 99°

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

(b) Deactivating Groups

Anionic transition states can be destabilised, and the system deactivated, by electron donating groups in the para position. This can be achieved by groups having a +I inductive effect such as methyl, or a +M mesomeric effect such as amino and methoxy groups.

Ground state effects are also important. An electron-releasing (+M) group $\ddot{Y}$ can interact with the benzene ring giving the following resonance structures (XXa and XXb).

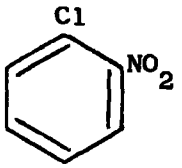
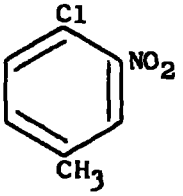


(XXa) (XXb)

The increased negative charge on the carbon atom at the point of substitution will hinder nucleophilic attack. Structures such as (XXb), where Y = NH_2, have been used to explain the low basicity of aniline.[39]

Inductive 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°[42] are shown in Table 1.4.

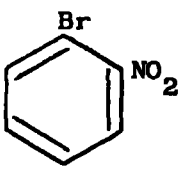
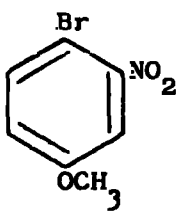
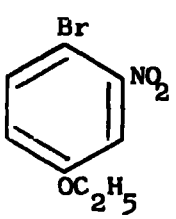
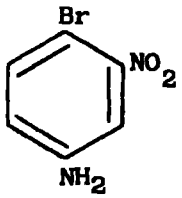
TABLE 1.4

Substrate	$k(l.mole^{-1}sec^{-1})$
	2.52×10^{-6}
	2.99×10^{-7}

Mesomeric deactivation: Groups which cause deactivation by mesomeric effects include NH_2, OCH_3, and OC_2H_5. Although found to be deactivating with respect to hydrogen, they have a -I effect,[39] which in itself would stabilise a negative charge. The effect is however swamped by the +M interaction.

Table 1.5 shows rate constants of reactions of some deactivated p-substituted-2-nitrobromobenzenes with piperidine in piperidine at 25°.[45]

TABLE 1.5

Substrate	$k(min^{-1})$
	2.90×10^{-3}
	5.22×10^{-5}
	4.38×10^{-5}
	3.60×10^{-7}

1.2.2 Ortho-Substituent Effects

As negative charge in the transition state is localised at positions ortho and para to the point of substitution, electronic effects in the transition state at the ortho and para positions are hence likely to be very similar. The previous discussion about substituent stabilisation and destabilisation at the para position is applicable to substituents at the ortho position, so it is expected that groups which activate with respect to hydrogen at the para position will also activate at the ortho position, and likewise by deactivating groups.

In the ortho position the +I methyl group is deactivating[46] and the -I trifluoromethyl group is activating.[46] The -M groups, NO_2,[47] CN,[48] $COCH_3$[49] and SO_2CH_3[49] are found to be activating towards nucleophilic attack, while the +M groups NH_2,[47] OCH_3[50] and OC_2H_5[50] are deactivating.

The ortho and para positions are, however, not entirely equivalent. The close proximity of the substituent in the ortho position to the point of substitution means that inductive effects are likely to be greater than at the para position, and steric effects caused by a bulky substituent will also be present. In the ortho position there is also the possibility of interaction of the substituent with the nucleophile.

Ortho steric effects: A measure of the activating or deactivating power of a substituent can be obtained from the relative rate constant. This is the ratio of rate constant of the substituted to that of the unsubstituted system.

Ortho steric effects of -COX groups have been investigated by comparison of relative rate constants for reactions of 2-COX-4-nitrochlorobenzenes and 2-nitro-4-COX-chlorobenzenes with methoxide ion in methanol at 50°. The results are shown in Table 1.6.

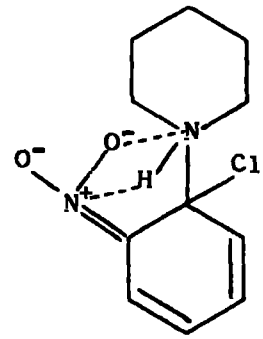
TABLE 1.6

Substituent	Relative Rate Constants		Ref.
	Para	Ortho	
H	1	1	49
CO_2Me	1560	174	49
COMe	1990	246	49
COPh	1655	21·6	49
CHO	2240	285	48

The lower relative rate constant caused by the substituent in the ortho position as compared to that in the para position is accounted for in terms of steric effects.[49]

The nitro group itself has been found to be less activating (by factors of between 2 and 4) in the ortho than in the para positions, for reactions of 2- and 4-nitrohalobenzenes with methoxide in methanol.[17,18] This again can be accounted for by the adverse steric effect of the nitro group in the ortho position.

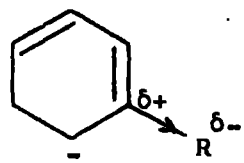
Substituent-nucleophile interactions: For reaction with piperidine in a variety of solvents ortho-nitrochlorobenzene has been found to react faster than para-nitrochlorobenzene.[51,52] In changing solvents from 75% methanol to benzene the rate constant of the o-nitro compound remained virtually constant while that of the p-nitro compound was reduced by a factor of 20.[51] These facts are explained[51,52] by 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 (XXI). For p-nitrochlorobenzene such interaction is not possible so that rate constants will be more greatly affected by solvent solvation, which will be less for benzene than for 75% methanol.



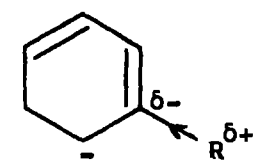
(XXI)

1.2.3 Meta-Substituent Effects

As substituents in the meta position can not interact with the negative charge in the transition state in the ortho or para position by a mesomeric process, the main electronic effects will be inductive. Inductive activation is shown in (XXII) and deactivation in (XXIII) for substituent R.

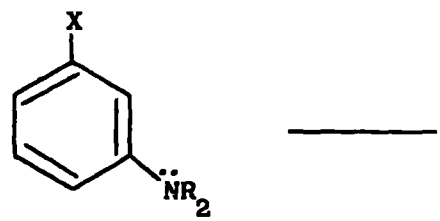


(XXII)

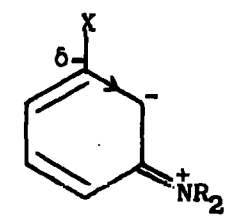


(XXIII)

Inductive relay of resonance effects may also be present. This process is shown in structures (XXIVa) and (XXIVb) for a meta amino substituent interacting with the benzene ring in the ground state.



(XXIVa)

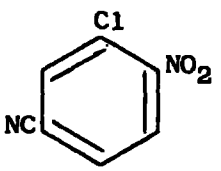
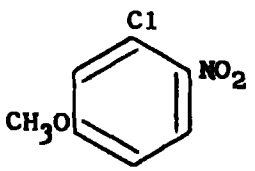
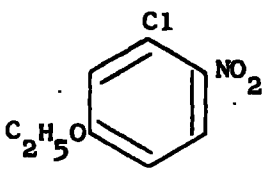
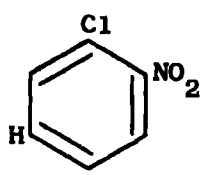
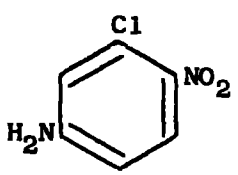
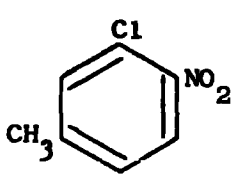


(XXIVb)

The effect of increasing the electron density at the point of substitution by an inductive process, as shown, will deactivate the system towards nucleophilic attack. A corresponding activating effect could arise for a -M substituent.

Investigation into the effect of meta substituents has been carried out in a series of 2-nitro-5-substituted-chlorobenzenes by measurements of rate constants for the reaction with piperidine in benzene at 45°.[43] Some of the values are shown in Table 1.7.

TABLE 1.7

Substrate	$k(l.mole^{-1}sec^{-1}) \times 10^5$
	21·2
	1·52
	1·34
	0·363
	0·311
	0·312

Activation and deactivation effects are not as great as for substituents in the ortho and para positions. The methoxide and ethoxide groups, in contrast to their effects in the ortho and para positions, are slightly activating, indicating that their -I properties are dominant, whereas the amino group is slightly deactivating. The methyl group is also deactivating, as it is in the ortho and para positions, owing to its +I effect.

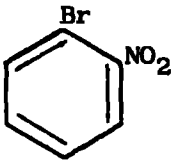
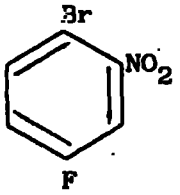
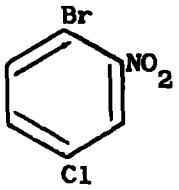
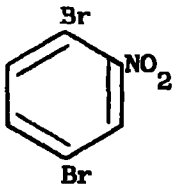
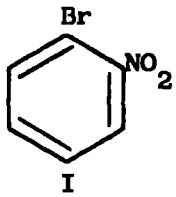
1.2.4 Halogen Substituent Effects

This section is concerned with the electronic effects of halogens as substituents as opposed to their being leaving groups. The -I effect of the halogens, decreasing along the series F < Cl < Br < I i.e. as the electronegativities of the halogen decrease, ought to lead to activation, whereas their +M effect due to their lone pairs would deactivate the system. (A fuller discussion of electronic interactions of halogens, especially fluorine, is given in Section 2.1.2).

(a) Para Postion

Rate constant measurements for the debromination reactions of 4-R-2-nitrobromobenzenes with piperidine in piperidine[45] and dechlorination reactions of 4-R-2-nitrochlorobenzenes with methoxide in methanol[53] (R = halogen or H) have shown chlorine, bromine and iodine to be activating whereas fluorine is slightly deactivating with respect to hydrogen. Table 1.8 shows the measured values for the former set of reactions. Rate constants refer to displacement of bromide.

TABLE 1.8

Substrate	$k(min^{-1})$ at 25°
	2.90×10^{-3}
	7.55×10^{-4}
	1.62×10^{-2}
	2.27×10^{-2}
	1.57×10^{-2}

(b) Ortho Position

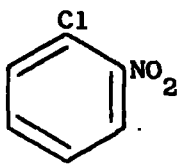
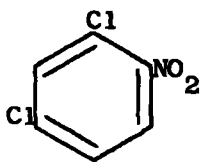
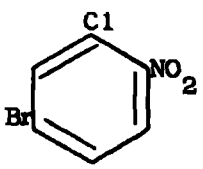
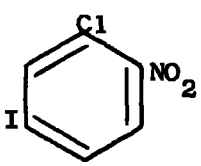
Few results have been published on the effect of halogens ortho to the position of attack. Chlorine has been found to be activating as the rate constant for the reaction of 1,2-dichloro-4-nitrobenzene with methoxide ions in methanol is 12·5 times greater than that for the analogous reaction of 4-nitrochlorobenzene.[54]

(c) Meta Position

Halogens show their greatest activating effect in the meta position[1,55]

where their inductive effects predominate. Table 1.9 shows the values of rate constants obtained for the reaction of 2-nitro-5-R-chlorobenzene (R = halogen or H) with piperidine in benzene at 45°.[43] The rate constants refer to displacement of chlorine ortho to the nitro group.

TABLE 1.9

Substrate	$k(l.mole^{-1}sec^{-1}) \times 10^5$
	0·363
	11·70
	12·50
	9·07

It can be seen that the activation of chlorine, bromine and iodine is greater in this position than in the para position (Table 1.8), and that the effect of the three halogens in the meta position are very similar.

1.2.4 Hammett Equation

In an attempt to relate the structure and reactivity of an aromatic system, Hammett[56] proposed the following expression for reactions in the side chain of para and meta substituted benzene derivatives:

$$\log \frac{K}{K_o} = \rho\sigma$$

K_o and K are the values of rate or equilibrium constants for the reaction of unsubstituted and substituted compounds respectively. The value of σ is a measure of the ability of the substituent to donate or attract electrons and has a negative value if the substituent is a better electron donor than hydrogen, and a positive value if a better electron attractor than hydrogen. The value of ρ is a measure of the susceptibility of the system towards substitution.

The ionisations of substituted benzoic acids in water at 25^o are taken as a standard,[56] and ρ for these reactions defined as unity. The σ value for hydrogen is defined as zero. It is hence possible, by calculation of σ values of various substituents in benzoic acids, to apply these values to the same substituents in other systems and obtain values of ρ for the substrates in question.

For reactions in a side chain, there is no conjugation between the reaction centre and the substituent, so electronic donation or attraction can only be transmitted to the reaction centre by inductive effects.

In reactions in which there is direct conjugation between the substituent and the reaction centre, e.g. for nucleophilic attack at the benzene ring possessing a para nitro group, the Hammett equation does not hold. To take account of mesomeric electron donation or attraction, new values of σ constants, σ^- (sometimes termed σ^*)[56] have been used. The form of the Hammett equation remains the same, but the ionisation of phenols or anilinium ions are usually taken as standard reactions (i.e. $\rho = 1$).

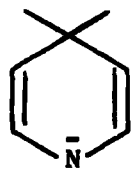
1.3 Nucleophilic Substitution in N-Heterocyclic Aromatic Compounds

1.3.1 General Considerations

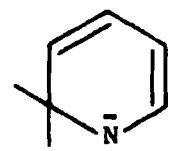
(a) Activation by Aza Group

The aza group, =N-, of heterocyclic aromatic compounds is found to have a profound activating effect in nucleophilic substitution reactions, similar

in magnitude to the effect of the nitro group in benzene systems Like the nitro group, the aza group has its greatest activating effect at positions ortho and para to itself, as at these positions negative charge in the transition state can be located on the nitrogen atom. This is shown for the pyridine nucleus in structures (XXV) and (XXVI).

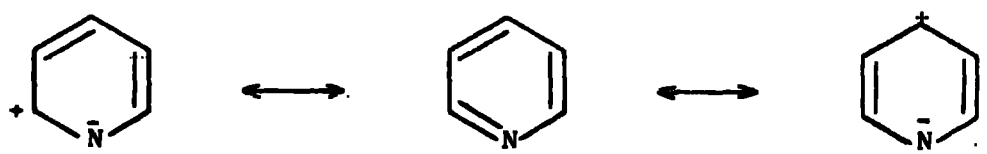


(XXV)



(XXVI)

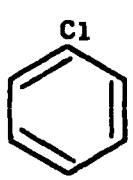
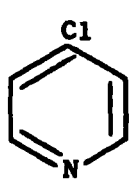
Ground state activation by the nitrogen can also occur, making the ortho and para positions more electrophilic, as shown for pyridine (XXVII).



(XXVII)

Comparison of the activating powers of the aza and nitro groups is shown in Table 1.10 which gives values of rate constants for the reactions with methoxide ions in methanol at 50°. (Values[58] calculated from original data[59]).

TABLE 1.10

Substrate	k(l.mole^{-1}sec^{-1})
	$1{\cdot}20 \times 10^{-16}$
	$8{\cdot}47 \times 10^{-6}$
	$8{\cdot}19 \times 10^{-7}$

The similarity between the activating effects of the aza and nitro groups relative to hydrogen is clearly seen.

(b) Mechanism of Substitution

The majority of nucleophilic substitution reactions in N-heterocyclic aromatic compounds 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 ion mobilities is often found to be F >> Cl as for the reactions of 2-halopyridines and 2-haloquinolines with piperidine in a variety of solvents.[59] Base catalysis has also been found for the reactions of 2-fluoro- and 2-chloro-5-nitropyridine with aniline and piperidine in acetone.[60]

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 give a mixture of 3- and 4-aminopyridine.[61]

(c) Substrate Basicity

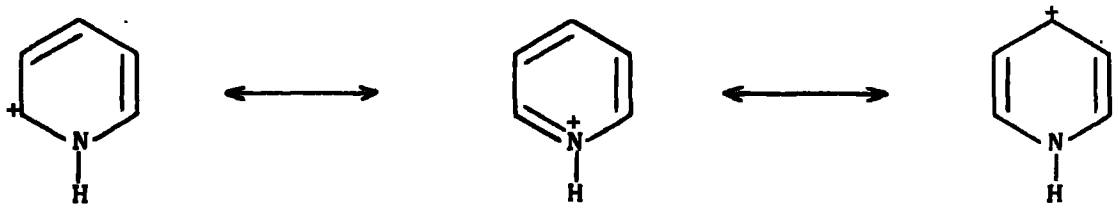
A property of N-heterocyclic compounds, which differentiates them from benzene compounds, is that the aza group of the former renders them basic. Table 1.11 shows the pK_a values for some heterocyclic compounds and their derivatives.

TABLE 1.11

Compound	pK_a	Ref.
Pyridine	5·17	62
Pyrimidine	1·30	63
Quinoline	4·81	64
2-Fluoropyridine	-0·44	63
2-Chloropyridine	0·72	63
4-Chloropyridine	3·71	64

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

Protonation of the ring nitrogen would greatly increase the electrophilicity of the aromatic nucleus (XXVIII).



(XXVIII)

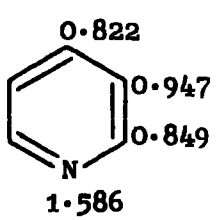
On account of this activation, nucleophilic substitution in these systems might be expected to be acid catalysed: many such cases are known.[1,65] For example, the amino-dehalogenation of pyrimidines has been found to proceed at a much greater rate in acid solution than in alkali.[66]

Nucleophilic substitution in monosubstituted pyridines, diazines, quinolines and isoquinolines will now be discussed in more detail.

1.3.2 Pyridines

As indicated above, the ground state activation of the pyridine nucleus by the nitrogen suggests that nucleophilic attack would be more favourable at the 2- and 4- than at the 3-position.

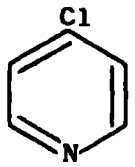
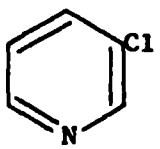
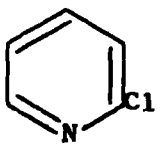
Calculation of the π-electron densities of the atoms of pyridine in the ground state give the values:[67]



Hence by ground state considerations alone, an order reactivity of positions 4 > 2 > > 3 is predicted.

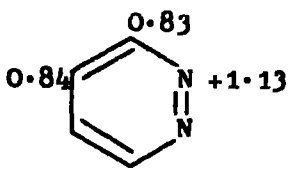
The rate constants shown in Table 1.12 for the reactions of 2-, 3- and 4-chloropyridines with methoxide ions in methanol are in accord with this prediction.[68]

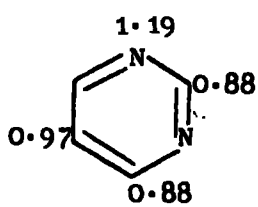
TABLE 1.12

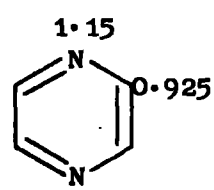
Substrate	$k(l.mole^{-1}sec^{-1})$
	$8{\cdot}91 \times 10^{-7}$
	$1{\cdot}09 \times 10^{-11}$
	$3{\cdot}31 \times 10^{-8}$

1.3.3 Pyrazines, Pyrimidines and Pyridazines

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. π-Electron densities for the three diazines have been calculated to be as follows:[69]



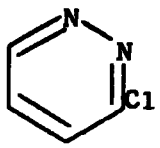
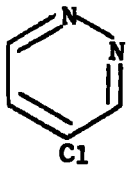
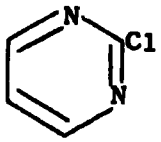
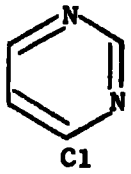
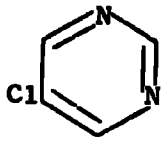
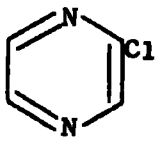
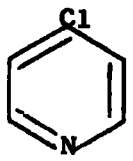
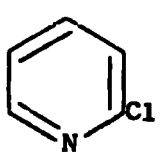




Rate measurements for the reactions of the six chlorodiazines with p-nitrophenoxide in methanol at 50° in the presence of added nitrophenol have been carried out.[69] The results are shown in Table 1.13, together with the

calculated values for the reactions of 2- and 4-chloropyridines under the same conditions.[70]

TABLE 1.13

Substrate	$k(l.mole^{-1}sec^{-1})$
	$1{\cdot}3 \times 10^{-6}$
	$2{\cdot}1 \times 10^{-6}$
	$6{\cdot}9 \times 10^{-4}$
	$1{\cdot}2 \times 10^{-5}$
	$1{\cdot}3 \times 10^{-7}$
	$4{\cdot}5 \times 10^{-6}$
	$3{\cdot}0 \times 10^{-12}$
	$8{\cdot}1 \times 10^{-11}$

As expected the results show a great increase of reactivity in going from the pyridine to the diazo compounds. On the assumption that ortho and para nitrogens are more activating than meta nitrogens it would be predicted that the reactivity of the diazines would be:

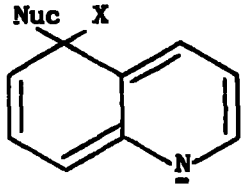
4-chloropyrimidine ~ 2-chloropyrimidine > 3-chloropyridazine ~ 4-chloropyridazine ~ 2-chloropyrazine > 5-chloropyrimidine

This order of reactivity is reflected reasonably well in Table 1.13, except that 2-chloropyrimidine is more than 50 times as reactive as 4-chloropyrimidine. This is accounted for[67] by the fact that the reactions are mildly acid catalysed, owing to the presence of added p-nitrophenol in the reaction mixture, and this catalysis is likely to be more effective at positions α to the ring nitrogen.

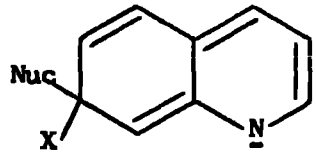
1.3.4 Quinolines and Isoquinolines

(a) Quinoline

For nucleophilic attack in halogenoquinolines, 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 positions 3 and 7 can lead to a transition state in which the charge is placed on nitrogen (XXIX) and (XXX).



(XXIX)



(XXX)

Attack at positions 6 and 8 can not lead to transition states in which negative charge is on the nitrogen. One would then predict a reactivity order for attack at the benzene ring of 5 ~ 7 > 6 ~ 8. As there is only weak conjugation between the two rings formation of (XXIX) and (XXX) would be expected to be not very favourable, and attack at these positions ought to be slower than in the heterocyclic ring.

Rate measurements for the reactions of chloro- and bromo-quinolines with piperidine as both nucleophile and solvent[72] have borne out the above postulates. Table 1.14 shows these rate constants corrected to 50° by Miller,[71] and also the values for 1-bromo- and 2-bromo-naphthalene;[73] and also corrected to 50°;[71] the latter results showing the activation due to the aza group in quinoline.

TABLE 1.14

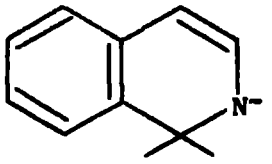
Substrate		$k(mole^{-1}sec^{-1})$
Naphthalene	1-Br	$5{\cdot}62 \times 10^{-13}$
Naphthalene	2-Br	$1{\cdot}15 \times 10^{-12}$
Quinoline	2-Cl	$3{\cdot}52 \times 10^{-6}$
Quinoline	3-Br	$3{\cdot}20 \times 10^{-10}$
Quinoline	4-Cl	$6{\cdot}10 \times 10^{-7}$
Quinoline	5-Br	$7{\cdot}29 \times 10^{-11}$
Quinoline	6-Br	$5{\cdot}67 \times 10^{-11}$
Quinoline	7-Br	$6{\cdot}55 \times 10^{-10}$
Quinoline	8-Br	$5{\cdot}66 \times 10^{-10}$

The fact that 2-chloroquinoline is more reactive than 4-chloroquinoline is accounted for by the hydrogen in position 5, which sterically hinders attack at position 4.[71]

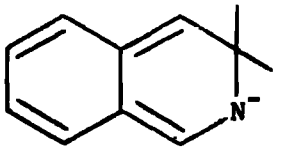
(b) Isoquinoline

By analogy with the quinoline system, the positions most susceptible to nucleophilic attack in isoquinoline ought to be those α to the nitrogen (i.e. positions 1 and 3). Rate measurements for the reactions of ethoxide ions in ethanol at 20° with 1-chloroisoquinoline and 3-chloroisoquinoline give rate constant values of $6{\cdot}90 \times 10^{-7}$ $l.mole^{-1}sec^{-1}$ and $1{\cdot}20 \times 10^{-11}$ $l.mole^{-1}sec^{-1}$ respectively.[28]

The much lower value for attack at position 3 than for position 1 can be explained by consideration of the transition states. In the transition state for attack at position 1 (XXXI) negative charge can be localised on nitrogen without loss of aromaticity in the benzene ring, whereas localisation of negative charge on nitrogen for attack at position 3 (XXXII) destroys the aromaticity of the benzene ring.



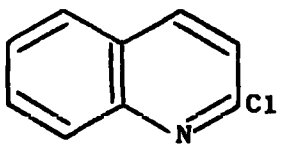
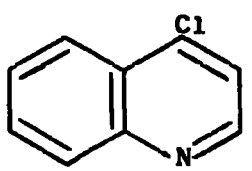
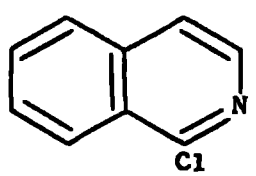
(XXXI)



(XXXII)

Great similarities in the reactivity of 2-chloro- and 4-chloro-quinoline and 1-chloroisoquinoline have been found for their reactions with ethoxide ions in ethanol at 20°,[28] (Table 1.15).

TABLE 1.15

Substrate	$k(l.mole^{-1}sec^{-1})$
	$6{\cdot}30 \times 10^{-7}$
	$6{\cdot}50 \times 10^{-7}$
	$6{\cdot}90 \times 10^{-7}$

CHAPTER 2

NUCLEOPHILIC ATTACK IN POLYHALO-AROMATIC COMPOUNDS

A. Polyfluoro-aromatic Compounds

2.1 Polyfluorobenzenes

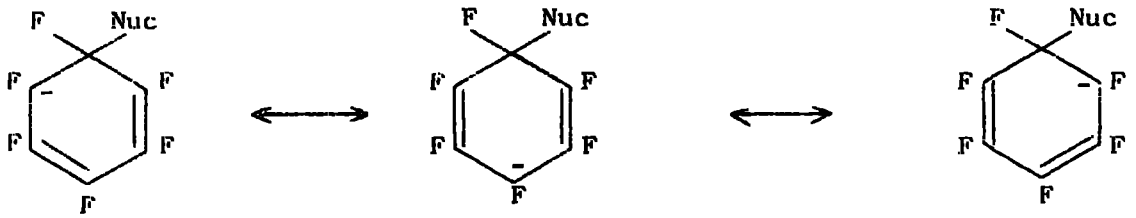
2.1.1 Introduction

Hexafluorobenzene reacts readily to give monosubstituted products with many nucleophiles, including methoxide ions,[74,75] hydroxide ions,[76,77] ammonia[78] and amines.[79]

Nucleophilic substitution reactions in monosubstituted pentafluorobenzenes (C_6F_5X) have been extensively investigated. In most cases, e.g. where X = H,[79] CH_3,[80] C_6H_5,[81] SC_6H_5,[82] CF_3,[83,84] C_2F_5,[85] CN[86] and halogens,[86] substitution occurs almost totally at the position para to X. (In the case of chlorine a small amount of ortho product is given[86,87]). When X = O^- or NH_2 attack occurs at the meta position,[88] and when X = NO[89] or NO_2[90] and the nucleophile is ammonia or an amine, attack occurs extensively at the ortho position.

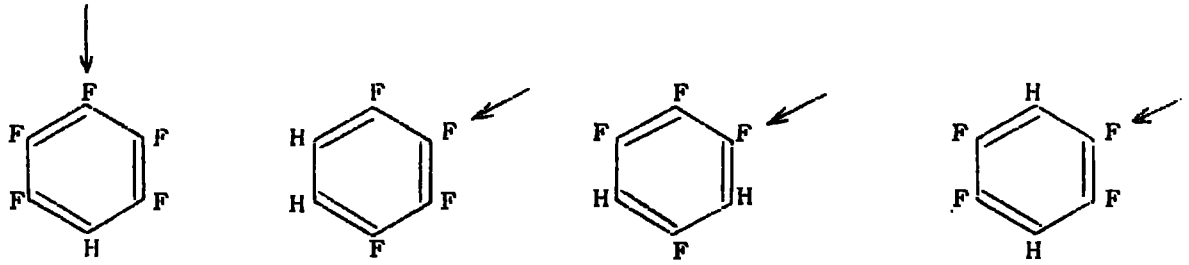
2.1.2 Rationalisation of Postion of Substitution

In order to explain the orientation of nucleophilic attack, the distribution of charge in the transition state and the effects of the substituents on that charge have been considered.[91,92] It has been proposed[91,92] that for substitution in polyfluoro-aromatic compounds, the transition state (I, II and III) of the rate determining step has the major component of its structure derived from II, with only small contribution from I and III, i.e. most charge in the transition state is on the atom para to the position of substitution.



(I) (II) (III)

Evidence for this charge distribution is obtained from molecular orbital calculations[93] and from the orientation of attack in pentafluorobenzene and the three tetrafluorobenzenes.[91] These four compounds react with nucleophiles in the positions arrowed.



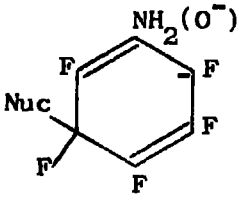
For the first three compounds, attack occurs only para to a hydrogen, which has been suggested stabilises a negative charge on an α carbon atom to a greater extent than fluorine (see below). The fact that no ortho product is formed suggests a non-equal distribution of charge in the transition state at positions ortho and para to the point of attack.

2.1.3 Effects of Substituents

Substituents which stabilise negative charge to a greater extent than fluorine, e.g. nitro, perfluoroalkyl and cyano groups, would be expected to direct nucleophilic attack to the position para to themselves, assuming that most of the charge in the transition state is on the carbon atom para to the position of substitution: this orientation is generally found.[79-84] The fairly high percentage (greater than 50% when the nucleophile is ammonia or methylamine) of ortho product for the reactions of pentafluoronitrobenzene

with amines has been explained by hydrogen bonding between the nitro group and the amine when attack occurs at the ortho position.[90]

The fact that pentafluoroaniline and pentafluorophenoxide react in the meta position[88] is to be expected from the discussion in Chapter 1. The most stable transition state for these compounds will be the one in which there is no negative charge on the carbon atom to which the substituents are attached. This is achieved by attack at the meta position, leading to transition state (IV).



(IV)

The halogens are often found to destabilise a negative charge on an α carbon atom in the order F > Cl > Br > I ~ H,[94] especially when the geometry of the carbanion is planar.

This order of capacity in destabilising a negative charge has been explained in terms of the Iπ effect,[94] which is a measure of the inductive repulsion between the non-bonding electrons of the halogens and the negative charge on carbon in a π system. For halogens the Iπ effect is in the opposite direction to the -Iσ effect arising from their electronegativities, but is in the same direction as, but is different from, their +M effects.

The Iπ repulsion results from coulombic interaction between the lone pairs on halogen and the electrons on the α carbon atom. The effect will be greater for fluorine than for the other halogens, as interaction will become less favourable as the size of the halogen increases, and will be at a maximum in aromatic systems owing to the enforced planar sp^2 geometry. This interaction is shown in Figure 2.1, which represents the effect in the

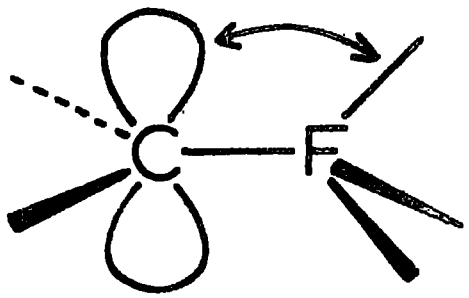
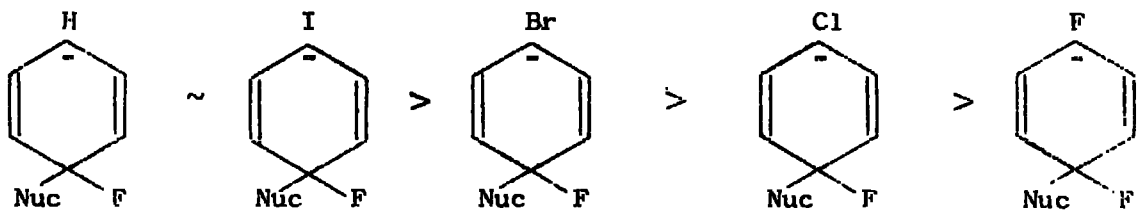


Figure 2.1

transition state for nucleophilic substitution. The effect is likely to be greater as the amount of charge on the carbon increases. Hydrogen will have no Iπ effect.

The dependence of the magnitude of the effect of an α fluorine, whether stabilising or destabilising, on the conformation of the carbanion can be seen in the following examples. Measurements of the kinetic acidities of $CHFX_2$ compounds,[95] which give tetrahedral carbanions, show them to be 10^4 to 10^5 times more acidic than the corresponding CH_2X_2 compounds. However, the sodium methoxide catalysed isotope exchange of fluorene is reduced by a factor of 8 by a 9-fluoro substituent:[96] in this case planar geometry is enforced.

By considering Iπ interactions the following order of stability of transition states (V-IX) has been proposed.[91]



This postulate readily explains why chloro-, bromo- and iodo-pentafluorobenzene and pentafluorobenzene react mainly at the para position.

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,[91] taking hexafluorobenzene as a standard, that substituents which can reduce the electron deficiency of the ring by electron donation by a +M effect such as NH_2 or 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 destabilise the initial state of the system, relative to hexafluorobenzene, making the molecule more susceptible to nucleophilic attack.

2.1.4 Kinetic Studies

In contrast to the great amount of kinetic data available for reactions of activated monohalobenzenes, very little kinetic investigation has been carried out in polyfluorinated benzene compounds.

Table 2.1 shows the relative rate constants for reactions of compounds C_6F_5X with methoxide in methanol at 60°.[97] Except where shown, fluorine is lost para to the substituent.

TABLE 2.1

Substrate	Relative Rate Constants
C_6F_6 [a]	0·90
C_6F_5H	1
C_6F_5Cl	4·6
C_6F_5Cl [b]	19
$C_6F_5CF_3$	$4·5 \times 10^3$
$C_6F_5NO_2$	$2·3 \times 10^6$
C_6H_5F	$5·2 \times 10^{-8}$
$p\text{-}FC_6H_4NO_2$	28

[a] Actual relative value = 5·4

[b] For attack ortho to chlorine

Table 2.2 shows values of rate constants for a further set of C_6F_5X compounds: group A for the reaction with methoxide ion in dioxan/methanol (5:1 v/v) at 50°, and group B for the reaction with methoxide ion in methanol at 50°.[98]

TABLE 2.2

	Substrate	Main Product	k(l.mole^{-1}sec^{-1})
A	C_6F_6 [a]		$3{\cdot}50 \times 10^{-3}$
	C_6F_5H	para to H	$4{\cdot}00 \times 10^{-3}$
	C_6F_5Br	para to Br	$6{\cdot}42 \times 10^{-2}$
	C_6F_5I	para to I	$3{\cdot}85 \times 10^{-2}$
	$C_6F_5OCH_3$	all positions	$2{\cdot}71 \times 10^{-4}$
	$C_6F_5NH_2$	meta to NH_2	$2{\cdot}15 \times 10^{-5}$
	$C_6F_5O^-$	meta to O^-	$8{\cdot}11 \times 10^{-8}$
B	C_6F_6 [a]		$5{\cdot}02 \times 10^{-5}$
	C_6F_5H	para to H	$8{\cdot}66 \times 10^{-5}$
	$C_6F_5CF_3$	para to CF_3	$3{\cdot}70 \times 10^{0}$
	C_6F_5CN	para to CN	$3{\cdot}45 \times 10^{1}$

[a] Actual value divided by 6

From both sets of results it can be seen that the groups CF_3, NO_2 and CN are highly activating with respect to fluorine and direct exclusively para to themselves. The last two compounds in Table 2.1 are included to show that the para nitro group in p-nitrofluorobenzene is somewhat more activating than five fluorines in hexafluorobenzene.

The groups NH_2 and O^- are strongly deactivating with respect to fluorine, and as expected direct meta to themselves. The OCH_3 group, although not as deactivating as the previous two, gives a mixture of products resulting from attack at all positions.

The halogens chlorine, bromine and iodine activate the position para to themselves, as compared to fluorine, by factors of approximately 21 (Table 2.1), 18 and 11 (Table 2.2) respectively. This is reasonably in accord with the arguments based on charge distribution in the transition state given earlier. Pentafluorobenzene, is however, only very slightly more reactive than hexafluorobenzene. If reaction rates were dependent solely on the stability of transition states (cf. V-IX), it would be expected that hydrogen would be more activating in the para position than the other halogens.

Competition experiments on the reactions of substituted pentafluorobenzenes with pentafluorophenoxide ion[99] give rate constant ratios which are in agreement with the kinetic data.[97,98] The results are shown in Table 2.3.

TABLE 2.3

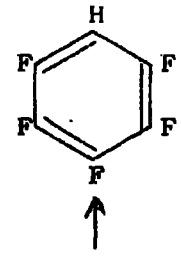
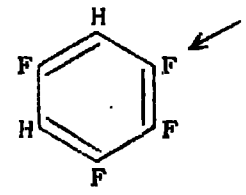
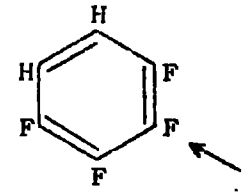
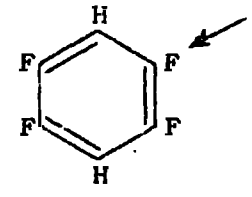
Substrate	Relative Rate Constants
$C_6F_5CF_3$	$2{\cdot}4 \times 10^4$
$C_6F_5{\cdot}C_6F_5$	$7{\cdot}3 \times 10^2$
C_6F_5Br	39
C_6F_5Cl	32
C_6F_5H	1
C_6F_6 [a]	0·91

[a] Actual value divided by 6

The relative rate constants refer to loss of fluorine para to the substituent. In these reactions bromine is slightly more activating than chlorine, in contrast to the rate constants in Table 2.2.

Kinetic measurements have also been made for the reactions of the three tetrafluorobenzenes with methoxide ion in methanol at 50°.[100] The rate constants are shown in Table 2.4 together with those for hexafluorobenzene and pentafluorobenzene under the same conditions.[100] The position of substitution is indicated by arrows. Comment on these results will be given in Chapter 3.

TABLE 2.4

Substrate	$k(l.mole^{-1}sec^{-1})^a$
	$1{\cdot}3 \times 10^{-4}$
	$1{\cdot}8 \times 10^{-4}$
	$9{\cdot}0 \times 10^{-6}$
	$1{\cdot}8 \times 10^{-6}$
	10^{-8}

[a] Values of k are corrected for statistical factors

Base catalysis: Base catalysis has been observed for the reaction of hexafluorobenzene with piperidine in N-hexane, dioxan and methanol at 100°.[101] The measured rate constant, k, was found to be sensitive to piperidine concentration and was expressed in the usual form:

$$k = k' + k''[B]$$

The extent of catalysis ($^{k''}/_{k'}$) decreased along the solvent series N-hexane - methanol - dioxan i.e. in the sequence of increasing specific solvation. By specific solvation is meant the ability of a solvent to co-ordinate to the reaction centre of a molecule and, in these cases, to act as a 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.

2.1.5 Reactions with Perfluoro-olefins and Fluoride Ion

These reactions are of synthetic value as they are involved in the preparation of perfluoroalkyl benzenes.

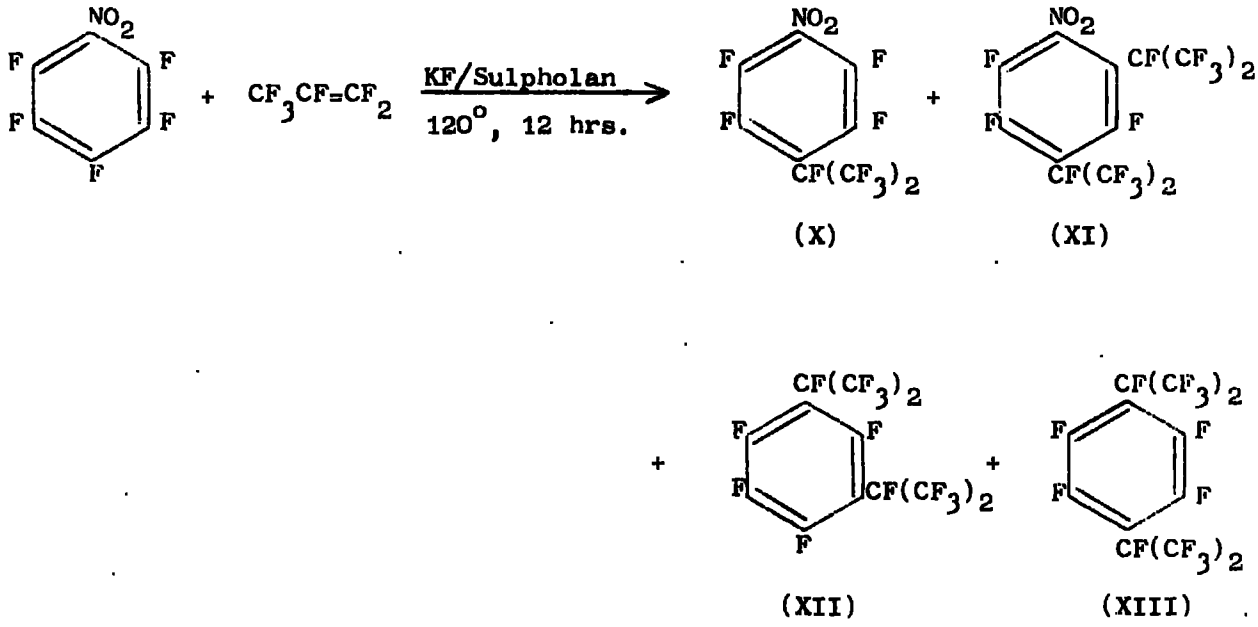
Miller[102] first showed that carbanions can be generated by the reaction of polyfluoro-olefins with fluoride ion in aprotic solvents.

$$F^- + CF_2{=}C\!\!<\!\!\!> \qquad\qquad CF_3\text{-}\overset{|}{C}\text{—}^-$$

Anions of this type have been used as nucleophiles for reactions with polyfluoroaromatic compounds.

The reaction of tetrafluoroethylene, potassium fluoride and hexafluorobenzene at 135° at 34 atmospheres has yielded a mixture of perfluoroethylbenzenes (mono to hexa).[103]

Perfluoropropene and potassium fluoride react with pentafluoronitrobenzene to give a number of products (X-XIII) in proportions depending upon the reaction conditions.[104]



Products (XII) and (XIII) were due to displacement of the nitro group.

The same reaction conducted at higher temperature[104] yielded perfluoroisopropylbenzene as the major product.

Octafluorobut-2-ene, caesium fluoride and pentafluoronitrobenzene react in sulpholan at 150° to give perfluoro-sec.-butylbenzene.[105]

Perfluoro-t-butylbenzene has recently been prepared by the reaction of perfluoroisobutene, caesium fluoride and pentafluoronitrobenzene in sulpholan.[106]

2.2 Polyfluoro-N-heterocyclic Compounds

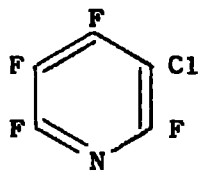
Polyfluoro-N-heterocyclic compounds react more readily with nucleophiles than perfluorobenzenoid compounds owing to the activating effect of the aza group. A survey of nucleophilic substitution reactions in polyfluoropyridines, diazines, quinolines and isoquinolines will be given, and rationalisation of the orientation of substitution will then be discussed.

2.2.1 Pentafluoropyridine and Its Derivatives

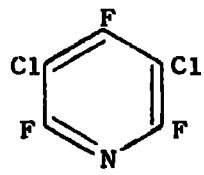
Pentafluoropyridine reacts with nucleophiles[107,108] including ^-OMe, CN^-,

$^-$OH and amines, to give the 4-substituted products. Further substitution in the case of methoxide ion[107,108] gives 2,4-dimethoxytrifluoropyridine and 2,4,6-trimethoxydifluoropyridine.

Both 3-chlorotetrafluoropyridine (XIV) and 3,5-dichlorotrifluoropyridine (XV) 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.[109]



(XIV)



(XV)

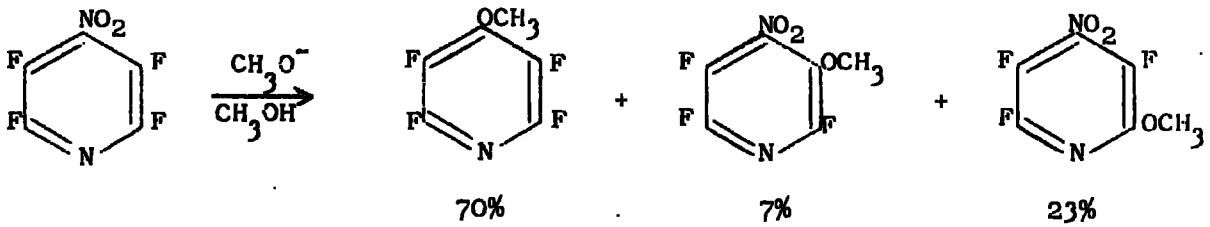
Steric effects in these two compounds, arising from the presence of chlorine, are evident. Aqueous potassium hydroxide with (XIV) gives a mixture of products with the hydroxyl group in the 4- and 6-position (90% and 10% respectively), and the same composition is given for the analogous reaction with (XV). In contrast to this, attack by hydroxide ion in t-butanol on (XIV) gives a mixture of the 2-, 4- and 6-hydroxy products (10%, 50% and 35% respectively), and the same reagent with (XV) 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-position. This has been attributed[109] to solvation of the hydroxide ion in t-butanol leading to an effectively larger nucleophile which would react preferentially at the less sterically hindered 6-position.

Competition experiments with aqueous ammonia[110] have shown that the susceptibility towards nucleophilic attack increases in the series pentafluoro-

pyridine < 3-chlorotetrafluoropyridine < 3,5-dichlorotrifluoropyridine in the ratio of 1 : 3·7 : 12·6 respectively. This is consistent with the differences in Iπ effect between chlorine and fluorine on the negative charge at the 3-position of the pyridine nucleus in the transition state.

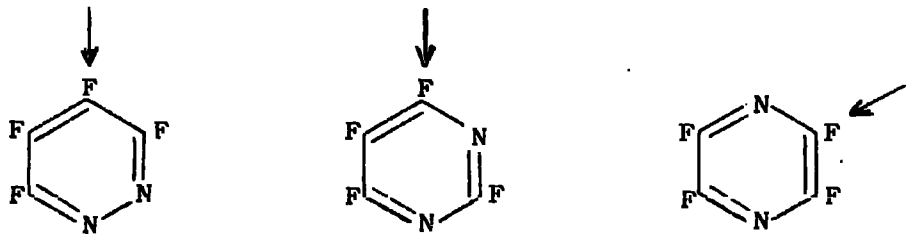
Both 4-chloro-[111] and 4-bromo-[112] tetrafluoropyridine react with nucleophiles to replace the 2-fluorine. The fact that neither bromide nor chloride is displaced is indicative of a two step mechanism.

Other 4-substituted tetrafluoropyridines react in the 2-position,[109] although 4-nitrotetrafluoropyridine with methoxide ion gave two minor products due to replacement of the 2- and 3-fluorines, and a major product due to the replacement of the nitro group.



2.2.2 Tetrafluorodiazines

Tetrafluoro-pyridazine (XVI)[114-117], -pyrimidine (XVII)[118-120] and -pyrazine (XVIII)[121,122] react with nucleophiles in the positions indicated, i.e. para to the ring nitrogen where possible.



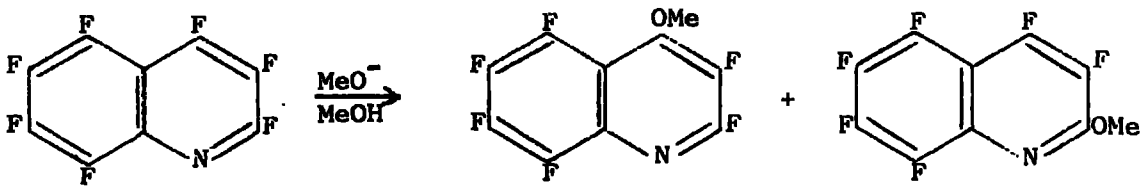
(XVI) (XVII) (XVIII)

Subsequent substitution in the pyridazine[114] and pyrimidine[119] occur para to the second nitrogen, although for monosubstituted trifluoropyrazines,

orientation of secondary attack depends on the substituent:[122] alkyl groups and chlorine direct para to themselves, and the methoxy group directs ortho to itself. Reasons for the observed orientation are discussed in the next section.

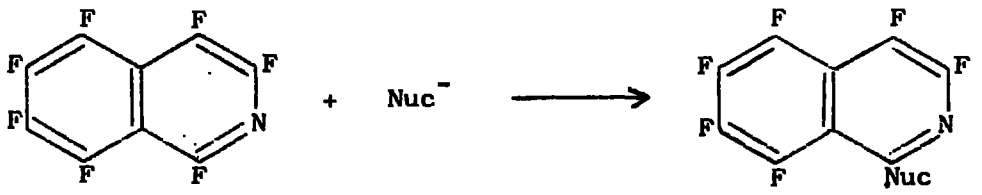
2.2.3 Perfluoro-quinoline and isoquinoline

Heptafluoroquinoline reacts with nucleophiles, including methoxide ions and ammonia, to give a mixture of products resulting from substitution in the 2- and 4-positions.[123]



Steric effects due to the fluorine in the 5-position appear to be important. The reaction of methoxide ion in methanol gives 75% of the 2-substituted product[123] (25% of the 4-isomer), while methoxide ion in t-butanol gives > 95% of the 2-methoxy product.[124]

Heptafluoroisoquinoline[124] reacts with nucleophiles exclusively in the 1-position.

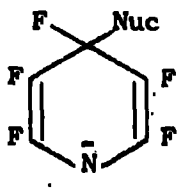


2.3 Rationalisation of Orientation of Substitution by Electronic Effects

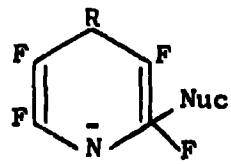
In the light of the observed positions of substitution in polyfluoro-N-heterocyclic compounds, it has been suggested[114] that orientation of substitution is controlled by the influence of the ring nitrogen atoms, rather than the effect of Iπ repulsion, on the stability of the transition state. This is in contrast to the rationalisation given for the polyfluoro-

benzene systems, but the orientating effect of nitrogen was considered to be dominant in the reactions of the corresponding N-heterocyclic compounds (Chapter 1).

The Iπ effect must obviously be considered, but high electron density on nitrogen in the transition state, as in (XIX) and (XX), reduces the electron densities on carbon atoms compared to substitution in polyfluorobenzenes, and hence lessens the importance of Iπ destabilisations.

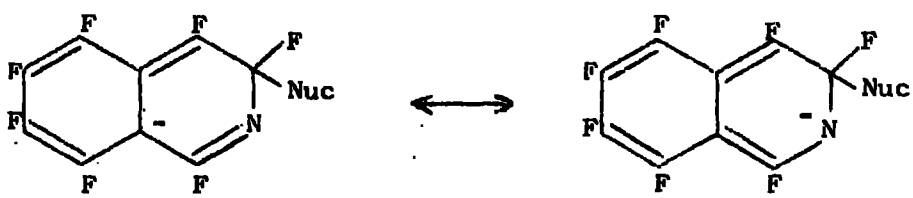


(XIX)



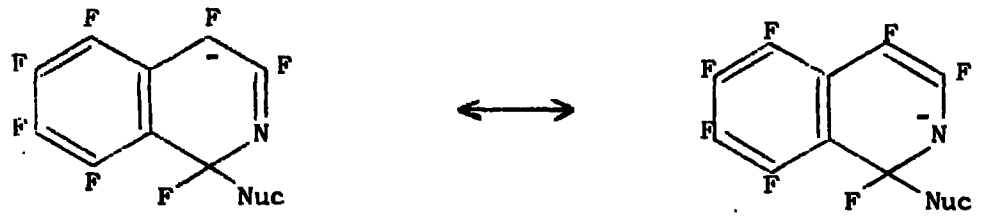
(XX)

Monosubstitution in perfluoro-pyridine, -pyridazine, -pyrimidine and -quinoline occurs in the position predicted by both activation by nitrogen and Iπ effects, i.e. attack occurs para to nitrogen. On the basis of the Iπ effect, however, it would be argued that heptafluoroisoquinoline would react in position 3, analogous to octafluoronaphthalene,[125] passing through a transition state (XXI).



(XXI)

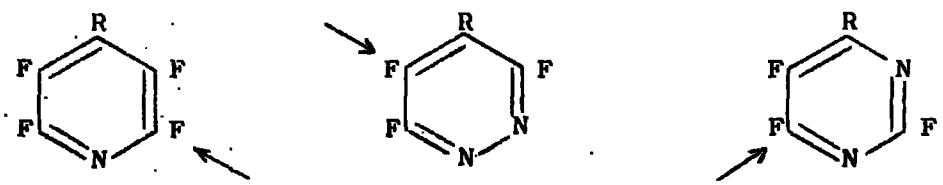
Instead, substitution occurs in the 1-position in spite of the apparently opposed Iπ effect in the transition state (XXII); this indicates control of orientation by nitrogen, with a high electron density on the nitrogen as in (XXIIb).



(XXIIa) (XXIIb)

Attack at the 3-position as in (XXI) causes loss of aromaticity of the carbocyclic ring, which is likely to be unfavourable (cf. difference in reactivity between 3- and 4-chloroisoquinoline in section 1.3.4).

The directions of attack in 4-substituted pyridines, pyridazines and pyrimidines (XXIII-XXV, direction of attack as arrowed) are explicable in

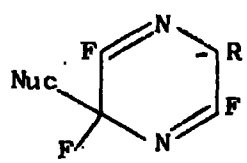


(XXIII) (XXIV) (XXV)

terms of either the Iπ effect or the activation caused by the ring nitrogen.

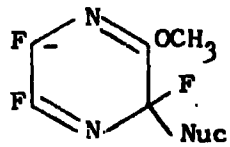
Orientation of substitution in monosubstituted trifluoropyrazines has been explained[122] in terms of the differences in Iπ effects between fluorine and the substituents.

In cases where the Iπ effect of the substituent is less than that of fluorine, e.g. for chlorine and alkyl groups, substitution occurs para to the substituents, leading to a transition state (XXVI) in which negative charge can be located on the carbon atom bearing the substituent R.



(XXVI)

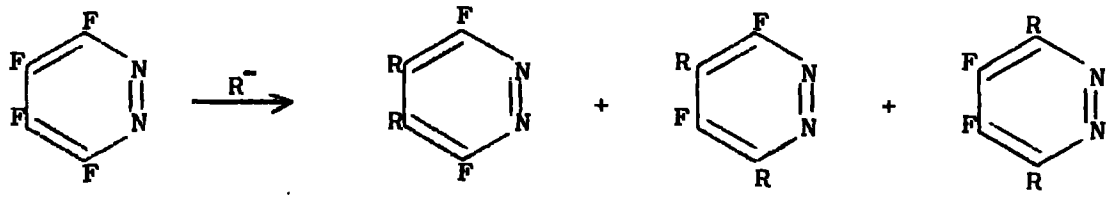
When R is the methoxyl group, substitution occurs in the ortho position. This is accounted for by supposing oxygen to have a greater Iπ repulsive effect than fluorine, and hence transition states of type (XXVI) would be less stable than (XXVII), in which negative charge can be localised on a carbon bearing fluorine.



(XXVII)

2.4 Reactions with Polyfluoroalkylanions

The reactions of $CF_3CF_2^-$, $(CF_3)_2CF^-$ and $(CF_3)_3C^-$ with tetrafluoropyridazine[126] are interesting in that they show a clear-cut variation from kinetic to thermodynamic control of products.



R = CF_3CF_2 (XXVIII)

R = $(CF_3)_2CF$ (XXIX) (XXX)

R = $(CF_3)_3C$ (XXXI)

Only the disubstituted derivatives, formed at 80°, will be considered. With $CF_3CF_2^-$, isomer (XXVIII) was formed exclusively, and was not rearranged by fluoride ion even up to 150°; $(CF_3)_2CF^-$ gave (XXIX) which gave a mixture of (XXIX) and (XXX) on heating with fluoride ion; while $(CF_3)_3C^-$ gave only (XXXI). Clearly, steric interactions are minimised with both the bulky $(CF_3)_3C$ groups adjacent to the ring nitrogen, rather than flanked by fluorine atoms attached to the ring. Therefore, across the series,

there is a complete transition from kinetic control, in reactions with $CF_3CF_2^-$ to thermodynamic control of products with the bulky $(CF_3)_3C^-$.

A similar state of affairs is also found for the reactions of the same perfluoroalkylanions with pentafluoropyridine.[126]

B. Polychloro-aromatic Compounds

2.5 Polychlorobenzenes

2.5.1 Hexachlorobenzene

Unlike hexafluorobenzene, which is planar, the steric effects of the six chlorine atoms in hexachlorobenzene cause the aromatic ring to exist in a buckled form.[127]

Hexachlorobenzene reacts readily with nucleophiles[128] including alkoxide ions, thioalkoxide ions 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 fluoride as compared to chloride ions.[98] Table 2.5 shows the rate constants for cations with hydroxide ion in dioxan/water (9:1 v:v) at 160°.[98]

TABLE 2.5

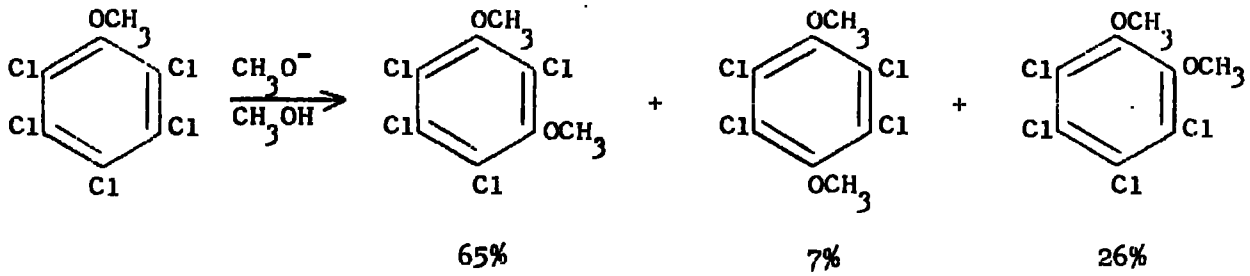
Substrate	$k(l.mole^{-1}sec^{-1})$
C_6F_6	$1{\cdot}03 \times 10^{-2}$
C_6Cl_6	$7{\cdot}40 \times 10^{-5}$

2.5.2 Monosubstituted Pentachlorobenzenes

Compared to the amount of data available for nucleophilic attack in pentafluorobenzene compounds, few results are available for substitution in pentachlorobenzenes.

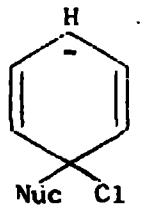
Pentachloronitrobenzene reacts with aqueous ammonia at 200° [129] giving, as the major product, pentachloroaniline (60%) plus a mixture of 2- and 4-aminotetrachloronitrobenzene. The displacement of the nitro group is in contrast to the analogous reaction with pentafluoronitrobenzene in which the nitro group is not displaced.

Yakobson and co-workers[129,130] 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[129] and methoxide ion[130] to give solely the 3-substituted product (meta to the NH_2 group), while pentachloroanisole with methoxide ion[130] gives products arising from attack at positions ortho, meta and para to the OCH_3 group:

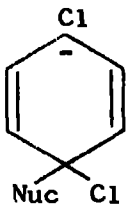


65% 7% 26%

Pentachlorobenzene reacts with nucleophiles in the position para to hydrogen,[131] as does pentafluorobenzene. This has been interpreted[92] in terms of the relative stabilities of transition states (XXXII) and (XXXIII) i.e. attack para to hydrogen gives a more stable transition state than for attack para to chlorine.



(XXXII)



(XXXIII)

Comparison between the rates of displacements of fluoride ion from hexafluorobenzene and pentachlorofluorobenzene has shown the latter to be more reactive. Table 2.6 shows the relative rate constants for reaction with methoxide ion in methanol at 60°.[132]

TABLE 2.6

Substrate	Relative Rate Constant
C_6F_6 [a]	1
C_6Cl_5F	40

[a] It is presumed that the measured rate constant was divided by the statistical factor of 6.

2.6 Polychloro-N-heterocyclic Compounds

2.6.1 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,[133] the 2-position being less sterically hindered than the 4-position. Table 2.7 shows the ratio of 4-:2-substitution with various nucleophiles.[133]

TABLE 2.7

Nucleophile	Solvent	Ratio of 4-:2-substitution
NH_3	EtOH	70:30
Me_2NH	EtOH	20:80
Et_2NH	EtOH	1:99
MeO^-	MeOH	85:15
EtO^-	EtOH	63:35
$nBuO^-$	nBuOH	57:43

The monosubstituted products are also subject to disubstitution, 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.[133]

Table 2.8 shows the ratio of the 2,6-:2,4-disubstituted products obtained for further substitution.

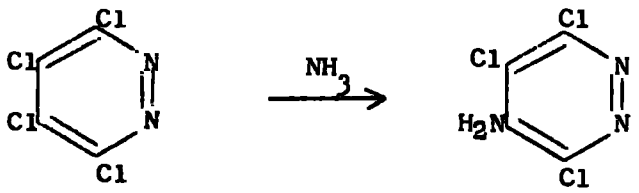
TABLE 2.8

Nucleophile	Ratio of 2,6-:2,4-disubstituted Product
NH_3	0:100
Me_2NH	70:30
MeO^-	0:100
EtO^-	1:99

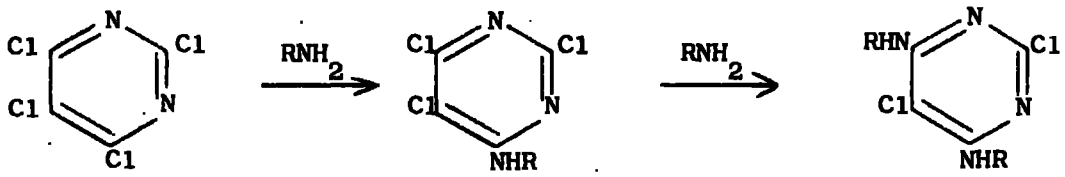
2.6.2 Tetrachlorodiazines

Scant information is available for reactions of tetrachlorodiazines with nucleophiles.

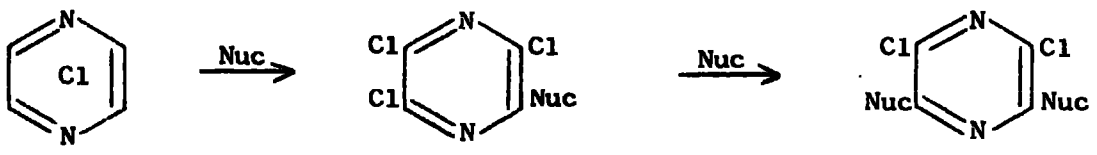
Tetrachloropyridazine reacts with aqueous ammonia in ethanol and sodium hydroxide in water to give 4-amino- and 4-hydroxy-trichloropyridazine respectively[134] i.e. substitution occurs para to the nitrogen. No other isomer was reported formed.



Tetrachloropyrimidine reacts with aqueous ammonia and primary aromatic amines in aqueous acetone to give the 4-substituted product.[135] Further substitution with amines leads to the 4,6-disubstituted product,[135,136] i.e. for both mono- and di-substitution attack occurs para to a ring nitrogen as for tetrafluoropyrimidine.



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).[137]

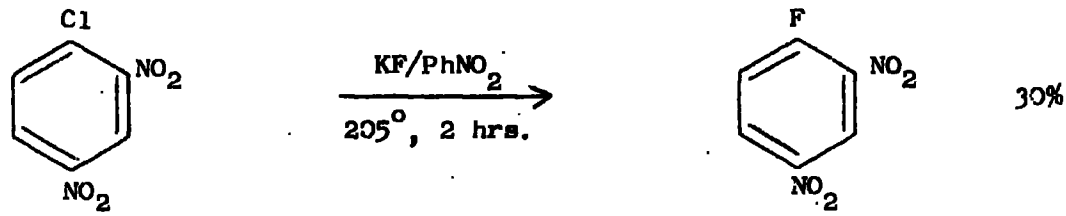


2.7 Reaction of Polychloro-aromatic Compounds with Fluoride Ion

An important route to the synthesis of polyfluorinated aromatic compounds is the halogen exchange reaction between the corresponding polychloro-

compound and fluoride ion.

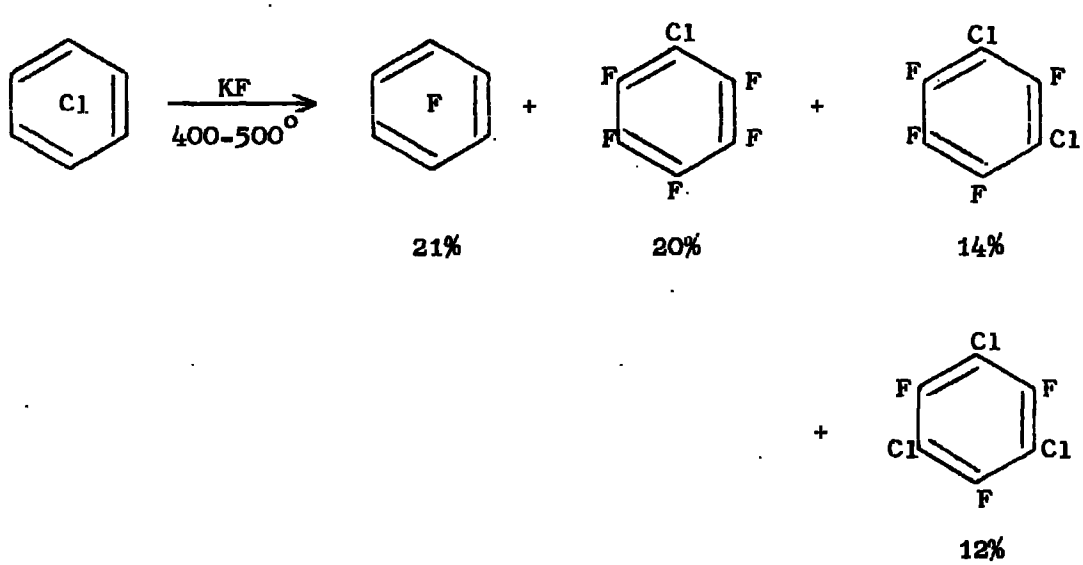
That halogen exchange reaction in aromatic compounds can occur, was first demonstrated by Gottlieb,[138] who reacted 2,4-dinitrochlorobenzene with potassium fluoride in nitrobenzene.



The best solvents for halogen exchange reactions have been found to be aprotic dipolar solvents such as dimethylformamide, dimethylsulphoxide and sulpholan.[139,140] In these solvents, fluoride ion acts as a very powerful nucleophile owing to its low degree of solvation.[141]

Attempts to synthesise hexafluorobenzene from hexachlorobenzene and potassium fluoride in various solvents have, however, failed to give the required product in high yield; a mixture of chlorofluorobenzenes being given.[142]

A general method to the preparation of perfluoro compounds from perchloro compounds is to heat the perchloro compound with potassium fluoride in the absence of a solvent. This method works for both benzene and N-heterocyclic chloro compounds, and a few examples are given below.



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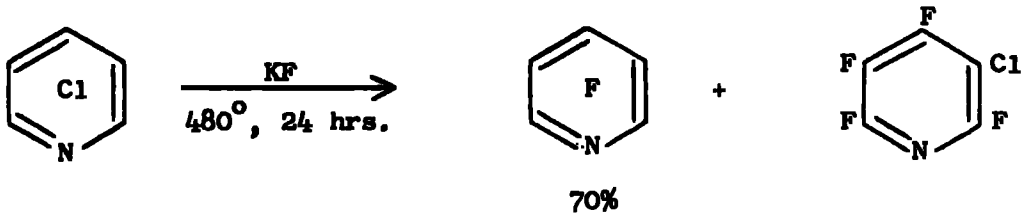
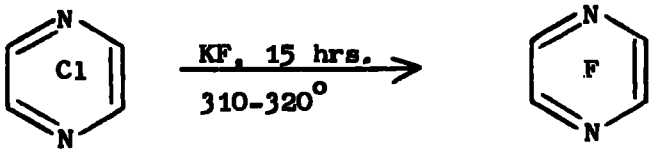


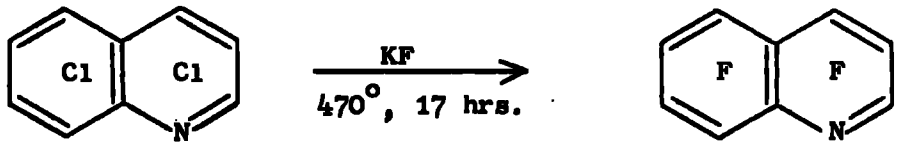
70%

107



95%

122



71%

144

DISCUSSION

CHAPTER 3

RATE MEASUREMENTS FOR REACTIONS OF POLYFLUORO- AND POLYCHLORO-HETEROCYCLIC COMPOUNDS WITH NUCLEOPHILES

3.1 Introduction

The discussion in Chapter 2 showed that much qualitative investigation has been carried out into the reactions of polyfluoroheterocyclic compounds with nucleophiles, although no rate measurements have been reported. The aim of the work described here has been to relate rates of reaction to the substituents in the aromatic nucleus and to the structure of the substrate.

The substrates investigated were a series of substituted polyfluoropyridines, tetrachloro- and tetrafluoro-diazines, and heptafluoro-quinoline and -isoquinoline.

3.2 Choice of Nucleophile and Solvent

Preliminary investigation of the reaction of pentafluoropyridine with methoxide ions in methanol showed that the rate constant was too high for accurate determination. Employing a spectrophotometric technique for following the course of the reaction, and using approximately equal initial concentrations of methoxide ion and pentafluoropyridine (c. 10^{-4} moles l^{-1}), rate constants in the region of 10^{3} $l.mole^{-1}min^{-1}$ were obtained. The low methoxide concentration and the inaccuracies involved in measuring such a high rate constant meant that rate constants obtained in different runs were usually not in agreement by a factor of less than 10%. A nucleophile and solvent which gave lower values of rate constant was hence sought.

The two nucleophile/solvent systems found to be most convenient for rate measurements were diethylamine in dioxan and ammonia in 60/40 (v:v) dioxan/water. Of these the latter was most frequently used, as in some reactions

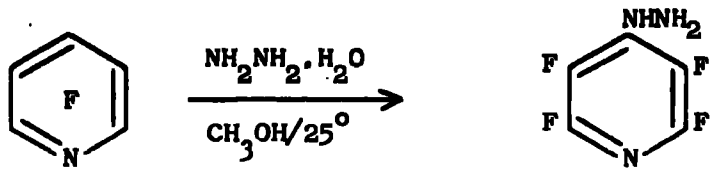
the great steric requirements of the two ethyl groups of diethylamine were dominant in determining the rate and orientation of substitution; this effect was not apparent with ammonia.

3.3 Preparation of Substrates

A brief description of the preparation of the heterocyclic starting materials will now be given. Some of the compounds prepared viz. 3,4-dichlorotrifluoropyridine, 3,4,5-trichlorodifluoropyridine and 2,6-dichlorotrifluoropyridine have not been previously reported. Compounds, the preparation of which are not described here, were provided in varying states of purity, and were all purified before use as described in Chapter 5.

(a) 4-Chlorotetrafluoropyridine

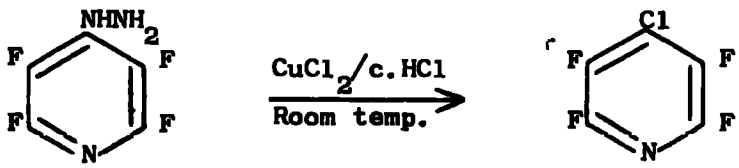
The starting material for the preparation, 4-hydrazinotetrafluoropyridine (2)*, was prepared in very high yield from the reaction of pentafluoropyridine (1) and hydrazine hydrate in methanol.[107]



(1) (2)

> 90%

4-Chlorotetrafluoropyridine (3) was obtained from the reaction of (2) with copper(II) chloride in concentrated hydrochloric acid.



(3)

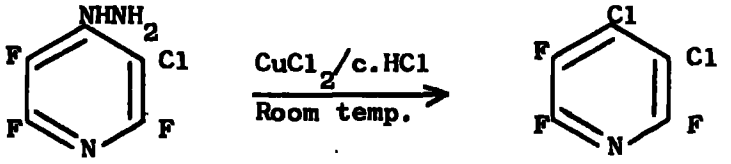
70%

---

* From this point, compounds will be numbered as shown, and each compound will be referred to by its corresponding number throughout.

(b) 3,4-Dichlorotrifluoropyridine

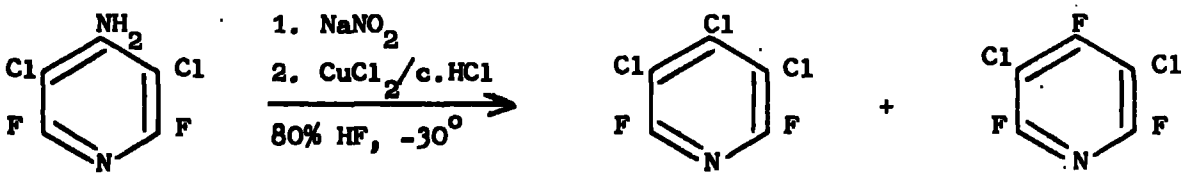
3,4-Dichlorotrifluoropyridine (4) was prepared by the reaction of 3-chloro-4-hydrazinotrifluoropyridine with copper(II) chloride in concentrated hydrochloric acid.



(4)
80%

(c) 3,4,5-Trichlorodifluoropyridine

3,4,5-Trichlorodifluoropyridine (5) was prepared by the diazotisation reaction of 4-amino-3,5-dichlorodifluoropyridine with sodium nitrite and copper(II) chloride in 80% aqueous hydrofluoric acid at -30°.



(5)
64%

15%

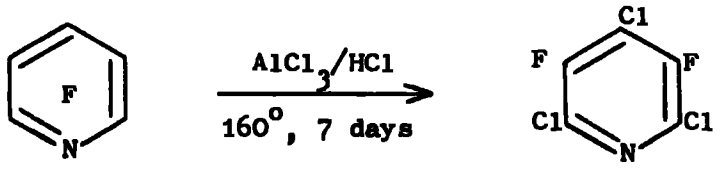
4-Amino-3,5-dichlorodifluoropyridine was prepared in good yield (> 90%) by the reaction of aqueous ammonia and 3,5-dichlorotrifluoropyridine.[109]

The above reaction was chosen for the preparation as opposed to using the method adopted for compounds (3) and (4) above, as it was known[145] that the reaction of aqueous hydrazine with 3,5-dichlorotrifluoropyridine gave a mixture of the 4- and 6-substituted product, whereas aqueous ammonia and 3,5-dichlorotrifluoropyridine gave only the 4-substituted isomer.

(d) 2,6-Dichlorotrifluoropyridine

The preparation of this compound was achieved in two stages. 2,4,6-Trichlorodifluoropyridine (6) was first prepared by a method similar to that

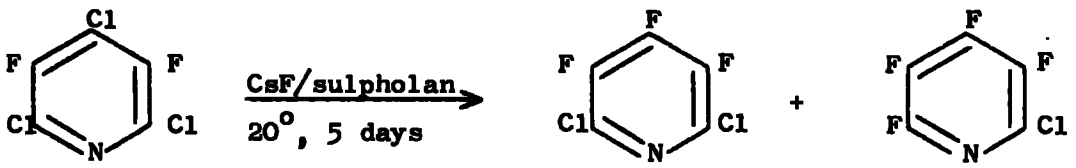
of Thorpe,[146] in which pentafluoropyridine, aluminium chloride and concentrated hydrochloric acid were heated in a sealed nickel tube. Excess chloride and acid were used in order to reduce the percentages of 4-chlorotetrafluoro- and 2,4-dichlorotrifluoro-pyridine which are found as by-products, the former being the major product when a 1:1:1 molar ratio of reactants was used.[146]



(6)
70%

Under the conditions used compound (6) was the only product formed in appreciable amount.

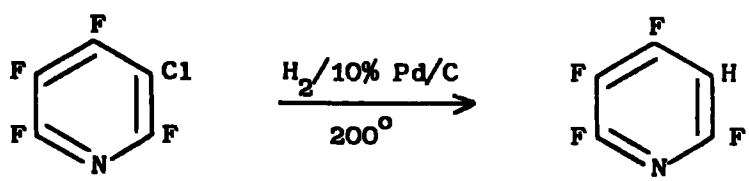
The preparation of 2,6-dichlorotrifluoropyridine (7) was achieved by stirring (6) with a 3 molar excess of dry caesium fluoride in dry sulpholan. A by-product, 2-chlorotetrafluoropyridine (8), was also formed.



(6) (7) 70% (8) 15%

(e) 2,4,5,6-Tetrafluoropyridine (9)

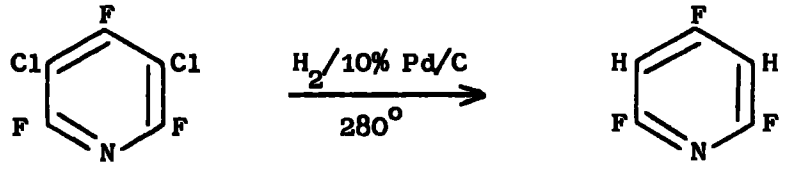
The method used was that of Chambers and co-workers.[147] 3-Chloro-tetrafluoropyridine was catalytically reduced by hydrogen over palladised charcoal.



(9)

(f) 2,4,6-Trifluoropyridine (10)

This compound was prepared by the catalytic hydrogen reduction of 3,5-dichlorotrifluoropyridine by a method analogous to the one above.[147]



(10)

3.4 Kinetic Methods and Rate Constant Calculations

Rate constant determinations for all reactions discussed in this chapter were carried out at 25·02° with either ammonia as nucleophile in 60/40 dioxan/water or diethylamine as nucleophile in dioxan. In all but two of the systems studied, reactions were followed by periodically titrating samples of the reaction solution against standard acid, and hence determining the concentration of nucleophile remaining.

For the reactions with ammonia, second order rate constants (k_{II}) were obtained from equation 3.1.

$$k_{II}t = \frac{1}{a-2b} \ln \frac{b}{a} \left(\frac{a-2x}{b-x}\right) \qquad 3.1$$

where

a = initial concentration of nucleophile

b = initial concentration of substrate

x = concentration of substrate reacted at time t.

For reactions with diethylamine, second order rate constants (k_{II}) were calculated from equation 3.2.

$$k_{II}t = \frac{1}{a-b} \ln \frac{b}{a} \left(\frac{a-x}{b-x}\right) \qquad 3.2$$

The terms are the same as for equation 3.1.

Equation 3.1 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. 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.

For reactions with diethylamine as nucleophile, equation 3.2 gives constant second order rate constants throughout the run; hence this implies that diethylamine is not appreciably protonated in dioxan during the course of the reaction. The proton presumably attaches itself to a fluoride ion and the equilibrium

$$HF + (C_2H_5)_2NH \rightleftharpoons (C_2H_5)_2\overset{+}{N}H_2.F^-$$

is far to the left.

Support for this interpretation arises from the observation that the pK_a of NH_4^+ does not change significantly from its value to water to that in 60/40 dioxan/water,[148] whereas n-pentylamine has been found not to be appreciably protonated during its reaction with 2-chloropyrimidine in the aprotic solvent dimethylsulphoxide.[149]

The reactions of tetrafluoropyrimidine and perfluoro-3,5-dimethylpyridine with ammonia were too fast to employ the titration technique, and these reactions were followed spectrophotometrically. A large excess of ammonia was used for each run, and first order rate constants (k_I) calculated from equation 3.3.

$$k_I t = \ln \frac{OD_\infty - OD_o}{OD_\infty - OD} \qquad 3.3$$

OD_∞ = optical density at infinity

OD_o = optical density at time zero

OD = optical density at time t.

Dividing by the ammonia concentration (assumed to be constant throughout the run), gives the second order rate constant, k_{II}.

In cases where two products arose, from attack at positions m and n in the nucleus, the rate constants for attack at these positions (k_m and k_n) were calculated from the observed rate constant, k, from the expressions:

$$k_m + k_n = k$$

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

Errors quoted are the 'standard errors of the mean' (r), and are calculated from the standard deviation (σ) by the expression:

$$r = \frac{\sigma}{n^{\frac{1}{2}}} \qquad \text{where n = number of readings.}$$

σ is obtained from the expression:

$$\sigma = \left[\frac{\Sigma(k_i-\bar{k})^2}{n-1}\right]^{\frac{1}{2}}$$

where

k_i = the ith value of rate constant for the run

$\bar{k}$ = the mean rate constant for the run.

Values of k_i for which $(k_i-\bar{k}) > 2{\cdot}5\sigma$ were rejected, and new values of $\bar{k}$ and σ calculated.

3.5 Reactions of Polyfluoro- and Polychloro-pyridines with Ammonia

The substrates investigated were a series of chlorofluoropyridines ranging from pentafluoro- to pentachloro-pyridine, 2,4,5,6-tetrafluoropyridine, 2,4,5-trifluoropyridine, perfluoro-3-methylpyridine and perfluoro-3,5-dimethylpyridine. All reactions were carried out in 60/40 dioxan/water at 25°, except

the reaction of pentachloropyridine. In this case 70/30 dioxan/water was used, owing to the insolubility of the substrate in the former solvent. It was thought that the change of solvent was unlikely to affect the rate constant significantly from its hypothetical value in 60/40 dioxan/water, especially as the quoted rate constant is only approximate. The position of substitution in pentachloropyridine was also not established, but from the discussion of section 2.4.1 it is likely that substitution occurs almost entirely at the 4-position.

Table 3.1 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 that of 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-chlorotetrafluoropyridine (3).

The rate data themselves will first be discussed, and then discussion will follow on the rationalisation of the observations.

3.5.1 Discussion of Rate Data

(a) Chlorofluoropyridines

The rate constants for the chlorofluoropyridines will now be considered. The first observation is that fluoride is displaced much more rapidly than chloride. This is deduced from the comparison of the rate constants for pentafluoropyridine (1) and pentachloropyridine (13), and from the fact that the 2-fluorine, and not the 4-chlorine, is displaced from those compounds containing a chlorine at the 4-position.

Chlorine is seen to be activating relative to fluorine in positions ortho and para to the position of substitution. A measure of the activating effect of chlorine relative to fluorine at the position ortho to the position of substitution is the ratio of the rate constant for the ortho chlorine

TABLE 3.1

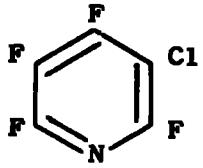
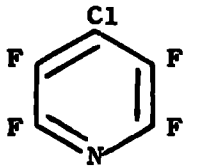
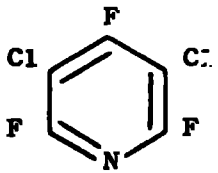
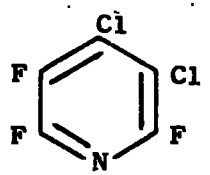
Substrate		Position of Substitution	k(l.mole^{-1}min^{-1})	Relative k	Relative k
	(1)	4	$(4{\cdot}08 \pm 0{\cdot}02) \times 10^{-2}$	1	
	(11)	4	$(1{\cdot}15 \pm 0{\cdot}01) \times 10^{-1}$	2·82	
	(3)	2[a]	$(9{\cdot}29 \pm 0{\cdot}05) \times 10^{-5}$	$2{\cdot}28 \times 10^{-3}$	1
	(12)	4	$(2{\cdot}85 \pm 0{\cdot}02) \times 10^{-1}$	7·00	
	(4)	2	$(2{\cdot}92 \pm 0{\cdot}01) \times 10^{-4}$	$7{\cdot}16 \times 10^{-3}$	3·14
		6	$(2{\cdot}46 \pm 0{\cdot}01) \times 10^{-3}$	$6{\cdot}03 \times 10^{-2}$	$2{\cdot}65 \times 10^{1}$

TABLE 3.1 (continued)

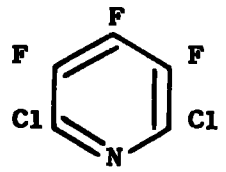
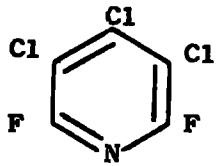
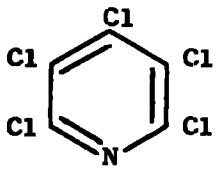
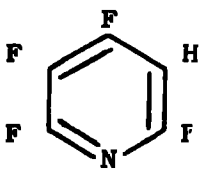
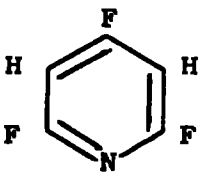
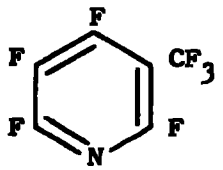
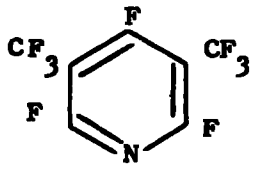
	(7)	4	$(3{\cdot}88 \pm 0{\cdot}02) \times 10^{-2}$	$9{\cdot}51 \times 10^{-1}$	
	(5)	2[a]	$(7{\cdot}77 \pm 0{\cdot}04) \times 10^{-3}$	$1{\cdot}90 \times 10^{-1}$	$8{\cdot}36 \times 10^{1}$
	(13)	4[c]	$\sim 10^{-5}$[b]	$\sim 2 \times 10^{-4}$	
	(9)	4	$(1{\cdot}33 \pm 0{\cdot}01) \times 10^{-3}$	$3{\cdot}26 \times 10^{-2}$	
		6	$(3{\cdot}52 \pm 0{\cdot}02) \times 10^{-4}$	$8{\cdot}63 \times 10^{-3}$	3·79
	(10)	4	$\sim 5 \times 10^{-5}$[b]	$\sim 10^{-3}$	

TABLE 3.1 (continued)

	(14)	4	$3{\cdot}26 \pm 0{\cdot}02$	$7{\cdot}99 \times 10^{1}$	
		6	$1{\cdot}46 \pm 0{\cdot}01$	$3{\cdot}58 \times 10^{1}$	$1{\cdot}57 \times 10^{4}$
	(15)	4	$(1{\cdot}29 \pm 0{\cdot}01) \times 10^{2}$	$3{\cdot}16 \times 10^{3}$	
		6[a]	$(8{\cdot}00 \pm 0{\cdot}06) \times 10^{1}$	$1{\cdot}96 \times 10^{2}$	$8{\cdot}61 \times 10^{5}$

[a] Observed rate constants divided by 2.

[b] Value only approximate owing to the slowness of the reaction. No errors are given.

[c] Position of attack inferred from earlier discussion.

compound to that of the ortho fluorine compound. This ratio will be termed $k_{o\text{-}Cl}/k_{o\text{-}F}$. The activating effect of a para chlorine relative to a para fluorine is obtained in an analogous way, and will be termed $k_{p\text{-}Cl}/k_{p\text{-}F}$. The relationship between the ortho and para halogens and the position of substitution is shown diagrammatically in Figure 3.1.

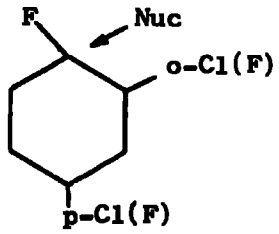


Figure 3.1

The values of $k_{o\text{-}Cl}/k_{o\text{-}F}$ and $k_{p\text{-}Cl}/k_{p\text{-}F}$ are shown in Tables 3.2 and 3.3 respectively. On the left hand side of the tables are the compounds from which the values are calculated, with the positions of substitution arrowed.

TABLE 3.2

Effect of Ortho Chlorine Relative to Ortho Fluorine

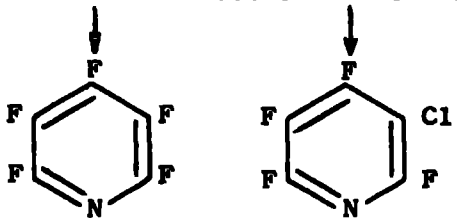
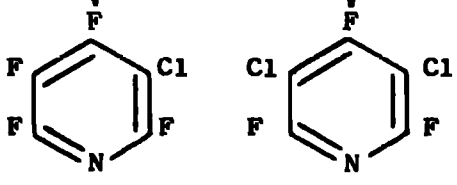
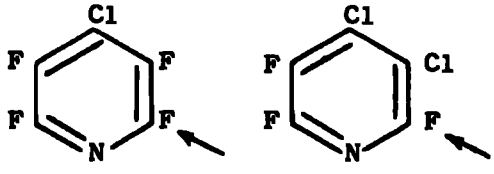
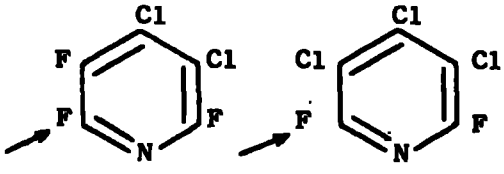
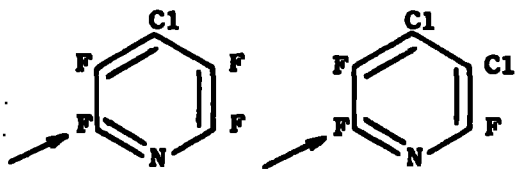
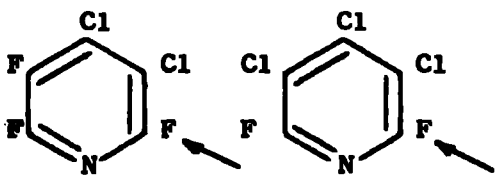
	$k_{o\text{-}Cl}/k_{o\text{-}F}$
	2·82
	2·48
	3·14
	3·16

TABLE 3.3

Effect of Para Chlorine Relative to Para Fluorine

	$k_{p\text{-}Cl}/k_{p\text{-}F}$
	26·5
	26·6

From Tables 3.2 and 3.3 it is seen that an ortho chlorine activates the system by a factor of approximately 3 relative to fluorine, while in the para position, the effect of chlorine is about 9 times as great as in the ortho position, and the system is activated by a factor of approximately 27. These values are similar to those quoted for reactions of polyfluorobenzene compounds (Tables 2.1 and 2.2) and dihalonitrobenzenes (Table 1.7).

The rate constant for the reaction of 2,6-dichlorotrifluoropyridine (7) is almost the same as that for pentafluoropyridine (1), and hence it can be concluded that for these systems a chlorine meta to the position of attack has virtually the same effect as a fluorine in the same position. From this fact an estimate for the rate constant for attack at the 2-position of pentafluoropyridine can be given as 10^{-4} l.mole^{-1}min^{-1}, as it will be virtually identical with the rate constant for attack at the 2-position of 4-chlorotetrafluoropyridine (3). There is therefore a difference in reactivity of approximately 400 between the 4- and 2-positions of pentafluoropyridine.

(b) 2,4,5,6-Tetrafluoropyridine (9) and 2,4,6-Trifluoropyridine (10)

Both of these compounds are less reactive than pentafluoropyridine. Although the rate constant for 2,4,6-trifluoropyridine is only approximate, it can be seen that its value is substantially less (by about a factor of 30) than the value for 2,4,5,6-tetrafluoropyridine.

Considering just the rate constants for 2,4,5,6-tetrafluoropyridine, attack at the 4-position is deactivated by a factor of 30·6 relative to attack at the 4-position in pentafluoropyridine. This deactivation arises from replacing a fluorine by a hydrogen at the position ortho to the position of substitution.

If it is assumed that the rate constant for attack at the 2-position of pentafluoropyridine is approximately 10^{-4} $l.mole^{-1}min^{-1}$, the rate constant for attack at the 6-position in 2,4,5,6-tetrafluoropyridine ($3·52 \times 10^{-4}$ $l.mole^{-1}min^{-1}$) is 3·5 times this figure. It can hence be concluded that in the position para to the position of substitution, a hydrogen will activate the system by a factor of approximately 3 relative to fluorine, i.e. fluorine is slightly deactivating in the para position, relative to hydrogen.

This value is of the same order as the values obtained from polyfluorobenzene compounds (Tables 2.1 and 2.2) and from halonitrobenzene compounds (Table 1.7).

From the data of Table 3.1 it is not possible to obtain a measure for the effect of hydrogen meta to the position of substitution. Attempts to prepare 3,4,5-trifluoropyridine failed.

(c) Perfluoro-3-methylpyridine (14) and Perfluoro-3,5-dimethylpyridine (15)

Rate constants for attack on both compounds shows the CF_3 group to be greatly activating in positions ortho and para to the position of attack.

A measure of the activating power of the CF_3 group in the ortho position, relative to F, is obtained by comparing the rate constants for attack at the

4-positions of pentafluoropyridine and perfluoro-3-methylpyridine: a factor of 79·9 is calculated.

An even greater activating effect is produced by a CF_3 group para to the position of substitution. The rate constant for attack at the 6-position of perfluoro-3-methylpyridine is approximately 10^4 times that for attack in the 2-position of pentafluoropyridine.

(d) Summary of Conclusions

(i) Fluoride ion is displaced much more readily than chloride ion.

(ii) Relative to fluorine, chlorine activates the system in the position ortho to the position of substitution by a factor of approximately 3, and by a factor of approximately 27 when para to the position of substitution.

(iii) Fluorine and chlorine meta to the position of substitution are virtually equivalent.

(iv) Relative to fluorine, hydrogen deactivates the system by a factor of about 30 when ortho to the position of substitution, but when para to the position of substitution, hydrogen is slightly activating by a factor of approximately 3.

(v) The CF_3 group activates the system relative to fluorine when ortho (by a factor of about 80) and para (by a factor of approximately 10^4) to the position of substitution.

(vi) The rate constant for attack at the 4-position of pentafluoropyridine is about 400 times that for attack at the 2-position.

The fact that fluoride is displaced more readily than chloride imples that the reactions are taking place by a two-step addition-elimination mechanism. The attempted rationalisations that follow have been formulated on the basis of such a mechanism.

3.5.2 Rationalisation of Results in Terms of the Iπ Effect

(a) Orientation of Substitution in Pentafluoropyridine

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 Iπ effects of the 3- and 5-fluorines. 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 (Figure 3.2), and this would be far less favourable than a transition state resulting from attack at the 4-position in which charge is accommodated on nitrogen.

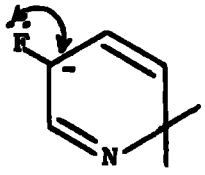


Figure 3.2

(b) Effect of Chlorine and the Trifluoromethyl Group as Substituents

On the basis of Iπ effects, replacement of the 3- and 5-fluorines by chlorine or the trifluoromethyl group will increase the rate of attack at the 4- and the 2- and 6-positions as chlorine will produce less lone pair destabilisation than fluorine, and CF_3 ought to produce no lone pair destabilisation. This activation is observed.

(c) Difficulties Arising from this Rationalisation

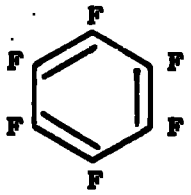
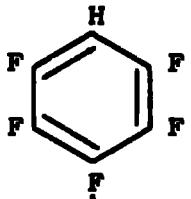
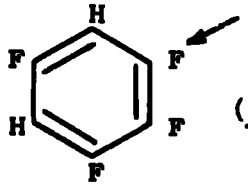
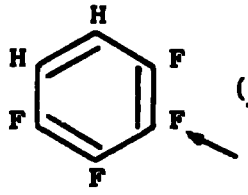
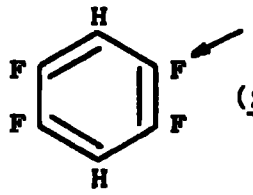
If the Iπ effect of fluorine were dominant in determining the rate and orientation of attack, hydrogen would be expected to be activating relative to fluorine at positions ortho and para to the position of substitution, as hydrogen has no Iπ effect. What has been found, however, is that the rate constants for attack at the 6-positions of pentafluoropyridine (1) and

2,4,5,6-tetrafluoropyridine (9) are comparable, and that rate reduction by a 3- or 5-hydrogen, relative to fluorine, is substantial.

Similar effects have been found for the rate constants of reactions of a series of hydrofluorobenzenes with methoxide ions in methanol. These will now be discussed.

3.5.3 Rates of Attack in Hydrofluorobenzenes

Rate constants for methoxide substitution in a series of hydrofluorobenzenes in methanol at 50° were quoted in Chapter 2 (Table 2.4) and the table is reproduced below (positions of substitution arrowed). The results were obtained by Hollyhead[100] (thesis kindly loaned by Professor J.C. Tatlow) and are also quoted in a paper by Streitwieser.[150]

Substrate		k(l.mole^{-1}sec^{-1})
	(16)	$1{\cdot}3 \times 10^{-4}$ [a]
	(17)	$1{\cdot}8 \times 10^{-4}$
	(18)	$9{\cdot}0 \times 10^{-6}$ [a]
	(19)	$1{\cdot}8 \times 10^{-6}$ [a]
	(20)	$\sim 10^{-8}$ [a]

[a] Values corrected for statistical factor

Taking the results at face value, an ortho hydrogen deactives the system by a factor of 20 (compare rate constants for pentafluorobenzene (17) and 1,2,3,5-tetrafluorobenzene (18)); a meta hydrogen deactivates the system by a factor of 100 (compare rate constants for pentafluorobenzene (17) and 1,2,3,4-tetrafluorobenzene (19)); and a para hydrogen has little effect (compare hexafluorobenzene (16) and pentafluorobenzene (17)).

The theories discussed in Chapter 2 to explain orientation of substitution in pentafluorobenzenes emphasise 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. What follows is an alternative view to account for the rate and orientation of attack. Both the polyfluoro-benzene and -pyridine systems will be considered.

3.5.4 An Alternative Rationalisation for Rate and Orientation of Substitution

(a) Hydrofluorobenzenes

(i) 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 polarisation of the sigma electrons by fluorine, leading to a build-up of positive charge at the point of substitution (Figure 3.3).

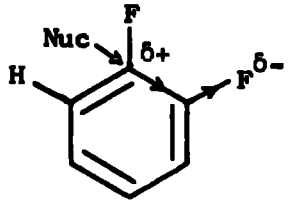


Figure 3.3

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.

(ii) Effect of Fluorine Meta to the Position of Substitution

The activating effect of fluorine relative to hydrogen at the position meta to the point of substitution results from inductive stabilisation of the negative charge in the transition state by fluorine, which is impossible in the case of hydrogen. This is shown in Figure 3.4.

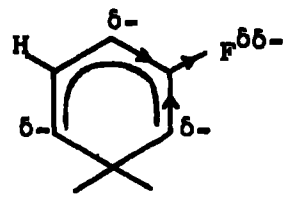
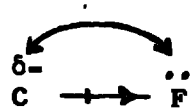


Figure 3.4

(iii) 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 destabilisation caused by electron pair repulsion of fluorine virtually cancelling out the stabilising effect of inductive electron withdrawal.



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

The orientation of substitution in pentafluorobenzene (17), 1,2,3,5-tetrafluorobenzene (18) and 1,2,3,4-tetrafluorobenzene (19) is in line with the above statement, and the low reactivity of 1,3,4,5-tetrafluorobenzene (20),

the lowest of the three tetrafluorobenzenes, is explained by its having the least number of fluorines ortho and meta to the point of substitution.

(b) Polyfluoropyridines

(i) Orientation of Attack in Pentafluoropyridine

The difference in reactivity of approximately 400 between the 2- and 4-positions, leading to exclusive replacement of the 4-fluorine in pentafluoropyridine, can be accounted for by the above hypothesis.

It is generally found that the nitrogen in the pyridine nucleus activates the 4-position more than the 2-position. In section 1.3.2 it is shown that the reactivity of 4-chloropyridine is between 1 and 10 times greater than that of 2-chloropyridine, and other results are also available to show this.[65] Attack at the 4-position in pentafluoropyridine maximises the number of ortho and meta fluorines: the 4-position has two ortho and two meta fluorines whereas the 2-position has one ortho and two meta fluorines. The observation in section 3.5.1 that in these systems an ortho fluorine is approximately 30 times more activating than hydrogen implies that the extra ortho fluorine associated with attack at position 4 increases the reactivity of that position relative to that of the 2-position by a factor of 30. The 2-position also has a para fluorine, and although its effect will be small, it will deactivate the 2-position by a factor of about 3. (This factor is obtained in section 3.5.1 from the differences in reactivity between the 6-positions of pentafluoropyridine (1) and 2,3,5,6-tetrafluoropyridine (9)).

Taking these three factors together, and assuming an approximate value of 5 for the intrinsic difference in reactivity between the 2- and 4-positions of the pyridine nucleus, a value of 450 is obtained between the reactivities of the 4- and 2-positions. This value is of the same order as that observed. (In section 3.5.1 the difference in reactivity between the 2- and 4-position of pentafluoropyridine was shown to be about 400).

(ii) Effect of Substituents

Hydrogen: This has been dealt with for the case of the hydrofluorobenzenes, and the same principles will apply for the hydrofluoropyridines.

Chlorine: It was seen in section 3.5.1 that chlorine and fluorine atoms meta to the position of substitution are virtually equivalent. As atoms at this position can only interact with negative charge in the transition state by inductive means, this implies that the inductive effects of chlorine and fluorine on a β carbon atom in these systems are also equivalent. Replacement of a fluorine by chlorine ortho to the position of attack, ought therefore not to significantly alter the charge density at the position of attack, and hence the activating effect of an ortho chlorine, relative to fluorine, can be discussed in terms of differences in transition state energy alone. The same also applies for a para chlorine, which, being removed from the point of substitution is unlikely anyway to have a significant effect on the charge density at that position.

In replacing an ortho or para fluorine by chlorine, the resulting loss of electron pair interaction with negative charge in the transition state more than compensates for the smaller stabilising (-I) effect of chlorine than fluorine. The overall effect is hence stabilising, and the system is activated.

resultant stabilising

Trifluoromethyl Group: The absence of lone pair interactions in the case of CF_3, coupled with an inductive (-I) effect of the same magnitude as that of fluorine (see discussion in Chapter 4), means that a CF_3 group ortho or para to the position of substitution will greatly stabilise the transition state relative to fluorine and will substantially activate the system.

$CF_3 \longleftarrow \overset{\delta-}{C}$ greatly stabilising

A more detailed discussion of the effects of perfluoroalkyl groups on nucleophilic substitution reactions is given in Chapter 4.

3.6 Reactions of Polychlorofluoropyridines with Diethylamine

Rate measurements were carried out for the reactions of diethylamine with the same set of chlorofluoropyridines as used for the reactions with ammonia, with the exception of pentachloropyridine. Reactions were carried out in dioxan at 25°, and the rate of reaction of pentafluoropyridine and diethylamine in nitrobenzene was also measured in order to determine the effect on the rate constant in changing to a solvent of higher dielectric constant than dioxan.

Rate constants are shown in Table 3.3. The rates are given relative to that of pentafluoropyridine, and also relative to that of 4-chlorotetrafluoropyridine for compounds in which attack occurs at the 2- or 6-position.

3.6.1 Discussion of Rate Data

Unlike the reactions with ammonia, the reactivity of the 4-position in pentafluoropyridine (1) is reduced when the 3- and 5-fluorines are exchanged for chlorine. In fact the reactivity of the 4-position in 3,5-dichlorotrifluoropyridine (12) has been so reduced that the only product observed is that resulting from attack at the 2-position.

4-Chloropyridine (3) is less reactive than pentafluoropyridine by a factor of about 80, which is not as great as the difference in reactivity of the two compounds with ammonia (a factor of about 400). For reaction at the 2- or 6-position, an ortho chlorine is also seen to be deactivating by

TABLE 3.3

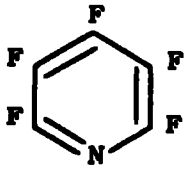
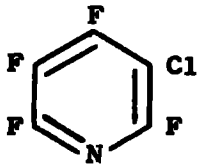
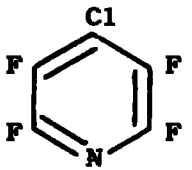
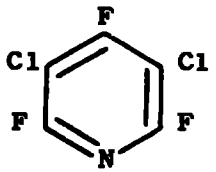
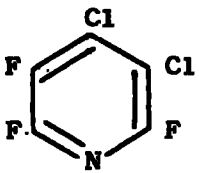
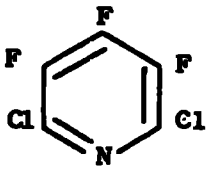
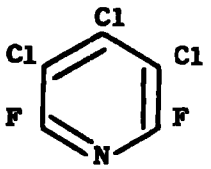
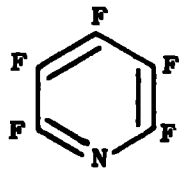
Substrate		Position of Substitution	k(l.mole^{-1}min^{-1})	Relative k	Relative k
	(1)	4	$(3{\cdot}05 \pm 0{\cdot}01) \times 10^{-1}$	1	
	(11)	4	$(5{\cdot}81 \pm 0{\cdot}03) \times 10^{-2}$	$1{\cdot}90 \times 10^{-1}$	
		6	$(1{\cdot}04 \pm 0{\cdot}01) \times 10^{-1}$	$3{\cdot}44 \times 10^{-1}$	$2{\cdot}35 \times 10^{1}$
	(3)	2 [a]	$(4{\cdot}46 \pm 0{\cdot}03) \times 10^{-3}$	$1{\cdot}46 \times 10^{-2}$	1
	(12)	2 [a]	$(6{\cdot}90 \pm 0{\cdot}04) \times 10^{-2}$	$4{\cdot}52 \times 10^{-1}$	$1{\cdot}55 \times 10^{1}$
	(4)	6	$(1{\cdot}17 \pm 0{\cdot}01) \times 10^{-1}$	$3{\cdot}34 \times 10^{-1}$	$2{\cdot}62 \times 10^{1}$

TABLE 3.3 (continued)

	(7)	4	$(1{\cdot}79 \pm 0{\cdot}01) \times 10^{-1}$	$5{\cdot}11 \times 10^{-1}$	
	(5)	2 [a]	$(4{\cdot}36 \pm 0{\cdot}02) \times 10^{-2}$	$1{\cdot}24 \times 10^{-1}$	9·98
In Nitrobenzene:					
	(1)	4	$(7{\cdot}35 \pm 0{\cdot}03) \times 10^{-1}$	2·41	

[a] Observed rate constants divided by 2.

comparison of the rate constants for 3,4-dichlorotrifluoropyridine (4) and 3,4,5-trichlorodifluoropyridine (5).

The effects of a meta chlorine relative to fluorine are variable. The reactivity of 2,6-dichlorotrifluoropyridine (7) is approximately half that of pentafluoropyridine and a smaller reduction in reactivity is produced in going from 3,5-dichlorotrifluoropyridine (12) to 3,4,5-trichlorodifluoropyridine (5). In these cases the meta chlorine causes some deactivation while the meta chlorine for the reactions with ammonia has virtually no effect. The rate constants for 3-chlorotetrafluoropyridine (11) and 3,4-dichlorotrifluoropyridine (4) (for attack at the 6-position in each case) are however virtually identical, showing in this case that a meta chlorine and meta fluorine are once again equivalent.

The effect of a para chlorine relative to fluorine is obtained by comparing the reactivities of 4-chlorotetrafluoropyridine (3) and 3,4-dichlorotrifluoropyridine (4). The latter is 26·2 times more reactive than the former. This factor for the activating effect of a para chlorine is in agreement with the factors obtained for the reactions with ammonia (26·5 and 26·6).

In changing the solvent from dioxan to nitrobenzene, the rate constant for the reaction of pentafluoropyridine is increased by a factor of 2·4.

3.6.2 Rationalisation of Results

Most of the results can be accounted for in terms of the large steric requirements of diethylamine as compared to ammonia. In many cases the steric effects far outweigh the electronic factors as discussed for the reactions of ammonia.

The effect of replacing the 3-fluorine in pentafluoropyridine by chlorine increases the steric crowding at the 4-position thus reducing the reactivity at that position for reaction with diethylamine, which then reacts

preferentially in the 6-position. This position is less sterically crowded and is activated by the para chlorine. Addition of a second chlorine, giving 3,5-dichlorotrifluoropyridine (12), reduces the rate of attack at the 4-position still further, to such a point that no product resulting from attack at this position is given. The rate of attack ortho to nitrogen is also reduced owing to the steric effect of the second chlorine.

It is likely that the 3- and 5-fluorines in pentafluoropyridine are also sterically affecting the rate of attack at the 4-position. This would explain the smaller difference in reactivity between pentafluoropyridine (1) and 4-chlorotetrafluoropyridine (3) for diethylamine than for ammonia. As there is only one fluorine atom ortho to the 2-position, the steric effects for substitution in 4-chlorotetrafluoropyridine will be less than in pentafluoropyridine.

The deactivation caused by a meta chlorine in the cases cited earlier can be explained in terms of a secondary steric effect. By replacing the 2- and 6-fluorines in pentafluoropyridine by chlorine, the greater steric effect of the chlorines displaces the 3- and 5-fluorines towards the 4-position, thus increasing the steric crowding at that position and reducing the reactivity (Figure 3.5).

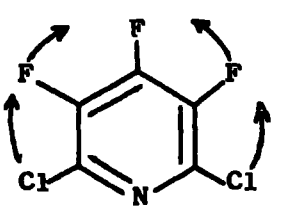


Figure 3.5

A similar effect occurs by replacing the 4-fluorine of 3,5-dichlorotrifluoropyridine (12) by chlorine. The resulting displacement of the 3- and 5-chlorines lowers the reactivity of the 2-position, relative to the 2-position in 3,5-dichlorotrifluoropyridine (Figure 3.6).

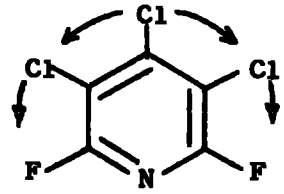


Figure 3.6

It is only when steric hindrance at the position of substitution is not altered by the replacement of fluorine by chlorine, that the relative effects of fluorine and chlorine are the same as for the reactions with ammonia. The rate constants for attack at the 6-position of 3-chlorotetrafluoropyridine (11) and 3,4-dichlorotrifluoropyridine (4) are almost the same because the steric effect of the 5-fluorine on the 6-position is not altered by replacing the 4-fluorine by chlorine. Similarly, the replacing of the 3-fluorine in 4-chlorotetrafluoropyridine by chlorine does not affect the steric environment of the 6-position, so the full activating effect of a para chlorine relative to fluorine is seen in comparing the reactivities of the 6-positions of 4-chlorotetrafluoropyridine (3) and 3,4-dichlorotrifluoropyridine (4).

3.6.3 Effect of Change of Solvent

The increase in rate constant (a factor of 2·5) for the reaction of pentafluoropyridine in changing the solvent from dioxan to nitrobenzene, is similar to the doubling of the rate constant observed with the same solvent change for the reaction of 2,4-dinitrochlorobenzene with p-toluidine as found by Shein.[143] It has been proposed[7] that an increase in polarity of the medium must make possible an increase in reaction rates for those reactions in which a larger charge separation occurs in the transition state than in the initial state: nucleophilic substitution reactions with amines fall into this category. Although the dielectric constants for nitrobenzene (ϵ = 34·8) and

dioxan (ϵ = 2·2) are different, in the reaction cited above there was only a doubling in rate in going from dioxan to nitrobenzene, whereas there has been found an 8-fold increase in rate constant for the same reaction in going from benzene to dioxan,[151] which have almost identical dielectric constants. The similarity in rate constants for reactions in dioxan and nitrobenzene has been explained[151,152] by the greater ability of dioxan than nitrobenzene to stabilise the transition state by hydrogen bonding to the protons of the amine. This partially compensates for the smaller dielectric constant of dioxan than nitrobenzene.

3.7 Reactions of Tetrafluoro- and Tetrachloro-diazines with Ammonia

Reactions were carried out in 60/40 dioxan/water at 25°. The aim of the rate measurements was to determine the effect of adding a second aza-group to the pyridine nucleus, and also to compare the reactivities of corresponding tetrafluoro- and tetrachloro-diazines. Rate measurements for the reaction of tetrachloropyrazine were not carried out owing to the assumed low reactivity of the compound.

Rate constants are shown in Table 3.4. Values for the fluorodiazines are given relative to the value for the 4-position in pentafluoropyridine, and those for the chlorodiazines relative to the approximate value for pentachloropyridine.

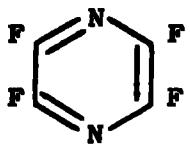
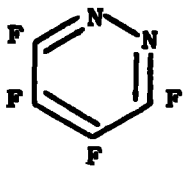
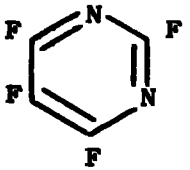
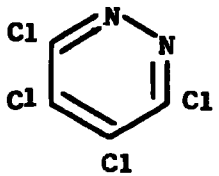
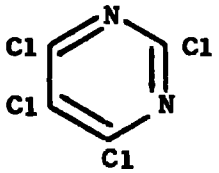
3.7.1 Discussion of Results

(a) Tetrafluorodiazines

(i) Activation Caused by the Second Aza Group

Where substitution occurs para to a nitrogen, i.e. in tetrafluoropyridazine (22) and -pyrimidine (23), the rate constants are higher than for pentafluoropyridine, showing that the second aza group is activating the system. The most reactive of the diazines, tetrafluoropyrimidine (23), has a nitrogen

TABLE 3.4

Substrate		Position of Substitution	k(l.mole^{-1}min^{-1})	k Relative to 	k Relative to 
	(21)	2	$(3{\cdot}04 \pm 0{\cdot}04) \times 10^{-3}$	$7{\cdot}45 \times 10^{-2}$	
	(22)	4	$1{\cdot}51 \pm 0{\cdot}03$	$3{\cdot}70 \times 10^{1}$	
	(23)	4	$(8{\cdot}07 \pm 0{\cdot}06) \times 10^{1}$	$1{\cdot}98 \times 10^{3}$	
	(24)	4	$(6{\cdot}45 \pm 0{\cdot}05) \times 10^{-4}$		$\sim 6 \times 10^{1}$
	(25)	4	$(1{\cdot}85 \pm 0{\cdot}02) \times 10^{-1}$		$\sim 2 \times 10^{4}$

All values of rate constant are corrected for statistical factors.

atom both ortho and para to the position of substitution, and as the nitrogens are directly co-ordinated to the reaction centre, they are in the optimum position for stabilisation of negative charge in the transition state. The 2-nitrogen in tetrafluoropyridazine is not in a position where charge is situated in the transition state, and so the major component of its activating ability will arise from inductive effects.

Tetrafluoropyrazine (21) is less reactive than pentafluoropyridine, but its rate constant is greater by a factor of about 30 than the rate constant for attack at the 2-position of pentafluoropyridine (c. 10^{-4} $l.mole^{-1}min^{-1}$). This increase in rate constant caused by placing an aza-group meta to the position of substitution, is similar in magnitude to the difference in rate constant between attack at the 4-positions of pentafluoropyridine and tetrafluoropyridazine (22), which is also caused by the insertion of an aza group meta to the point of substitution.

(ii) Difference in Reactivity between Tetrafluoropyridazine and Tetrafluoropyrazine

It was seen in section 1.3.3 that the reactivities of 2-chloropyrazine and 4-chloropyridazine were similar, and although there is no data available for the analogous fluoro compounds, it is reasonable to assume that these, too, will be similar to each other. The comparatively great difference in reactivity between the 4-position of tetrafluoropyridazine (22) and the 2-position of tetrafluoropyrazine (21) is explicable in terms of the principles outlined previously i.e. rate and orientation of attack are determined largely by the number of ortho and meta fluorines. Tetrafluoropyridazine, having two fluorines ortho and one meta to the position of substitution, would be expected to be more reactive than tetrafluoropyrazine, which has only one fluorine ortho and one meta to the position of substitution.

(iii) Orientation of Substitution

The orientation of substitution in tetrafluoro-pyrimidine (23) and -pyridazine (22) is also explicable in terms of the principles developed in section 3.5.4, i.e. orientation is such as to maximise the number of ortho and meta fluorines

(b) Tetrachlorodiazines

The ratio of reactivities of tetrachlorpyrimidine (25): tetrachloro-pyridazine (24) : pentafluoropyridine (1) is found to be approximately 20,000 : 60 : 1, which reflects the activating effect of a second aza-group ortho (in the case of pyrimidine) and meta (in the case of pyridazine) to the position of substitution.

The tetrachlorodiazines both react more slowly than the corresponding tetrafluorodiazines: a factor of about $2{\cdot}5 \times 10^3$ for the pyridazines and a factor of about $4{\cdot}5 \times 10^2$ for the pyrimidines. This difference in reactivity can be largely attributed to the reactions operating by an addition-elimination mechanism.

It has been found that 4-chloropyrimidine is only 2·5 times more reactive than 2-chloropyrimidine for the reaction with piperidine in ethanol,[153] whereas in both tetrachloro-pyrimidine and -pyridazine attack appears to occur exclusively at the 4-positions with no observable product arising from attack at the 2-positions. The reason for the orientation is not as obvious as for the tetrafluoro-diazines, as a para chlorine is activating relative to both fluorine and hydrogen. It was observed in the chlorofluoropyridine compounds that a para chlorine was about 27 times more activating than a para fluorine, which in turn was about 3 times less activating than hydrogen. Hence relative to hydrogen, a para chlorine is activating by a factor of about 9. Similarly an ortho chlorine, relative to hydrogen, activates by a factor of about 90

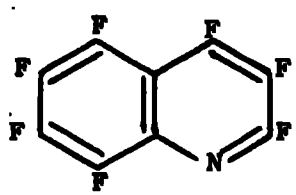
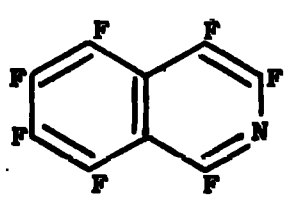
(a factor of 3 relative to fluorine which is 30 times more activating than an ortho hydrogen).

If in going from the monochloro-pyrimidines and -pyrazines to the tetrachloro compounds, the slightly greater reactivity of the 4- than 2-position (about a factor of 3) is preserved, then application of the above values for the activating power of an ortho and para chlorine relative to hydrogen leads to the conclusion that the 4-positions in tetrachloro-pyrimidine and -pyridazine are about 30 times more reactive than the 2-positions. A difference in reactivity of this magnitude would lead to the formation of only 3 or 4% of products arising from attack at the 2-position in each case.

3.8 Reactions of Heptafluoro-quinoline and -isoquinoline with Ammonia

Rate measurements were carried out in 60/40 dioxan/water at 25°, and the rate constants are shown in Table 3.5.

TABLE 3.5

Substrate	Position of Substitution	k(l.mole^{-1}min^{-1})	k Relative to 
 (26)	4	(2·56 ± 0·02) x 10^{-1}	6·27
	6	(1·13 ± 0·01) x 10^{-1}	2·80
 (27)	1	(9·47 ± 0·04) x 10^{-2}	2·32

It can be seen that both the compounds are more reactive than pentafluoro-pyridine, which shows the activation caused by the benzene ring.

The 2- and 4-positions in heptafluoroquinoline (26) and the 1-position in heptafluoroisoquinoline (27) were found to have similar reactivities. This is in line with the similar reactives of 2- and 4-chloroquinoline and 1-chloroisoquinoline (Tables 1.12 and 1.13).

3.9 A Note on Base Catalysis

In the foregoing discussion, it has been assumed that the nucleophilic substitution reactions take place by an addition-elimination process. This assumption is based on the fact that chloride is displaced much less readily than fluoride from the systems. It might be expected, then, that as amines were used as nucleophiles, base catalysis would occur, and the rate constants be dependent on nucleophile concentration. This effect was not encountered in the reactions studied, as rate constants remained effectively constant throughout each run in dioxan, 60/40 dioxan/water and nitrobenzene, even though the base concentration, about 0·07 moles l^{-1}, more than halved during the percentage of the reaction (about 75%) thoughout which instantaneous rate constants were measured. Doubling the initial base concentration did not obviously increase the rate constants. If these reactions are sensitive to base concentration, it would need a much greater change in base concentration than encountered in the reactions studied to noticeably effect the rate constants.

That the rate constants are insensitive to base concentration in the range of base concentration used is supported by the results of Shein and Rodionov[101] who showed that rate constants for the reaction of hexafluorobenzene and piperidine in ethanol were increasingly sensitive to base concentration above about 1 mole l^{-1} base concentration, but below a piperidine concentration of about 0·2 moles l^{-1}, rate constants varied very little with piperidine concentration.

CHAPTER 4

RATE MEASUREMENTS FOR REACTIONS OF PERFLUOROALKYLBENZENES WITH AMMONIA

4.1 Introduction

Octafluorotoluene[83,84] and decafluoroethylbenzene[85] are known to react with nucleophiles exclusively in the position para to the perfluoroalkyl group. Rate measurements for the reactions of octafluorotoluene with nucleophiles have shown the CF_3 group to increase the rate of reaction relative to fluorine by a factor of 10^4-10^5 (see Tables 2.1, 2.2 and 2.3). Rate measurements for the reactions of other perfluoroalkylbenzene compounds have not been reported.

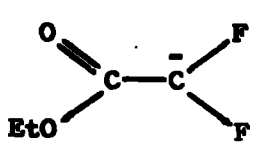
The aim of the present investigation was to observe the effects of the CF_3, CF_2CF_3, $CF(CF_3)_2$ and $C(CF_3)_3$ groups on the reactivities of the perfluoroalkylbenzene series, and to determine whether there was any evidence for the occurrence of the process of fluoride ion hyperconjugation.

Evidence for and against the general occurrence of fluoride ion hyperconjugation will be discussed, followed by rationalisation of the observations by alternative mechanisms.

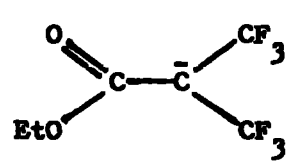
4.2 Evidence For and Against the Occurrence of Fluoride Ion Hyperconjugation

4.2.1 Aliphatic Systems

It is generally found that a β fluorine is able to stabilise a negative charge to a much greater extent than an α fluorine: the estimated pK_a values for species (28) and (29) are 25 and 14 respectively.[155]

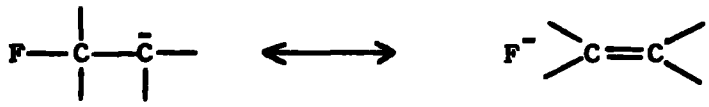


(28)



(29)

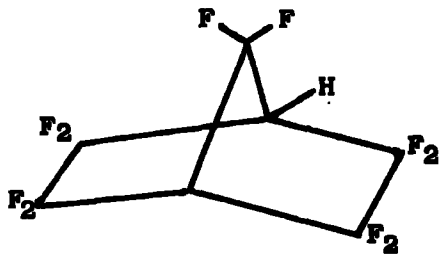
Andreades[156] has attributed this stabilising ability of a β fluorine to the occurrence of fluoride ion hyperconjugation, which is not possible in the case of an α fluorine. The process is represented by the following resonance canonicals (30):



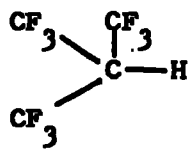
(30)

The same effect has also been proposed to explain the large barrier to rotation about the carbon-carbon bond found for the species $F\text{-}CH_2\text{-}\bar{C}H_2$.[157]

The significance of fluoride ion hyperconjugation has been investigated by the measurement of the relative rates of base catalysed hydrogen-tritium exchange for 1-H-undecafluorobicyclo[2.2.1]heptane (31) and tris(trifluoromethyl)methane (32).[150]



(31)



(32)

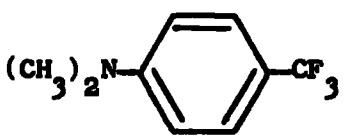
As the intermediate carbanion from (31) is forced to remain pyrimidal, there is far less chance of stabilisation by hyperconjugation than for (32), so for the rate of exchange, it is predicted that $k_{(32)} >> k_{(31)}$ if hyperconjugation is involved to any significant degree. It was found[158] that $k_{(31)}$ was larger than $k_{(32)}$ by a factor of about 5, which was explained by stabilisation of the intermediate carbanion from (31) by inductive effects. It would therefore appear that fluoride ion hyperconjugation were not playing a significant role in these reactions.

4.2.2 Aromatic Systems

Methods used to obtain evidence for and against fluoride ion hyperconjugation in aromatic compounds have been dipole moment measurements, n.m.r. studies, and investigations into chemical reactivities. These will be discussed in turn.

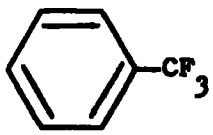
(a) Dipole Moment Measurements

It has been found[159] that the dipole moment of p-dimethylaminobenzotrifluoride (33) is greater by 0·43D than that calculated from the vector sum of the dipole moments of benzotrifluoride (34) and dimethylaniline (35).



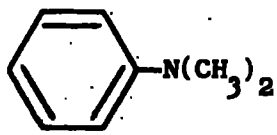
(33)

μ = 4·62D



(34)

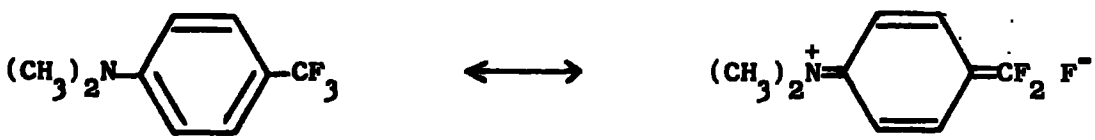
μ = 2·61D



(35)

μ = 1·58D

This difference has been interpreted in terms of the following resonance forms, (33a) and (33b).[159]

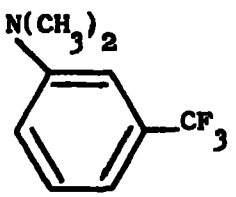


(33a) (33b)

The suggestion that fluoride ion hyperconjugation is responsible for the increase in dipole moment is not, however, compatible with other results. Sheppard[160] has shown that p-$(CF_3)_2CF\cdot C_6H_4\cdot N(CH_3)_2$ also has an enhanced dipole moment. In this case the difference between the observed value (4·71D) and the calculated value (4·26D) is 0·45D which is very similar to the difference found for (33). Were hyperconjugation occurring to any major

extent, no-bond resonance involving C-CF_3 would have to be as important as for C-F to account for the observations. This is obviously not the case as the acidity of HF is at least 10^{30} times greater than HCF_3.

Another observation which throws doubt on the involvement of fluoride ion hyperconjugation in determining the size of dipole moments, is that the dipole moment of N-N-dimethyl-3-trifluoromethylaniline (36) is enhanced to a similar extent (0·30D) to those of the previous two compounds.[161]

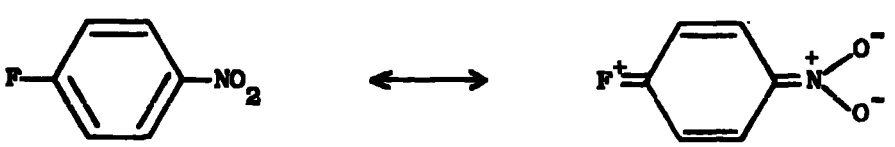


(36)

In this case resonance interaction of the CF_3 and $N(CH_3)_2$ groups is impossible.

(b) N.m.r. Investigations

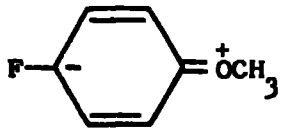
The fluorine chemical shifts of para-substituted fluorobenzenes have been found to be dependent on solvent polarity when the substituents are electron-withdrawing and capable of resonance interaction with the para fluorine.[162] As the polarity of solvent increases, the fluorine peak is shifted to lower field. The phenomenon has been interpreted[162] as arising from an enhancement in polar solvents of resonance forms such as (37b).



(37a) (37b)

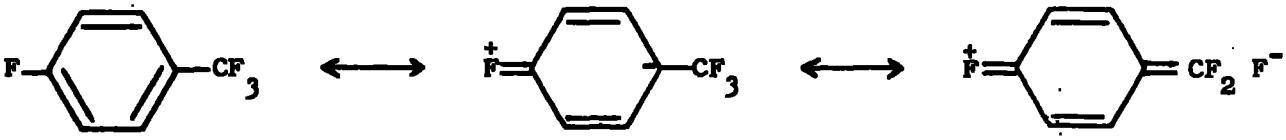
It has also been found that the charges need to be at the periphery of the molecule to produce solvent response;[163] hence fluorine resonances of

structures such as (38) are solvent insensitive.



(38)

It would now seem possible to use this information to distinguish between structures (39b) and (39c) in p-fluorobenzotrifluoride (39a).



(39a) (39b) (39c)

The chemical shift of the ring fluorine in p-fluorobenzotrifluoride does show small solvent dependence,[163] which suggests some participation of fluoride ion hyperconjugation. However, it has also been found[160] that the trifluoromethyl fluorines of (39a) have chemical shifts which are solvent insensitive. It would be expected that if structure (39c) were important all the fluorine peaks would undergo solvent shifts. The importance of fluoride ion hyperconjugation to the observed chemical shifts is thus open to question.

(c) Chemical Reactivity Investigations

Hammett reactivity parameters (σ values) can be used in determining whether resonance interaction of a substituent with the rest of the molecule is affecting the reactivity of the molecule. The σ values determined for substituents from ionisation constants of benzoic acids are found to be unsuitable to describe the behaviour of substituents such as the para nitro group, in reactions in which they can co-ordinate by resonance to the reaction centre, as in the ionisations of para substituted phenols. The sigma constants

in these cases (termed σ^-) are larger than the σ values obtained where resonance interaction is not possible e.g. were the substituent is meta to the reaction centre.

An indication of the importance of hyperconjugation for the CF_3 group would be if σp values for CF_3 were greater for reactions in which delocalisation of negative charge in the benzene ring occurred (ionisation of phenols and anilines) than for reactions in which no such delocalisation occurred (ionisation of benzoic acids).

The σ values for p-CF_3 are found to be greater in the first class of reactions than the second,[164] which would appear to indicate participation of fluoride ion hyperconjugation. However, σ values for the m-CF_3 group also increase to a similar extent.[164] This is not the case for groups such as NO_2, which delocalise charge by classical resonance: for these groups only the para isomer shows enhanced σ-values. From these observations the occurrence of hyperconjugation is not substantiated.

Of greater significance are the inductive (σ_I) and resonance (σ_R) components of the reactivity parameters. These have been calculated for the CF_3, CF_2CF_3 and $(CF_3)_3CF$ groups from pK_a measurements of benzoic acids and anilines.[160] The values are shown in Table 4.1.

TABLE 4.1

Substituent	σ_I	σ_R
CF_3	0·33-0·44	0·18
CF_2CF_3	0·41	-
$CF(CF_3)_2$	0·39	0·17-0·26

The resonance and inductive effects of the CF_2CF_3 and $CF(CF_3)_2$ groups are similar to those of the CF_3 group. It would appear, then, that fluorine

no-bond resonance is not contributing significantly to the electronic structures of the molecules; if it were, the σ_R values for CF_3 would be expected to be greater than for the other groups.

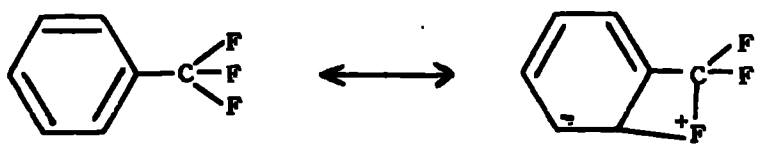
Recent measurements of the thermodynamic parameters (ΔH^o, ΔS^o and pK_a) for the ionisations in aqueous solution of m- and p-hydroxybenzotrifluorides have shown that fluoride ion hyperconjugation is of little importance in these compounds,[165] as values of the individual parameters were found to be very similar for both compounds. Resonance interaction between the CF_3 group and the reaction site could only occur for a p-CF_3 substituent, so if such interaction were appreciable, differences in the values of the corresponding parameters in each compound would be expected.

4.2.3 Alternative Rationalisations

Rationalisation of the effects of perfluoroalkyl groups, in particular the CF_3 group, will now be discussed in terms other than fluoride ion hyperconjugation. Two major mechanisms have been advocated to explain the observations: the p-π mechanism and the π-inductive mechanism. These will be discussed in turn.

(a) The p-π Mechanism

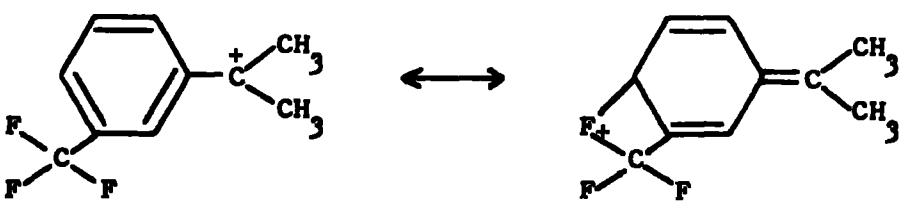
This process has been proposed by Sheppard,[160] who suggests that interaction occurs between the unshared p-electrons of fluorine and the π-system of the aromatic ring. Electron density is returned to the ring, partly counteracting the normal electron withdrawing power of fluorine. The p-π effect is represented as structures (40a) and (40b).



(40a) (40b)

This interpretation is based on the correlation of ^{19}F chemical shifts of the fluorines of benzotrifluoride with σ parameters. It has been criticised[164] in that such a relationship between chemical shift and σ values is quite normal, and that there appears to be no reason for postulating the p-π mechanism to rationalise such behaviour.

Also, if the p-π mechanism were important, then the value of σ^+ should be less than σ (the smaller the value of σ^+, the greater the +M effect of the group) for m-CF_3, i.e. contribution from resonance structure (41b) should accelerate the rate of solvolysis of m-trifluoromethylcumyl chloride.

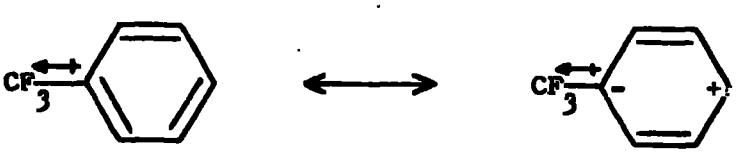


(41a) (41b)

It is found, however, that $\sigma^+ > \sigma$ for both m- and p-CF_3.[164]

(b) The π-inductive Mechanism

This mechanism has been favoured by a number of workers as a rationalisation of the substituent effects of the CF_3 group.[161,164] The powerful electron-withdrawing effect of the trifluoromethyl group produces a dipole external to the benzene ring, which polarises the π-electrons of the ring so as to enhance delocalisation of negative charge. This is shown in structures (42a) and (42b).



(42a) (42b)

The mechanism explains the enhanced dipole moments of molecules such as p-dimethylaminobenzotrifluoride, and can also be used to account for the enhanced dipole moment of N-N-dimethyl-3-trifluoromethylbenzene,[161] in which the CF_3 group is meta to the amine group.

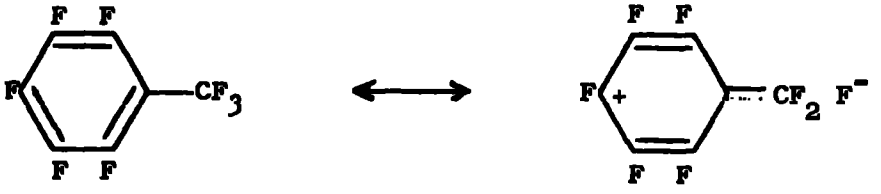
The more than normal enhancement of reactivity (shown by greater σ values) caused by a p-CF_3 group in reactions requiring delocalisation of negative charge is accounted for by this mechanism. Also, as the inductive effects of the perfluoroalkyl groups are known to be approximately equal,[154] the similarities in the σ_R values of the perfluoroalkyl groups and the dipole moments of $p\text{-}CF_3 \cdot C_6H_4 \cdot N(CH_3)_2$ and $p\text{-}(CF_3)_2CF \cdot C_6H_4 \cdot N(CH_3)_2$ are consistent with the π-inductive mechanism.

The mechanism is also in line with the simple inductive effects used to rationalise reactivity differences in highly fluorinated aliphatic systems (e.g. Reference 158).

4.3 Consequences of the Occurrence of Hyperconjugation in Nucleophilic Substitution Reactions of Perfluoroalkylbenzenes

The above discussion has been concerned mainly with the effects of the possible occurrence of fluoride ion hyperconjugation on the ground states of molecules. In nucleophilic substitution reactions it is necessary to discuss the possible effects of hyperconjugation on both the ground and transition states in order to determine the overall effect on the reaction.

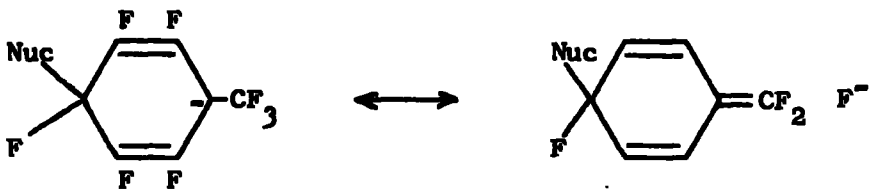
For octafluorotoluene, ground state canonicals (43a) and (43b) could be written if fluoride ion hyperconjugation were appreciable.



(43a) (43b)

The existence of canonical (43b) will increase the electrophilicity of the point of substitution and hence will activate the system towards nucleophilic attack.

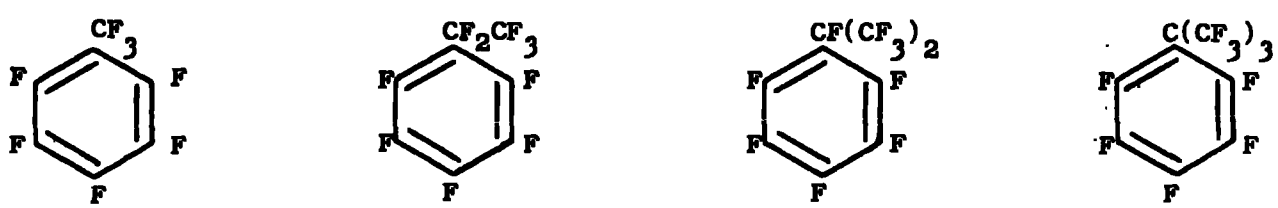
In the transition state, occurrence of fluoride ion hyperconjugation would lead to the formation of canonical (44b).



(44a) (44b)

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

If this were the case, successive replacement of the fluorines of the CF_3 group by CF_3 groups would reduce the magnitude of fluoride ion hyperconjugation and correspondingly reduce the reactivities of the resulting compounds. Determination of rate constants for the nucleophilic substitution reactions of octafluorotoluene (45), perfluoroethylbenzene (46), perfluoroisopropylbenzene (47) and perfluoro-t-butylbenzene (48) under the same conditions, ought to reveal whether such a situation were occurring, i.e. whether the reactivities of the compounds decreased down the series (45)-(48).



(45) (46) (47) (48)

The aim of the present work was to investigate this.

4.4 Choice of System in Present Study

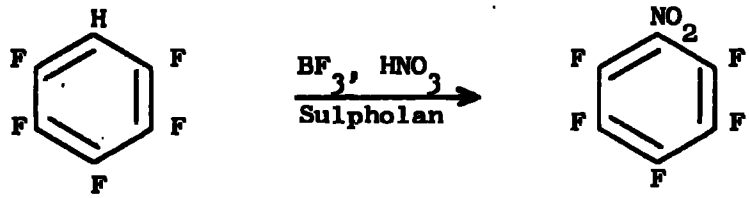
In an attempt to relate the reactions of the perfluoroalkylbenzenes with those of the substrates discussed in Chapter 3, ammonia was chosen as nucleophile. Both perfluoroisopropylbenzene and perfluoro-t-butylbenzene were found to be insoluble in 60/40 dioxan/water (v:v) and so a solvent of 77/23 dioxan/water (v:v) was used for all the substrates.

Preliminary investigation of the reaction of perfluorotoluene with ammonia in 77/23 dioxan/water at 25° showed the reaction to be too slow for accurate determinations: the most suitable temperature was found to be 92° (accurate value: 92·23°). This temperature was used in all rate measurements.

4.5 Preparation of Substrates

It was necessary to prepare perfluoroisopropyl- and perfluoro-t-butylbenzene. Both perfluorotoluene and perfluoroethylbenzene were provided, and these were purified before use.

Pentafluoronitrobenzene (49) was the precursor for the preparation of the first two compounds, and this was prepared by the method of Tatlow and co-workers,[166] from the reaction of pentafluorobenzene (17) with boron trifluoride and fuming nitric acid in sulpholan.

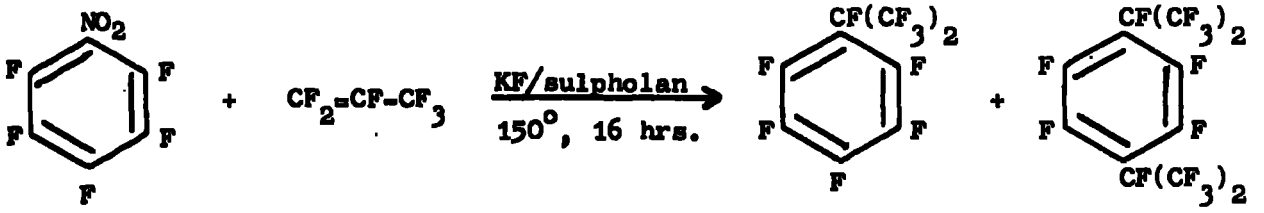


(17) (49)

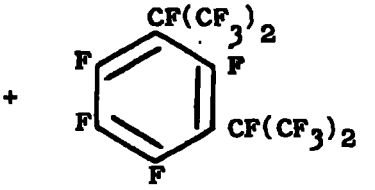
80%

(a) Perfluoroisopropylbenzene

This was prepared by the fluoride ion-initiated reaction of hexafluoropropene and pentafluoronitrobenzene in dry sulpholan.



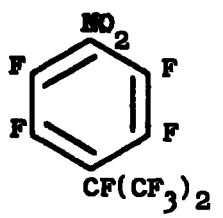
(47) (50)



(51)

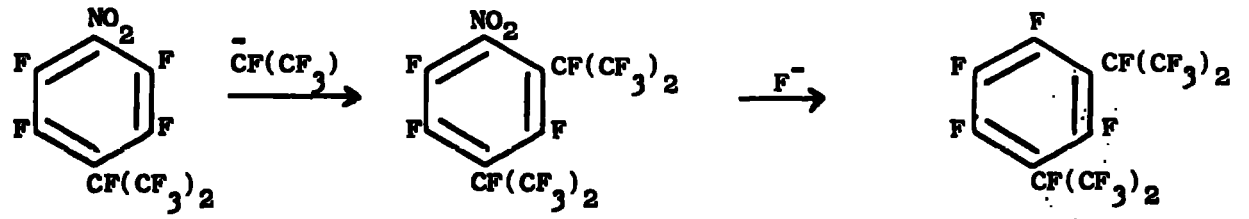
Perfluoroisopropylbenzene (47) and a mixture of disubstituted products, (50) and (51), were obtained.

The products obtained for the same reaction at 120° are shown in Section 2.1.4. It would appear that the reaction proceeds with initial substitution by $\bar{C}F(CF_3)_2$ para to the NO_2 group to give (52), which can then lose NO_2 by displacement with either F to give (47), or $\bar{C}F(CF_3)_2$ to give (50).



(52)

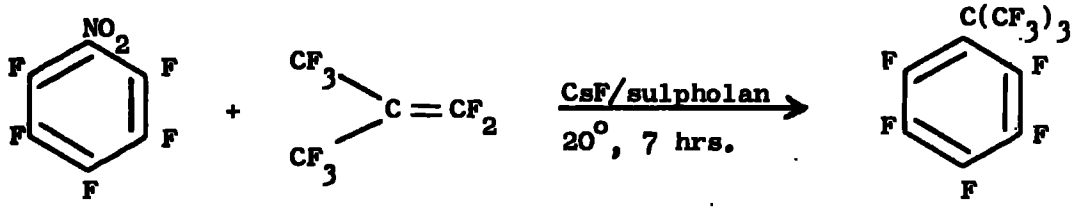
Compound (51) is formed by substitution ortho to NO_2 by $\bar{C}F(CF_3)_2$ in (52), followed by displacement of the nitro-group by fluoride ion:



(52) (51)

(b) Perfluoro-t-butylbenzene

Perfluoro-t-butylbenzene (48) was prepared via a method similar to that of Jackson,[105] by the reaction of perfluoroisobutene, caesium fluoride and pentafluoronitrobenzene. The product consisted of perfluoro-t-butylbenzene plus starting material. This compound has recently been prepared by Knunyants and co-workers.[106]



(48)

28%

4.6 Kinetic Methods and Rate Constants Calculations

Reactions were followed by titrating the residual ammonia against standard acid. (Details are given in Section 5.6). Second order rate constants (k_{II}) were evaluated using the formula:

$$k_{II}.t = \frac{1}{a-2b} \ln \frac{b}{a} \left(\frac{a-2x}{b-x}\right)$$

where a, b and x have their usual meanings (see Section 3.4). Using this equation, constant second order rate constants were obtained throughout each run.

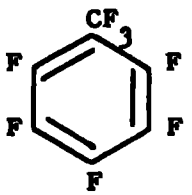
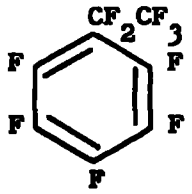
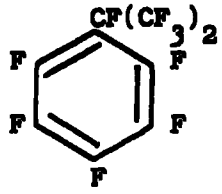
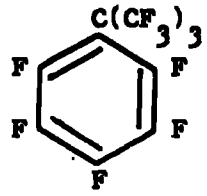
Errors were calculated by the procedure described in Section 3.4.

4.7 Discussion of Results

Rate constants for the reaction of perfluoroalkylbenzene with ammonia in 77/23 dioxan/water at 92·23° are shown in Table 4.2. Attack occurred 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

TABLE 4.2

Substrate		10^2 k(l.mole^{-1}min^{-1})
	(45)	4·02 ± 0·02
	(46)	8·62 ± 0·05
	(47)	6·02 ± 0·03
	(48)	10·4 ± 0·1

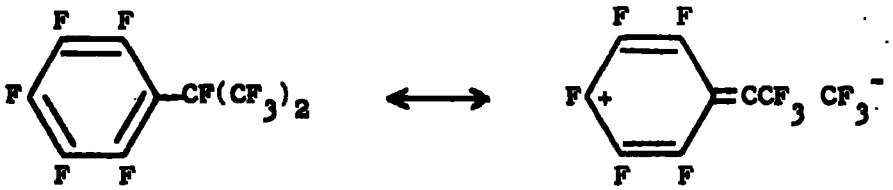
proceed over a period of one week. This is perhaps not surprising, as the data of Tables 2.2 and 2.3 show there to be a difference in reactivity of about 4 x 10^4 between perfluorotoluene and pentafluorobenzene. Such a difference in the system under study would give a rate constant of about 10^{-6} l.mole^{-1}min^{-1} for the reaction of pentafluorobenzene. Owing to the similarity in reactivity between hexafluoro- and pentafluoro-benzene, this figure would also represent the value of rate constant for hexafluorobenzene (for attack at one position in the ring).

4.8 Interpretation of Rate Data

(a) In Terms of Negative Ion Hyperconjugation

It can be seen from Table 4.2 that all four substrates are of similar reactivity, especially when compared to the estimated value for pentafluorobenzene: in fact, octafluorotoluene is the least reactive of the four. It was proposed in Section 4.3 that if fluoride ion hyperconjugation were important, octafluorotoluene would be expected to be the most reactive of the perfluoroalkylbenzenes, with rate constants decreasing down the series from octafluorotoluene to perfluoro-t-butylbenzene. The observations are in direct contrast to this situation, suggesting that the process of fluoride ion hyperconjugation is unimportant.

It might be suggested that hyperconjugation involving CF_3^- is as important as that involving F^-. This process would lead to the formation of species (47b) from perfluoroisopropylbenzene (47a).



(47a) (47b)

If hyperconjugation involving F^- and CF_3^- were occurring to the same extent, the reactivities of the four alkyl benzenes would be similar, and this could account for the observed situation. Hyperconjugation involving CF_3 is, however, highly unlikely. As stated before, the acidity of HF is at least 10^{30} times greater than that of HCF_3.

From the results obtained, it would appear that negative ion hyperconjugation is playing little or no role in the reactions of perfluoroalkylbenzenes with nucleophiles.

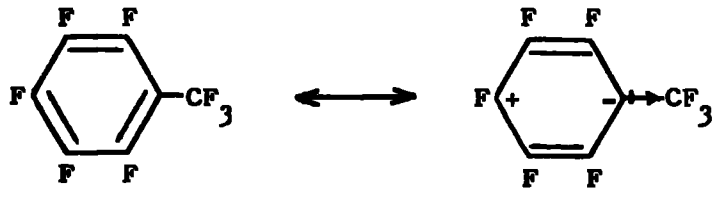
(b) In Terms of Inductive Effects

It was stated earlier that the inductive effects of F and CF_3 have been found to be very similar. Evidence for the similarity of the inductive (-I) effects of F and CF_3[154] is obtained from the similarity of their σ_I values, and also from the σ_I values of the groups OCF_3 (0·47) and OCF_2CF_3 (0·48).[154] (The σ values are calculated from the dissociation constants of the meta substituted benzoic acids).

In aliphatic systems, measurements of acid dissociation constants also indicate similarities in the inductive effects of F and CF_3. Although it has not been possible to find the dissociation constant of pentafluoropropionic acid, the K_a values of CF_3CO_2H and $n\text{-}C_3F_7CO_2H$ (0·59 and 0·68 respectively at 25°),[167] indicate that replacement of F by CF_3 has comparatively little effect on acid strength.

It is possible to account for the similarities in rate constants of the perfluoroalkylbenzenes and also for the great activation caused by the perfluoroalkyl groups, solely in terms of inductive effects.

In Section 4.2.3, the π-inductive effect was used to explain certain properties of trifluoromethylbenzene compounds, such as enhanced dipole moments. Application of this effect to the ground state of octafluorotoluene would lead to structures (45a) and 45b).

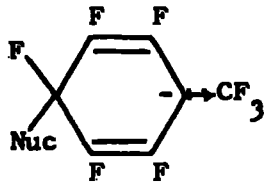


(45a) (45b)

Formation of structure (45b) 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

π-electrons. Exchange of the fluorines of the CF_3 group for CF_3, i.e. in moving along the series CF_3, CF_2CF_3, $CF(CF_3)_2$, $C(CF_3)_3$, will not appreciably alter this inductive activation, as the inductive effects of F and CF_3 are similar.

In the transition state, stabilisation of the negative charge by CF_3 is achieved by a simple -I effect (53), and the magnitude of the stabilisation will be the same for the other perfluoroalkyl groups.



(53)

Such stabilisation is impossible in the case of hexafluorobenzene, owing to the destabilisation caused by the lone pairs of fluorine, which is discussed in Section 3.5.4, offsets the -I stabilisation of fluorine.

The result of the above effects is that the perfluoroalkylbenzenes are greatly activated towards nucleophilic attack as compared to hexafluorobenzene or pentafluorobenzene, and also that the individual perfluoroalkylbenzenes have very similar reactivities.

Any trend in the measured rate constants may be due to a number of minor effects.

4.9 Rationalisation of Orientation of Substitution

The orientation of substitution in perfluoroalkylbenzenes, i.e. exclusively para to the substituent, can be accounted for in terms of the ideas developed in Section 3.5.4: the nucleophile attacks in such a position as to maximise the number of ortho and meta fluorines.

EXPERIMENTAL

Instrumentation

(i) Preparative Work

Infra-red spectra were recorded on a Grubb-Parsons 'Spectromaster' spectrometer. Liquid samples were 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 a Varian A56/60D spectrometer, operating at 60 and 56·4 MHz. respectively, and at a temperature of about 40°, the standard temperature of the probe.

Mass spectra were recorded using an A.E.I. M.S.9 spectrometer, and all molecular weights were determined using this instrument.

Ultra-violet spectra were recorded using a Unicam S.P.800 spectrophotometer.

Carbon, nitrogen and hydrogen analyses were obtained using a Perkin-Elmer 240 Elemental Analyser, and analysis for halogens was as described in the literature.[168]

Analytical vapour phase chromatography (v.p.c.) was performed on a Perkin-Elmer 'Fractometer', model 451 or a Pye Chromatograph, series 104, using columns packed with silicone elastomer on Celite (column 'O') and di-n-decylphthalate on Celite (column 'A'). Quantitative v.p.c. was carried out on a Griffin and George, D6, Gas Density Balance using columns 'O' and 'A'. For this instrument, when correctly standardised, the number of moles of any compound in a mixture is directly proportional to its peak area. Preparative scale v.p.c. was performed on either a Varian 'Aerograph' instrument or a Perkin-Elmer 'F-21' instrument, using columns 'O' and 'A' in both.

(ii) Rate Measurements

Thermostat baths were of conventional design. Temperature control was to ±0·01 C° by contact thermometer, and heating achieved by the means of

electric light blubs. Thermometers standardised to ±0·02° by the National Physics aboratory were used for temperature measurement. For the 25° bath (accurate temperature = 25·02°) water was used as liquid, and for the 92° bath (accurate temperature = 92·23°) lissapol was used.

When reaction rates were determined spectrophotometrically, absorbances were measured using a Unicam SP 600 spectrophotometer, the cell compartment of which was thermostatted at 25°.

General Experimental Method for Preparative Work

Except for reactions in which water was present in the reactants, or in which dry conditions were not necessary, all apparatus was oven-dried above 120° prior to use.

Ether extracted solutions were dried over anhydrous magnesium sulphate, and the ether subsequently removed on a rotary evaporator.

Determination of Product Isomer Ratios

In a number of reactions two products were formed and the isomer ratios had to be accurately measured. This was especially important in the case of 3,4-dichlorotrifluoropyridine as o:p chlorine:fluorine rate ratios depended on rate constants for attack at the 2- and 6-positions. The product mixture from this compound was subject to analytical v.p.c. investigations, and the product ratios determined from the peak areas. At least six separate injections were made and the percentage of each isomer was found to be constant within 1-2%.

CHAPTER 5

EXPERIMENTAL FOR CHAPTER 3

5.1 Preparation and Purification of Starting Materials

5.1.1 Substrates

In cases where substrates were provided, but not commercially obtained, a description of their purification is given, and a reference cited after the name of each such compound, for its method of preparation. Full characterisation is given for compounds not previously synthesised.

(a) Pentafluoropyridine[169]

This was purified prior to use by preparative scale v.p.c. ('Aerograph', column 'A', 140°).

(b) 3-Chlorotetrafluoropyridine[169]

Purified by preparative scale v.p.c. ('Aerograph', column 'A', 140°).

(c) 3,5-Dichlorotrifluoropyridine[169]

This was purified by preparative scale v.p.c. ('Aerograph', column 'A', 130°).

(d) 4-Chlorotetrafluoropyridine

This was obtained by a two-step preparation; the first stage being the preparation of 4-hydrazino-tetrafluoropyridine.

(i) Pentafluoropyridine (18g., 0·11 mole) was added dropwise to a stirred solution of hydrazine hydrate (9g.) in methanol (30 ml.). The solution was refluxed for 2 hrs., then poured into excess water (150 ml.) and ether extracted (2 x 20 ml.). The ethereal solution was washed several times with water and dried. Removal of the ether gave a yellow solid shown to be 4-hydrazino-tetrafluoropyridine (16g., 83%) by comparison of its i.r. spectrum

with that of an authentic sample.[107] This was used without further treatment.

(ii) 4-Hydrazino-tetrafluoropyridine (16g., 0·05 mole) was added slowly to a stirred solution of copper(II) chloride (80·4g., 0·60 mole) in concentrated hydrochloric acid (550 ml.). The mixture was stirred at room temperature for 2 hrs., then refluxed for 30 mins., after which time nitrogen ceased to be evolved. The mixture was distilled, and the organic layer separated from water in the distillate. The distillate was ether extracted, and working up the ethereal solution as described above gave a liquid product (12g., 76%), which was shown to be 4-chlorotetrafluoropyridine by comparison of its i.r. spectrum with that of an authentic sample.[111] Before use, this was purified by quantitative v.p.c. ('Aerograph', column 'A', 140°).

(e) 3,4-Dichlorotrifluoropyridine

3-Chloro-4-hydrazino-trifluoropyridine[109] was purified by recrystallisation (twice) from methanol followed by vacuum sublimation.

3-Chloro-4-hydrazino-trifluoropyridine (10g., 0·052 mole) was added to a solution of copper(II) chloride (45g., 0·33 mole) in concentrated hydrochloric acid (300 ml.). The mixture was refluxed with stirring until nitrogen ceased to be evolved (several hours), and then distilled. The distillate was neutralised by careful addition of sodium bicarbonate, and ether extracted (2 x 20 ml.). The combined ethereal solutions were washed several times with water and dried. Removal of the ether left a liquid product shown by analytical v.p.c. (column 'A', 150°) to consist almost entirely of one compound (> 90%). This was shown to be 3,4-dichlorotrifluoropyridine (8·2g., 80%) b.pt. 156°. (Found: C, 29·5; N, 6·7%; M, 201. $C_5Cl_2F_3N$ requires C, 29·7; N, 6·9%; M, 201). I.r. spectrum no. 3, n.m.r. spectrum no. 3.

(f) 3,4,5-Trichlorodifluoropyridine

This was a two stage preparation, the first stage being the preparation of 4-amino-3,5-dichlorodifluoropyridine.

(i) 3,5-Dichlorotrifluoropyridine (12g., 0·059 mole) and ammonia solution (20 ml., 0·880 s.g.) were heated at 80° for 15 mins. On cooling, the organic layer solidified. This was ether extracted (2 x 10 ml.), and the combined ethereal solution washed several times with water and dried. Removal of the ether gave a solid product shown to be 4-amino-3,5-dichlorodifluoropyridine (11·2g., 95%) by comparison of its i.r. spectrum with that of an authentic sample.[109] Its ^{19}F n.m.r. spectrum only consisted of one peak, showing the 4-amino isomer to be present.

(ii) To a stirred solution of 4-amino-3,5-dichlorodifluoropyridine (7·3g., 0·036 mole) in aqueous HF (80% w/w, 50 ml.) was added sodium nitrite (6g., 0·087 mole) at -25° over a period of 30mins. With the temperature maintained between -25° and -30°, a solution of copper(I) chloride in concentrated HCl (made by the addition of hydrated copper(II) chloride (30g.) and hydrated sodium sulphite (45·6g.) to concentrated HCl (60 ml.)), was added dropwise over a period of 30 mins.

After a further two hours, when the solution had reached room temperature, the mixture was diluted with water (750 ml.), neutralised by the careful addition of sodium bicarbonate, and ether extracted (2 x 50 ml.). The combined ethereal solutions were washed several times with water and dried. Removal of the ether gave a colourless liquid (6·8g.). V.p.c. analysis of the liquid (G.D.B., column 'O', 220°) showed it consisted of two major products (90% of mixture), one of which was 3,5-dichlorotrifluoropyridine (16% of mixture). The other product was separated by preparative scale v.p.c. (F21, column 'O', 200°) and shown to be 3,4,5-trichlorodifluoropyridine (5g., 64%) b.pt.[189]. (Found: C, 27·2; N, 6·2%; M, 217. $C_5Cl_3F_2N$ requires

C, 27·4; N, 6·4%; M, 217). I.r. spectrum no. 4, n.m.r. spectrum no. 4.

After separation, the compound was found to be pure enough to use, by v.p.c. investigation, without further treatment.

(g) 2,6-Dichlorotrifluoropyridine

The first step was the preparation of 2,4,6-trichlorodifluoropyridine performed by a similar method to that of Thorpe.[146]

(i) Pentafluoropyridine (5g., 0·031 mole), aluminium chloride (10g., 0·074 mole), and hydrogen chloride (5g., 0·137 mole) were heated for 9 days at 160° in a sealed nickel tube. The resulting complex was cautiously hydrolysed in water, and ether extracted (2 x 20 ml.). The combined ether extracts were washed and dried, and removal of the ether gave a solid product. Vacuum sublimation of the product gave a white solid (4·6g.) shown to be 2,4,6-trichlorodifluoropyridine (70% yield) by comparison of its i.r. spectrum with that of an authentic sample.[139] The compound was used without further treatment.

(ii) 2,4,6-Trichlorodifluoropyridine (4·3g., 19·8 mmole) and dried caesium fluoride (7g., 46·0 mmole) were stirred in dry sulpholan (20 ml.) under an atmosphere of dry nitrogen at room temperature for 9 days. The volatiles were removed from sulpholan by vacuum distillation (80°, 0·01 m.m.) giving a liquid product (3·8g.). Chromatographic analysis (column 'A', 150°) showed the latter to consist of unreacted starting material (5% of mixture) and two other compounds. These two compounds were separated by fractional distillation and were shown to be (i) 2,6-dichlorotrifluoropyridine (70% yield), b.pt. 156-7°. (Found: C, 30·0; N, 7·3%; M, 201. $C_5Cl_2F_3N$ requires C, 29·7; N, 6·9%; M, 201). I.r. spectrum no. 2, n.m.r. spectrum no. 2; and (ii) 2-chlorotetrafluoropyridine (15% yield), b.pt. 119-120°. (Found: C, 32·5; N, 7·6%; M, 185. C_5ClF_4N requires C, 32·4; N, 7·6%; M, 185). I.r. spectrum no. 1, n.m.r. spectrum no. 1.

Prior to use, 2,6-dichlorotrifluoropyridine was further purified by preparative scale v.p.c. (F21, column 'A', 125°).

(h) 2,4,5,6-Tetrafluoropyridine

This was prepared by the method of Chambers and co-workers.[147]

3-Chlorotetrafluoropyridine (5g., 0·027 moles) was dropped at a rate of 0·1g.min^{-1} into a flask heated to 200°, through which a stream of hydrogen (50 ml.min^{-1}) was passing. The chlorotetrafluoropyridine vapourised immediately, and was carried in the gas stream through a silica tube (½ in. diam. x 12 in.). The central 6 in. of this tube was heated by an electric furnace to 250° and contained palladised charcoal (10% Pd, 90% C). The product emerging from the catalyst was condensed in a trap cooled by liquid air and then dried by distillation under vacuum from P_2O_5. This liquid (3·2g.) was shown by v.p.c. (column 'A', 80°) to consist of one major product. This was separated by preparative scale v.p.c. (F21, column 'A', 80°) and shown to be 2,4,5,6-tetrafluoropyridine by comparison of its i.r. spectrum with that of an authentic sample as previously prepared.[147] The compound was used in kinetic runs without further treatment.

(i) 2,4,6-Trifluoropyridine

The same technique was employed as in the previous preparation. 3,5-Dichlorotrifluoropyridine (5g., 0·025 mole) was flash-distilled at 240° and passed in the stream of hydrogen over the catalyst at 280°. The product (2g.) was found to consist of one major component by v.p.c. analysis (column 'A', 80°), which on separation (F21, column 'A', 80°) was shown to be 2,4,6-trifluoropyridine (60% yield) by comparison of its i.r. spectrum with that of an authentic compound as previously prepared.[147] After separation the compound was found to be free of impurities and was used without further treatment.

(j) Attempted Preparation of 3,4,5-Trifluoropyridine

By the same technique as used above, 2,6-dichlorotrifluoropyridine (1·5g., 7·4 mmole) was flash-distilled at 210° and passed in a stream of hydrogen over the catalyst at 280°. The product (0·7g.) was obtained as a dark, viscous liquid. Chromatographic analysis (column 'A', 80°) showed only the presence of unreacted starting material and water (due to condensation during the collection of product).

(k) Pentachloropyridine

The commercial product was purified by two recrystallisations from ethanol followed by vacuum sublimation (100°, 0·02 mm.).

(l) Perfluoro-3-methyl- and Perfluoro-3,5-dimethyl-pyridine[170]

A mixture of perfluoro-3-methylpyridine and perfluoro-3,5-dimethyl-pyridine was separated into its components by repeated use of preparative scale v.p.c. (F21, column 'A', 120°). It was necessary to pass each component through the column a number of times before each was obtained in a pure state.

(m) Tetrafluoropyrazine[121]

This was purified by preparative scale v.p.c. (F21, column 'A', 120°).

(n) Tetrafluoropyridazine[114] and Tetrafluoropyrimidine[119]

These were provided in a pure state and were not further treated.

(o) Tetrachloropyridazine[114]

This was purified by two recrystallisations from ethanol followed by vacuum sublimation (0·01 mm.). M.pt. 87° (lit.,[144] 87-89°).

(p) Tetrachloropyrimidine

The commercial product was purified as above. M.pt. 67° (lit. 67°).

(q) Heptafluoroquinoline[144] and Heptafluoroisoquinoline[144]

These were both purified by two recrystallisations from ethanol followed

by vacuum sublimation (100°, 0·01 mm.). Heptafluoroquinoline m.pt. 89° (lit.,[144] 89-90°), heptafluoroisoquinoline m.pt. 44° (lit.,[144] 45·5°).

5.1.2 Solvents

(a) Dioxan

The method adopted was that of Vogel.[172] Commercial dioxan (2·5 l.) was refluxed for 8 hrs. with concentrated hydrochloric acid (35 ml.) and water (200 ml.) with a steady stream of nitrogen 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 layer was left standing over fresh potassium hydroxide pellets for a further 20 hrs. The dioxan was refluxed with excess sodium for about 8 hrs., until the surface of the sodium was bright, and then distilled into an oven-dried flask under dry nitrogen. The fraction boiling between 101-2° was collected.

When not in use, the dioxan was stored under nitrogen in a refrigerator (-5°) in the dark.

(b) Water

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

(c) Nitrobenzene

Analytical grade nitrobenzene was used without further treatment. On shaking a 5 ml. sample of the nitrobenzene with 20 ml. of water, the neutrality of the water was found not to be affected.

5.1.3 Reagents

(a) Ammonia

Analytical grade ammonia was used without further treatment.

(b) Diethylamine

Commercial diethylamine was fractionally distilled immediately before use: the fraction boiling between 55·8-56° was collected.

5.2 Methods of Rate Measurements

5.2.1 Reactions with Ammonia

(a) Titrimetric Methods

Stock solutions of ammonia in water and substrate in dioxan were prepared, usually being approximately 1·5 moles l^{-1} and 0·5 moles l^{-1} respectively. Occasionally stock solutions of double these concentrations were used, and for the reaction of 4-chlorotetrafluoropyridine, which was very slow, concentrations of c. 6·0 moles l^{-1} for ammonia and 2·0 moles l^{-1} of substrate were used.

Dioxan (60 ml.) and water (40 ml.) were pipetted into a stoppered conical flask and immersed in the thermostat bath (25·02°). Then 5 ml. of the stock ammonia solution were added and the contents of the flask mixed. Two 5 ml. aliquots of the solution were removed separately, quenched in distilled water (100 ml.) and titrated against standardised hydrochloric acid, (usually 0·0251M, and double this concentration if the stock ammonia solution was 3·0M) using methyl red as indicator. From these two titrations, an initial titration reading for the reaction was calculated, allowing for subsequent dilution by the substrate solution, and from this, the initial ammonia concentration found.

The reaction was initiated by the addition of 5 ml. substrate solution, having thermostatted at 25·02°, to the reaction vessel (resulting solution was a 60/40 dioxan/water (v:v) mixture), and the reaction followed, up to at least 75% of total reaction, by periodically quenching 5 ml. aliquots of reaction solution in 100 ml. distilled water and titrating against the

standard hypochloric acid using methyl red as indicator. Infinity titres were taken after at least 10 half lives, and the initial substrate concentration calculated from the initial and infinity titres.

The titrating acid was prepared by diluting commercial 0·1M hydrochloric acid, and standardising the resulting solution against standard sodium hydroxide solution.

For the reaction of pentachloropyridine, the procedure was the same except that the solvent was initially prepared from 70 ml. dioxan and 30 ml. water.

Second order rate constants were calculated as outlined in Section 3.4.

(b) Spectrophotometric Method

This method was used to follow the reactions of tetrafluoropyrimidine and perfluoro-3,5-dimethylpyridine.

Comparison of the u.v. spectra of the starting materials and respective products showed that the wavelengths 258 nm in the case of tetrafluoropyrimidine and 240 nm in the case of perfluoro-3,5-dimethylpyridine gave the greatest range of optical density throughout the reaction. These wavelengths were used for optical density measurements in the kinetic runs.

Stock solutions of ammonia in water ($7{\cdot}07 \times 10^{-3}$M for reaction with tetrafluoropyrimidine and $6{\cdot}78 \times 10^{-3}$M for reaction with perfluoro-3,5-dimethylpyridine) and substrate in dioxan (c. 10^{-4}M for each substrate) were prepared. The high concentration of ammonia relative to the substrate meant that the reaction took place under first order conditions.

The stock solutions were immersed in a 25° thermostat bath, water from which passed through the cell compartment of the spectrophotometer (Unicam SP600) which was used for absorbance measurements. 1·20 Ml. of the stock ammonia solution and 1·80 ml. of the substrate solution were pipetted into a 1 cm. silica u.v. cell, giving a solvent composition of 60/40 dioxan/water

(v:v). The cell was immediately stoppered, shaken, and placed in the spectrometer. The instrument was standardised at the wavelength used with a blank solution of 1·20 ml. water and 1·80 ml. dioxan.

Values of optical density were read as rapidly as possible, owing to the speed of the reaction, 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 by titration against standard hydrochloric acid (0·025M), and the ammonia concentration in the cell calculated from this allowing for dilution by the substrate solution.

First and second order rate constants were calculated as described in Section 3.4.

5.2.2 Reactions with Diethylamine

(a) Reactions in Dioxan

Stock solutions of diethylamine in dioxan (c. 1·5 moles l^{-1}) and substrate in dioxan (c. 0·5 mole l^{-1}) were prepared. 100 Ml. dioxan were pipetted into a stoppered conical flask, which had been painted black to prevent light-induced deterioration of the amine, and placed in the thermostat bath (25·02°). Then 5 ml. of amine solution were added, the contents of the flask mixed, and two 5 ml. aliquots separately removed, quenched in 100 ml. water and titrated against standardised 0·025M hydrochloric acid using methyl red as indicator. The resulting titration figure, after correcting for dilution by the added substrate solution, gave an initial titre figure and the initial amine concentration for the run was calculated from this.

The reaction was started by adding 5 ml. substrate solution, after thermostatting at 25·02°, and the reaction followed as described for the analogous reactions with ammonia in 60/40 dioxan/water. Initial substrate

concentration was obtained from the initial and infinity titres, and second order rate constants calculated as described in Section 3.4.

(b) Reaction in Nitrobenzene

Rate constants for the reaction of diethylamine and pentafluoropyridine were determined by the same procedure as for the reaction in dioxan. When titrating the residual amine against standard acid, the 5 ml. solution sample was quenched in 100 ml. water, and the resulting nitrobenzene/water mixture agitated continuously during titration to ensure complete neutralisation of the amine in the aqueous layer. Although the end-point was not as sharp as for the previous titrations, it led to adequately constant rate values throughout the run.

5.3 Product Identifications

Unless otherwise stated, reaction products were isolated by pouring the remaining reaction solution after 'infinity time' into excess water (150 ml.) and ether extracting (2 x 20 ml.). The combined ethereal solutions were washed with water, dried, and removal of the ether left the product. Previously known products were usually identified by comparison of their i.r. spectra with those of the authentic compounds.

In the cases of 4-chlorotetrafluoro-, 3,4-dichlorotrifluoro-, and 3,4,5-trichlorodifluoro-pyridine, for reactions with both ammonia and diethylamine, titration of 5 ml. of reaction solution after 'infinity time' against standardised 0·01M silver nitrate solution, using silver and glass electrodes, showed no measurable concentration of chloride ions present; hence substitution did not occur at the 4-positions in these compounds.

Each product was carefully examined, normally by v.p.c., in order to determine the number of components present. In the majority of reactions studied only one product was formed, but in a few cases, attack occurred at two positions in the molecule, giving rise to a product mixture.

5.3.1 Reactions with Ammonia in 60/40 Dioxan/Water:

(a) With Pentafluoropyridine

The crude solid product, prepared as described above, was shown to consist of one component (apart from remaining solvent) by chromatographic investigation (column 'O', 250°). After recrystallisation from ethanol the product was shown to be 4-aminotetrafluoropyridine by comparison of its i.r. spectrum with that of an authenticated sample.[107]

(b) With 3-Chlorotetrafluoropyridine

The crude solid product was shown to consist of one product component by chromatography investigation (column 'O', 250°). After recrystallisation from ethanol followed by vacuum sublimation, its i.r. spectrum was shown to be identical to that of an authentic sample[109] of 4-amino-3-chlorotetrafluoropyridine.

(c) With 3,5-Dichlorotrifluoropyridine

3,5-Dichlorotrifluoropyridine (3·03g., 0·015 mole) was added to a stirred mixture of ammonia solution (2 ml., 0·880 s.g.), dioxan (24 ml.) and water (16 ml.) in a flask set in a water bath at room temperature. The solution was stirred for 30 mins and poured into excess water (150 ml.). The product was ether extracted (2 x 20 ml.) and the combined ether extracts washed with water and dried. Removal of the ether gave a solid product, chromatographic investigation of which (column 'O', 250°) showed only one product component. After recrystallisation from ethanol, the product was shown to be 4-amino-3,5-dichlorodifluoropyridine by comparison of its i.r. spectrum with that of an authentic specimen.[109]

(d) With 4-Chlorotetrafluoropyridine

The reaction product was isolated in the usual manner. The crude product was shown to contain one product component by v.p.c. investigation

(column 'O', 220°) and after recrystallisation from ethanol was shown to be 2-amino-4-chlorotrifluoropyridine by comparison of its i.r. spectrum with that of an authentic sample.[111]

(e) With 3,4-Dichlorotrifluoropyridine

The crude, solid product was shown to be a mixture of two components in the ratio of 88·7 : 11·3 by chromatographic investigation (G.D.B., column 'O', 200°). The ^{19}F n.m.r. spectrum of the product showed each component to have two fluorines. The downfield peak of the major component is assignable to a fluorine ortho to the ring nitrogen and ortho to a carbon bearing chlorine, and the peak to higher field assignable to a fluorine meta to the ring nitrogen; this is consistent with the compound being 6-amino-3,4-dichlorodifluoropyridine. The peaks of the minor component are also assignable to fluorines ortho and meta to the ring nitrogen, but the shifts of these two peaks are higher than those of the corresponding peaks of the other product, and this is consistent with the minor product being 2-amino-3,4-dichlorodifluoropyridine. The elemental analysis of the mixture, after vacuum distillation, was also consistent with the product being composed of the two isomers. (Found: C, 30·2; N, 14·1; H, 1·1%. $C_5H_2Cl_2F_2N_2$ requires C, 30·2; N, 14·1; H, 1·0%). Rate constants were calculated using the observed percentage of each isomer.

Repeated recrystallisations of the mixture from aqueous ethanol gave a pure sample of 6-amino-3,4-dichlorodifluoropyridine, m.pt. 128-129°. (Found: C, 30·2; N, 14·4; H, 1·3%; M, 198. $C_5H_2Cl_2F_2N_2$ requires C, 30·2; N, 14·1; H, 1·0%; M, 198). I.r. spectrum no. 5, n.m.r. spectrum no. 5.

A pure sample of 2-amino-3,4-dichlorodifluoropyridine was not obtained and its n.m.r. spectrum (no. 6) obtained from that of the mixture.

(f) With 3,4,5-Trichlorodifluoropyridine

The crude product was found to consist of one component, apart from

remaining solvent, by chromatographic analysis (column 'O', 250°). The product was recrystallised from ethanol, vacuum sublimed (80°, 0·01 mm.), and shown to be 2-amino-3,4,5-trichlorofluoropyridine, m.pt. 144°. (Found: C, 27·9; N, 13·2; H, 1·0%; M, 214. $C_5H_2Cl_3FN_2$ requires C, 27·8; N, 13·0; H, 0·9%; M, 214). I.r. spectrum no. 7, n.m.r. spectrum no. 8.

(g) With 2,6-Dichlorotrifluoropyridine

The crude solid product was shown to consist of one component by chromatographic analysis (column 'O', 220°). It was recrystallised from ethanol, vacuum sublimed (80°, 0·01 mm.), and shown to be 4- amino-2,6-dichlorotrifluoropyridine, m.pt. 167-8°. (Found: C, 30·1; N, 14·4; H, 0·8%; M, 198. $C_5H_2Cl_2F_2N_2$ requires C, 30·2; N, 14·1; H, 1·0%; M, 198). I.r. spectrum no. 6, n.m.r. spectrum no. 7.

(h) With 2,4,5,6-Tetrafluoropyridine

The ^{19}F n.m.r. spectrum of the crude solid product showed it to consist of two compounds. The major component (79% by integration) showed two downfield peaks assignable to fluorine ortho to the ring nitrogen, and a peak at higher field assignable to a fluorine meta to nitrogen; this is consistent with the compound being 4-amino-2,5,6-trifluoropyridine (n.m.r. spectrum no. 9).

The second component (21% by integration) showed three peaks assignable to fluorines ortho, meta and para to the ring nitrogen: this is consistent with its being 6-amino-2,4,5-trifluoropyridine (n.m.r. spectrum no. 10).

It was not possible to obtain pure samples of each compound for characterisation, but elemental analysis of the mixture after vacuum sublimation (80°, 0·01 mm.) was consistent with its being composed of the two above isomers. (Found: C, 40·3; N, 18·9; N, 18·9; H, 2·2%. $C_5H_3F_3N_2$ requires C, 40·5; N, 18·9; H, 2·0%). Rate constants were calculated using the measured percentage of each isomer.

(i) With 2,4,6-Trifluoropyridine

2,4,6-Trifluoropyridine (1·0g., 7·3 mmole), aqueous ammonia (30 ml., 0·880 s.g.), dioxan (30 ml.) and water (20 ml.) were sealed in a glass ampoule and heated at 80° for 3 weeks. The solution was poured into excess water (100 ml.) and ether extracted (2 x 20 ml.). The combined ethereal solutions were washed with water, dried, and removal of the ether left the solid product (0·85g., 87%).

The product was recrystallised from cyclohexane and shown to be 4-amino-2,6-difluoropyridine, m.pt. 124-5°. (Found: C, 46·4; N, 20·9; H, 3·4%; M, 130. $C_5H_4F_2N_2$ requires C, 46·2; N, 20·5; H, 3·1%; M, 130). I.r. spectrum no. 8, n.m.r. spectrum no. 11.

The n.m.r. spectrum of the compound showed one singlet peak.

(j) With Perfluoro-3-methylpyridine

The solid product was isolated in the usual manner, and its ^{19}F n.m.r. spectrum was the same as that for the mixture 4-amino-2,5,6-trifluoro-3-trifluoromethylpyridine and 6-amino-2,4,5-trifluoro-3-trifluoromethylpyridine reported previously for the same reaction.[170] Integration of the peaks showed the two products to be in the ratio of 69·2 : 30·8 respectively. This ratio was used to calculate rate constants for attack at the 4- and 6-positions.

(k) With Perfluoro-3,5-dimethylpyridine

The ^{19}F n.m.r. spectrum of the solid product was the same as that of the mixture 4-amino-2,6-difluoro-3,5-bistrifluoromethylpyridine and 6-amino-2,6-difluoro-3,5-bistrifluoromethylpyridine obtained from the same reaction previously.[170] Integration of the peaks showed the two products to be in the ratio of 55·3 : 44·7 respectively. The ratio was used to calculate the rate constants for attack at the two positions.

(l) With Tetrafluoropyrazine

The product, after recrystallisation from ethanol followed by vacuum sublimation (100°, 0·005 mm.) was shown to be 2-aminotrifluoropyrazine by comparison of its i.r. spectrum with that of an authentic sample.[122]

(m) With Tetrafluoropyridazine

The crude solid product was found to consist of one component by chromatographic analysis (column 'O', 230°). It was recrystallised from light petroleum (b.pt. 80-100°) and shown to be 4-aminotrifluoropyridazine by comparison of its i.r. with that of an authentic sample.[114]

(n) With Tetrafluoropyrimidine

Tetrafluoropyrimidine (1·0g., 6 mmoles) were added to 0·880 aqueous ammonia (2 ml.) in a 60/40 dioxan/water mixture (20 ml.). The mixture was allowed to stand at room temperature for 1 hr. It was then poured into excess water (150 ml.) and ether extracted (2 x 30 ml.). The combined ethereal solutions were washed and dried, and removal of the ether left the solid product. This was shown by chromatographic analysis (column 'O', 230°) to consist of one component. This was recrystallised from ethanol and shown to be 4-aminotrifluoropyrimidine by comparison of its i.r. spectrum with that of an authentic sample.[119]

(o) With Tetrachloropyridazine

The solid product was isolated in the usual manner. It was recrystallised from ethanol and shown to be 4-aminotrichloropyrazine, m.pt. 201° (lit.,[134] 204°).

(p) With Tetrachloropyrimidine

The crude product was recrystallised from ethanol and shown to be 4-aminotrichloropyrimidine, m.pt. 169° (lit.,[135] 168°).

(q) With Heptafluoroquinoline

The ^{19}F n.m.r. spectrum of the solid product was the same as that of the mixture of 2- and 4-aminohexafluoroquinoline reported for the product of the same reaction.[123] The percentages of each isomer were obtained by integration of the peak of the spectrum by the method of C.A.T. (spectrum run by Dr. R. Matthews), and the isomer ratio was found to be 69 : 31 respectively for the 4- and 2-amino isomers. This ratio was used in the calculation of rate constants for attack at the two positions.

(r) With Heptafluoroisoquinoline

The ^{19}F n.m.r. spectrum of the product was identical to that of 1-aminohexafluoroisoquinoline reported for the product of the same reaction.[123] The crude product was recrystallised from ethanol and its i.r. spectrum found to be identical to that of an authentic specimen of 1-aminohexafluoroisoquinoline.[173]

5.3.2 Reactions with Diethylamine in Dioxan:

(a) With Pentafluoropyridine

Pentafluoropyridine (2g., 0·012 mole) was added to diethylamine (2·6g., 0·036 mole) in dioxan (25 ml.). The mixture was stirred in a water bath at room temperature for 2 hrs., then poured into water (100 ml.) and ether extracted (2 x 15 ml.). The combined ethereal solutions were washed with water, dried, and removal of the ether left an oily liquid, chromatographic analysis of which (column 'O', 220°) showed it to consist of one component. The product was vacuum distilled (80°, 0·005 mm.) and shown to be 4-diethylaminotetrafluoropyridine. (Found: C, 48·9; N, 13·0; H, 4·8%; M, 222. $C_9H_{10}F_4N_2$ requires C, 48·6; N, 12·6; H, 4·5%; M, 222). I.r. spectrum no. 9, n.m.r. spectrum no. 12.

(b) With 3-Chlorotetrafluoropyridine

3-Chlorotetrafluoropyridine (2·82g., 0·015 mole) was added to diethylamine (2·92g., 0·04 mole) in dioxan (25 ml.). (The resulting solution had the same ratio of substrate to amine as in the kinetic runs). The solution was stirred in a water bath at room temperature for 1 hr., poured into water (100 ml.) and the liquid product obtained by the method described in the previous preparation.

Chromatographic analysis of the product (column 'O', 170°) showed two poorly resolved peaks. The ^{19}F n.m.r. spectrum of the mixture showed the major product (64·4% by integration) to have three peaks, the chemical shifts of which implied that the three fluorines were ortho, meta and para to the ring nitrogen, and this is consistent with the product being 3-chloro-6-diethylaminotrifluoropyridine (n.m.r. spectrum no. 15).

The ^{19}F n.m.r. spectrum of the second component (35·6%) showed two low field peaks assignable to fluorines ortho to the ring nitrogen, and one peak to higher field assignable to a fluorine meta to nitrogen. This is consistent with the product being 3-chloro-4-diethylaminotrifluoropyridine (n.m.r. spectrum no. 14).

Separation of the isomers by preparative scale v.p.c. or low temperature crystallisation from hexane and light petroleum (b.pt. 40-60°) was found not to be possible, but the elemental analysis of the mixture was consistent with its being composed of the two isomers. (Found: C, 45·5; N, 12·1; H, 4·4%. $C_9H_{10}ClF_3N_2$ requires C, 45·3; N, 11·7; H, 4·2%). Rate constants were calculated using the observed percentage of each isomer.

(c) With 3,5-Dichlorotrifluoropyridine

3,5-Dichlorotrifluoropyridine (3·03g., 0·015 mole) was added to diethylamine (2·92g., 0·04 mole) in dioxan (25 ml.). The solution was stirred in a water bath at room temperature for 1 hr. and poured into water (150 ml.).

The product was ether extracted (2 x 20 ml.), the combined ethereal solution washed with water, dried, and the ether removed to give an oily liquid product. Chromatographic analysis (column 'O', 220°) of the liquid showed it to consist of one component. The product was purified by vacuum distillation (100°, 0·005 mm.) to give a colourless oily liquid shown to be 3,5-dichloro-2-diethylaminodifluoropyridine. (Found: C, 42·4; N, 11·3; H, 3·7%; M, 254. $C_9H_{10}Cl_2F_2N_2$ requires C, 42·4; N, 11·0; H, 3·9%; M, 254). I.r. spectrum no. 11, n.m.r. spectrum no. 16. The n.m.r. spectrum consisted of two doublet peaks.

(d) With 4-Chlorotetrafluoropyridine

The product was obtained from the kinetic reaction solution after 'infinity time' in the usual manner. The resulting yellow oily liquid was found to consist of one component by chromatographic analysis (column 'O', 200°), and was purified by distillation (100°, 0·01 mm.). The product, a colourless liquid, was shown to be 4-chloro-2-diethylaminotrifluoropyridine. (Found: C, 45·4; N, 12·1; H, 4·0%; M, 238. $C_9H_{10}ClF_3N_2$ requires C, 45·3; N, 11·7; H, 4·2%; M, 238). I.r. spectrum no. 10, n.m.r. spectrum no. 13.

(e) With 3,4-Dichlorotrifluoropyridine

The liquid product obtained from the kinetic reaction solution was shown by chromatographic analysis (column 'O', 230°) to consist of one component. The product was purified by vacuum distillation (100°, 0·01 mm.) to give a colourless, oily liquid, shown to be 3,4-dichloro-6-diethylamino-difluoropyridine. (Found: C, 42·3; N, 11·3; H, 4·2%; M, 254. $C_9H_{10}Cl_2F_2N_2$ requires C, 42·4; N, 11·0; H, 3·9%; M, 254). I.r. spectrum no. 13, n.m.r. spectrum no. 18.

(f) With 3,4,5-Trichlorodifluoropyridine

The liquid product obtained by the normal method was shown by chromatographic analysis (column 'O', 250°) to consist of one component.

The product was purified by vacuum distillation to give a colourless, oily liquid, shown to be 3,4,5-trichloro-2-diethylaminofluoropyridine. (Found: C, 40·1; N, 10·4; H, 3·7%; M, 270. $C_9H_{10}Cl_3FN_2$ requires C, 39·8; N, 10·3; H, 3·7%; M, 270). I.r. spectrum no. 14, n.m.r. spectrum no. 19.

(g) With 2,6-Dichlorotrifluoropyridine

The crude liquid product was shown to consist of one component by chromatographic analysis (column 'O', 220°). It was purified by vacuum distillation to give a colourless, oily liquid, shown to be 2,6-dichloro-4-diethylaminodifluoropyridine. (Found: C, 42·2; N, 11·4; H, 4·1%; M, 254. $C_9H_{10}Cl_2F_2N_2$ requires C, 42·4; N, 11·0; H, 3·9%; M, 254). I.r. spectrum no. 12, n.m.r. spectrum no. 17.

CHAPTER 6

EXPERIMENTAL FOR CHAPTER 4

6.1 Preparation and Purification of Starting Materials

6.1.1 Preparation of Pentafluoronitrobenzene

Boron trifluoride was bubbled through a mixture of sulpholan (100 ml.) and fuming nitric acid (25 ml.) at room temperature, cooling in an ice bath when necessary, until a saturated solution was formed (about 1 hr.). Pentafluorobenzene (50g., 0·30 mole) was added and the mixture stirred at 60-70° for 2 hrs. The homogeneous yellow solution was poured onto crushed ice (800g.), diluted with water (500 ml.) and steam distilled. The distillate was ether extracted (2 x 30 ml.), the combined ethereal solutions dried, and removal of the ether gave pentafluoronitrobenzene (57g., 90%).

6.1.2 Substrates

(a) Octafluorotoluene

The commercial product was purified by preparative scale vapour phase chromatography ('Aerograph', column 'A', 125°).

(b) Perfluoroethylbenzene

The commercial product was purified by preparative scale vapour phase chromatography ('Aerograph', column 'A', 125°).

(c) Perfluoroisopropylbenzene

Pentafluoronitrobenzene (5g., 0·025 mole), anhydrous potassium fluoride (5g., 0·086 mole) and dry sulpholan (20 ml.) were placed in a glass Carius tube, which had been previously oven-dried and purged with dry nitrogen, and hexafluoropropene (6g., 0·04 mole) condensed in. The tube was sealed and heated at 150° for 16 hrs. After cooling, the contents of the tube were

poured into excess water (150 ml.) and ether extracted (2 x 20ml.) The combined ether extracts were washed several times with water and dried. Removal of the ether left a dark brown liquid, which was vacuum distilled (80°, 0·02 mm.) to give a colourless liquid (2·5g.), leaving a tarry residue. Quantitative chromatographic analysis (G.D.B., column 'A', 80°) showed the product to consist mainly (> 90%) of perfluoroisopropylbenzene (50% of product) and an unresolved mixture of the 1,4- and 1,3-disubstituted benzene compounds (43% of product), by analogy with the products of the same reaction previously reported.[173]

Perfluoroisopropylbenzene was separated and purified by preparative scale v.p.c. ('Aerograph', column 'A', 140°), and its identity confirmed by comparison of its i.r. spectrum with that of an authentic sample.[173]

(d) Perfluoro-t-butylbenzene

Owing to the very high toxicity of perfluoroisobutene, great care was taken when using it. The preparation was carried out in a well-ventilated area, and breathing apparatus worn when perfluoroisobutene was used. Any apparatus which had been in contact with perfluoroisobutene was immersed in a bath of aqueous alkaline acetone which readily hydrolyses the gas.

Pentafluoronitrobenzene (9g., 0·042 mole) and dry caesium fluoride (7g., 0·046 mole) were added against a counter current of dry nitrogen to sulpholan (25 ml.) in an oven-dried 50 ml. conical flask equipped with a magnetic stirrer and a two-arm adaptor. To one arm of the adaptor was attached a variable volume reservoir (a football bladder), and the other arm was used for nitrogen inlet or for attachment to a vacuum line. The flask was immersed in liquid air and evacuated. After warming to room temperature, perfluoroisobutene (10g., 0·05 mole) was condensed in, partially inflating the bladder. The mixture was stirred at room temperature for 7 hrs., after which the mixture was frozen, the apparatus disassembled and aqueous alkaline acetone (20 ml.)

added to the flask to destroy any remaining perfluoroisobutene.

The contents of the flask were poured into water (150 ml.) and ether extracted (2 x 20 ml.). The combined extracts were washed several times with water and dried. Removal of the ether gave a brown liquid (9g.). Quantitative chromatographic analysis (G.D.B., column 'A', 120°) showed the liquid to consist of an equal mixture of unreacted starting material (50% recovery) and a product (4·5g., 28% yield). A small percentage of hexafluorobenzene (< 5%) was also detected.

The product was removed and purified by preparative scale v.p.c. (F21, column 'O', 120°) and shown to be perfluoro-t-butylbenzene, b.pt. 145°. (Found: C, 30·8; F, 68·6%; M, 386. $C_{10}F_{14}$ requires C, 31·1; F, 68·9%; M, 386). I.r. spectrum no. 15, n.m.r. spectrum no. 23.

(e) Pentafluorobenzene

The commercial product was purified by preparative scale v.p.c. ('Aerograph', column 'A', 120°).

6.1.3 Solvents and Reagents

Dioxan was purified as described earlier (Section 5.1.2) Distilled water and reagent grade ammonia solution were used.

6.2 Method of Rate Measurements

Stock solutions of ammonia in water (about 1·5 moles l^{-1}) and substrate in dioxan (about 0·5 moles l^{-1}) were prepared. Dioxan (80 ml.) and water (20 ml.) were pipetted into a flask and 5 ml. of the stock ammonia solution added. After mixing, two 5 ml. aliquots were removed, and if desired, titrated against standardised 0·0251M hydrochloric acid using methyl red as indicator.

5Ml. of the substrate solution were added to the flask and the solution mixed. (Resulting solvent was a 77/23 dioxan/water (v:v) mixture). 5 Ml. aliquots of the reaction solution were then sealed in glass tubes and immersed

simultaneously in the thermostat bath (92·23°). After 15 min. a tube was removed and plunged into liquid air to stop the reaction. The time of immersion in liquid air was taken as the zero time for the reaction. The tube was removed, washed, and broken under the surface of 100 ml. water in a stout glass jar. The residual ammonia was titrated against standard hydrochloric acid (0·0251M) using methyl red as indicator. This titre was taken as the initial reading for the run, and the initial ammonia concentration calculated from it. The reaction was followed by removing tubes periodically, plunging them in liquid air (this time being taken as the time of the reading), and titrating against acid as described above. The infinity reading for the reaction was taken as the average titre of three tubes which were left in the bath for at least 10 half lives. The initial substrate concentration was calculated from the initial and infinity titres, and second order rate constants calculated as described in Section 4.5.

The titrating acid was prepared and standardised as described earlier (Section 5.2.1).

6.3 Identification of Products

(a) From Octafluorotoluene

Octafluorotoluene (0·75g., 3·18 mmole) and 1·5M aqueous ammonia (5 ml.) in a mixture of dioxan (80 ml.) and water (20 ml.) were sealed in a glass ampoule and heated in the thermostat bath (92°) for 4 days. The contents were poured into water (150 ml.) and ether extracted. The ether extract was washed with water and dried, and removal of the ether left an oily liquid (0·73g., 96%) which was found by chromatographic investigation (column 'O', 230°) to have only one component. The product was purified by vacuum distillation to give a colourless, oily liquid and shown to be 4-aminohepta-fluorotoluene. (Found: C, 36·3; N, 6·1; H, 1·0%; M, 233. Calculated for $C_7H_2F_7N$: C, 36·1; N, 6·0; H, 0·86%; M, 233). The compound has been

reported previously,[83] but no spectra data were given. I.r. spectrum no. 16, n.m.r. spectrum no. 20.

(b) From Perfluoroethylbenzene

Perfluoroethylbenzene (0·9g., 3·14 mmole) and 1·5M aqueous ammonia (5 ml.) were reacted and the product obtained, as described in (a) above.

The liquid product (0·80g., 90%) was found to consist of one component by chromatographic analysis (column 'O', 230°) and was shown to be 4-amino-nonafluoroethylbenzene. (Found: C, 33·9; N, 5·3; H, 1·0%; M, 283. Calculated for $C_8H_2F_9N$: C, 33·9; N, 5·0; H, 0·7%; M, 283). The compound has been previously reported[85] but no spectra data were given. I.r. spectrum no. 17, n.m.r. spectrum no. 21.

(c) From Perfluoroisopropylbenzene

The reaction solution prepared for the kinetic run, as described in Section 6.2, after removal of the 5 ml. samples, was sealed in a glass ampoule and the product obtained as described in (a) above.

The liquid product was found to consist of one component by chromatographic analysis (column 'O', 220°) and was shown to be 4-aminoundecafluoroisopropyl-benzene. (Found: C, 32·4; N, 4·2; H, 0·6%; M, 333. $C_9H_2F_{11}N$ requires C, 32·4; N, 4·2; H, 0·6%; M, 333). I.r. spectrum no. 18, n.m.r. spectrum no. 22.

(d) From Perfluoro-t-butylbenzene

The product was obtained from the remaining reaction solution used for the kinetic runs as described in (c) above. The liquid product was found to consist of one component by chromatographic analysis (column 'O', 220°) and was shown to be 4-aminotridecafluoro-t-butylbenzene. (Found: C, 31·1; N, 3·8; H, 0·3%; M, 383. $C_{10}H_2F_{13}N$ requires C, 31·3; N, 3·7; H, 0·5%; M, 383). I.r. spectrum no. 19, n.m.r. spectrum no. 24.

APPENDIX I

RATE DATA

Pentafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	11·40	
25·58	10·91	4·04
42·0	10·62	4·12
70·0	10·20	4·12
100·0	9·81	4·14
125·5	9·53	4·13
175·0	9·10	4·06
220·58	8·74	4·13
282·6	8·41	4·04
360·0	8·06	4·06
∞	6·90	

$[NH_3]_o$ = 0·1140 moles l^{-1}

$[Substrate]_o$ = 0·02250 moles l^{-1}

k = (4·09 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k = (4·06 ± 0·03) x 10^{-2} $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (4·08 ± 0·03) x 10^{-2} $l.mole^{-1}min^{-1}$

3-Chlorotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	14·62	
10·1	13·85	1·17
20·0	13·18	1·18
35·0	12·36	1·15
56·42	11·36	1·16
75·0	10·70	1·14
100·45	9·90	1·15
131·0	9·20	1·13
171·0	8·49	1·12
234·0	7·61	1·14
289·0	7·10	1·13
398·0	6·40	1·14
∞	5·10	

$[NH_3]_o$ = 0·07339 moles l^{-1}

$[Substrate]_o$ = 0·02390 moles l^{-1}

k = (1·15 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (11 readings)

Duplicate k = (1·15 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (14 readings)

Mean k = (1·15 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$

4-Chlorotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^4 k (l.mole^{-1}min^{-1})
0		
1542	10·91	1·82
3012	10·44	1·84
4603	9·95	1·89
6054	9·64	1·80
7656	9·20	1·87
10080	8·70	1·85
12960	8·19	1·84
17310	7·55	1·82
21900	7·00	1·81
25020	6·65	1·83
∞	2·58	

$[NH_3]_o$ 0·229 moles l^{-1}

$[Substrate]_o$ = 0·0887 moles l^{-1}

k = (1·84 ± 0·01) x 10^{-4} l.mole^{-1}min^{-1} (10 readings)

Duplicate k = (1·88 ± 0·01) x 10^{-4} l.mole^{-1}min^{-1} (10 readings)

Mean k = (1·86 ± 0·01) x 10^{-4} l.mole^{-1}min^{-1}

3,5-Dichlorotrifluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	13·68	
5·0	12·85	2·78
10·0	12·10	2·86
16·0	11·32	2·91
24·0	10·50	2·88
34·5	9·60	2·91
45·0	9·00	2·80
59·25	8·25	2·81
74·0	7·58	2·88
89·17	7·20	2·76
119·0	6·42	2·84
128·0	6·30	2·79
∞	4·30	

$[NH_3]_o$ = 0·06867 moles l^{-1}

$[Substrate]_o$ = 0·02354 moles l^{-1}

k = (2·84 ± 0·02) x 10^{-1} $l.mole^{-1}min^{-1}$ (11 readings)

Duplicate k = (2·86 ± 0·03) x 10^{-1} $l.mole^{-1}min^{-1}$ (10 readings)

(2·84 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (13 readings)

Mean k = (2·85 ± 0·02) x 10^{-1} $l.mole^{-1}min^{-1}$

3,4-Dichlorotrifluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^3 k ($l.mole^{-1}min^{-1}$)
0	13·11	
302	12·20	2·82
728	11·19	2·75
1384	9·99	2·73
1851	9·28	2·77
2915	8·15	2·75
3350	7·80	2·74
4340	7·18	2·69
6125	6·30	2·75
∞	4·18	

$[NH_3]_o$ = 0·1311 mole l^{-1}

$[Substrate]_o$ = 0·04465 mole l^{-1}

k = (2·75 ± 0·01) x 10^{-3} $l.mole^{-1}min^{-1}$ (8 readings)

Duplicate k = (2·78 ± 0·01) x 10^{-3} $l.mole^{-1}min^{-1}$ (8 readings)

Mean k = (2·77 ± 0·01) x 10^{-3} $l.mole^{-1}min^{-1}$

2,6-Dichlorotrifluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	13·63	
31·0	13·06	3·97
80·25	12·31	3·89
129·1	11·66	3·92
185·0	10·09	3·83
256·0	10·43	3·87
341·0	9·83	3·85
450·0	9·21	3·85
568·0	8·72	3·81
724·0	8·20	3·83
∞	6·41	

$[NH_3]_o$ = 0·06842 moles l^{-1}

$[Substrate]_o$ = 0·01807 moles l^{-1}

k = (3·87 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k = (3·88 ± 0·04) x 10^{-2} $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (3·88 ± 0·03) x 10^{-2} $l.mole^{-1}min^{-1}$

3,4,5-Trichlorodifluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^2 k (l.mole^{-1}min^{-1})
0	12·20	
50·0	11·82	1·55
115·0	11·35	1·59
218·0	10·70	1·59
373·0	9·91	1·57
533·0	9·26	1·54
705·0	8·66	1·54
954·0	7·95	1·54
1295·0	7·23	1·53
1580·0	6·73	1·55
1875·0	6·33	1·55
∞	3·88	

$[NH_3]_o$ = 0·06124 moles l^{-1}

$[Substrate]_o$ = 0·02088 moles l^{-1}

k = (1·56 ± 0·01) x 10^{-2} l.mole^{-1}min^{-1} (10 readings)

Duplicate k = (1·55 ± 0·01) x 10^{-2} l.mole^{-1}min^{-1} (10 readings)

Mean k = (1·55 ± 0·01) x 10^{-2} l.mole^{-1}min^{-1}

2,4,5,6-Tetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^3 k (l.mole^{-1}min^{-1})
0	13·32	
388	12·95	1·71
1405	12·11	1·69
2013	11·70	1·65
3150	10·96	1·68
7225	9·20	1·64
10140	8·33	1·65
11595	7·89	1·72
17340	6·94	1·70
∞	4·69	

$[NH_3]_o$ = 0·06687 moles l^{-1}

$[Substrate]_o$ = 0·02166 moles l^{-1}

k = (1·68 ± 0·01) x 10^{-3} l.mole^{-1}min^{-1} (8 readings)

Duplicate k = (1·68 ± 0·01) x 10^{-3} l.mole^{-1}min^{-1} (8 readings)

Mean k = (1·68 ± 0·01) x 10^{-3} l.mole^{-1}min^{-1}

Perfluoro-3-methylpyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	k ($l.mole^{-1}min^{-1}$)
0	12·64	
0·80	10·96	4·72
1·35	10·08	4·77
1·88	9·38	4·81
2·33	8·77	4·67
3·12	8·23	4·74
3·95	7·61	4·82
5·17	7·03	4·68
6·58	6·50	4·61
7·95	6·08	4·64
∞	4·23	

$[NH_3]_o$ = 0·06345 moles l^{-1}

$[Substrate]_o$ = 0·02111 moles l^{-1}

k = (4·72 ± 0·02) $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k = (4·72 ± 0·02) $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (4·72 ± 0·02) $l.mole^{-1}min^{-1}$

Perfluoro-3,5-dimethylpyridine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	O.D.	10 k_I (min^{-1})
0	0·312	
0·233	0·346	(3·53)
0·50	0·375	2·99
0·80	0·411	3·08
1·08	0·441	3·09
1·60	0·490	3·12
1·87	0·513	3·14
2·20	0·538	3·14
2·70	0·567	3·07
3·23	0·599	3·11
3·87	0·630	3·13
4·63	0·660	3·16
5·25	0·678	3·14
10·0	0·742	2·98
∞	0·765	

$[NH_3]_o$ = $1{\cdot}084 \times 10^{-3}$ moles l^{-1}

k_I = $(3{\cdot}09 \pm 0{\cdot}02) \times 10^{-1}$ min^{-1} (12 readings)

k_{II} = $(2{\cdot}86 \pm 0{\cdot}02) \times 10^{2}$ $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k_{II} = $(2{\cdot}93 \pm 0{\cdot}03) \times 10^{2}$ $l.mole^{-1}min^{-1}$

Mean k_{II} = $(2{\cdot}89 \pm 0{\cdot}03) \times 10^{2}$ $l.mole^{-1}min^{-1}$

Pentafluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	12·97	
5·50	11·99	3·00
8·83	11·42	3·09
13·00	10·83	3·04
17·95	10·15	3·08
23·05	9·60	3·02
28·33	9·09	2·98
33·62	8·53	3·05
39·30	8·04	3·07
45·17	7·56	3·12
58·92	6·80	3·03
67·92	6·33	3·05
76·42	5·92	3·10
86·42	5·59	3·06
102·08	5·10	3·08
∞	3·23	

$[(C_2H_5)_2NH]_o$ = 0·06563 moles l^{-1}

$[Substrate]_o$ = 0·02464 moles l^{-1}

k = (3·05 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (14 readings)

Duplicate k = (3·05 ± 0·03) x 10^{-1} $l.mole^{-1}min^{-1}$ (10 readings)

Mean k = (3·05 ± 0·02) x 10^{-1}

3-Chlorotetrafluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	13·05	
10·0	12·10	1·67
20·0	11·37	1·60
30·15	10·62	1·61
40·0	10·00	1·62
50·5	9·50	1·57
60·0	8·97	1·61
75·0	8·34	1·60
90·0	7·71	1·64
120·0	6·81	1·65
140·0	6·40	1·62
160·0	6·00	1·63
180·0	5·70	1·61
210·2	5·26	1·64
291·2	4·56	1·65
∞	3·37	

$[(C_2H_5)_2NH]_o$ = 0·06551 moles l^{-1}

$[Substrate]_o$ = 0·02339 moles l^{-1}

k = (1·62 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (14 readings)

Duplicate k = (1·64 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (13 readings)

Mean k = (1·63 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$

4-Chlorotetrafluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10^3 k (l.mole^{-1}min^{-1})
0	12·95	
120	12·31	8·86
270	11·63	8·56
345	11·22	9·08
495	10·64	8·87
630	10·17	8·75
780	9·61	8·96
930	9·20	8·79
1110	8·66	8·92
1290	8·30	8·67
1560	7·63	8·91
1920	6·97	8·91
2520	6·20	8·67
∞	3·25	

$[(C_2H_5)_2NH]_o$ = 0·06501 moles l^{-1}

$[Substrate]_o$ = 0·02435 moles l^{-1}

k = (8·83 ± 0·04) x 10^{-3} l.mole^{-1}min^{-1} (12 readings)

Duplicate k = (8·98 ± 0·06) x 10^{-3} l.mole^{-1}min^{-1} (13 readings)

Mean k = (8·91 ± 0·05) x 10^{-3} l.mole^{-1}min^{-1}

3,5-Dichlorotrifluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	12·94	
15·0	11·82	1·41
23·0	11·40	1·31
30·0	10·96	1·34
40·0	10·44	1·34
50·0	10·01	1·31
60·0	9·52	1·34
70·0	9·10	1·35
80·0	8·72	1·36
90·0	8·35	1·38
105·0	7·90	1·38
120·0	7·53	1·37
135·0	7·16	1·38
155·0	6·78	1·38
175·0	6·41	1·39
195·0	6·10	1·40
∞	4·06	

$[(C_2H_5)_2NH]_o$ = 0·06496 moles l^{-1}

$[Substrate]_o$ = 0·02229 moles l^{-1}

k = (1·37 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (15 readings)

Duplicate k = (1·39 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (16 readings)

Mean k = (1·38 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$

3,4-Dichlorotrifluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	13·81	
15·0	12·97	1·14
30·0	12·17	1·21
45·0	11·56	1·18
65·0	10·82	1·18
85·0	10·19	1·19
112·0	9·50	1·19
131·0	9·11	1·18
160·0	8·62	1·17
201·0	8·05	1·17
∞	6·21	

$[(C_2H_5)_2NH]_o$ = 0·06933 moles l^{-1}

$[Substrate]_o$ = 0·01908 moles l^{-1}

k = (1·18 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$

Duplicate k = (1·16 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$

Mean k = (1·17 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$

2,6-Dichlorotrifluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	13·55	
8·17	13·08	1·79
17·0	12·63	1·79
25·0	12·30	1·73
40·0	11·70	1·76
55·0	11·22	1·76
70·2	10·81	1·77
90·5	10·35	1·78
111·0	10·02	1·76
130·0	9·72	1·80
∞	8·55	

$[(C_2H_5)_2NH]_o$ = 0·06802 moles l^{-1}

$[Substrate]_o$ = 0·01255 moles l^{-1}

k = (1·77 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k = (1·80 ± 0·02) x 10^{-1} $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (1·79 ± 0·02) x 10^{-1} $l.mole^{-1}min^{-1}$

3,4,5-Trichlorodifluoropyridine + Diethylamine in Dioxan at 25·02°

Time (min.)	Titre (ml.)	10^2 k (l.mole^{-1}min^{-1})
0	13·24	
14·92	12·65	(7·97)
30·0	12·02	8·67
50·0	11·31	8·83
75·0	10·60	8·69
103·0	9·89	8·74
143·0	9·05	8·81
180·0	8·49	8·68
220·0	7·93	8·71
275·0	7·40	8·65
330·0	6·95	8·71
∞	5·39	

$[(C_2H_5)_2NH]_o$ = 0·06647 moles l^{-1}

$[Substrate]_o$ = 0·01970 moles l^{-1}

k = (8·73 ± 0·02) x 10^{-2} l.mole^{-1}min^{-1} (9 readings)

Duplicate k = (8·71 ± 0·03) x 10^{-2} l.mole^{-1}min^{-1} (9 readings)

Mean k = (8·72 ± 0·03) x 10^{-2} l.mole^{-1}min^{-1}

Pentafluoropyridine + Diethylamine in Nitrobenzene at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	12·48	
3·55	11·40	7·36
7·17	10·51	7·31
11·30	9·63	7·46
15·17	8·98	7·46
30·0	7·40	7·24
35·0	7·03	7·26
40·0	6·70	7·36
∞	5·18	

$[Substrate]_o$ = 0·06265 moles l^{-1}

$[(C_2H_5)_2NH]_o$ = 0·01832 moles l^{-1}

k = (7·35 ± 0·03) x 10^{-1} $l.mole^{-1}min^{-1}$ (7 readings)

Tetrafluoropyrazine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	14·95	
20·0	14·73	1·18
52·17	14·35	1·29
95·25	13·92	1·28
155·75	13·41	1·25
216·0	12·99	1·22
306·5	12·41	1·22
405·3	11·89	1·21
532·5	11·31	1·23
684·5	10·83	1·21
∞	8·55	

$[NH_3]_o$ = 0·1498 moles l^{-1}

$[Substrate]_o$ = 0·03210 moles l^{-1}

k = (1·23 ± 0·01) x 10^{-2} $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k = (1·20 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (1·22 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$

Tetrafluoropyridazine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	k ($l.mole^{-1}min^{-1}$)
0	9·75	
1·25	8·44	3·15
2·25	7·62	3·19
3·50	6·82	3·22
5·18	6·11	3·08
6·58	5·54	3·16
8·05	5·11	3·15
10·42	4·66	3·00
12·72	4·25	3·00
15·92	3·90	2·87
19·83	3·50	2·88
25·58	3·05	2·97
31·20	2·80	2·92
∞	1·81	

$[NH_3]_o$ = 0·04933 moles l^{-1}

$[Substrate]_o$ = 0·02009 moles l^{-1}

k = (3·05 ± 0·04) $l.mole^{-1}min^{-1}$ (12 readings)

Duplicate k = (2·99 ± 0·06) $l.mole^{-1}min^{-1}$ (8 readings)

Mean k = (3·02 ± 0·05) $l.mole^{-1}min^{-1}$

Tetrafluoropyrimidine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	O.D.	10 k_I (min^{-1})
0	0·409	
0·25	0·449	4·71
0·55	0·487	4·44
0·83	0·520	4·44
1·05	0·545	4·52
1·33	0·572	4·53
1·63	0·597	4·53
1·85	0·617	4·66
2·22	0·632	4·56
2·52	0·658	4·67
2·95	0·675	4·55
3·35	0·689	4·49
3·68	0·700	4·49
∞	0·769	

$[NH_3]_o$ = $2·833 \times 10^{-3}$ moles l^{-1}

k_I = $(4·55 \pm 0·031) \times 10^{-1}$ min^{-1} (12 readings)

Duplicate k_I = $(4·59 \pm 0·04) \times 10^{-1}$ min^{-1} (12 readings)

Mean k_I = $(4·57 \pm 0·04) \times 10^{-1}$ min^{-1}

k_{II} = $(8·07 \pm 0·06) \times 10^{1}$ $l.mole^{-1}min^{-1}$

Tetrachloropyridazine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^3 k (l.mole^{-1}min^{-1})
0	14·60	
308	14·36	1·34
1320	13·64	1·34
2724	12·82	1·32
4405	12·00	1·32
5970	11·41	1·30
9960	10·24	1·28
14850	9·28	1·28
20100	8·44	1·33
∞	6·46	

$[NH_3]_o$ = 0·07329 moles l^{-1}

$[Substrate]_o$ = 0·02043 moles l^{-1}

k = (1·31 ± 0·01) x 10^{-3} l.mole^{-1}min^{-1} (8 readings)

Duplicate k = (1·27 ± 0·01) x 10^{-3} l.mole^{-1}min^{-1} (8 readings)

Mean k = (1·29 ± 0·01) x 10^{-3} l.mole^{-1}min^{-1}

Tetrachloropyrimidine + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	13·67	
3·83	12·87	3·81
9·08	11·97	3·77
14·33	11·22	3·76
20·17	10·57	3·68
27·75	9·85	3·65
38·25	8·97	3·77
49·83	8·38	3·64
90·17	6·93	3·67
∞	5·03	

$[NH_3]_o$ = 0·06862 moles l^{-1}

$[Substrate]_o$ = 0·02169 moles l^{-1}

k = (3·72 ± 0·02) x 10^{-1} $l.mole^{-1}min^{-1}$ (8 readings)

Duplicate k = (3·68 ± 0·01) x 10^{-1} $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (3·70 ± 0·02) x 10^{-1} $l.mole^{-1}min^{-1}$

Heptafluoroquinoline + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	12·58	
10·0	10·62	3·73
15·27	9·82	3·77
20·0	9·21	3·79
27·0	8·50	3·74
35·0	7·80	3·75
45·0	7·11	3·75
56·25	6·51	3·73
66·25	6·10	3·68
80·25	5·60	3·67
100·25	5·04	3·69
133·0	4·43	3·65
207·0	3·64	3·61
304·0	3·12	3·65
∞	2·50	

$[NH_3]_o$ = 0·06315 moles l^{-1}

$[Substrate]_o$ = 0·02530 moles l^{-1}

k = $(3·71 \pm 0·01) \times 10^{-1}$ $l.mole^{-1}min^{-1}$ (13 readings)

Duplicate k = $(3·68 \pm 0·01) \times 10^{-1}$ $l.mole^{-1}min^{-1}$ (14 readings)

$(3·67 \pm 0·03) \times 10^{-1}$ $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = $(3·69 \pm 0·01) \times 10^{-1}$ $l.mole^{-1}min^{-1}$

Heptafluoroisoquinoline + Ammonia in 60/40 Dioxan/Water at 25·02°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	15·03	
10·0	14·35	9·46
22·0	13·60	9·68
37·0	12·83	9·56
55·0	11·99	9·72
75·0	11·30	9·49
101·0	10·49	9·52
129·0	9·76	9·62
164·33	9·12	9·40
206·25	8·37	9·70
246·0	7·87	9·73
∞	5·01	

$[NH_3]_o$ = 0·07065 moles l^{-1}

$[Substrate]_o$ = 0·02535 moles l^{-1}

k = (9·58 ± 0·04) x 10^{-2} $l.mole^{-1}min^{-1}$ (10 readings)

Duplicate k^1 = (9·35 ± 0·04) x 10^{-2} $l.mole^{-1}min^{-1}$ (11 readings)

Mean k = (9·47 ± 0·04) x 10^{-2} $l.mole^{-1}min^{-1}$

Perfluorotoluene + Ammonia in 77/23 Dioxan/Water at 92·23°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	14·06	
15·0	13·70	4·00
45·0	13·08	3·86
85·0	12·32	3·93
130·0	11·58	4·00
180·0	10·89	4·03
240·0	10·29	3·91
315·0	9·52	4·04
395·0	9·02	3·90
520·0	8·20	4·07
644·0	7·68	4·07
∞	5·27	4·05

$[NH_3]_o$ = 0·07058 $l.mole^{-1}min^{-1}$

$[Substrate]_o$ = 0·02206 $l.mole^{-1}min^{-1}$

k = (3·98 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$ (11 readings)

Duplicate k = (4·05 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$ (11 readings)

Mean k = (4·02 ± 0·02) x 10^{-2} $l.mole^{-1}min^{-1}$

Perfluoroethylbenzene + Ammonia in 77/23 Dioxan/Water at 92·23°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	14·70	
10·0	14·22	8·67
25·0	13·57	8·75
45·0	12·84	8·71
65·0	12·21	8·73
90·0	11·60	8·55
125·0	10·82	8·70
160·0	10·30	8·44
205·0	9·62	8·72
265·0	9·05	8·59
335·0	8·59	8·36
∞	6·83	

$[NH_3]_o$ = 0·07379 moles l^{-1}

$[Substrate]_o$ = 0·01975 moles l^{-1}

k = $(8·62 \pm 0·04) \times 10^{-2}$ $l.mole^{-1}min^{-1}$ (10 readings)

Duplicate k = $(8·62 \pm 0·05) \times 10^{-2}$ $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = $(8·62 \pm 0·05) \times 10^{-2}$ $l.mole^{-1}min^{-1}$

Perfluoroisopropylbenzene + Ammonia in 77/23 Dioxan/Water at 92·23°

Time (min.)	Titre (ml.)	10^2 k ($l.mole^{-1}min^{-1}$)
0	12·08	
15·0	11·74	5·92
35·0	11·30	6·15
65·0	10·75	6·08
100·0	10·20	6·06
140·0	9·72	5·87
190·0	9·12	6·04
240·0	8·68	5·99
315·0	8·11	6·05
375·0	7·88	5·93
465·0	7·40	5·86
∞	5·50	

$[NH_3]_o$ = 0·06064 moles l^{-1}

$[Substrate]_o$ = 0·01652 moles l^{-1}

k = (6·00 ± 0·03) x 10^{-2} $l.mole^{-1}min^{-1}$ (10 readings)

Duplicate k = (6·03 ± 0·08) x 10^{-2} $l.mole^{-1}min^{-1}$ (10 readings)

Mean k = (6·02 ± 0·05) x 10^{-2} $l.mole^{-1}min^{-1}$

Perfluoro-t-butylbenzene + Ammonia in 77/23 Dioxan/Water at 92·23°

Time (min.)	Titre (ml.)	10 k ($l.mole^{-1}min^{-1}$)
0	12·63	
10·0	12·11	1·03
25·0	11·41	1·05
45·0	10·66	1·02
70·0	9·86	1·03
105·0	8·96	1·04
140·0	8·27	1·04
185·5	7·63	1·02
245·5	6·93	1·03
342·5	6·15	1·05
∞	4·25	

$[NH_3]_o$ = 0·06340 $l.mole^{-1}min^{-1}$

$[Substrate]_o$ = 0·02103 $l.mole^{-1}min^{-1}$

k = (1·03 ± 0·003) x 10^{-1} $l.mole^{-1}min^{-1}$ (9 readings)

Duplicate k = (1·05 ± 0·005) x 10^{-1} $l.mole^{-1}min^{-1}$ (9 readings)

Mean k = (1·04 ± 0·004) x 10^{-1} $l.mole^{-1}min^{-1}$

APPENDIX II

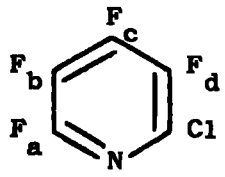
^{19}F N.M.R. SPECTRA

Index to n.m.r. spectra

1. 2-chlorotetrafluoropyridine
2. 2,6-dichlorotrifluoropyridine
3. 3,4-dichlorotrifluoropyridine
4. 3,4,5-trichlorodifluoropyridine
5. 6-amino-3,4-dichlorodifluoropyridine
6. 2-amino-3,4-dichlorodifluoropyridine
7. 4-amino-2,6-dichlorodifluoropyridine
8. 2-amino-3,4,5-trichlorofluoropyridine
9. 4-amino-2,5,6-trifluoropyridine
10. 6-amino-2,4,5-trifluoropyridine
11. 4-amino-2,6-difluoropyridine
12. 4-diethylaminotetrafluoropyridine
13. 4-chloro-2-diethylaminotrifluoropyridine
14. 3-chloro-4-diethylaminotrifluoropyridine
15. 3-chloro-6-diethylaminotrifluoropyridine
16. 3,5-dichloro-2-diethylaminodifluoropyridine
17. 2,6-dichloro-4-diethylaminodifluoropyridine
18. 3,4-dichloro-6-diethylaminodifluoropyridine
19. 3,4,5-trichloro-2-diethylaminofluoropyridine
20. 4-aminoheptafluorotoluene
21. 4-aminononafluoroethylbenzene
22. 4-aminoundecafluoroisopropylbenzene
23. perfluoro-t-butylbenzene
24. 4-aminotridecafluoro-t-butylbenzene

All spectra, unless otherwise stated, were run as pure liquid at 40^{o}. Chemical shifts are in p.p.m. relative to external $CFCl_3$.

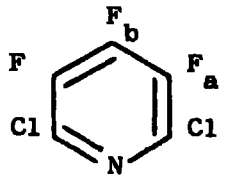
1.



Shift	Assignment
84·4 (Broad S)	a
137·0 (TD)	c
140·1 (DDD)	d
159·3 (DDD)	b

J_{ab} = 23; J_{ac} = 16; J_{ad} = 26; J_{bc} = 16; J_{bd} = 4; J_{cd} = 18

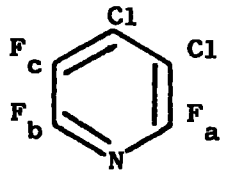
2.



Shift	Assignment
138·5 (D)	a
140·5 (T)	b

J_{ab} = 17

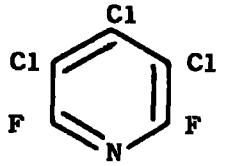
3.



Shift	Assignment
72·2 (DD)	a
85·5 (DD)	b
142·5 (DD)	c

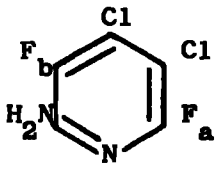
J_{ab} = 13; J_{ac} = 26; J_{ab} = 20

4.



Shift
68·6 (S)

5.

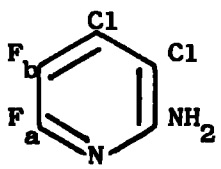


Shift	Assignment
74·9 (D)	a
143·8 (D)	b

J_{ab} = 26

Spectrum run as solution in acetone

6.

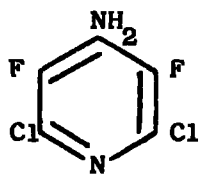


Shift	Assignment
91·3 (D)	a
157·3 (D)	b

J_{ab} = 25

Spectrum run as solution in acetone

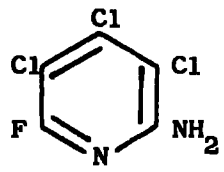
7.



Shift
140·9 (S)

Spectrum run as solution in acetone

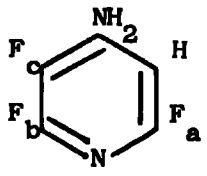
8.



Shift
72·9 (S)

Spectrum run as solution in acetone

9.

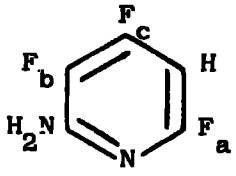


Shift	Assignment
76·4 (DD)	a
95·0 (DD)	b
173·7 (TD)	c

J_{ab} = 13; J_{ac} = J_{bc} = 20

Spectrum run as solution in acetone

10.

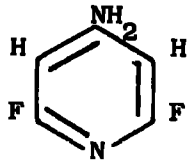


Shift	Assignment
70·9 (T)	a
124·6 (TD)	c
172·6 (DDD)	b

J_{ab} = 24; J_{ac} = J_{bc} = 18

Spectrum run as solution in acetone

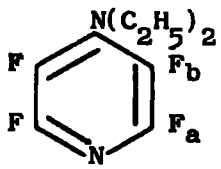
11.



Shift
68·7 (S)

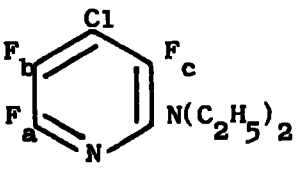
Spectrum run as solution in acetone

12.



Shift	Assignment
96·6 (S)	a
158·0 (S)	b

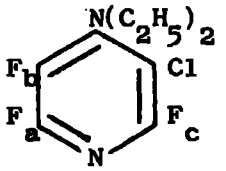
13.



Shift	Assignment
87·0 (DD)	a
136·3 (DD)	c
156·2 (DD)	b

$J_{ab} = 24$; $J_{ac} = 29$; $J_{bc} = 8$

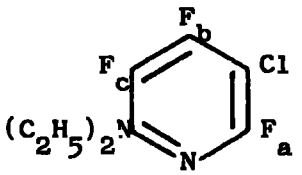
14.



Shift	Assignment
74·4 (DD)	c
92·5 (DD)	a
154·0 (T)	b

$J_{ab} = 21$; $J_{ac} = 14$; $J_{bc} = 23$

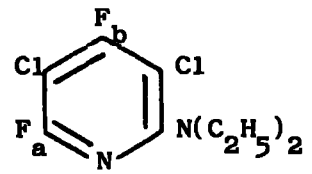
15.



Shift	Assignment
72·8 (DD)	a
124·4 (DD)	b
163·2 (DD)	c

$J_{ab} = 12$; $J_{ac} = 26$; $J_{bc} = 17$

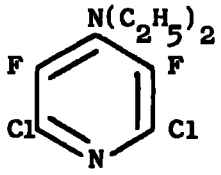
16.



Shift	Assignment
70·9 (D)	a
97·6 (D)	b

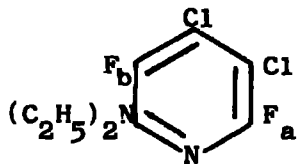
$J_{ab} = 16·5$

17.



Shift
129·3 (S)

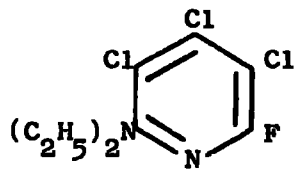
18.



Shift	Assignment
75·7 (D)	a
139·8 (D)	b

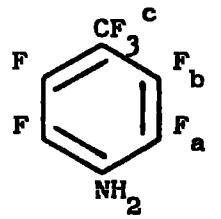
J_{ab} = 27·5

19.



Shift
70·0 (S)

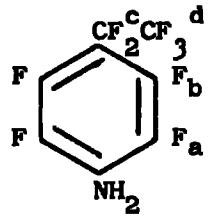
20.



Shift		Assignment
56·8	(T)	c
147·0	(M)	b
165·3	(D)	a

J_{ab} = 12; J_{cb} = 22

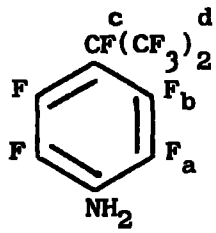
21.



Shift	Assignment
86·9 (Broad S)	d
109·9 (T)	c
143·6 (M)	b
163·3 (D)	a

J_{ab} = 12; J_{cd} = 30

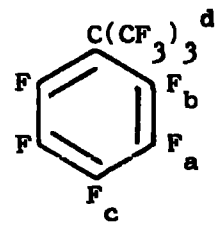
22.



Shift	Assignment
76·1 (Broad S)	d
141·3 (Broad)	b
162·2 (D)	a
177·2 (T)	c

J_{ab} = 15; J_{cd} = 42

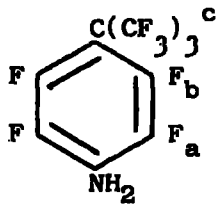
23.



Shift	Assignment
64·9 (T)	d
129·9 (M)	b
150·8 (M)	c
164·2 (DD)	a

J_{ab} = 12; J_{ac} = 20; J_{bd} = 25; J_{bc} = 12

24.



Shift	Assignment
61·8 (T)	c
132·4 (M)	b
165·4 (D)	a

J_{ab} = 11; J_{bc} = 26

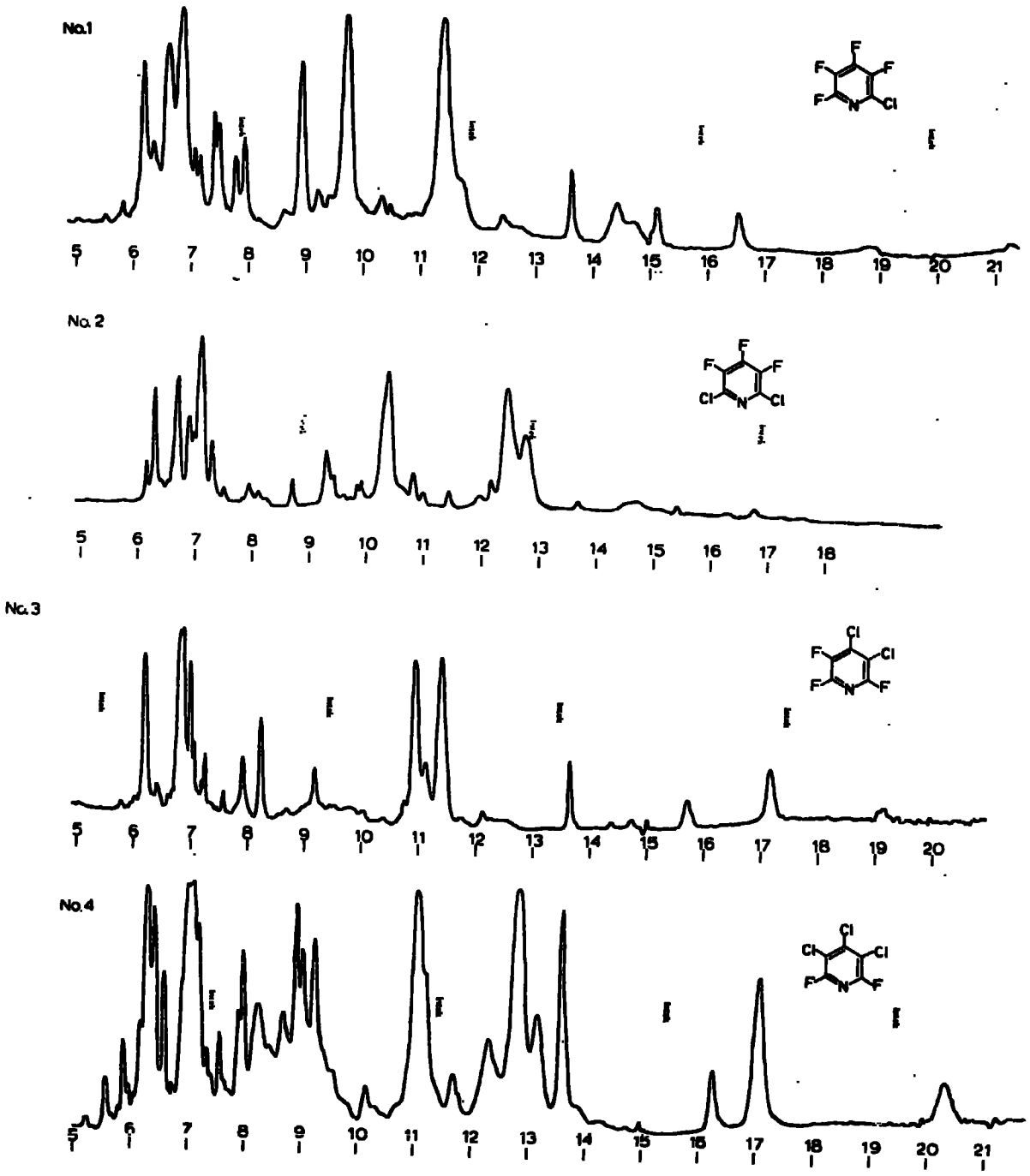
APPENDIX III

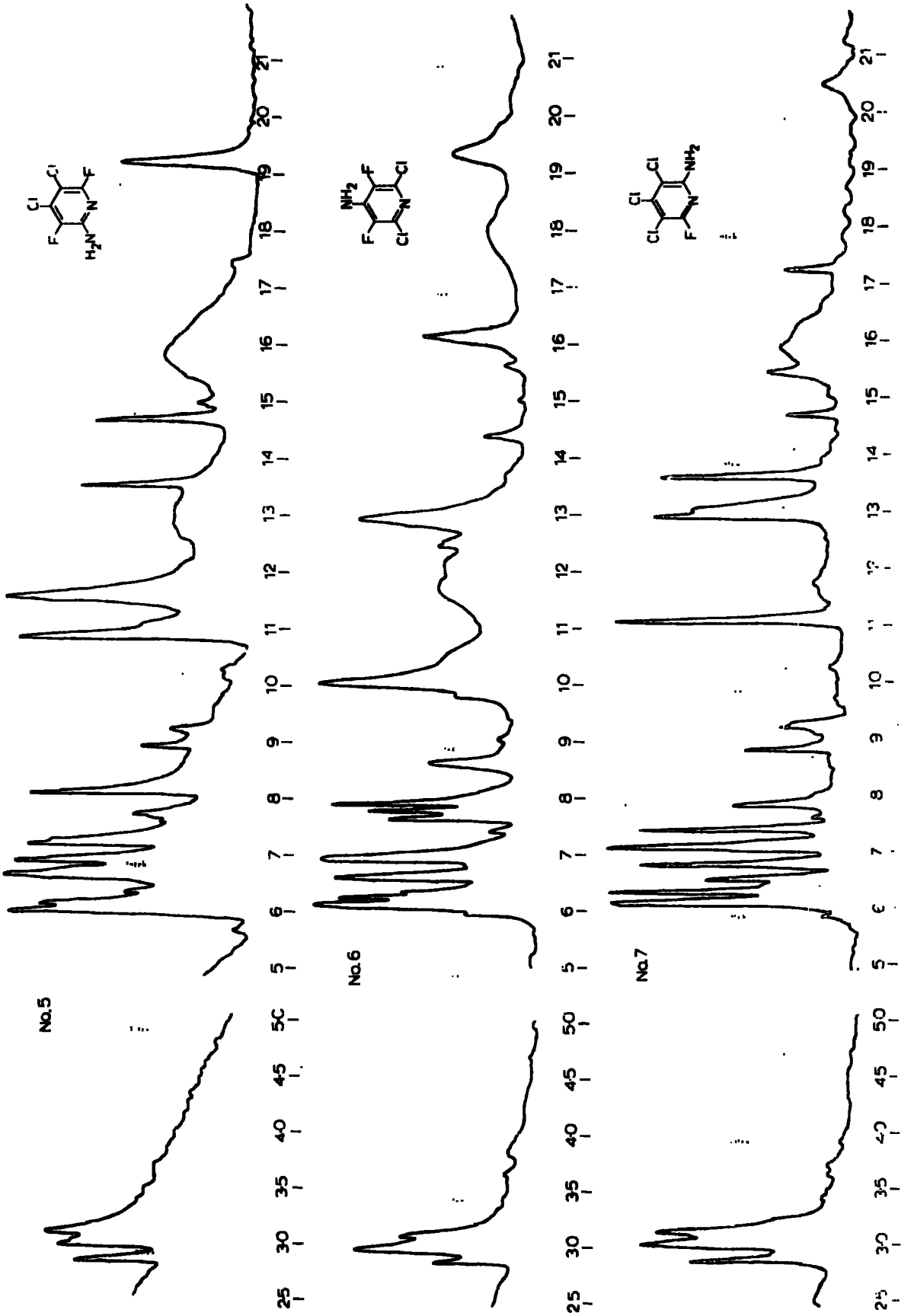
INFRA-RED SPECTRA

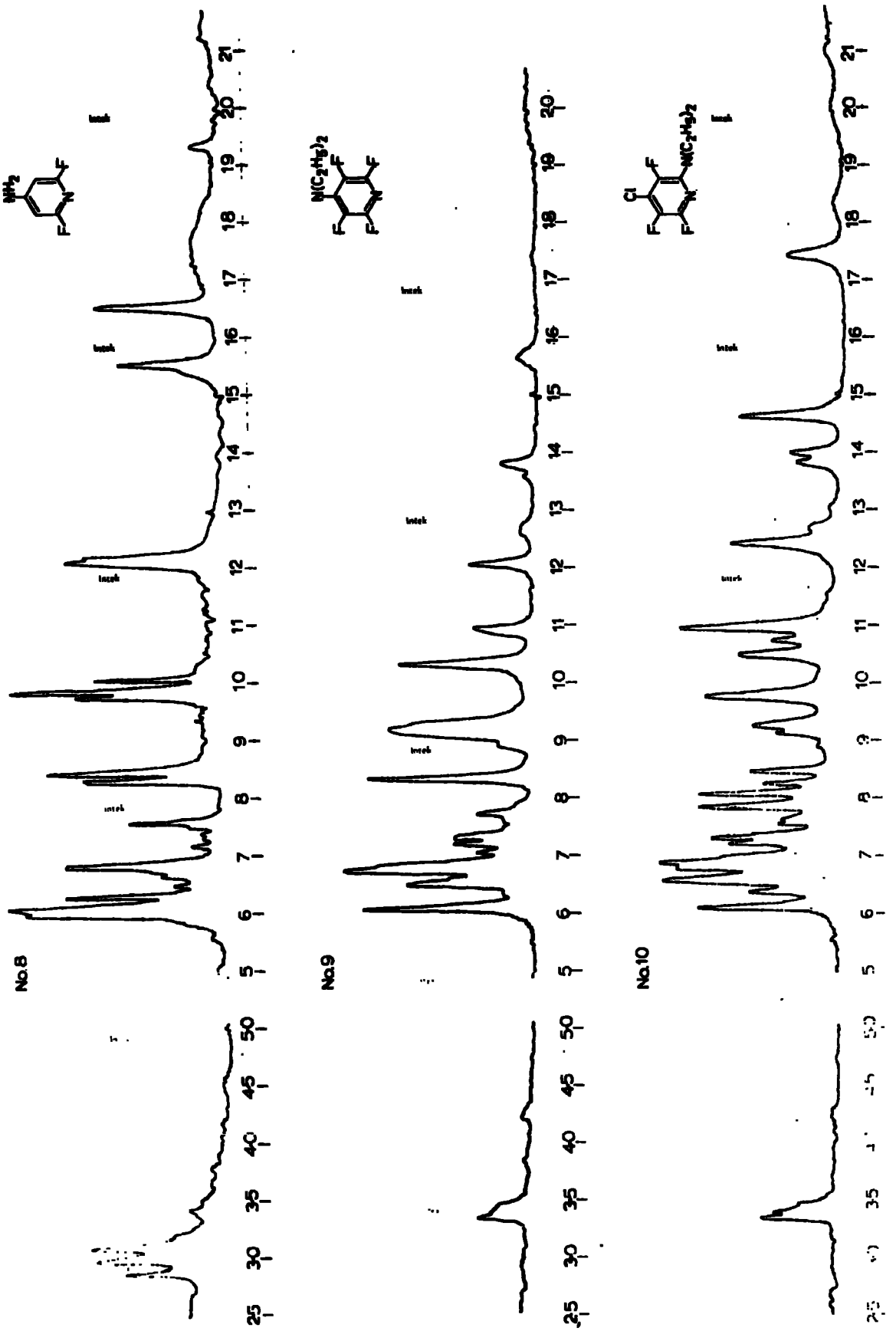
Spectrum No.	Compound	
1.	2-chlorotetrafluoropyridine	(1)
2.	2,6-dichlorotrifluoropyridine	(1)
3.	3,4-dichlorotrifluoropyridine	(1)
4.	3,4,5-trichlorodifluoropyridine	(1)
5.	6-amino-3,4-dichlorodifluoropyridine	(s)
6.	4-amino-2,6-dichlorodifluoropyridine	(s)
7.	2-amino-3,4,5-trichlorofluoropyridine	(s)
8.	4-amino-2,6-difluoropyridine	(s)
9.	4-diethylaminotetrafluoropyridine	(1)
10.	4-chloro-2-diethylaminotrifluoropyridine	(1)
11.	3,5-dichloro-2-diethylaminodifluoropyridine	(1)
12.	2,6-dichloro-4-diethylaminodifluoropyridine	(1)
13.	3,4-dichloro-6-diethylaminodifluoropyridine	(1)
14.	3,4,5-trichloro-2-diethylaminofluoropyridine	(1)
15.	perfluoro-t-butylbenzene	(1)
16.	4-aminoheptafluorotoluene	(1)
17.	4-aminononafluoroethylbenzene	(1)
18.	4-aminoundecafluoroisopropylbenzene	(1)
19.	4-aminotridecafluoro-t-butylbenzene	(1)

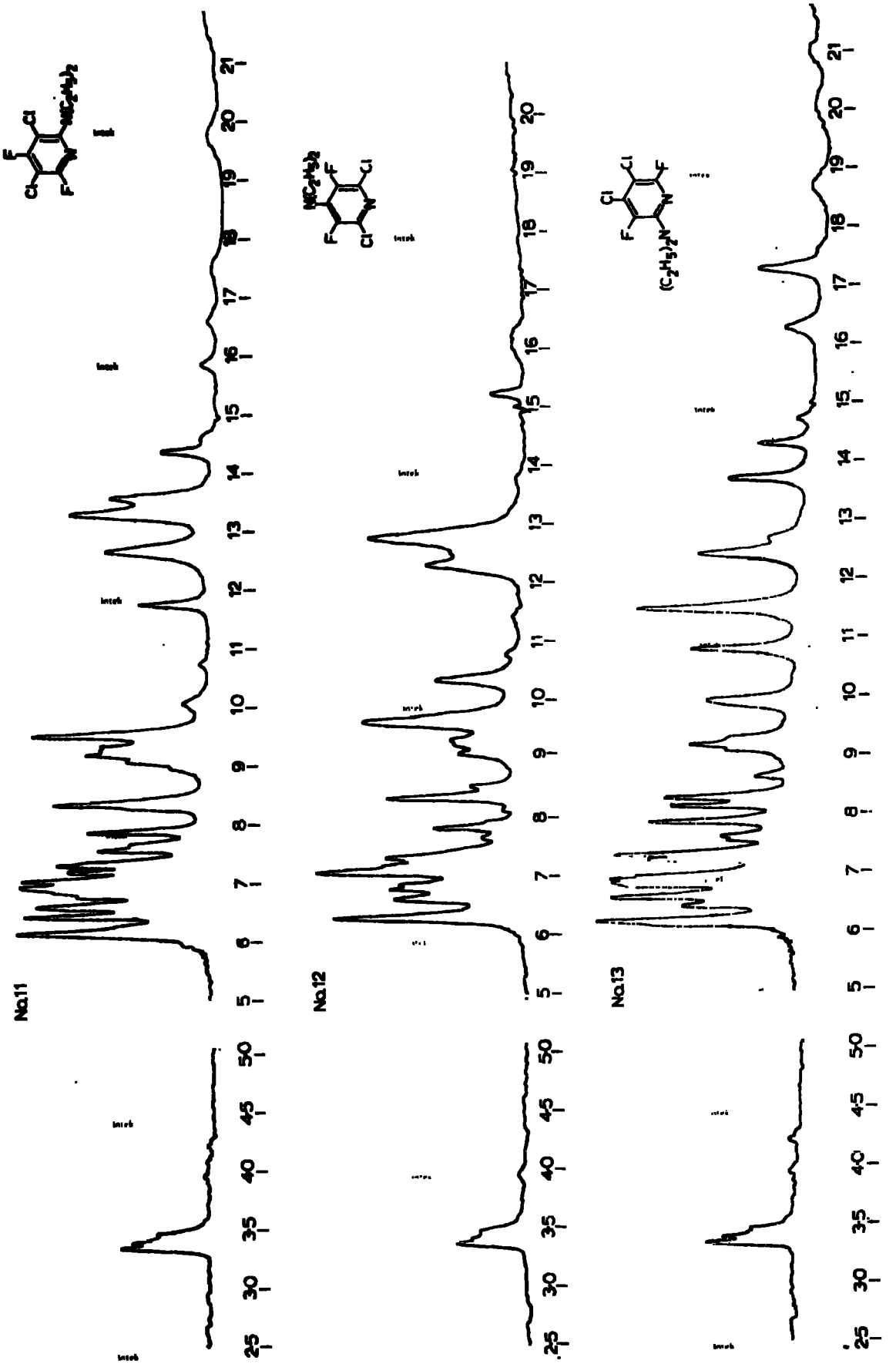
(1) - sample as contact film between potassium bromide discs.

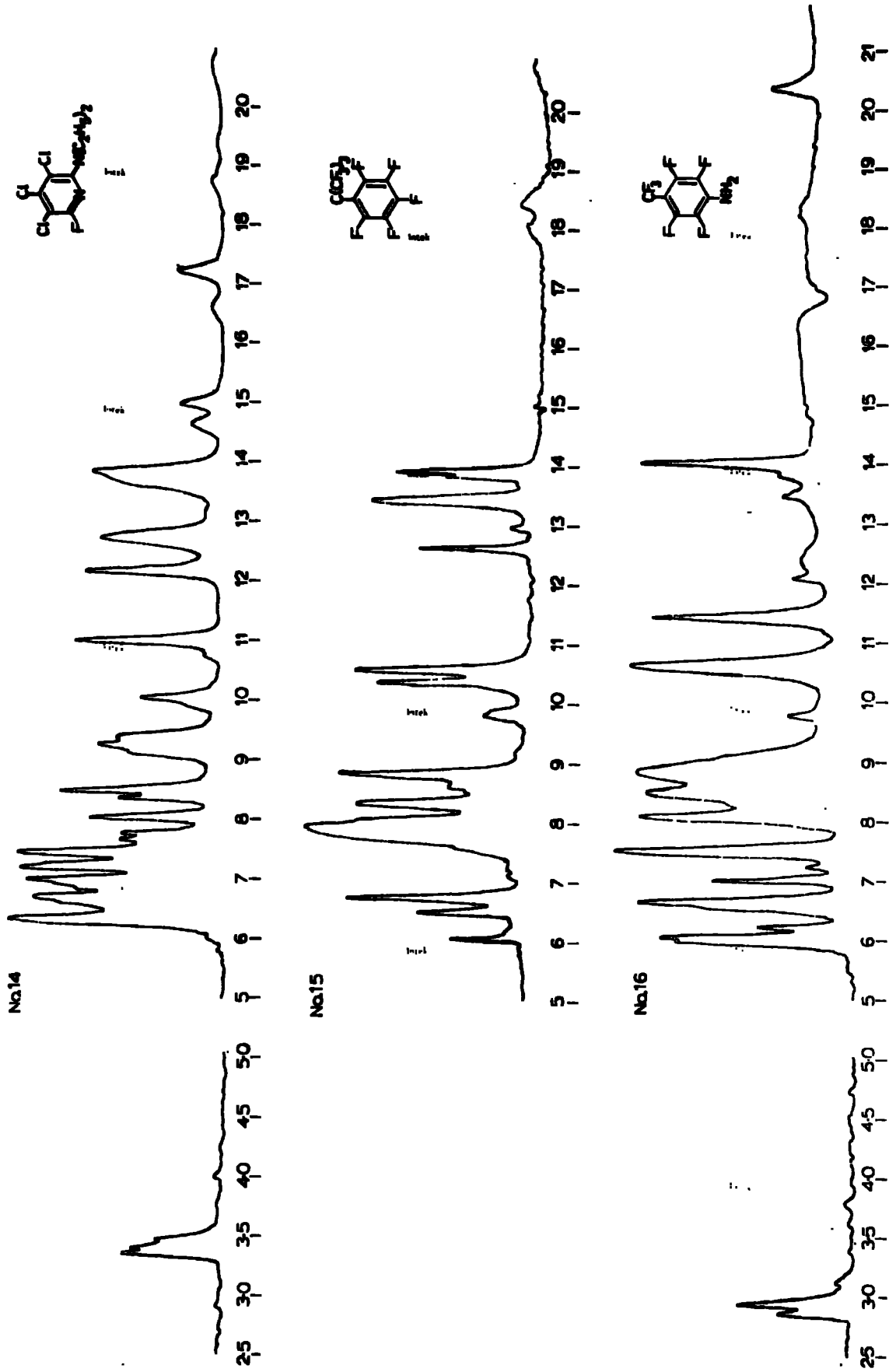
(s) - sample compressed into thin disc with potassium bromide.

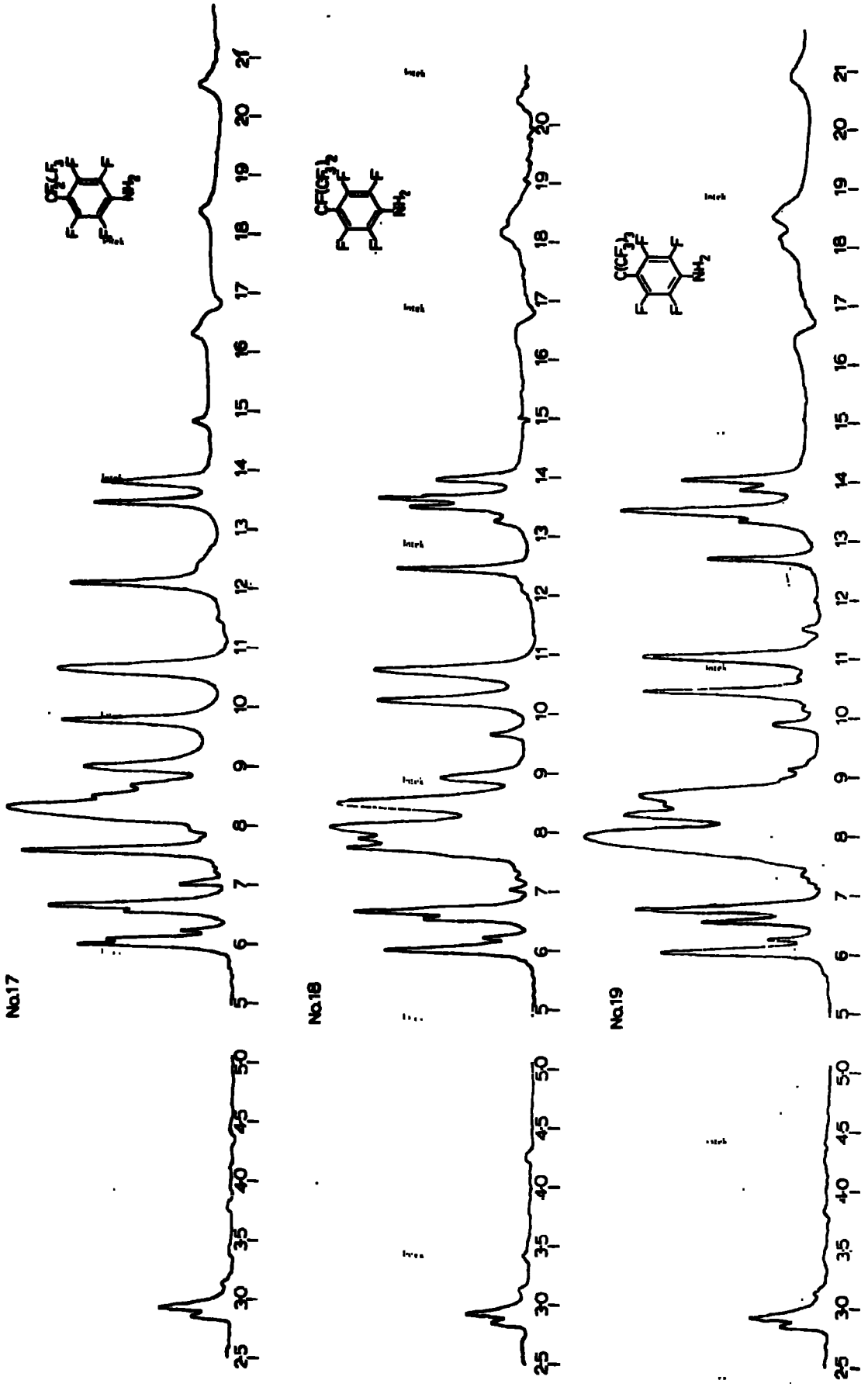

No.1
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
No. 2
5 6 7 8 9 10 11 12 13 14 15 16 17 18
No. 3
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
No.4
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21


No.5
No.6
No.7


No.8
No.9
No.10


No.11
No.12
No.13


No.14
No.15
No.16


No.17
No.18
No.19

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