Nucleophilic substitution in polyhaloaromatic systems

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NUCLEOPHILIC SUBSTITUTION IN POLYHALOAROMATIC SYSTEMS

Submitted by

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MEMORANDUM

The work described in this thesis was carried out at the University of Durham between October 1981 and August 1984 and is original except where stated by reference. This work has not previously been submitted, either wholly or in part, for a degree at this or any other university.

SUMMARY

An approach has been developed from which it has been possible to elucidate the separate activating effect of substituent groups or atoms to nucleophilic attack in a number of ring systems. Using this approach it has been possible to determine the effects of a number of potentially activating groups to nucleophilic substitution in the pyridine ring system. A number of groups were studied and these were found to be activating in the order NO_2>$\overset{+}{N}$=$\simeq$CN>CF_3>halogens for attack at any given site.

The activating effect of fluorine, relative to hydrogen, was determined for attack by ammonia and by sodium methoxide in the pyridine and pyrimidine systems. The ratio of *ortho/meta* fluorine activation was found to increase as the reactivity of the system increased. From these observations, the nature of the "*ortho*-effect" was in part explained as a consequence of an initial-state ion-dipole interaction. Evidence was also provided which suggested that *ortho*-fluorine is σ-complex stabilising. *Ipso*-fluorine was found to have a marked σ-complex-stabilising influence.

It has been possible to extend the empirical approach to account for the orientation of nucleophilic substitution in the polyfluoronaphthalene eystem. *Ortho* and "*pseudo-meta*" fluorines were found to be activating relative to hydrogen by factors of about 25 and 30 respectively, whereas the effect of a "*pseudo-para*" fluorine was much less significant being similar in activating power to hydrogen. Thus the orientation of nucleophilic attack in this system may be predicted; attack takes place at the site at which the activating effects of fluorine are

maximised. For very large polycyclic systems it was suggested that the orientation of attack may be predicted from a consideration of localisation energy.

The synthesis and some reactions of 2H-pentafluoropropene were studied. Its fluoride ion-induced reaction with pentafluoronitrobenzene yielded a number of unusual products including perfluoro-3-methyl-2,1-benzisoxazole. The reaction of 2H-PFP with pentafluoropyridine in the presence of fluoride ion gave mainly perfluoro-4-(prop-2-enyl)pyridine). This in turn reacted with caesium fluoride in dry tetraflyme to give a very stable carbanion, observable by n.m.r., which could be trapped with bromine to give the expected product. However, trapping of the anion with iodine gave tetrafluoro-4-(2H-hexafluoroisopropyl)pyridine, tetrafluoro-4-(2-hydroxyhexafluoroisopropyl)-pyridine and tetrafluoro-4-(2,2,2-trifluoroethyl)pyridine as the major products. Mechanisms for the formation of these products were proposed.

Rate measurements for the reactions of pentafluorotoluene, pentafluoro-(2,2,2-trifluoroethyl)benzene and perfluoro-t-butylbenzene showed a marked increase in reactivity along the series. This was interpreted in terms of an increase in the substituents' inductive effect as the number of CF_3 groups was increased, rather than as a consequence of trifluoromethyl ion hyperconjugation. Pentafluoro-(2H-hexafluoroisopropyl)benzene was found to rapidly dehydrofluorinate in the presence of sodium methoxide.

CONTENTS

INTRODUCTION

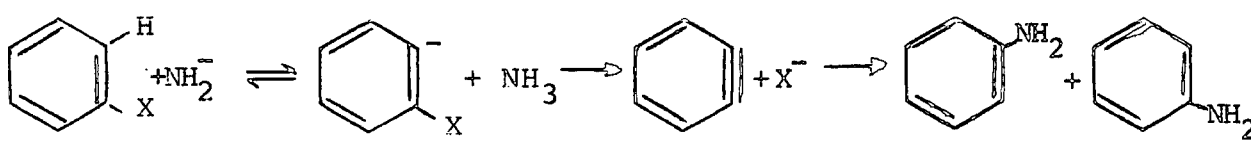
CHAPTER ONE

NUCLEOPHILIC AROMATIC SUBSTITUTION

Nucleophilic aromatic substitution reactions may proceed by a number of different pathways. Many of these mechanistic possibilities are familiar and have been extensively reviewed.[1,2] The following Sections are intended to give a brief summary of some of the mechanisms which may occur in both aromatic and N-heteroaromatic systems; discussion will be concerned mainly with halogenated species. Some recent developments within the field will also be considered.

1.1 Introduction - A Summary of Possible Mechanisms for Nucleophilic Aromatic Substitution

Aryl halides not activated by strongly electron-withdrawing groups are generally unreactive towards nucleophiles[3] but, with very strong bases such as potassium amide in liquid ammonia, reaction may occur *via* the so-called "benzyne" mechanism. The initial step is a reversible proton abstraction, *ortho* to the halogen substituent, forming an aryl anion. This is followed by halide-ion elimination to give the "aryne", which is rapidly captured by any nucleophiles present. For example, (Equation 1.1):



X = F, Cl, Br, I (1.1)

The radical-chain $S_{RN}1$ mechanism provides another means for nucleophilic substitution in unactivated aryl halides; there have been reviews both of the scope[4] and synthetic applications[5] of this mechanism. The reaction is initiated by electron transfer to the substrate, giving a radical anion. This process may be chemically,[6] electrochemically,[7] thermally[8] or photochemically[9] induced. The radical anion is then propagated in steps (1)-(3) as shown in the following generalised process (Equation 1.2):

$$ArX + e^- \longrightarrow [ArX]^{\cdot -} \quad \text{(initiation)}$$

$$[ArX]^{\cdot -} \longrightarrow Ar^{\cdot} + X^- \quad \text{(1)}$$

$$Ar^{\cdot} + Y^- \longrightarrow [ArY]^{\cdot -} \quad \text{(2)}$$

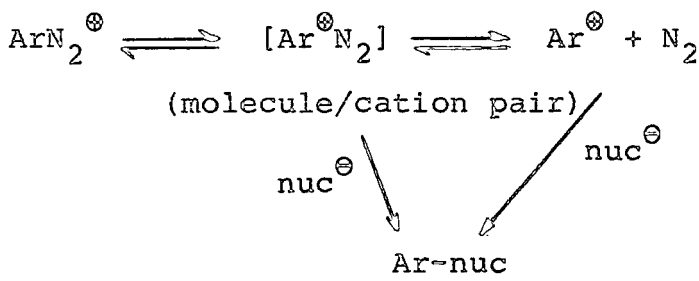
$$[ArY]^{\cdot -} + ArX \longrightarrow ArY + [ArX]^{\cdot -} \quad \text{(3)}$$

(Y^- = nucleophile) (1.2)

Summation of the three propagation steps gives the overall equation: $ArX + Y^- \longrightarrow ArY + X^-$, and therefore the overall reaction is a nucleophilic substitution of the leaving group X by the nucleophile Y. More general opportunities for electron-transfer chain catalysis (ETC) are discussed in Section 1.3.1.

A third mechanism for nucleophilic aromatic substitution is found in the dediazoniation reactions of arene diazonium salts. An understanding of this process is complicated by the fact that the mechanism is dependent upon the reaction conditions;[10] both ionic and free-radical pathways are available.[11] It has been suggested[12] that the overall process

of the reaction, *via* an ionic intermediate, can be represented by the following equation (Equation 1.3):



(1.3)

This process, analagous to the S_N1 mechanism observed in aliphatic compounds, is considered to be the only example of an aryl-cation mechanism.[12] Various mechanisms for the reaction of diazonium salts *via* radical intermediates have been suggested;[14,15,16] it is generally agreed that the key step is a redox process involving electron transfer from an electron donor to the diazonium cation.[17,18] For example (Equation 1.4):

$$ArN_2^+ + Cu^+ \longrightarrow Ar^\circ + N_2 + Cu^{2+}$$

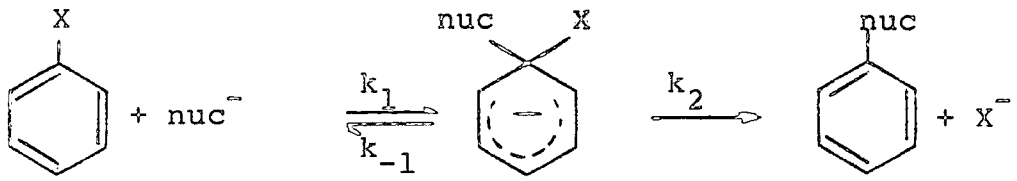
$$Ar^\circ + CuX_2 \longrightarrow ArX + CuX$$

(X = halogen) (1.4)

Aspects of the chemistry of diazonium compounds have been reviewed.[19]

Aromatic systems may also react with nucleophiles *via* a bi-molecular addition-elimination, or S_NAE mechanism, which usually results in the *ipso*-substitution of a leaving group. In order for this mechanism to occur, a system must be suitably activated and possess a leaving group that can exist as a stable anion. The reaction proceeds *via* the formation of a covalently-bonded anionic σ-complex, in which negative

charge is delocalised into the ring; this is represented as structure (1) below (Equation 1.5):



(1) (1.5)

Evidence for the occurrence of this mechanism with activated systems has been well documented.[20] There is overwhelming evidence for the formation of anionic σ-complexes,[21,22] which can sometimes be isolated as salts.[22]

In polyfluoroaromatic systems, which are activated to nucleophilic substitution and possess an excellent leaving group in F^-, reaction with nucleophiles normally takes place by this two-step bi-molecular process. It is thought that formation of the intermediate complex (1) is rate-limiting (*i.e.* $k_2 >> k_{-1}$ in (1.5)), which implies that little C-F bond breaking occurs in this step. Evidence in support of this assumption has been the order (F>>Cl>Br>I) of halide ion mobility found in the nucleophilic substitution reactions of polyfluoroaromatic compounds;[20] this point has been fully discussed.[20,23]

Except where stated otherwise, it has been assumed that all nucleophilic aromatic substitution reactions discussed in subsequent Chapters occur *via* the S_NAE mechanism, with the first step rate-determining. Other pathways are available for the reaction of activated aromatic species with nucleophiles; some of these are discussed in Section 1.3.

1.2 Mechanism for Nucleophilic Aromatic Substitution in N-Heterocyclic Compounds

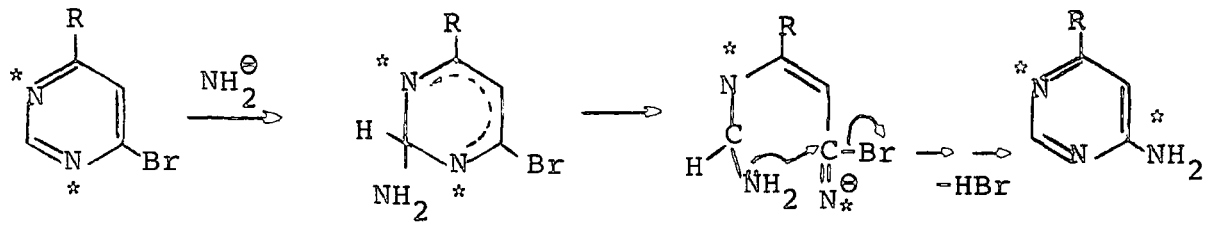
Nitrogen heterocyclic systems are all activated, relative to the corresponding benzenoid compounds, towards nucleophilic aromatic substitution. The effect of the ring nitrogen is greatest at positions *ortho* and *para* to this group. The nature and magnitude of this activation is discussed in Section 2.6.1.

As a consequence of this activation, the majority of nucleophilic substitutions in N-heterocyclic aromatic compounds proceed by the well-recognised two-step S_NAE mechanism, as discussed in Section 1.1. Evidence for this mechanism is the same as for the benzene derivatives; for example, several studies of σ-adduct formation from heterocyclic compounds have been reported.[24,25] Similarly, the order of halogen mobilities is usually found to be F>>Cl>Br in these systems.[26,27]

However, the reactions of N-heterocyclic compounds with nucleophiles are often complicated by processes other than straightforward substitution. In the presence of strong bases, unactivated substrates may sometimes react by the elimination-addition mechanism; this area has recently been reviewed.[28]

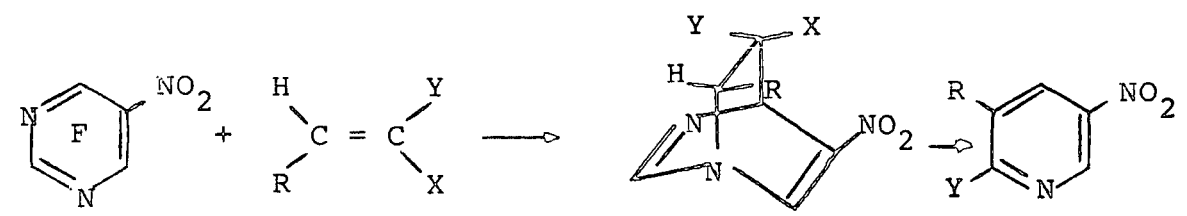
Another method by which unactivated N-heterocyclic systems may react with strong bases is by the S_N(ANRORC) mechanism. The mechanism occurs by a series of reaction steps, involving an Addition of the Nucleophile, Ring Opening, and Ring Closure. This process was first observed in the

reaction of 6-bromo-4-alkyl-pyrimidines with potassium amide in liquid ammonia.[29] Although the final product may conceivably have been formed by the more standard elimination-addition mechanism, labelling experiments[30] indicated the occurrence of a ring degenerate transformation in which the ring-N= in the product was different from that in the substrate (Equation 1.6):



R=C_6H_5, t-C_4H_9) (Addition of Nucleophile) (Ring Opening) (Ring Closure) (1.6)

Ring transformations that are non-degenerate (*i.e.* that lead to the formation of a new heterocyclic system) also take place by the S_N(ANRORC) mechanism; there is however recent evidence suggesting that, in a few systems, this process may occur by a cycloaddition mechanism.[31] For example[32]



(R=H,CH_3,$(CH_2)_4$; X=Y=OCH_3, morpholino, piperidino) (1) - HCN (2) - HX

The scope of the S_N(ANRORC) mechanism has been reviewed.[33] both S_N(ANRORC) and S_NEA pathways are available for the reactions of unactivated N-heterocyclic systems with strong

bases; in some cases both mechanisms occur simultaneously.[23]

1.3 Some Recent Developments in the Field of Nucleophilic Aromatic Substitution

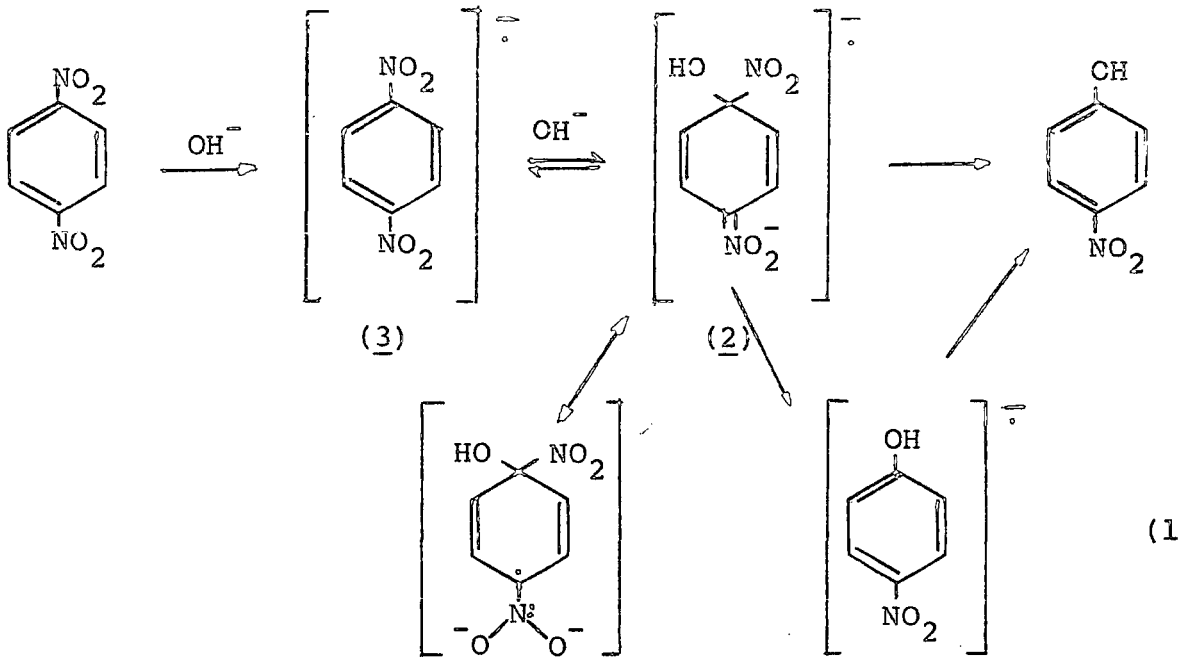
1.3.1 The Role of Electron Transfers in Nucleophilic Aromatic Substitution

That unactivated aromatic species may react with nucleophiles by the $S_{RN}1$ mechanism, in which the initial step involves electron transfer to the substrate, is well known and has been discussed (Section 1.1). The possibility that single electron transfer (SET) is the primary step in nucleophilic displacements in general (*i.e.* preceding the formation of the covalent bond) has been proposed.[34,35,36] For example, the reaction of alkyl halides with nucleophiles has been shown to take place by the following procedure[37] (Equation 1.7):

$$Nu^- + RX \longrightarrow Nu^\circ + RX^{\bullet -} \longrightarrow Nu^\circ + R^\circ + X^- \longrightarrow R\text{-}Nu + X^- \qquad (1.7)$$

However, the occurrence of such SET processes in activated aromatic systems is more questionable; competing processes such as proton abstraction[38,39] and σ-complex formation[39] are other alternatives.

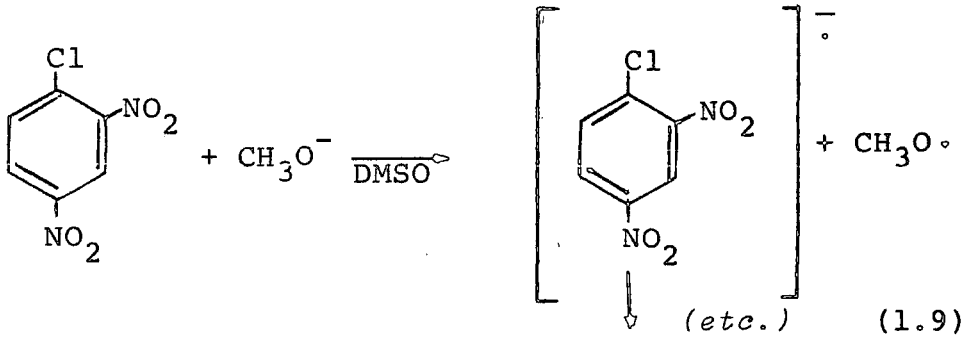
The formation of radical anions in activated nucleophilic substitution has been substantiated in only a few examples. One such case is the reaction of 1,4-dinitrobenzene with OH^-, which has been studied by esr. spectroscopy.[40] The proposed mechanism[40] involves electron transfer from OH^- to the substrate, followed by addition of OH^- to form the radical dianion (2) (Equation 1.8):



(1.8)

This electron transfer pathway is facilitated by the relative stabilities of the radical anions (2) and (3), and also by the low oxidation potential of OH^-. Consequently, the reaction of 1,3,5-trinitrobenzene with bases occurs primarily by the S_NAE mechanism because of the enhanced stability of the intermediate σ-complex.[39]

Further evidence regarding the importance of one-electron transfers in activated aromatic substitution reactions has been derived from kinetic studies.[41,42] The reactions of various nitroarenes with bases proceed *via* a radical chain mechanism in which the initiation step involves electron-transfer from the base to the substrate, for example[41] (Equation 1.9):



(1.9)

However, in the above example, appreciable quantities of anion radicals are detected only under carefully controlled conditions (*e.g.*, in the presence of a large excess of base and in the absence of oxygen). Clearly then, there are several important factors regarding the general occurrence of SET processes in activated nucleophilic aromatic substitution. Firstly, the oxidation potential of the nucleophile and the electron affinity of the substrate must be favourable. The nature of the solvent is important, as is the nature of the leaving group. The relative stabilities of any reaction intermediates, be they anion radicals or σ-complexes, are also important. Whether or not these criteria are met in the majority of nucleophilic substitution reactions and consequently the general occurrence of SET processes is open to question.

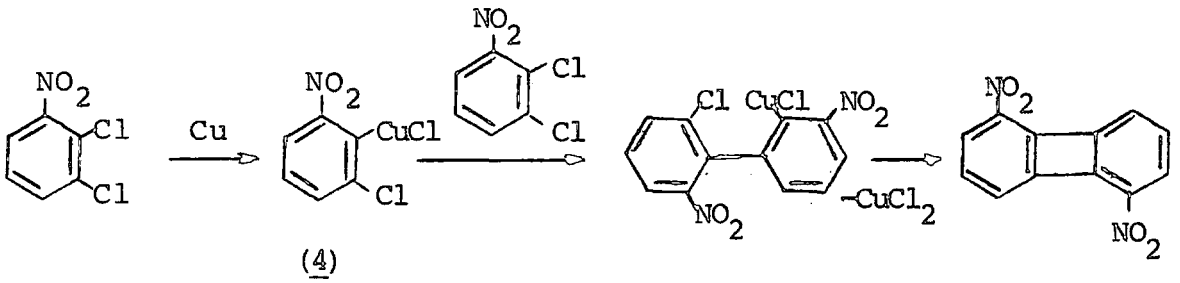
Recently, evidence for the occurrence of an electron-transfer chain (ETC) process, in which the substrate suffers a one-electron oxidation (forming an aryl radical cation) before entering the chain, has been presented.[43,44] This $S_{ON}2$ mechanism has been compared with the analagous $S_{RN}1$ process for anion radical propagation.[45] However, there are very few known examples of this mechanism.

1.3.2 The Scope of Catalysis in Nucleophilic Aromatic Substitution

(a) Catalysis by Metals/Metal Salts

There have been several recent reports of the catalysis of nucleophilic substitution processes by copper compounds.[46,47,48]

The copper-catalysed substitution reactions of aryl halides are known as Ullmann condensations. The scope of this industrially-important reaction has been reviewed.[48] For example, the reaction of 2,3-dichloronitrobenzene in the presence of copper-bronze[49] proceeds *via* the initial formation of an organo-copper intermediate (4) (Equation 1.10):



(4)

(1.10)

Ullmann condensations have been reported for a number of systems and catalysts, with copper in the 0, +1 or +2 oxidation states.[48] A number of mechanistic pathways for these processes have been proposed. However, a general feature is the formation of a complex between the aryl halide and the copper.[48] For example, the Ullmann condensation of 1-bromoanthraquinone with ethylenediamine in the presence of CuBr (where Cu(I) is the effective catalyst) proceeds by a one-electron transfer from Cu(I) to the anthraquinone *via* an organo-copper complex.[50,52] This has also been proposed in the halogen-exchange reactions of aryl halides with Cu(I) salts.[51]

Recently, reports of the use of transition metal salts and complexes as catalysts in nucleophilic substitution reactions have been published.[52,53] Thus polyhalogenated aromatic compounds may be dehalogenated using a low-valent transition metal complex such as $Pd(PPh_3)_4$ in the presence

of alkoxides,[53] or by using salts such as $PdCl_3$ in the presense of PPh_3 and hydroxide ions, where a Pd(0) complex is generated *in situ*.[54] Pd(0) will also catalyse the reaction between aryl halides and thiolate ions (giving aryl sulphides) *via* the oxidative addition of aryl halide to Pd(0)[55] (Equation 1.11):

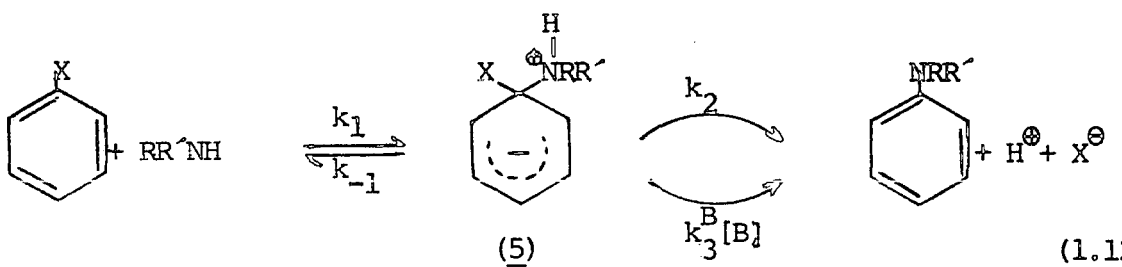
$$ArX + Pd(0) \longrightarrow ArPdX$$

$$ArPdX + RS^- \longrightarrow ArSR + Pd(0) + X^- \qquad (1.11)$$

The cyanation of aryl halides is catalysed by nickel,[56] palladium[57] and cobalt[58] complexes.

(b) Base Catalysis

The observation of base catalysis in the reactions of amines with certain activated aromatic substrates has provided overwhelming kinetic evidence for the two-step bimolecular mechanism of nucleophilic substitution in these systems. This point has been discussed.[20,59] Base catalysis is traditionally represented by the following mechanism[60] (Equation 1.12):



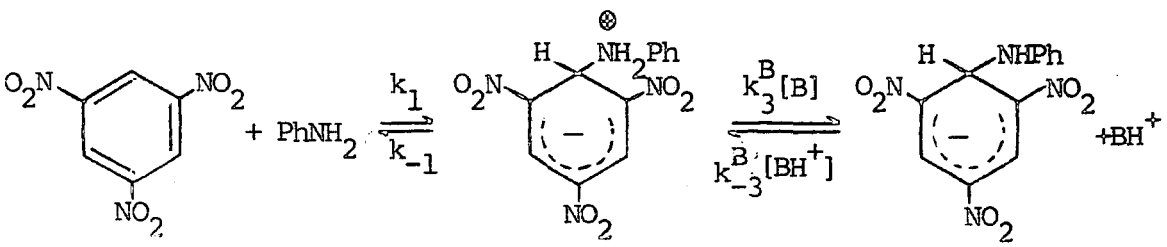
(1.12)

The initially formed zwitterionic σ-adduct (5) contains a labile N-H proton, and thus the system may undergo base catalysis through partitioning of (5) along the available pathways. A rate expression for equation (1.12) can readily be derived, and its application to account for the pronounced

observation of base catalysis in, for example, 1-fluoro-2,3-dinitrobenzene compared to the non-observation of this effect in 1-chloro-2,4-dinitrobenzene, has been discussed.[61,62]

Recent studies have concentrated on the actual mechanism of the k_3^B base-catalysed step, and there has been considerable controversy about this. It is generally agreed that two mechanisms exist. These are, (1) rate-limiting deprotonation, and (2) rate-limiting leaving group expulsion.

The rate-limiting deprotonation mechanism has been found in the formation of the σ-complex (6) from 1,3,5-trinitrobenzene and aniline, which is base catalysed by 1,4-diazabicyclooctane (DABCO) in DMSO[63,64,65] (Equation 1.13):

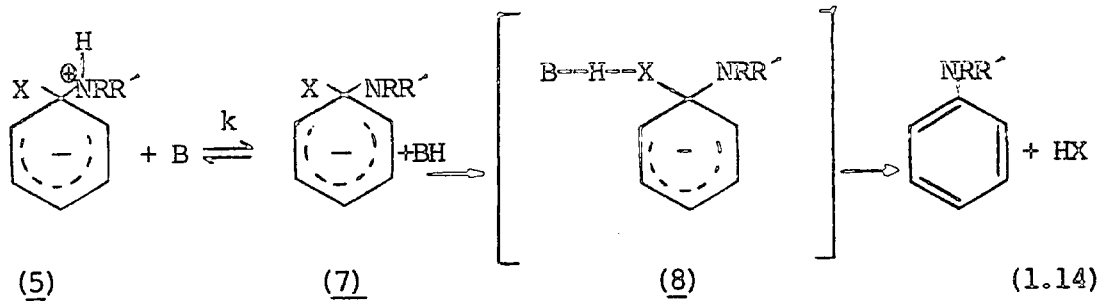


(6) (1.13)

This process generally applies when the reaction is carried out in protic solvents. Detailed kinetic analyses of rate-limiting deprotonations in the reactions of 1,3,5-trinitrobenzene with bases have been reported.[66,67]

In the rate-limiting leaving group expulsion mechanism, the initially formed zwitterionic intermediate (5) undergoes a fast proton transfer, yielding the σ-complex (7). This is followed by a rate-determining general acid-catalysed removal of the leaving group by BH^+ *via* transition state (8).

For example (Equation 1.14):



(5) (7) (8) (1.14)

This process has been termed "SB-GA" catalysis (specific base-general acid).[59] A number of examples of this mechanism have been reported.[68,69,70]

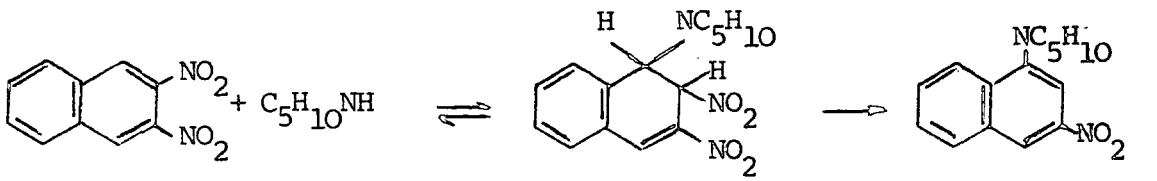
(c) Micellar Catalysis

There have been several recent reports of reactions subject to micellar catalysis.[71,72,73] In aqueous solution, cationic micelles generally enhance complex stability by increasing the forward rate of complex formation, at the same time decreasing the reverse rate. Thus, the reaction of 2,4-dinitrofluorobenzene with aniline is catalysed by the micellar surfactant hexadecyltrimethylammonium bromide (CTABr).[74] In contrast, anionic micelles strongly decrease the rates of complex formation. Several models to account for the catalytic effect of micelles have been forwarded.[74,75]

1.3.3 Cine and Tele Substitution

Activated nucleophilic aromatic substitution by the addition-elimination pathway usually involves an *ipso* attack of the nucleophile; that is, the entering group occupies the same position as that vacated by the leaving group.

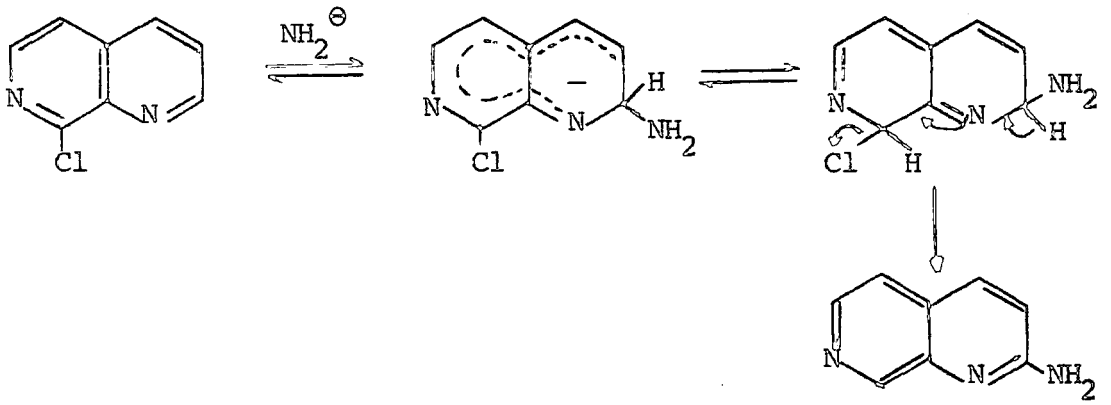
Recently, however, a new class of substitution reaction has been reported. When the incoming group enters *ortho* to the leaving group, then cine-substitution is said to have taken place. There are several known examples of nucleophilic aromatic cine substitutions. An example is the reaction of 2,3-dinitronaphthalene with piperidine, which is believed to take place by the following mechanism[76] (Equation 1.15):



(1.15)

Other known cine substitutions occur in the reaction of 2,3-dinitroaniline with secondary amines,[77] and in the reaction of pyrazole with 1,4-dinitropyrazole.[78]

When the incoming group occupies a position separated by more than one atom from that vacated by the leaving group, then tele substitution is said to have occurred.[79] This has also been termed the "abnormal addition-elimination", or $S_N(AE_a)$ mechanism.[80] Tele substitutions are known in both mono- and polycyclic aromatic systems. An example is the reaction of 8-chloro-1,7-naphthyridine with potassium amide which gives, apart from the "normal" substituted product, an adduct arising from the following mechanism[81], (Equation 1.16):



(1.16)

Other tele substitutions occur in the reactions of secondary amines with 2,3-dinitroaniline,[77] 4-alkoxy-2,3-dinitroaniline[82] and 1,4-dimethyl-2,3-dinitronaphthalene.[79] Both cine and tele processes have also been identified in the S_N(ANRORC) mechanism where, for example, S_N(ANRORC)^{cine} symbolises a process in which an incoming amino group appears adjacent to the position vacated by the halogen in the final product.[33]

CHAPTER TWO

SUBSTITUENT EFFECTS IN NUCLEOPHILIC AROMATIC SUBSTITUTION

2.1 Types of Electronic Substituent Effect

The electronic effect of a substituent, X, on a σ-bonded system is generally referred to as its polar or inductive effect. This effect results directly from a difference in electronegativity between the substituent and the adjacent carbon chain. Transmission of the effect through the molecule can occur by two means:

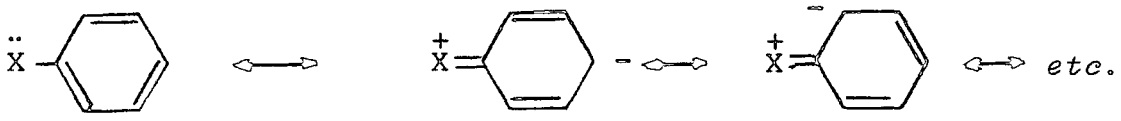
(a) A progressive, but diminishing, relay of the effect through the chain (9):

$$\underset{\text{(X electron attracting)}}{X \xleftarrow{\delta-\ \delta+} CH_2 \xleftarrow{\delta\delta+} CH_2 \longleftarrow CH_2 \longrightarrow} \qquad (9)$$

This is referred to as the σ-inductive effect.

(b) A direct, through space, electrostatic effect, known as the field effect. The relative importance of field and σ-inductive mechanisms has been discussed.[83,84]

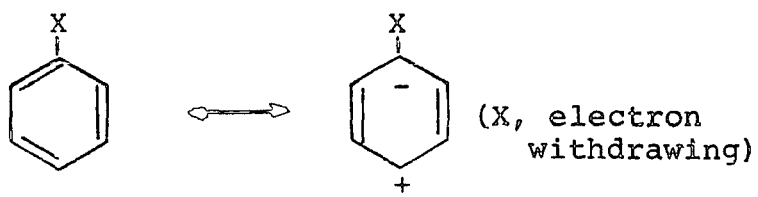
In aromatic systems, additional mechanisms for the transmission of electronic effects exist. The resonance, or mesomeric, effect involves a conjugative transfer of π-electron density between the substituent and the aromatic ring. This results in a change in the π-electron density of the system; the process may be illustrated by the following canonical structures (10a,b,c) (π-donating substituent):



(10a) (10b) (10c)

Molecular orbital calculations have confirmed this process.[85]

A substituent may also perturb an aromatic π-system without actual π-electron transfer between the substituent and the aromatic ring. Substituent effects of this kind are known as π-inductive effects; the overall effect observed is in fact a composite of several interactions which are mutually dependent and experimentally inseparable. These interactions have been fully discussed.[84] The net effect is a polarisation of the π-system so as to enhance the delocalisation of negative charge. This may be represented by the following structures (11, 11a):



(X, electron withdrawing)

(11) (11a)

The nature of substituent electronic effects in general has been reviewed.[84,86,87,88]

2.2 Effect of Substituent on Carbanion Stability

A number of techniques are available for the examination of substituent effects in carbanions. The measurement of equilibrium (K_a) and kinetic (k_1) acidity in solution is well

known and has been reviewed;[89,90] however the empirical pK_a values obtained (Equation 2.1) are complicated by factors such as solvent effects and other inter -

$$RH + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^- + HB \qquad pK_a = -\log k_1/k_{-1} \qquad (2.1)$$

molecular interreactions which may obscure the intrinsic properties of the carbanion. More recently however measurements of CH-acidity in the gas phase have been reported for a number of systems.[91,92] The standard free energy change, G^o, for a process such as (Equation 2.2) gives a measure of the acid-

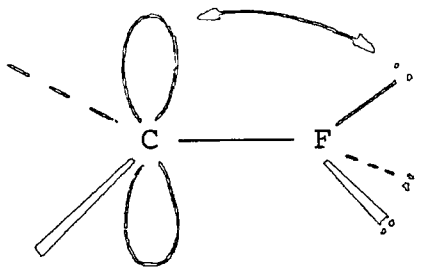
$$HX_{(gas)} \rightleftharpoons H^+_{(gas)} + X^-_{(gas)} \qquad (2.2)$$

ity of HX, and thus a measure of the stability of the carbanion X^-, in the absence of solvent effects. The determination of substituent effects from gas-phase data has been reviewed.[93] Carbanion geometry and stability as a function of substituent effects has also been determined theoretically.[94,95]

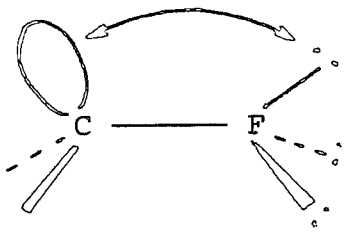
2.2.1 Fluorine Substituents

The stabilising influence of a fluorine atom directly attached to a carbanionic centre is generally difficult to predict. Base-catalysed deuterium exchange reactions of haloforms have shown that α-halogens are carbanion stabilising in the order I~Br>Cl>F.[96,97] As this is the reverse order of halogen inductive effects, then clearly destabilising electron pair repulsions must be important in these systems. The interaction between halogen lone pairs and a carbanionic centre is known as the "I_π effect",[98] and

is maximised in planar, sp^2 hybridised species where orbital overlap is greatest[99] (12); I_π destabilisation is minimised in sp^3 hybridised species [99] (13):



(12)



(13)

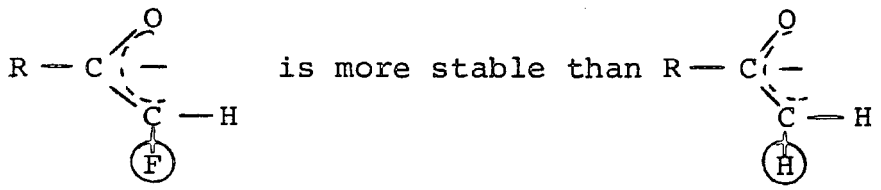
As a result of this interaction, halogen substituents exhibit a greater stabilising influence in pyramidal carbanions.[100] This is consistent with the known weak acid-strengthening effect of fluorine attached to an sp^3-centre;[101] carbanions containing more than one α-fluorine substituent are generally destabilised however.[97,101] Calculated inversion barriers for simple pyramidal carbanions also confirm this effect [102] (Table 2.1).

TABLE 2.1 Energy Barriers to Inversion, from Pyramidal to Planar Configurations, for some Simple Carbanions.[102]

Species	E_{inv}(kcal mol^{-1})
CH_3^-	19.2
FCH_2^-	32.6
F_2CH^-	53.3

Replacement of H by F in CH_3^- increases the barrier to inversion which may be interpreted solely in terms of I_π repulsions. The preferred pyramidal geometry of this type of α-fluorocarbanion has been shown by other M·O studies.[95,100]

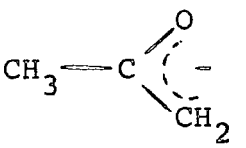
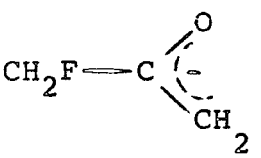
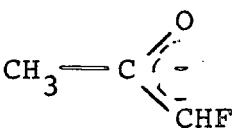
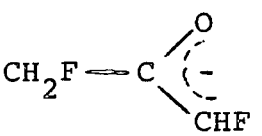
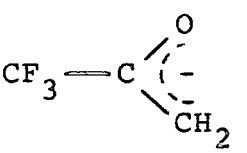
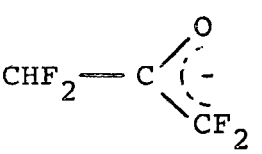
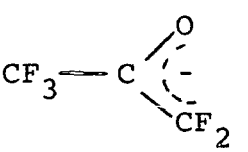
Rates of deuterium exchange reactions in α-halomethyl esters,[97] and ionisation constants of some nitrohalomethanes,[103] have been reported. In these systems the carbanion generated is essentially sp^2 hybridised. Consequently, I_π interactions are at a maximum, with the net result that fluorine is found to be destabilising to carbanion formation, relative to hydrogen. Recently however, a gas phase study of some fluorinated sp^2 hybridised carbanions has been published,[104] in which the acidity of a series of fluoroacetones was determined. The results show that α-fluorine substituents stabilise planar carbanions in the gas phase (Table 2.2), *i.e.*



The difference between gas-phase and solution data indicate an ambiguity in the effect of α-fluorine on sp^2 carbanions; this has been attributed to solvent effects in the solution acidity data.[104]

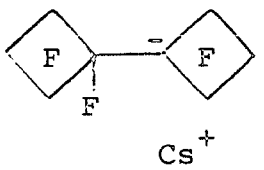
It is well established that a fluorine atom adjacent to a carbanionic centre is strongly stabilising;[105] results (Table 2.2) have also shown this effect in the gas phase.[104] In this situation, I_π repulsions are effectively removed and stabilisation takes place by inductive means. A number of recent thermodynamic studies have confirmed this effect.[106-109] Thus the stability of the anion[108] (14) and of hexafluorocyclobutane ylids[107,110] (15) are both attributable to the inductive effect of the β-fluorine substituents.

TABLE 2.2 Gas Phase Acidities of Some Fluorinated Acetones[104]

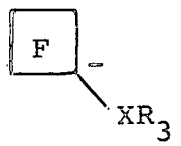
Compound	Anion Generated	Gas Phase acidity,[(a)] (k cal mol^{-1})
CH_3COCH_3		54.9
CH_3COCH_2F		49±2
CH_3COCH_2F		43.5±0.5
$(CH_2F)_2CO$		36.0±0.5
CH_3COCF_3		35.2±0.1
$(CHF_2)_2CO$		26±3
CF_3COCHF_2		17.5±1

(a) Gas phase acidity = Enthalpy change for the reaction

$AH \longrightarrow A^- + H^+$



(14)

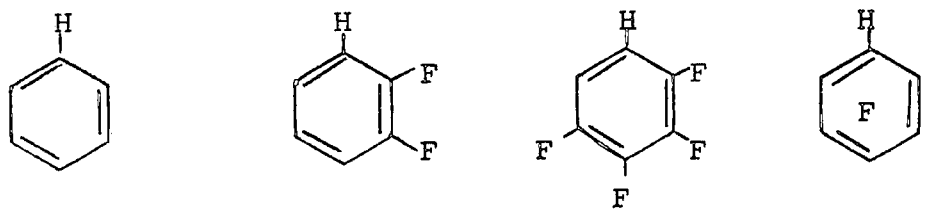


X = N, P

R = Et, Ph

(15)

Similarly, the increase in kinetic acidity along the following series is also due to this effect:[111]



pK_a	43	35	31.5	25.8

2.2.2 Other Substituents

Substituents may be classified in terms of their ability to donate or attract σ- and π-electrons by the various processes already described (Section 2.1). The electronic properties of a given substituent are reflected in the stabilisation energy of a given carbanion and also in its geometry. A recent M.O study[95] has calculated these parameters for a number of α-substituted, XCH_2^- - type carbanions. The results are shown in Table 2.3.

The carbanion XCH_2^- may be stabilised inductively by X, and also by interaction of the CH_2^- lone pair with an empty π-orbital on X.[95] Thus, for π-accepting substituents

TABLE 2.3 Calculated and Experimental Stabilisation Energies for XCH_2^- Carbanions[95]

X	Carbanion Geometry	Stabilisation Energy, kcal mol^{-1}	
		Calculated[95]	Experimental[91]
CH_3	Pyr.	1.4 - 3.3	
CH_3CH_2	Pyr.	4.4 - 5.6	
NH_2	Pyr.	3.3 - 5.6	
OH	Pyr.	7.9 -15.7	
F	Pyr.	14.6 -24.6	
CN	Pla.	55.0 -61.1	44.4
NO_2	Pla.	75.9 -98.1	57.9
CH_2=CH	Pla.	31.8 -37.5	25.8
CH≡C	Pla.	42.9 -46.5	35.2
CF_3	Pyr.	37.0 -57.0	
CHO	Pla.	60.5 -71.5	50.2
C_6H_5	Pla.	44.4	37.6

pla. = planar; pyr. = pyramidal.

(NO_2, CN, CHO, *etc.*) the carbanion is essentially planar, which maximises this stabilising interaction; this is reflected in the large stabilisation energies in these systems.

This interaction is unfavourable for π-donating substituents (OH, NH_2, *etc.*) where I_π effects are significant; consequently, pyramidal geometries and smaller stabilisation energies are observed.

2.3 Linear Free-Energy Relationships

The effect of a substituent on the reactivity of an aromatic system may be expressed in terms of the Hammett Equation which, in its simplest form, is shown in Equation[112] (2.3)

$$\log k/k_o = \sigma\rho \qquad (2.3)$$

where the substituent constant, σ, is a measure of the electron withdrawing properties of the substituent. The equation was first used to examine substituent effects in monosubstituted benzoic acids.[112] However, in many cases, especially when conjugative interaction between the substituent and the reaction centre is possible, the basic equation fails. In these situations, σ^- constants, derived from the ionisation of substituted phenols or anilinium ions, must be used.[113]

The scope of the Hammett Equation may be improved further upon resolution of the substituent constant into inductive (σ_I) and resonance (σ_R) components.[84] The basic Hammett Equation then becomes[114] (Equation 2.4):

$$\log k/k_o = \rho_I\sigma_I + \rho_R\sigma_R \qquad (2.4)$$

where ρ_I, ρ_R are transmission factors for each effect.

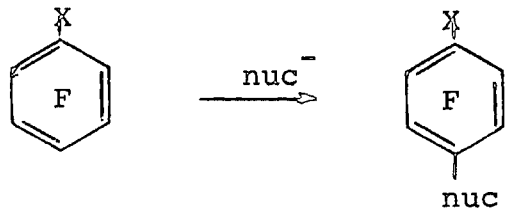
This Dual Substituent Parameter (DSP) approach has been fully discussed.[84,114] The σ_R values have been further refined,[86,114] depending on the electronic nature of the reaction considered. Thus, σ_R^- constants have been applied to substituents directly conjugated with electron rich systems. The σ_R^o, $\sigma_{R(BA)}$ and σ_R^+ scales have also been defined.[86]

In both dual and single substituent parameter approaches it is assumed that, for a given system, the transmission factor, ρ, remains constant for different substituents.[84] Another problem is the rigid division of substituents into either π-donors or π-acceptors, regardless of the electron demand of the system. A recent theoretical study has shown that classical π-acceptors (NO_2, CN, CHO, *etc*) become π-donors in electron deficient systems.[115]

2.4 Nucleophilic Substitution in Polyfluorobenzene Derivatives

2.4.1 An Early Theory. Orientation in Monosubstituted Polyfluorobenzenes

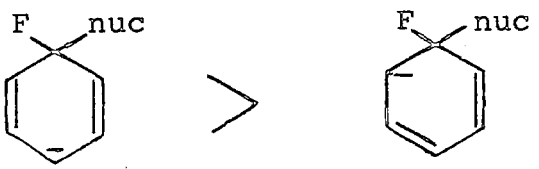
It is well known that, with few exceptions, monosubstitution in pentafluorobenzene derivatives results in preferential replacement of the fluorine atom *para* to the substituent[116] (Equation 2.3),



X = H, Ph, R_F, alkyl, halogen, CN, *etc*.

(2.3)

This orientation has been explained by considering the distribution of charge in the transition state of the rate-determining step, where it was proposed that charge is greatest *para* to the position of nucleophilic attack.[117] This assumption is supported by *ab initio* M.O calculations.[118] In valence bond terms, the order of canonical importance was thought to be



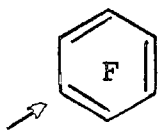
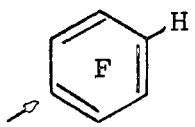
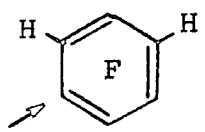
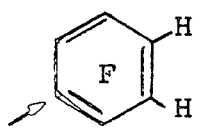
Thus destabilising I_π interactions should be greatest at the *para* position and, consequently, any substituent capable of stabilising negative charge better than fluorine would direct nucleophiles *para* to itself. This is the basis of the "I_π repulsion theory", where the major orientating influence in fluorobenzene systems is attributed to the need to avoid transition states in which charge is localised next to fluorine.[117]

2.4.2 Rate and Orientation in Mono- and Dihydropolyfluorobenzenes

The I_π repulsion theory gives a reasonable explanation for the observed orientation of nucleophilic substitution in polyfluorinated benzenes. However, with hindsight it is clear that the rôle of *para* fluorine has been greatly exaggerated; little attention is paid to the influence of fluorine atoms *ortho* and *meta* to the point of substitution. In a recent kinetic study,[119] the rate constants for the reaction of sodium methoxide with a series of hydrofluoro-

benzenes were determined. From these results it was possible to deduce the separate activating influences of fluorine atoms at different positions in the benzene system. The experimentally determined rate constants are shown in Table 2.4.

TABLE 2.4 Second-Order Rate Constants for Reactions of Some Hydrofluorobenzenes with Sodium Methoxide in Methanol at 58.0°C. [119]

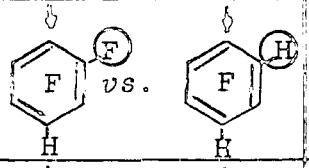
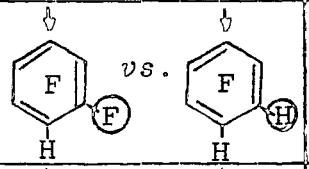
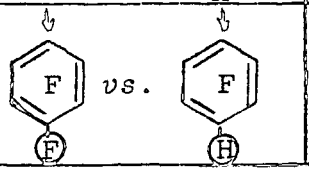
Substrate [(a)]	k, 1 mol^{-1} s^{-1}
	1.29×10^{-4} [(b)]
	3.02×10^{-4}
	5.28×10^{-6} [(b)]
	2.85×10^{-6} [(b)]

(a) Position of substitution arrowed

(b) Rate constant statistically adjusted.

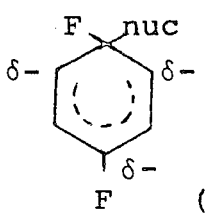
By making the appropriate comparisons in the above rate consants, the influence of fluorine, relative to a hydrogen atom at the same position, may be determined; this is shown in Table 2.5.

TABLE 2.5 Evaluation of the Separate Activating Influences of Fluorine Atoms in the Benzene System

Comparison	Effect determined	value ($^{kF}/_{kH}$)	Relative activating influence
	*ortho*-F / *ortho*-H	57	133
	*meta*-F / *meta*-H	106	246
	*para*-F / *para*-H	0.43	1

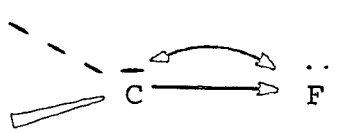
The results indicate that a *para*-fluorine atom is slightly deactivating relative to a hydrogen atom at this position. However, it is clear that this is only a small effect when compared to the significant influence of fluorine *ortho* and *meta* to the reaction site.

The results may be interpreted on the basis of what is known about the effect of fluorine on carbanion stability (Section 2.2.1). If (18) is considered to be a reasonable model for the transition state of the reactions under discussion, then a fluorine atom *para* to the point of substitution is effectively in the situation (19), where I_{π} interactions are maximised owing to the enforced sp^2 geometry of the system,



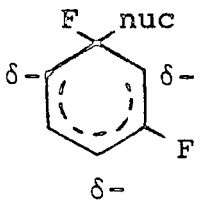
(18)

(unmarked bonds to F)



(19)

However, these interactions are effectively balanced by inductive electron withdrawal, so that the overall effect is that fluorine and hydrogen are of comparable activating ability. The substantial activating influence of fluorine *meta* to the point of attack may similarly be rationalised (20); in this position, a fluorine atom is effectively in the situation (21) which is known to be carbanion stabilising,

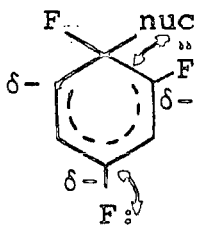


(20)

$$\bar{C} \rightarrow C \rightarrow F$$

(21)

The large activating influence of *ortho* fluorine is somewhat more difficult to account for, however, as in the transition state (22) the effects of *ortho* and *para* fluorine should, on the basis of I_{π} repulsions, be similar,

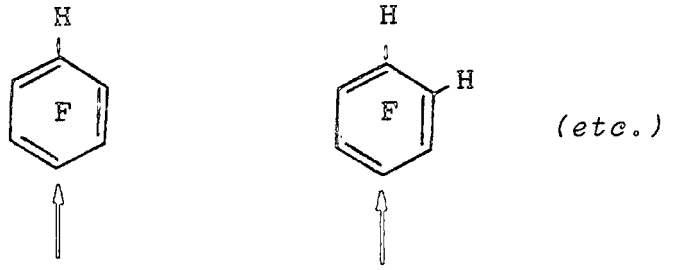


(22)

Nevertheless, it is clear that the overall effect of *ortho* fluorine is strongly activating in these systems. The precise nature of this "*ortho* effect" is discussed in Chapter Four.

The separation of fluorine activating influences in this study enables an alternative rationalisation for the rate and orientation of nucleophilic substitution in polyfluorobenzenes to be made. That is, nucleophilic attack

occurs so as to maximise the number of *ortho* and *meta* fluorines, largely ignoring the *para* fluorine. This rationale explains the observed orientations of substitution in a number of polyfluorobenzenes. For example, (position of substitution arrowed.

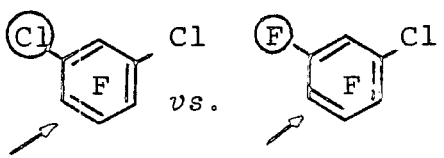
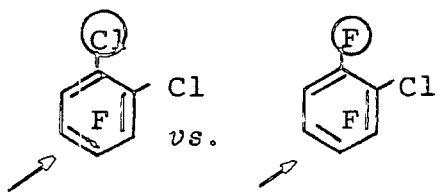
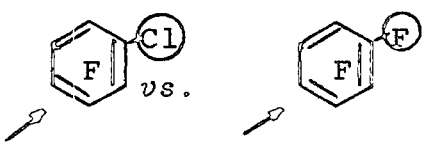


(etc.)

2.4.3 Activating Influence of Chlorine in the Benzene System

The empirical approach, described in the previous Section, for the separation of substituent activating influences, may be applied to other systems. Thus, by determination of the second-order rate constants for the reaction of sodium methoxide with a series of chlorofluorobenzenes, the activating effect of chlorine relative to fluorine may be evaluated. This is shown in Table 2.6. The results show that a chlorine atom, in the *para* position is much more activating than fluorine; this is consistent with the known stabilising influence of chlorine directly attached to a carbanionic centre ($\overline{C}$-Cl).[96] Although chlorine has a smaller inductive effect than fluorine, the decrease in electron pair repulsions compared with fluorine means that this substituent is net activating in the *para* position. In the *meta* position, chlorine and fluorine have a comparable activating effect, implying that the inductive effects on a β-carbon atom in

TABLE 2.6 Evaluation of the Separate Activating Influences of Chlorine in the Benzene System.[119] (Methoxide Ion, -7.6°C)

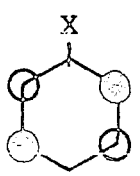
Comparison	Effect determined	value ($^{kCl}/_{kF}$)	Relative activating influence
	*ortho*-Cl / *ortho*-F	3.2	4.6
	*meta*-Cl / *meta*-F	0.69	1
	*para*-Cl / *para*-F	35	51

these systems are similar. In the *ortho* position, chlorine is found to be slightly more activating than fluorine, and therefore strongly activating relative to hydrogen. As in the previous Section, this "*ortho* effect" cannot be described simply in terms of carbanion stabilities; a reduction in I_π destabilisation accounts for the difference in *ortho* activation between chlorine and fluorine, but not the whole effect.

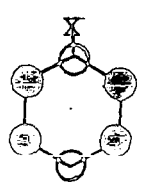
2.5 Alternative Theories on the Orientation of Nucleophilic Substitution in Polyhalogenated Aromatic Systems

2.5.1 Frontier Orbital Theory

An M.O study has predicted the nucleophilic substitution patterns of polyhalobenzenes by regarding the interaction between the halobenzene LUMO and the nucleophile HOMO to be the only transition state-stabilising interaction.[120,121] In monosubstituted perfluorobenzenes there are two degenerate LUMOs (23), (24); this degeneracy may be lifted depending on the nature of the substituent X. For poor π-donor substituents (X=H, CH_3, halogen, *etc.*) calculations show that (24)



(23)



(24)

becomes the LUMO,[121] so that nucleophilic substitution *para* to X is correctly predicted. However the approach fails for strong π-donor substituents ($X=O^-$, NH_2) where (23) is the LUMO. Thus nucleophilic attack is predicted *ortho* and

meta to X[121] whereas, experimentally, only *meta* is found. Incorrect substitution patterns are also predicted for a number of perfluoropolycyclic species.[122]

This variation of the FO approach[121] is rather oversimplified since other important transition state-stabilising interactions are not considered. In addition to the favourable HOMO-LUMO interaction there is also a stabilising Coulombic term (especially important for polar molecules) affecting the activation energy that must be considered.[238] The FO approach is discussed further in Section 4.5.1.

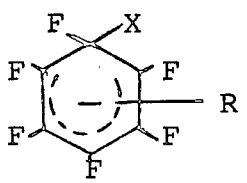
2.5.2 Prediction of Orientation Ignoring I_π Repulsions

A series of papers has been published in which it is argued that the electronic effect of a halogen substituent in an aromatic system may be described simply in terms of inductive and resonance contributions.[123] The I_π effect is not considered because it is regarded as an alternative to the resonance effect. By this approach the relative activation, to electrophilic substitution of each carbon atom in a given polyhalobenzene is calculated from an empirical three-parameter expression derived from the Hammett Equation; substituent effects are taken to be completely additive.[123] The carbon atom with the least electrophilic activation is then assumed to be that most susceptible to nucleophilic attack.[123-126] This method correctly predicts the predominant *para* orientation of nucleophilic substitution in the pentafluorohalobenzenes C_6F_5X[123] and has also been used to predict the rates of nucleophilic displacement reactions of polyhalo-

benzenes,[123-126] though with limited success. Halogen activating effects, called "substituent rate factors" have been evaluated from experimental rate constants;[126] these values are in general agreement with the effects quoted in Table 2.7, although the division of these factors into inductive and resonance contributions[126] does not reflect the absolute value of these effects.

2.5.3 Prediction of Orientation by the MNDO Method

In a recent publication[127] the isomer distributions for nucleophilic attack were predicted from a consideration of anions of the type (25),



(25)

X = H, F, NH_2, OH

R = H, OH, NH_2

However, the calculations generally did not fit the experimental results. For example, attack by NH_2^- on pentafluoroaniline is predicted to give almost exclusive *ortho* substitution when in fact *meta* is expected. Refinements to this simple model to include solvent effects and the possibility of hydrogen bonding would improve the results;[127] such modifications would however necessitate much more complex calculations.

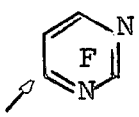
Prediction of the orientation of nucleophilic substitution in perfluoropolyaromatic systems by the "amplified" I_π repulsion theory will be discussed in Chapter Five.

2.6 Nucleophilic Substitution in Polyfluoropyridines

2.6.1 Influence of Ring Nitrogen on Reactivity

N-Heterocyclic polyfluoroaromatic compounds are strongly activated to nucleophilic substitution, as shown in Table 2.7,

TABLE 2.7 Relative Rate Constants for Attack by NH_3 on Some Perfluoro-N-heterocyclic Aromatic Systems.[128] (aq.dioxan, 25°C)

System	$k_{relative}$ (b)
 (a)	1
	37.4
	2×10^3
	$>10^5$

(a) Position of substitution arrowed;

(b) Corrected for statistical factor.

The activating effect of ring nitrogen in these systems is greatest at positions *ortho* and *para* to itself, *i.e.* at positions which result in the localisation of negative charge on the ring nitrogen in the transition state. Ground state activation by the nitrogen can also take place; this results in an increase in the electrophilicity of the *ortho* and *para*

positions. Quantitatively, the relative activating influence of ring nitrogen has been determined in a recent kinetic study[129] and it is also shown in the Hammett σ^- constants[130] for this group (Table 2.8).

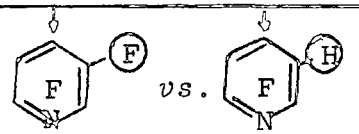
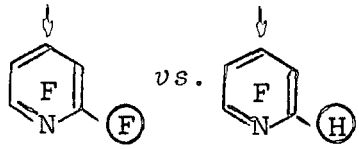
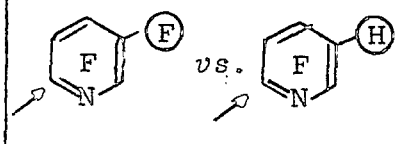
TABLE 2.8 Activating Effect of Ring Nitrogen in the Pyridine Ring System

-N=	Activating effect,[129] (relative to C-H)	σ^- [130]
ortho	6.2×10^4	1.00
meta	8.5×10^2	0.59
para	2.3×10^5	1.17

2.6.2 Separation of the Activating Effect of Fluorine in the Pyridine Ring System

Using an experimental technique similar to that discussed in Sections 2.4.2 and 2.4.3 it has been possible to determine the influence of a fluorine atom at positions *ortho*, *meta* and *para* to the reaction site in the pyridine system.[131] Two sets of reaction conditions have been used, and the results are summarised in Table 2.9. Several important observations may be made from these results. Firstly, it is clear that *ortho* and *meta* fluorines are activating to nucleophilic attack, whereas a *para* fluorine is slightly deactivating, relative to hydrogen. It is also noticeable that the order of activating influence is not very dependent on the nucleophile/solvent system used. The activating

TABLE 2.9 Ratios of Measured Rate Constants from Reactions of Some Hydrofluorpyridines[131] (a) With NH_3 in aqueous Dioxan at 25°C, (b) with MeO^- in Methanol at -7.6°C.

Comparison	Effect Determined	k_F/k_H (NH_3, 25°C)	k_F/k_H (MeO^-, -7.60°C
	*ortho*-F / *ortho*-H	31	79
	*meta*-F / *meta*-H	23	30
	*para*-F / *para*-H	0.26	0.33

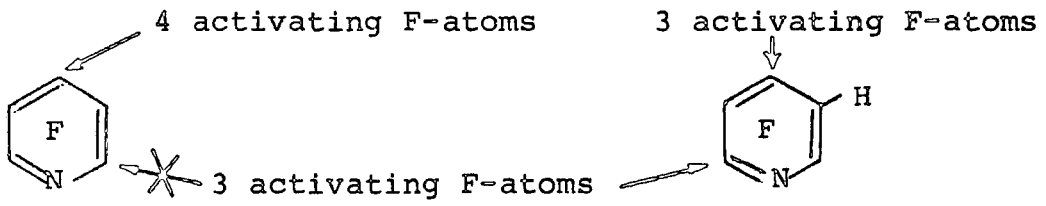
influence of fluorine in the pyridine and benzene systems may be compared (methoxide ion/methanol):

	ORTHO		*META*		*PARA*	
BENZENES	133	:	246	:	1	(Table 2.5)
PYRIDINES	239	:	91	:	1	(Table 2.9)

The most important feature of this comparison is that, in each system, both *ortho* and *meta* fluorines are substantially activating to nucleophilic attack, whereas a *para* fluorine clearly exerts only a small deactivating influence, relative to hydrogen. In the pyridine ring system, activation by the ring nitrogen is a major influence, with sites *ortho* and *para* to the ring nitrogen strongly activated (Table 2.8). However, it is clear that a negligible orientating preference

between these two sites occurs, since $\frac{k_{-N=(para)}}{k_{-N=(ortho)}} \simeq 4$.[129,131]

Therefore, we can extend the empirical approach developed in Section 2.4.2 to account for the orientation of nucleophilic attack in polyfluoropyridines. Thus nucleophilic substitution in pentafluoropyridine (26) occurs exclusively at the 4-position because the number of *ortho* and *meta* fluorines is maximised. A consideration based purely on ring nitrogen activation would have predicted attack at the 2-position also to take place. Similarly, the observation of attack at both the 4- and 6-positions in 3H-tetrafluoropyridine (27) can be rationalised, as attack at these positions results in the same number of activating fluorines.

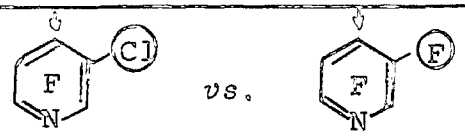
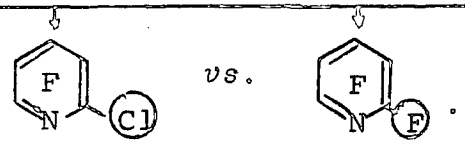
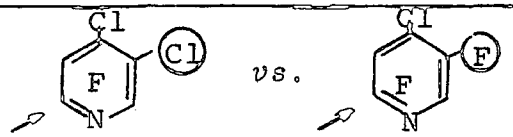


(26) (27)

2.6.3 Activating Influence of Chlorine in the Pyridine System

This has been determined from a recent kinetic study in which the rates of attack by ammonia on a series of chlorofluoropyridines were measured (Table 2.10).[132] If the results are compared with the activating effects determined in the benzene series (Table 2.6) then it may be concluded that the activating influence of chlorine is in the order *ortho>meta>para* for both pyridine and benzene series. The nature of this activating influence has been discussed (Section 2.4.3).

TABLE 2.10 Ratios of Measured Rate Constants from the Reactions of Some Chlorofluoropyridines with NH_3 in Aqueous Dioxan at 25.0°C [132]

Comparison	k_{Cl}/k_F	k_{Cl}/k_H
	2.82	86
	1.05	24
	26.5	6.9

2.7 Steric Effects

The basic Hammett Equation (Equation 2.1) cannot be used to examine *ortho* substituent effects since in this position various proximity effects may operate. Primary steric effects, defined by the Taft E_s constant, are due to the space-filling property of an *ortho* substituent. Such effects may be studied by the following relationship, [133] (Equation 2.4):

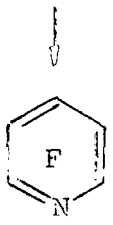
$$\log {}^{k}/_{k_{ortho}} = \delta E_s + \rho_I \sigma_I + \rho_R \sigma_R \qquad (2.4)$$

where δ is the transmission factor of the steric effect. A rough measure of steric "bulk" is also given by MR_D constants, [134] which are determined from molar refractivity experiments. Typical steric constants are shown in Table 2.11.

TABLE 2.11 Steric Substituent Constants[129]

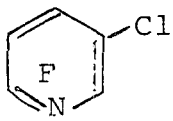
Substituent	E_s^e	MR_D
H	0	1
F	-0.46	0.8
Cl	-0.97	5.8
Br	-1.16	8.7
I	-1.4	14
OH	-0.55	2.6
CN	-0.51	5.5
NH_2	-0.61	4.4
CH_3	-1.24	5.7
Et	-1.31	10.3
t-Bu	-2.78	19.7
CF_3	-2.4	5
NO_2	-1.01	6.7
NO_2	-2.52	6.7
Ph	-3.82	25.4
CPh_3	-5.92	78.7

Secondary steric effects, such as steric inhibition of resonance, are also known;[135] allowances for this type of electronic effect have been made in the above E_s constants.[134] Steric effects are often manifested as a steric retardation of reactivity; thus monosubstitution by ammonia occurs exclusively at the 4-position in both pentafluoropyridine (26) and 3-chlorotetrafluoropyridine (28) (Table 2.11), whereas the reaction of (28) with diethylamine gives monosubstitution at both 4- and 6-positions,[132]



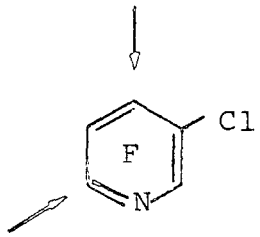
nuc = NH_3, Et_2NH.

(26)



nuc = NH_3

(28)



nuc = Et_2NH

(28)

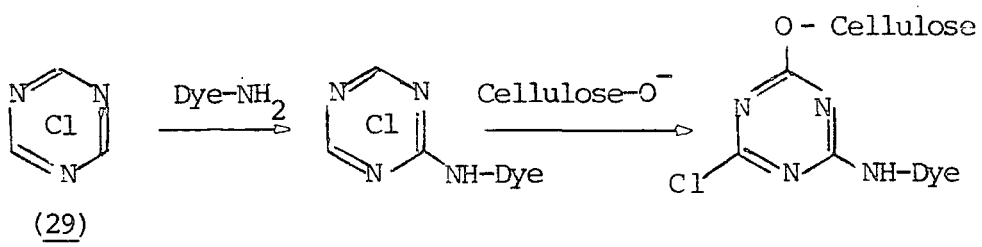
This reflects a steric deactivation of the 4-position by the 3-chlorine atom which becomes apparent when a nucleophile with large steric requirement is used.[132]

CHAPTER THREE

ACTIVATING EFFECTS OF SUBSTITUENT GROUPS TO NUCLEOPHILIC SUBSTITUTION IN POLYFLUOROAROMATIC SYSTEMS

3.1 Introduction

A range of fibre-reactive dyes - the "Procion" range - has been developed, in which the dye molecule is chemically bonded to the fibre *via* a reactive linking molecule.[136] The principle is outlined below (Equation 3.1). The linking molecule (in this case, cyanuric chloride (29)) is first attached to the dye through an amine function and then to the fibre, where the attacking species is cellulose-O^-.



(29) (3.1)

Recently, alternative linking agents have been developed.[136] Obviously, the planning and design of more effective reagents requires an understanding of the factors affecting the reactivity and orientation of nucleophilic substitution in these systems. In the previous Chapter, an approach was developed in which the activating influence of fluorine and chlorine atoms to nucleophilic attack could be empirically determined. The aim of the work described here was to use a similar technique so that the influence of a number of other, potentially activating, groups may also be determined.

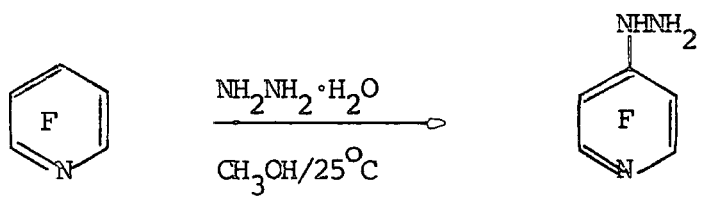
The substrates investigated were a series of substituted polyfluorobenzenes, pyridines and diazines.

3.2 Preparation of Substrates

A brief description of the preparation of the substrates under study will now be given. All the compounds have been previously reported; however, a new route to perfluoro-4-methyl pyridine is described. Other compounds used, the preparations of which are not discussed here, were provided, and were purified before use as described in Chapter Eight.

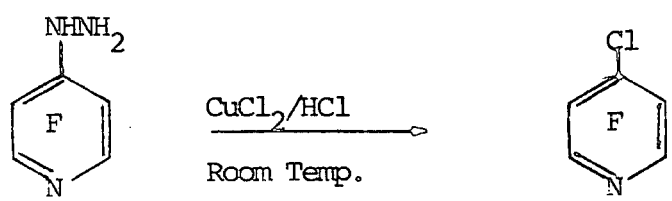
(a) 4-Chlorotetrafluoropyridine (31)

This was prepared by a two-step synthesis, according to the method of Chambers and co-workers.[137] Firstly, 4-hydrazinotetrafluoropyridine (30) was obtained in high yield from the reaction of pentafluoropyridine with hydrazine hydrate.



(30)
(~95%)

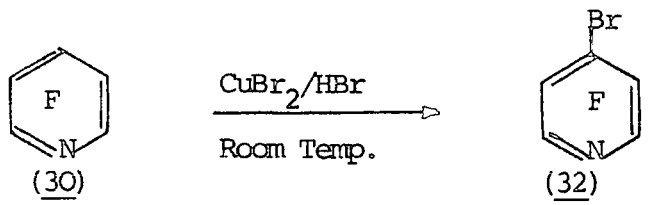
The required product was obtained from the reaction of (30) with a concentrated solution of copper (II) chloride in concentrated hydrochloric acid.



(30) (31)
(70%)

(b) 4-Bromotetrafluoropyridine (32)

This was prepared by the reaction of (30) with copper (II) bromide in 50% hydrobromic acid.[138]

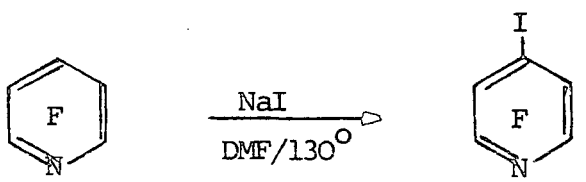


(30) (32)

(61%)

(c) 4-Iodotetrafluoropyridine (33)

This was prepared, in low yield, from the reaction of pentafluoropyridine with sodium iodide in N,N-dimethylformamide.[139]

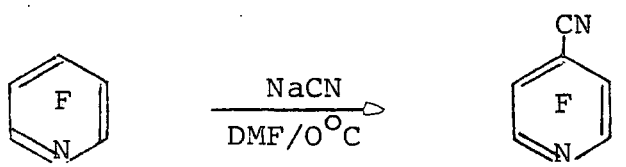


(33)

(40%, based on recovered starting material)

(d) 4-Cyanotetrafluoropyridine (34)

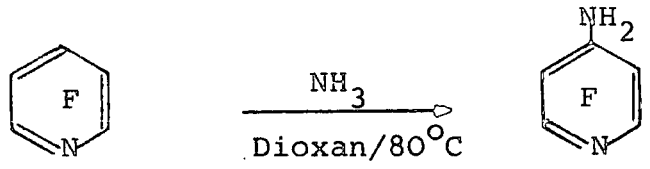
This was prepared, in low yield, from the reaction of pentafluoropyridine with sodium cyanide in N,N-dimethylformamide at 0°C.[140]



(27%, based on recovered starting material)

(e) 4-Nitrotetrafluoropyridine (36)

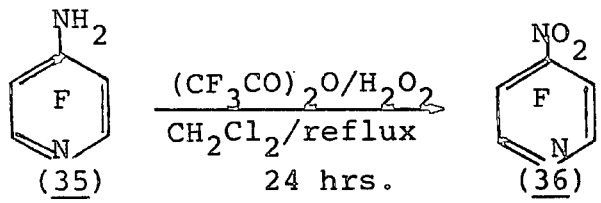
This was prepared by a two-step synthesis. Firstly, 4-aminotetrafluoropyridine (35) was obtained, in high yield, from the reaction of aqueous ammonia with pentafluoropyridine.[137]



(35)

(88%)

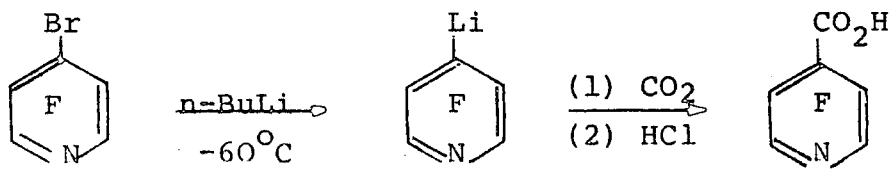
The desired compound (36) was obtained by oxidation of (35) with peroxytrifluoroacetic acid in methylene chloride.[141]



(35) (36)

(f) Perfluoro-4-methyl pyridine (38)

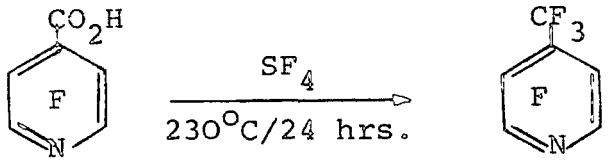
This was prepared *via* a two-step synthesis. Metallation of 4-bromotetrafluoropyridine (32) (n-butyl lithium), followed by reaction with carbon dioxide and acidificiation gave tetrafluoropyridine-4-carboxylic acid (37).[142]



(37)

(85%)

Reaction of (37) with SF_4 in an autoclave gave perfluoro-4-methyl pyridine (38) in reasonable yield.



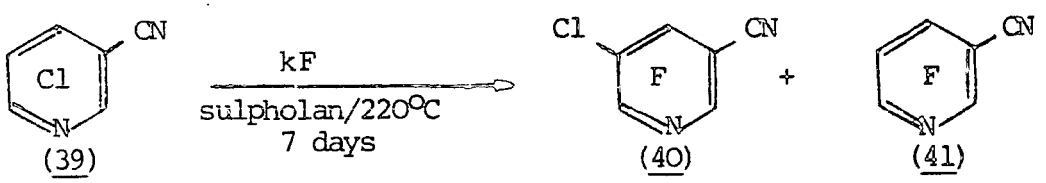
(37) (38)

(50%)

This method gives a higher yield of (38) than other[143,144] preparations in the literature.

(g) 3-Cyanotetrafluoropyridine (41)

This was synthesised by the prolonged heating of 3-cyanotetrachloropyridine (39) (provided; see Reference 145 for preparation) with anhydrous potassium fluoride.



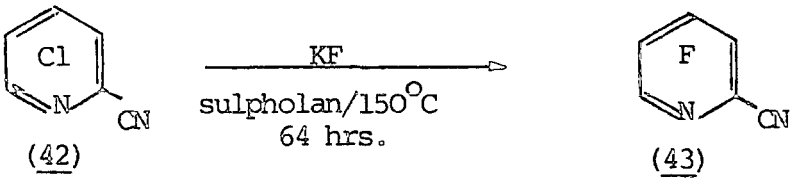
(39) (40) (41)

(74%) (17%)

The major product was 3-chloro-5-cyanotrifluoropyridine (40); no attempt was made to optimise the reaction conditions.

(h) 2-Cyanotetrafluoropyridine (43)

This was prepared by a similar method to that described in 3.2(g) above. Thus reaction of 2-cyanotetrachloropyridine (42) (provided[145]) with potassium fluoride in sulpholan gave the desired product (43) in reasonable yield.

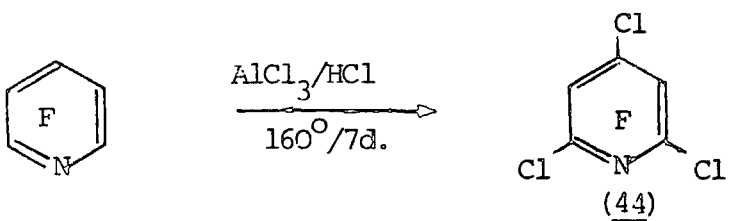


(42) (43)

(65%)

(i) 2,4,6-Trichlorodifluoropyridine (44)

This was prepared by a method similar to that of Thorpe,[146] in which pentafluoropyridine was heated with an excess of aluminium chloride and concentrated hydrochloric acid in a sealed nickel tube.

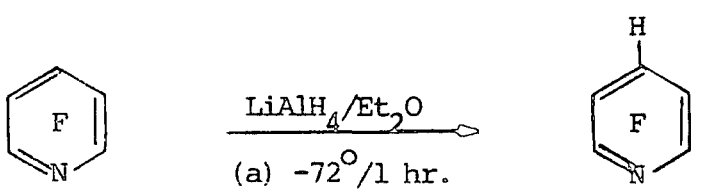


(44)

(70%)

(j) 4-Hydrotetrafluoropyridine (45)

This was prepared by the reaction, under anhydrous conditions and in an atmosphere of dry nitrogen, of pentafluoropyridine with lithium aluminium hydride in ether.[147]



(45)

(64%)

3.3 Kinetic Methods and Rate Constant Calculations

Rate constant determinations for all reactions discussed in this Chapter were carried out at 25.0°C, with ammonia as the nucleophile, in 60/40 (V/V) dioxan/water. All reactions were followed by periodically titrating samples of the reaction mixture against standard acid and hence determining the concentration of unreacted ammonia. Second-order rate constants were then calculated from Equation 3.2.[148]

$$k_{II} = \frac{1}{t} \cdot \frac{1}{a-2b} \cdot \ln \left[\frac{b(a-2x)}{a(b-x)} \right] \qquad (3.2)$$

where, k_{II} = second-order rate constant

a = initial concentration of ammonia

b = initial concentration of substrate

x = concentration of substrate reacted at time t.

Equation 3.2 implies that the acid liberated during any kinetic run extensively protonates the unreacted ammonia; the result is that, for every molecule of substrate reacted, two molecules of ammonia are needed.

The reaction of 3-cyanotetrafluoropyridine with ammonia was found to be too fast to successfully employ the titration technique; this reaction was followed spectrophotometrically. The runs were carried out in a large excess of ammonia, with first-order rate constants (k_I) calculated from Equation 3.3.

$$k_I t = \ln \frac{O{\cdot}D_\infty - O{\cdot}D_O}{O{\cdot}D_\infty - O\ D_t} \qquad (3.3)$$

where,

$O{\cdot}D_\infty$ = optical density at infinity

$O{\cdot}D_O$ = optical density at time zero

$O{\cdot}D_t$ = optical density at time t

k_1 = first-order rate constant

Dividing k_I by the ammonia concentration (assumed to be constant throughout the run) gave the second-order rate constant.

In cases where monosubstitution at two positions ("y" and "z", say) was observed, the rate constants for attack at these sites (k_y and k_z) were calculated from the observed rate constant, k_{obs}, using Equations 3.4 and 3.5.

$$k_{obs} = k_y + k_z \qquad (3.4)$$

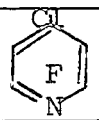
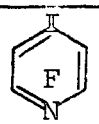
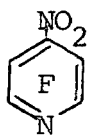
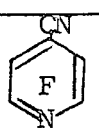
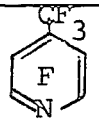
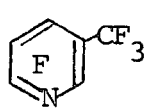
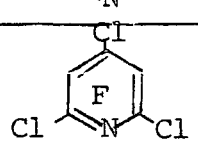
$$\frac{k_y}{k_z} = \frac{\text{\% product resulting from attack at y-position}}{\text{\% product resulting from attack at z-position}} \qquad (3.5)$$

Errors quoted are the "standard errors of the mean" and were calculated from the usual expressions.[149]

3.4 Reactions of Polyfluoropyridines with Ammonia

The substrates investigated were a series of 4-substituted tetrafluoropyridines and 2,4,6-trichlorodifluoropyridine. The positions of substitution were established using standard techniques as discussed in Chapter Eight. Table 3.1 shows the experimental 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.

TABLE 3.1 Rate Constants for the Reactions of Ammonia with Some Substituted Polyfluoropyridines in 60/40 (V/V) Dioxan/Water at 25.0°C

Substrate	Position of attack	k_{II} (l mol^{-1} s^{-1})
	4-	$(6.80\pm0.03)\times10^{-4}$
 (a)	2-	$(1.56\pm0.02)\times10^{-6}$
 (a)	2-	$(1.39\pm0.01)\times10^{-6}$
 (a)	2-	$(1.00\pm0.04)\times10^{-6}$
 (a)	2-	$(6.10\pm0.1)\times10^{-8}$
 (a)	4- 3- 2-	$(5.65\pm0.06)\times10^{-4}$ $(1.83\pm0.06)\times10^{-4}$ $(6.44\pm0.06)\times10^{-4}$
 (a)	3- 2-	$(2.77\pm0.05)\times10^{-5}$ $(8.58\pm0.05)\times10^{-5}$
 (a)	2-	$(2.11\pm0.02)\times10^{-5}$
 (a,b)	4- 6-	$(5.31\pm0.02)\times10^{-2}$ $(2.66\pm0.01)\times10^{-2}$
	4-	$(3.68\pm0.03)\times10^{-7}$

(a) Rate constants corrected for statistical factor.

(b) Rate constants from Reference 129.

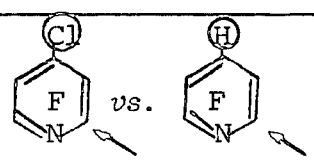
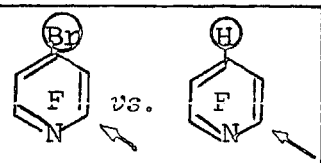
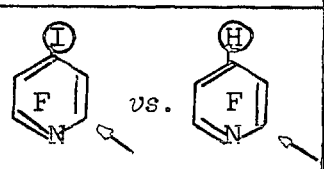
3.5 Discussion of Rate Data

3.5.1 4-Halotetrafluoropyridines

In these systems nucleophilic substitution was observed exclusively at the 2- or 6-position, *i.e. meta* to the halogen substituent. Attack does not occur at the 4-position, although at this position the activating effect of the fluorine substituents is maximised; this is indicative of the poor leaving group mobility of the larger halogens.

Chlorine, bromine and iodine substituents are seen to be activating relative to hydrogen, *meta* to the point of attack. The activating effect of these *meta* substituents may be determined from an empirical approach, as developed in the previous Chapter. This is shown in Table 3.2, where the observed "*meta*-effects" are compared with the corresponding Hammett σ_m values.

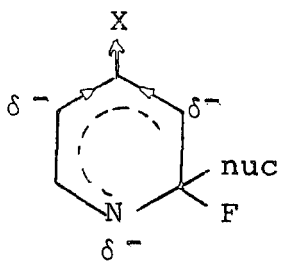
TABLE 3.2 Activating Effect of *Meta* Halogen Atoms

Comparison	Effect Determined	k_{Hal}/k_H	σ_{meta} [113]
	*meta*-Cl / *meta*-H	25.6	0.37
	*meta*-Br / *meta*-H	22.8	0.39
	*meta*-I / *meta*-H	16.4	0.35

(a) Position of substitution arrowed

(b) σ_m values from phenol dissociation constants at 25.0°C.

From Table 3.2 it is seen that the activating effects of the *meta* halogens are very similar. The activating effect of *meta* chlorine, deduced above from comparisons of nucleophilic attack at the 2-position, agrees very well with a previous study[132] (Section 2.6.3) where comparisons of attack at the 4-position were made. This shows the additive nature of halogen substituent effects. There is a slight decrease in the magnitude of the *meta*-effect along the series Cl>Br>I; this is broadly speaking mirrored by the σ_m constants quoted. The activating influence of a *meta*-substituent results mainly from an inductive stabilisation of the negative charge in the transition state (46). Thus, from Table 3.2, it must be



(all unmarked bonds to F)

(46)

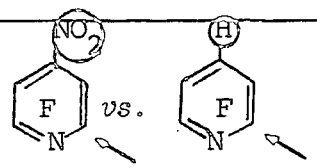
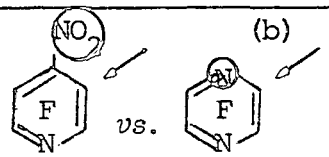
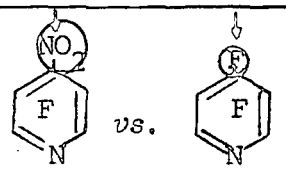
concluded that, in the pyridine system, *meta* halogens have similar inductive effects.

3.5.2 4-Nitrotetrafluoropyridine

Nucleophilic attack by ammonia in 4-nitrotetrafluoropyridine was observed at the 2- and 3-positions and also at the 4-position, where the NO_2 group was substituted. This in in agreement with a previous study on this compound.[141] The NO_2 group is seen to have a profound activating effect to nucleophilic substitution; it is also seen to have a substantial leaving group mobility, in agreement with the literature.[150] Quantitative measures of these effects have been calculated as shown in Table 3.3, where a comparison with the

relevant Hammett σ^- constants is made.

TABLE 3.3 Activating Effect and Leaving Group Mobility of the Nitro Group

Comparison	Effect determined	k_{NO_2}/k_H	σ^- (position) (a)
	*meta*-NO_2 / *meta*-H	1.06×10^4	0.71 *(meta)*
 (b)	*ortho*-NO_2 / *ortho*-N=	(c) 2.2×10^5	1.40 *(ortho)*
	L.G mobility-NO_2 / L.G mobility-F	(k_{NO_2}/k_F) 0.83	—

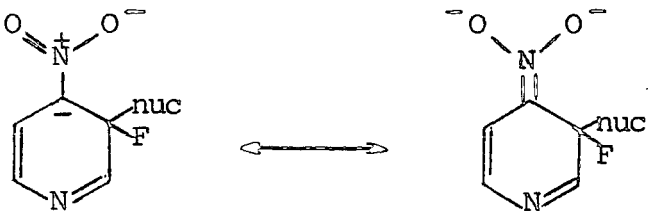
(a) σ^- values from phenol dissociation constants at 25.0°C.[113]

(b) Rate constant from Reference 129.

(c) Cannot calculate k_{NO_2}/k_H ratio <u>directly</u>. However, as substituent effects in these systems are generally additive, we may obtain the desired value from the known k-N=/k_H value (Table 2.8),[129] *i.e.* $k_{NO_2}/k_H = k_{NO_2}/k\text{-}N= \times (6.2 \times 10^4)$.

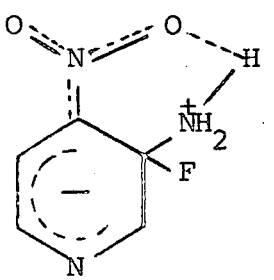
From Table 3.3 it is seen that the leaving group mobility of the NO_2 group is comparable to that of fluorine. However, the most striking observation is the substantial *ortho*- and *meta* activation of the NO_2 group relative to hydrogen; Hammett σ^- constants confirm this effect as do theoretical calculations. The NO_2 group is known to be a strong σ^- and π-electron acceptor,[88,95] and thus these effects

may be explained in terms of the relative stabilisation, by inductive and resonance means, of the transition state by NO_2 substituents *ortho* and *meta* to the reaction site. Resonance stabilisation is not likely for *meta* substituents, which accounts for the greater activation observed for *ortho* NO_2 (47, 47a).



(47) (47a)

Part of this *ortho* activating influence has been attributed to hydrogen bonding between ammonia and the nitro group in the transition state (48).[151,152]



(unmarked bonds to F)

(48)

The importance of initial state activation is discussed in Chapter Four.

3.5.3 Perfluoro-4-methylpyridine

Nucleophilic attack was observed exclusively at the 2-position in this compound. Thus a comparison of the rate constants of perfluoro-4-methylpyridine and 4-H-tetrafluoropyridine gives a measure of the activating influence of a *meta* CF_3 group, relative to hydrogen; a value of 346 is

calculated. The effect of *ortho* and *para* CF_3 has been calculated in an earlier study;[129,153] the total activating influence of this group is shown in Table 3.4.

TABLE 3.4 Activating Effect of the CF_3 Group

Effect	k_{CF_3}/k_H	σ^- (position) (a)
ortho-CF_3 / *ortho*-H	2.4×10^3	-
meta-CF_3 / *meta*-H	346	0.47 (*meta*)
para-CF_3 / *para*-H	4.4×10^3	0.54 (*para*)

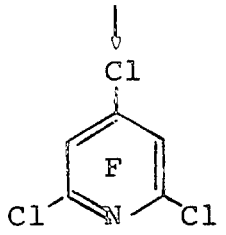
(a) σ^- values from phenol dissociation constants at 25.0°C[113]

From Table 3.4 it is seen that CF_3 is strongly activating at all positions; however, the magnitude of this effect is smaller than that observed for the nitro group. This trend is confirmed by the σ^- constants, which also predict a *para*-CF_3 group to be more activating than a *meta*-CF_3 as observed in this study.

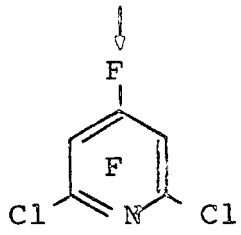
3.5.4 2,4,6-Trichlorodifluoropyridine

Nucleophilic displacement of chlorine at the 4-position, with slow rate, was observed in this system. This is in accord with the known[20] poor leaving group mobility of chlorine relative to fluorine. The effect may be quantified by a comparison of the rate constants, for attack at the

4-position, of 2,4,6-trichloropyridine and 2,6-dichlorotrifluoropyridine; this latter rate constant has been determined previously.[132]



(44)



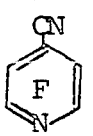
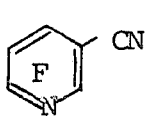
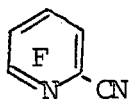
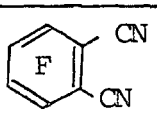
(49)

A value of 1.75×10^3 for the leaving group mobility of fluorine relative to chlorine is obtained.

3.6 Reactions of Some Polyfluorocyano Benzene and Pyridine Derivatives with Ammonia

The substrates investigated were 2-, 3- and 4-cyanotetrafluoropyridine and 1,2-dicyanotetrafluorobenzene. The experimental rate constants are shown in Table 3.5, together with the position(s) of nucleophilic attack.

TABLE 3.5 Rate Constants of Some Polyfluorocyano Benzene and Pyridine Derivates with Ammonia in 60/40(V/V) Dioxan/Water at 25.0°C

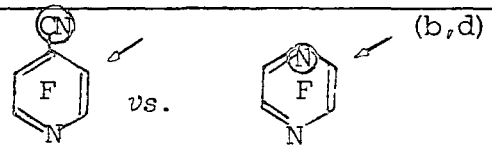
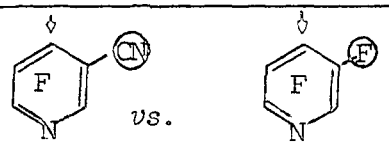
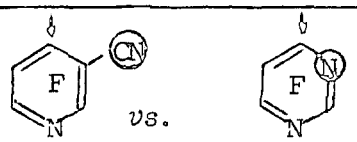
Substrate	Position of attack	k_{II} (l $mol^{-1}s^{-1}$)
 (a)	3-	$(2.77\pm0.05)\times10^{-5}$
	2-	$(8.58\pm0.05)\times10^{-5}$
	4-	1.56±0.04
	6-	0.77±0.04
	4-	$(8.18\pm0.04)\times10^{-3}$
 (a)	4-	$(1.80\pm0.01)\times10^{-3}$

(a) Rate constant corrected for statistical factor.

3.6.1 Discussion of Rate Data

The complete activating influence of the cyano group may be determined from the rate constants given in Table 3.5 by using the usual empirical technique. *Ortho*, *meta* and *para* effects were obtained from a number of comparisons; these are shown in Tables 3.6, 3.7 and 3.8 respectively.

TABLE 3.6 Activating Effect of *Ortho*-CN[a]

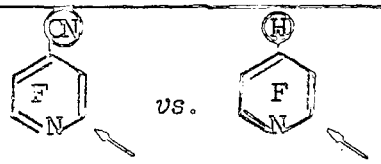
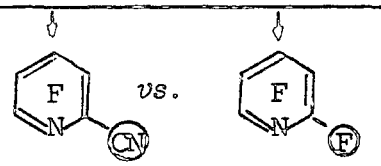
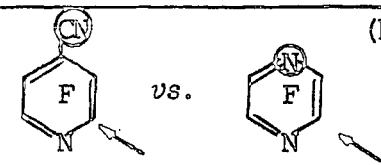
Comparison	k_{CN}/k_H
 (b,d)	3.4×10^4
 (b)	7.2×10^4
 (b,c)	7.1×10^4

(a) $\sigma^-_{ortho} = 1.32$ (Phenol dissociation, 25°C)[113]

(b) Direct calculation of k_{CN}/k_H not possible. Effect determined from known k_N/k_H and k_F/k_H values at *ortho* position.

(c) Rate Constant from Reference 129.

TABLE 3.7 Activating Effect of *Meta*-CN[a]

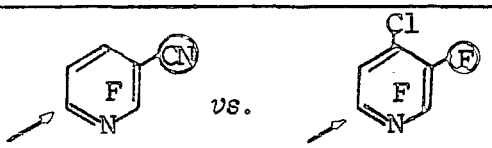
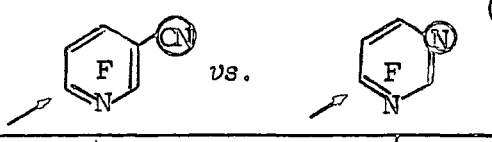
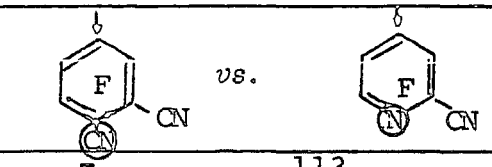
Comparison	k_{CN}/k_H
	1.41×10^3
 (b)	277
 (b,c)	1.44×10^3

(a) $\sigma_m = 0.61$.[113]

(b) Direct calculation of k_{CN}/k_H not possible. Effect determined from known k_F/k_H and k_N/k_H values at *meta* position.

(c) Rate constant from Reference 129.

TABLE 3.8 Activating Effect of *Para*-CN[a]

Comparison	k_{CN}/k_H
 (b)	1.3×10^5
 (b,c)	1.3×10^5
	5.1×10^4

(a) $\sigma^-_{para} = 0.89$[113]

(b) Direct calculation of k_{CN}/k_H not possible. Effect determined from known k_F/k_H values at *para* position.

(c) Rate constant from Reference 129.

Tables 3.6, 3.7 and 3.8 show that the cyano group is substantially activating at all positions relative to hydrogen. The magnitude of this activation is comparable with that of ring nitrogen (Table 2.9) but is less than that of the NO_2 group (Table 3.4). Generally speaking, activating effects deduced from substitutions at a number of different positions and from a variety of substrates were in reasonable agreement. This again shows the additive nature of substituent effects in these systems. The rather low value for the effect of *meta*-CN derived from the rate constant of 2-cyanotetrafluoropyridine is difficult to explain however. Activation by the cyano group is greatest at positions *ortho* and *para* to the substituent. This general trend is followed by the Hammett σ^- constants, although activation by *para*-CN determined in the current study is greater than might have been expected on this basis.

The cyano group, like the nitro group, is known to be a strong σ- and π-electron acceptor.[88,95] Consequently, the large activating effect of the CN group may be explained in similar terms as described in Section 3.5.2.

3.7 Summary of Conclusions

(i) The activating effects of the groups studied are summarised in Table 3.9:

TABLE 3.9 Activating Effects of Some Substituent Groups to Nucleophilic Aromatic Substitution

Group	$k_{substituent}/k_H$		
	ORTHO	*META*	*PARA*
NO_2	2.2×10^5	1.06×10^4	-
CF_3	2.4×10^3	346	4.4×10^3
-N= (a)	6.2×10^4	850	2.3×10^5
CN	$3.4-7.2 \times 10^4$	1.4×10^3	$5.1 \times 10^4 - 1.3 \times 10^5$
Halogen	-	16 - 25	-

(a) From Table 2.8.

(ii) Halogen substituents *meta* to the point of attack are of comparable activating effect.

(iii) Substituent effects are generally additive.

(iv) Hammett σ^- constants give a reasonable guide to the substituent activating effect.

(v) Leaving group mobilities of F and NO_2 are comparable; both are displaced much more readily than Cl.

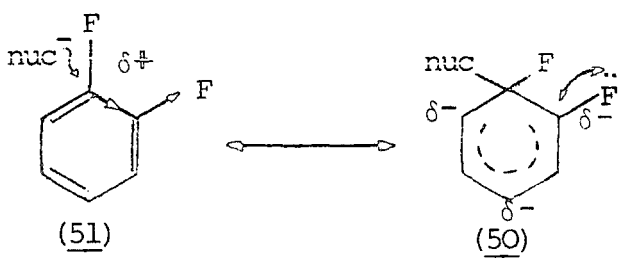
(vi) Rate constants determined are insensitive to base concentration in the range of base concentration used in any kinetic run. The occurrence of base catalysis is thus not substantiated in these systems.

CHAPTER FOUR

THE NATURE OF THE *ORTHO*-EFFECT

4.1 Introduction

The discussion in Chapter Two showed how, using an empirical approach, the activating influence of fluorine atoms on an aromatic nucleus may be separated into *ortho*, *meta* and *para* effects, relative to the position of nucleophilic attack. In the systems considered it was found that *ortho* and *meta* fluorines were strongly activating, whereas *para* fluorine was deactivating, relative to hydrogen at the same position. The *meta* and *para* effects were rationalised by considering the influence of fluorine on the stability of the anionic transition state, for which (50) was an approximate model. However, this simple explanation did not account for the activating effect of *ortho* fluorine. It has therefore been argued[132] that the Wheland intermediate (50) is an inadequate model for these systems. Initial state contributions (51) must also be considered, so that the transition state for nucleophilic substitution is more accurately represented by (51) ⟷ (50). Consequently the activating effect of *ortho* fluorine may be explained by an ion-dipole



(51) (50)

interaction in (51) whereby the polar nature of the C-*ortho* F bond encourages the approach of the nucleophile by enhancing the electrophilicity of the carbon atom under attack.[132]

This interaction more than compensates for the destabilising I_{π} repulsions in (50) with the net result that *ortho* fluorine is activating.

This hypothesis may be probed by a consideration of the Hammond postulate.[154] On this basis a more reactive system should lead to an earlier transition state for nucleophilic substitution, which means a greater contribution from (51) to the structure of the transition state. This in turn implies that, for more reactive systems, an increase in the importance of the *ortho* effect relative to the *meta* effect is expected, because of the increased importance of initial state polarisation.

Evidence in favour of this kinetic argument is the relative importance of activation by *ortho* and *meta* fluorine in the pyridine and benzene systems (Section 2.6.2); *ortho* fluorine is more activating than *meta* fluorine in the more reactive pyridine derivatives, whereas this order is reversed in the benzene system.

The aim of the work described here was to determine the activating effect of *ortho* and *meta* fluorine atoms in a number of systems of different reactivity. Thereby it was hoped that some conclusion could be reached as to the general applicability of the above kinetic argument in the description of the *ortho* effect.

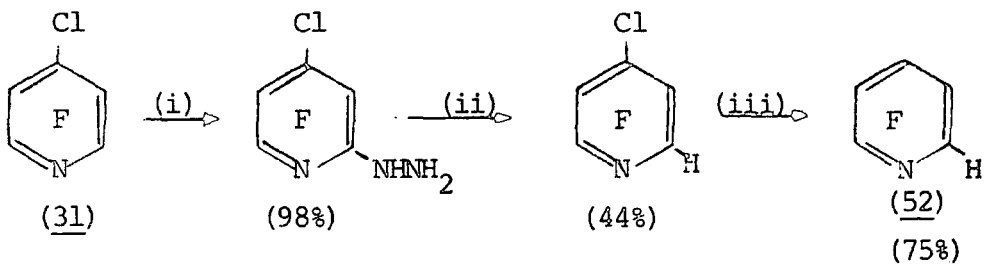
The substrates under investigation were a series of hydro-substituted polyfluoropyridines and pyrimidines.

4.2 Preparation of Substrates

A brief description of the preparation of the starting materials will now be given. All the compounds prepared have been previously reported. Pentafluoropyridine and tetrafluoropyrimidine were provided; these were purified before use as described in Chapter Nine.

(a) 2H-tetrafluoropyridine (52)

This was prepared from 4-chlorotetrafluoropyridine (31) by the route shown[131]:



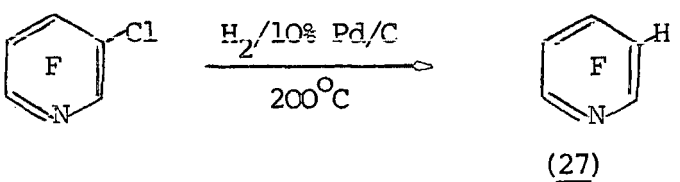
(i) $NH_2 \cdot NH_2 - H_2O$/EtOH/Room Temperature.

(ii) Conc. $CuSO_4$ (aq.).

(iii) CsF/Sulpholan/100°C for 6 hrs.

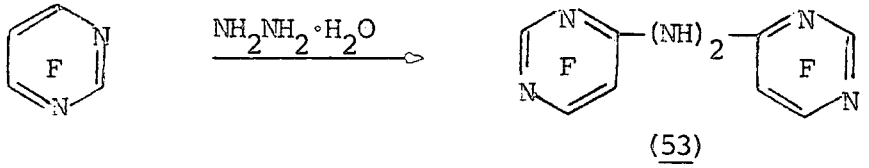
(b) 3H-tetrafluoropyridine (27)

This was prepared by the catalytic reduction, over palladised charcoal, of 3-chlorotetrafluoropyridine.[142]



(c) 4H-trifluoropyrimidine (54)

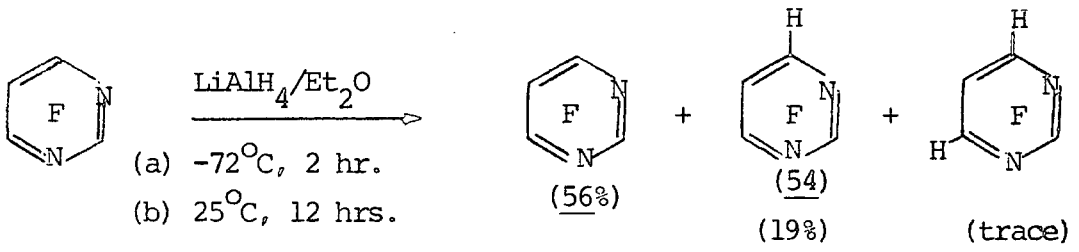
An attempt to synthesise (54) *via* the reaction of hydrazine hydrate with tetrafluoropyrimidine was unsuccessful owing to the formation of N,N´-(bis-4,4´-perfluoropyrimidino) hydrazine (53).



(53)

(85%)

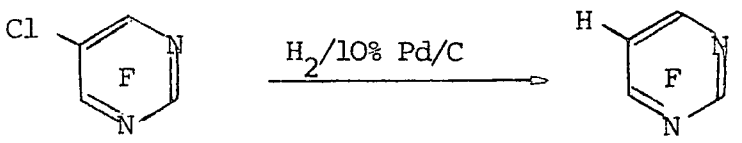
The reaction of lithium aluminium hydride with excess tetrafluoropyrimidine gave 4H-trifluoropyrimidine (54) in low yield.[155]



(based on recovered tetrafluoropyrimidine)

(d) 5H-trifluoropyrimidine (55)

This was prepared by the catalytic reduction of 5-chlorotrifluoropyrimidine over palladised charcoal.[156]



(55)

4.3 Rate Measurements for the Reactions of Substrates with Ammonia and Sodium Methoxide

Rate constants for the reaction of polyfluoropyridines with sodium methoxide and polyfluoropyrimidines with ammonia

and with sodium methoxide are shown in Tables 4.1 and 4.2 respectively. All reactions were carried out at 25.0°C; details of the calculations and experimental methods are described in Section 3.3 and in Chapter Nine.

In 4H-trifluoropyrimidine (54) where the orientation of nucleophilic attack has not previously been reported, it was established that monosubstitution by both ammonia and methoxide ion occurred exclusively at the 6-position. Nucleophilic substitution by methoxide ion in 3H-tetrafluoropyridine (27) occurred predominantly at the 4-position; this differs from the observed orientation of attack by ammonia in this compound, where a considerable amount of 6-substitution has been observed.[132] The orientation of nucleophilic attack in all other compounds discussed in this Chapter was in agreement with the literature.[132,157,158]

TABLE 4.1 Rate Constants for the Reaction of Sodium Methoxide in Methanol with Some Polyfluoropyridines at 25.0°C

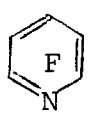
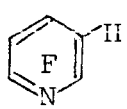
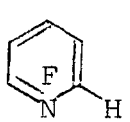
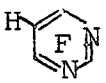
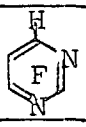
Substrate	Position of Substitution	k_{II} (l $mol^{-1}s^{-1}$)
	4-	$(1.42\pm0.01)\times10^{1}$
	4- 6-	$(5.94\pm0.04)\times10^{-1}$ $(0.30\pm0.06)\times10^{-1}$
	4-	$(9.34\pm0.03)\times10^{-1}$

TABLE 4.2 Rate Constants for the Reaction of (a) Ammonia in 60/40 (V/V) Dioxan/Water and (b) Sodium Methoxide in Methanol with Some Polyfluoropyrimidines at 25.0°C

Substrate	Position of Substitution	Rate Constant, k_{II} ($l\ mol^{-1}s^{-1}$)	
		(a) Attack by Ammonia	(b) Attack by MeO^-
	4-	1.35±0.01 (b)	(3.90±0.02)x10^3
	2-	(1.89±0.04)x10^{-1}	(1.48±0.03)x10^2
	4- (a)	(0.33±0.04)x10^{-1}	(1.34±0.03)x10^2
	6-	(4.49±0.02)x10^{-1}	(1.61±0.02)x10^3

(a) Rate constant statistically adjusted.

(b) Rate constant from Reference 129.

4.4 Discussion of Rate Data

The activating effect of *ortho* and *meta* fluorine atoms in the pyridine and pyrimidine ring systems, for each nucleophile/solvent system studied, is shown in Tables 4.3 and 4.4 respectively.

TABLE 4.3 Activating Influence of Fluorine in the Pyridine Ring System (Methoxide ion/Methanol, 25.0°C

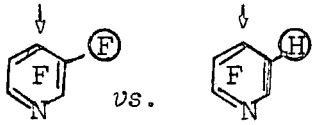
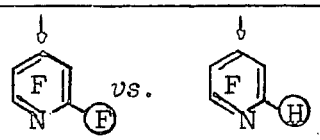
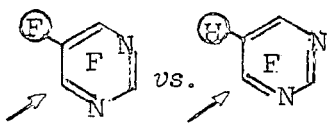
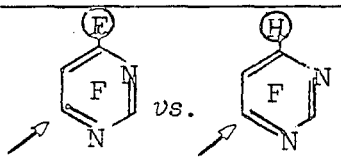
Comparison	Effect determined	k_F/k_H
	*ortho* -F / *ortho*-H	23.9
	*meta*-F / *meta*-H	15.2
	ortho-F / *meta*-F	1.57

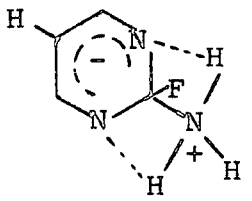
TABLE 4.4 Activating Influence of Fluorine in the Pyrimidine Ring System

Comparison	Effect determined	k_F/k_H (Ammonia)	k_F/k_H (Methoxide)
	*ortho*-F / *ortho*-H	41	29
	*meta*-F / *meta*-H	3.0	2.4
	ortho-F / *meta*-F	13.6	12.1

The orientation of nucleophilic substitution in polyfluoropyridines is governed by the effects of both the ring nitrogen and the fluoro-substituents, as discussed in Section 2.6.2. However, rather more discrimination by ring nitrogen between the 4- and the 2-/6-position is observed for attack by methoxide ion than for attack by ammonia.[132] This is indicated by the predominant attack by methoxide ion at the 4-position in 3H-tetrafluoropyridine (27), although attack at the 6-position leads to an equivalent number of activating *ortho* and *meta* fluorine substituents.

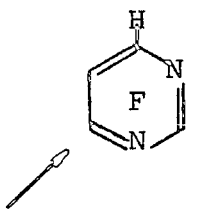
The orientation of substitution in polyfluoropyrimidines is similarly governed by the ring nitrogen and fluorine substituents. Activation of the system by ring nitrogen is substantial; there is, however, little discrimination by the nitrogen between the 2- and the 4-/6-positions. Thus the rate constants for attack by methoxide ion at these positions

in 5H-trifluoropyrimidine (55), where attack at each site is associated with the same number of activating F-atoms, are very similar. Attack by ammonia in (55) leads to preferential substitution of the 2-fluorine; this has been explained by a stabilisation of the transition state for 2-substitution by intramolecular hydrogen-bonding (56).[158]



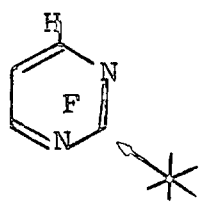
(56)

Consequently, the observation of exclusive nucleophilic substitution at the 4-position in tetrafluoropyrimidine may be attributed to the additional activating influence of an *ortho*-fluorine at this position. A similar argument may be used to explain the exclusive 6-substitution observed in 4H-trifluoropyrimidine (54).



2 activating=N-
1 *ortho* F

(54)



2 activating=N-only.

(54)

The effect of a *meta*-fluorine in the pyrimidine system is seen to be negligible.

The activating influence of *ortho* and *meta* fluorine has now been determined for three different fluoroaromatic systems. These effects are shown in Table 4.5, together

TABLE 4.5 Relative Activating Influence of *ortho* and *meta* Fluorines in Some Polyfluoroaromatic Systems

System (Nucleophile/°C)	k_{F}/k_{H} *ORTHO*	k_{F}/k_{H} *META*	*ORTHO* F / *META* F
 (a) (MeO^-/58°)	57	106	0.54
 (b) (NH_3/25°)	31	23	1.35
 (MeO^-/25°)	24	15	1.57
 (NH_3/25°)	41	3.0	13.6
 (MeO^-/25°)	29	2.4	12.1

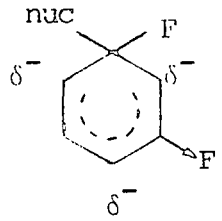
(a) From Table 2.5; Reference 119.

(b) From Table 2.10; Reference 131.

---

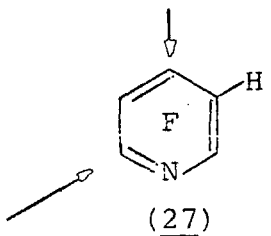
with the ratio of *ortho* to *meta* activation. Considering reactions with methoxide ion, it is clear that as the reactivity of the system increases there is a corresponding increase in the relative importance of the *ortho* effect. Thus, in fluorobenzenes, the ratio of *ortho* to *meta* fluorine activation is 0.54; this ratio increases to 1.57 in fluoropyridines and to 12.1 in fluoropyrimidines (the most reactive system studied) where the effect of *meta* fluorine is negligible. This general trend is followed by the reactions of these systems with ammonia.

The magnitude of the *ortho*-effect is seen (Table 4.5) to remain remarkably consistent with each system considered. There is however a marked decrease in the activation by *meta*-fluorine as the reactivity of the system increases. *Meta*-effects can be rationalised in terms of an inductive stabilisation of charge in the Wheland intermediate-type representation of the transition state (20), (Section 2.4.2). Consequently the decrease in *meta*-activation may be explained in terms of a reduction of charge delocalisation into the ring in the transition state as electron-withdrawing ring-N= substituents are added.



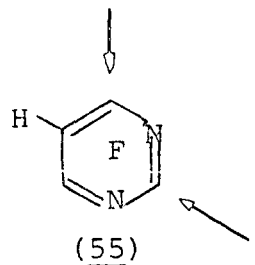
(20)

It was noted earlier in this Section that, for attack by methoxide ion, ring nitrogen is discriminating in favour of the 4-position in the pyridine system but not in the pyrimidine system. This is shown below, where attack at the arrowed position leads to an equivalent fluorine activation in each substrate:



(27)

$$\frac{k_{II}(4\text{-attack})}{k_{II}(6\text{-attack})} = 19.8$$



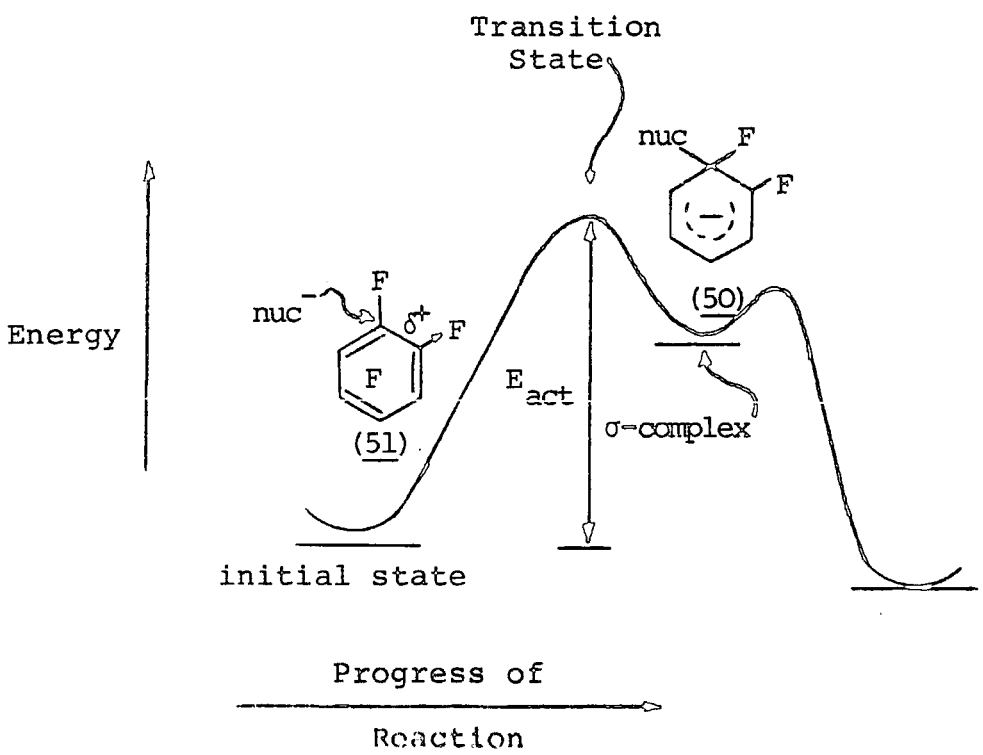
(55)

$$\frac{k_{II}(4\text{-attack})}{k_{II}(2\text{-attack})} = 0.91$$

As the ratio of 4- to 2- attack in (55) effectively reflects the relative activating effect of *ortho*- to *para*-ring nitrogen in the pyrimidine system, the above observations may be

equated with a large increase in the importance of *ortho*-ring nitrogen activation in this system. Therefore the same trend is observed for both ring nitrogen and fluorine (Table 4.5), *i.e.* the relative importance of the *ortho* effect increases with the reactivity of the system.

The nature of the activation by *ortho*-fluorine will now be discussed. In Section 4.1 it was suggested that this effect could be described in terms of an initial state ion-dipole interaction. For the purposes of this argument, the transition state of a given nucleophilic aromatic substitution reaction is represented by the two extreme cases (51), (50) with the actual situation being somewhere in between these extremes, depending on the nature of the system. This may conveniently be represented by the potential energy diagram below,[159] in which the first step of the reaction is rate-determining:

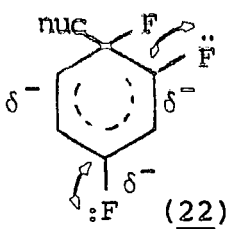


On the basis of the Hammond postulate,[154] the above transition state occurs earlier along the reaction pathway for a more reactive system. Effectively, this implies that the structure of this transition state should more closely resemble (51) for very reactive substrates. Similarly, for relatively unreactive substrates, the structure of the transition state should resemble (50). This may in turn be interpreted in terms of an increase in the relative importance of ion-dipole interactions as the reactivity of the system is increased.

The results shown in Table 4.5 clearly show this effect; the ratio of *ortho*- to *meta*-fluorine activation increases along the series benzenes<pyridines<pyrimidines, *i.e.* as the reactivity of the substrate increases. Consequently, it may be concluded that, at least in part, the nature of activation by *ortho*-fluorine is a kinetic effect arising from an ion-dipole interaction.

4.5 *Ortho*-Effects in σ-Complexes

When electronic effects in the transition state of a nucleophilic aromatic substitution reaction are considered it is usually assumed that fluorine atoms *ortho*- and *para*- to the reaction site are destabilising in the Wheland intermediate because of I_π repulsions (22). The observation that *ortho*-fluorine is activating to substitution is therefore

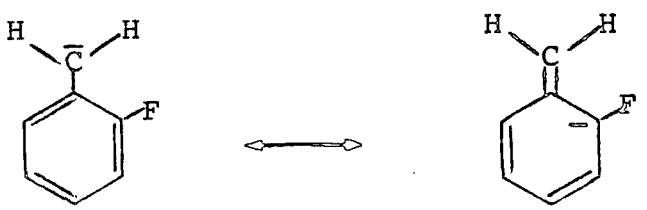


(22)

attributed to the predominance of initial state ion-dipole effects at this position as discussed in the previous Section.

However, while initial state activation by *ortho*-fluorine is undoubtedly a real effect, there is now considerable evidence to suggest that *ortho*-fluorine in the situation (22) is also stabilising, *i.e.* this substituent confers a thermodynamic stability on the σ-complex in addition to the kinetic effect just discussed. This evidence is now considered.

Exchange rates of some *ortho*-substituted toluenes have been measured by Streitwieser and Koch.[160] In these systems, the rate of exchange depends on the stability of the anion (57) ⟷ (58) and it was found that *ortho*-fluorine was anion stabilising (Table 4.6), whereas *para*-fluorine was slightly destabilising.



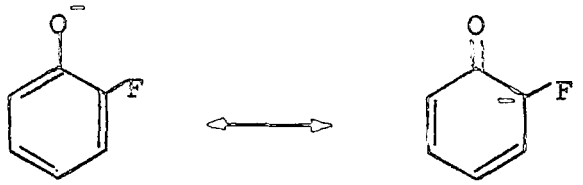
(57) (58)

TABLE 4.6 Relative Reactivities of Substituted Toluenes[160]

Substituent	Relative (H = 1) Rate		
	Ortho-	*Meta-*	*Para-*
CH_3	0.60	0.60	0.31
F	12	22	0.73
CF_3	—	60	∿180

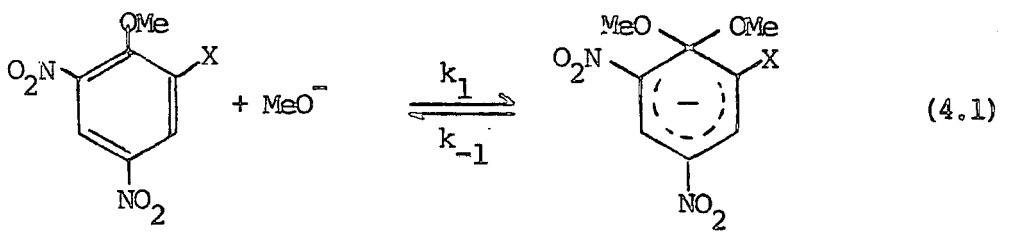
Similarly, the dissociation constants of fluorine-substituted phenols[113] show that *ortho*-fluorine is anion-stabilising

(59) ⟷ (60)



(59) (60)

More recently the reactions of some 1-methoxy-2,4-dinitro-6X-benzenes (61) with sodium methoxide have been reported.[161,162] Rate constants from this study are quoted in Table 4.7, where the reaction studied is shown in Equation 4.1:



(61) (52) (4.1)

TABLE 4.7 Rate Constants for the Reactions of Some 1-Methoxy-2-4-dinitro-6X-benzenes with Methoxide Ion in Methanol at 25°C.[161,162]

X	k_1 ($l\ mol^{-1}s^{-1}$)	k_{-1} (s^{-1})	K ($l\ mol^{-1}$)
H	2×10^{-3}	42	5×10^{-5}
Cl	0.18	0.06	3
F	0.10	0.40	0.3

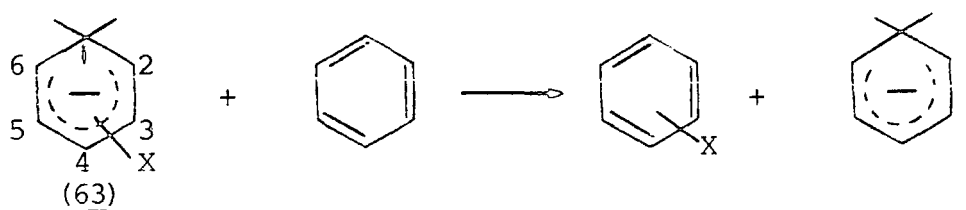
These results may be interpreted in the thermodynamic stabilisation of the anion (62) by *ortho*-fluorine; *ortho*-chlorine is

found to be more stabilising than fluorine, as expected on the basis of I_π repulsions (Section 2.4.3).

Theoretical calculations have estimated the stabilisation energies of a number of substituted cyclohexadienyl anions (63) relative to the substituted benzene as defined by Equation 4.2.[163,164] A selection of these results are shown in Table 4.8.

TABLE 4.8 Stabilisation Energies (kJ mol^{-1}) of Some Substituted Cyclohexadienyl Anions.[163]

Substituent	Position			
	1-	2-	3-	4-
H	0	0	0	0
F	29.0	10.4	27.9	-6.6
CN	54.1	125.8	69.6	148.6
NO_2	129.9	178.9	87.5	201.8
NH_2	15.8	-47.6	-9.5	-78.8



(63) (4.2)

Positive values in Table 4.8 indicate a greater stability of the substituted anion relative to the unsubstituted one. Negative charge has been shown to be localised mainly at the 2-/6- and 4-positions in (63);[163] however the results confirm

that *ortho*-fluorine is stabilising the anion. Similarly, *meta*-fluorine is also seen to be stabilising and *para*-fluorine destabilsing in accord with the empirically-determined results quoted in Table 2.5.

Table 4.8 shows that *ipso*-substituents have a marked anion stabilsing effect. For fluorine, this has been attributed to the operation of σ-inductive effects in the absence of I_π repulsions at this position.[163,164] The importance of this effect has received little attention in the literature although it has been invoked to account for the preferential substitution of aromatic fluorine in some systems.[164]

For the various substituents, at any given position, the calculated stabilisation energies are in the order NO_2>CN>F, which is in agreement with the results discussed in Chapter Three.

However, the important conclusion from this Section is that *ortho*-fluorine, in the systems considered, stabilises anionic σ-complexes. This stabilisation is clearly shown by experiment and by calculation. Nevertheless, there is no descriptive model that accounts satisfactorily for this effect.

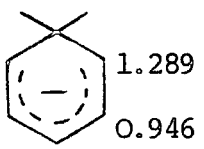
4.5.1 The Nature of σ-Complex Stabilisation by *Ortho*-Fluorine

In considering the effect of a fluorine atom directly attached to a carbanionic centre it could be argued that the balance between I_π and σ-inductive effects in (64) varies with δ. For small values of δ it is therefore

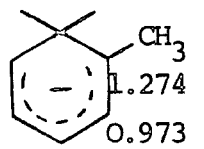
(64)

conceivable that in (64) fluorine would be carbanion stabilising.

In anionic σ-complexes, charge has been shown by ^{13}C n.m.r. spectroscopy to be localised mainly at the *ortho*- and *para* positions.[165,166] Theoretical calculations have confirmed this effect, where it has been shown that the greatest π-charge is located on the *para*-carbon atom.[118,163,164] For example, the predicted π-electron populations for some substituted cyclohexadienyl anions (65),[118] (66)[167] are shown below. For fluorinated systems, the charges on carbon



(65)

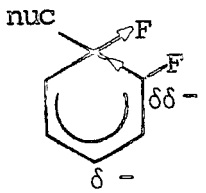


(66)

are thought to be of the same order as in (65).[164,165]

On the basis of these π-electron populations, destabilising I_π interactions should be marginally more important at the *para*- than at the *ortho*-position in a fluorinated σ-complex. However, it is unlikely that these differences in π-electron densities can substantiate the significant relief in I_π interactions necessary to account fully for the difference in the effect of fluorine at these positions. This point of view is reinforced when the π-densities at the *ortho*- and *meta*-positions in (65) (*i.e. ortho*>*meta*) are compared with the fluorine activating effects at these positions (*i.e. ortho*≈ *meta*). However, it is conceivable that fluorine at the *ipso*-position plays an important and as yet unrecognised rôle in these systems by inductively

removing charge density from the *ortho*-position (67). Recent calculations have indeed shown that *ipso*-fluorine is

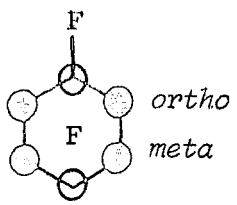


(67)

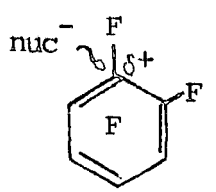
strongly σ-complex stabilising,[163,164] which has been attributed to the operation of inductive effects.[237]

An alternative explanation for the *ortho*-effect is based on a Frontier Orbital (FO) approach. This formalism has been used[121] to account for the orientation of nucleophilic substitution in polyhaloaromatics (Section 2.5.1) although this has been criticised.[122] However, it was not recognised[121,122] that there are in fact two major interactions which affect the activation energy that must be considered; in addition to the favourable HOMO-LUMO interaction, there is also a stabilising Coulombic term affecting reactivity.[238] The latter interaction is especially significant in the reactions of polar molecules.[238]

An attractive implication of this FO treatment is that *ortho*- and *meta*-fluorine atoms are predicted to have roughly the same activating influence, as observed in polyfluorobenzenes (24). However, for more reactive systems, it has been shown (Table 4.5) that the relative importance of *ortho*- to *meta*-fluorine increases. This observation may be explained



(24)



(51)

by the FO approach in terms of an increase in the importance of the Coulombic term in the transition state as the reactivity of the system increases. In other words as the system becomes more reactive, the structure of the transition state tends to (51) (Hammond postulate)[154] increasing the importance of ion-dipole (*i.e. ortho*) effects.

4.6 Conclusions

(i) The activating influences of *ortho*- and *meta*-fluorine in the pyridine and pyrimidine systems are:

	ortho	*meta*	
pyridines	24	15	(methoxide ion/25°)
pyrimidines	29	2.4	(aq. ammonia/25°)
	41	3.0	(methoxide ion/25°)

(ii) The relative activating effect of *ortho*- to *meta*-fluorine increases along the series benzenes<pyridines<pyrimidines, *i.e.* with the reactivity of the system.

(iii) The nature of the *ortho*-effect may in part be explained, from the above observations, on the basis of the Hammond postulate. The effect is a consequence of an initial state ion-dipole interaction.

(iv) *Ortho*-fluorine is also σ-complex stabilising, although no satisfactory descriptive model for this effect exists.

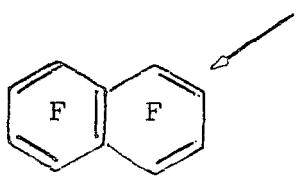
(v) *Ipso*-fluorine has been calculated to have a marked stabilising influence on σ-complexes.

CHAPTER FIVE

NUCLEOPHILIC SUBSTITUTION IN THE POLYFLUORONAPHTHALENE SYSTEM

5.1 Introduction

In Chapter Two it was shown how the orientation of monsubstitution in polyfluorinated monocyclic systems could be predicted by an empirical approach in which the number of activating *ortho*- and *meta*-fluorine atoms at each possible site of attack was considered. A logical extension of this approach would also enable the orientation of nucleophilic attack in polyfluoropolycyclic systems to be predicted. Thus it could reasonably be argued that nucleophilic substitution at the 2-position in octafluoronaphthalene (68) is preferred because at this position the number of activating fluorine atoms is maximised. However, the individual activating influence of fluorine in the naphthalene system must



(68)

be known before the orientation of nucleophilic attack in this system may be accounted for with confidence.

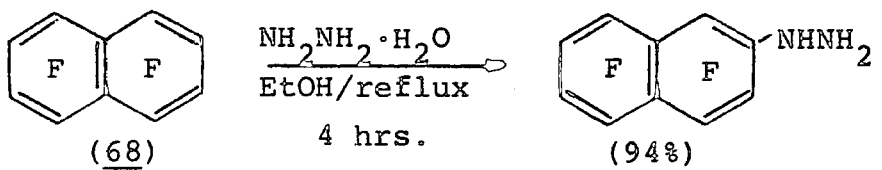
In this Chapter, the determination of the separate activating influences of fluorine in the naphthalene ring system is described. The results are then applied to account for the gross features of nucleophilic attack in perfluoropolycyclic systems in general. The substrates under investigation were octafluoronaphthalene (68), 2H-heptafluoronaphthalene (70), 1,2-dihydrohexafluoronaphthalene (71) and 2,6-dihydrohexafluoronaphthalene (72).

5.2 Preparation of Substrates

It was necessary to prepare all substrates with the exception of octafluoronaphthalene. This was provided and was purified before use. The preparation of 2,6-dihydrohexafluoronaphthalene has been briefly commented on,[167] though no characterisation of this compound has been reported. All other substrates have been previously reported.

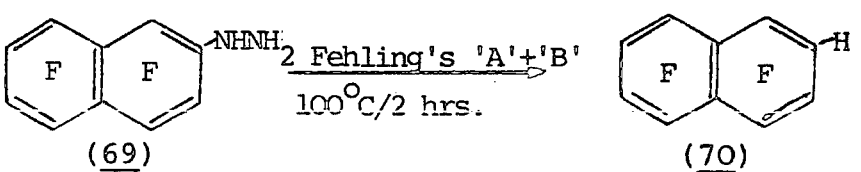
(a) 2H-heptafluorohaphthalene (70)

This was prepared by a two-step synthesis according to the literature.[168] Firstly, 2-hydrazinoheptafluoronaphthalene (69) was prepared in good yield by the reaction of octafluoronaphthalene (68) with hydrazine hydrate.



(68) (94%)

2H-heptafluoronaphthalene (70) was produced by reduction of (69) with Fehling's solutions 'A' and 'B'.

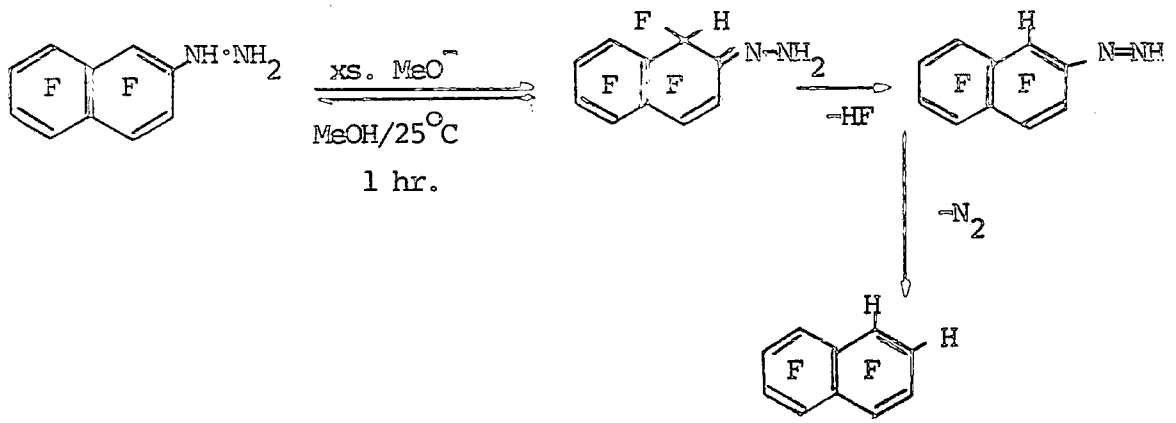


(69) (70)
(69%)

(b) 1,2-Dihydrohexafluoronaphthalene (71)

This was prepared by the reaction of (69) with an excess of methanolic sodium methoxide.[170] The formation of the product may be rationalised by a base-catalysed prototropic

shift, followed by successive loss of HF and nitrogen:[169,170]



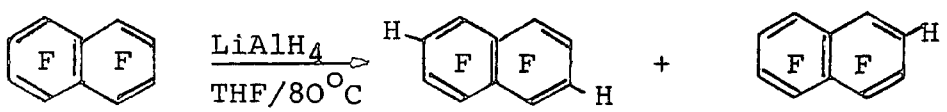
(71)

64%

A similar mechanism has been reported for the reaction of 4-hydrozinotetrachloropyridine with aqueous copper (I) oxide.[171]

(c) 2,6-Dihydrohexafluoronaphthalene (72)

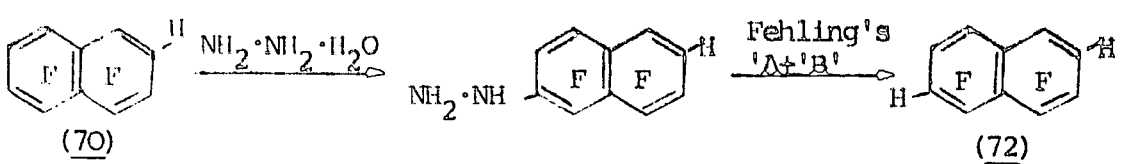
This was prepared by the reaction of octafluoronaphthalene (68) with lithium aluminium hydride in THF. The products were separated by preparative scale gas chromatography as discussed in Chapter Ten.



(68) (72) (70)

(+ other unidentified products)

Compound (72) may also, in principle, be synthesised *via* the following route:



(70) (72)

However, this approach was abandoned owing to incomplete conversions and poor yields.

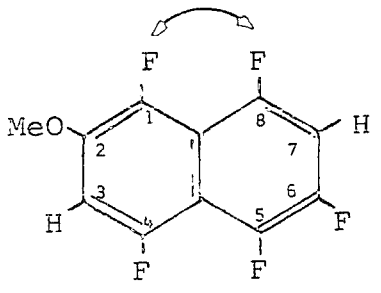
5.3 Kinetic Methods and Rate Constant Calculations

Rate measurements for all reactions discussed in this Chapter were carried out at 25.0°C with sodium methoxide as the nucleophile in dry AnalaR methanol. An excess of substrate was used in each run to avoid disubstitution by methoxide ion as discussed in Chapter Ten. Second-order rate constants and standard errors were calculated from the usual expressions as described in Section 3.3. The reactions were followed by the titrometric method.

5.4 Reactions of Polyfluoronaphthalenes with Sodium Methoxide

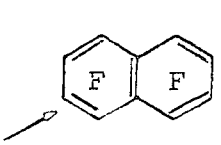
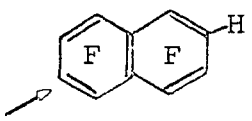
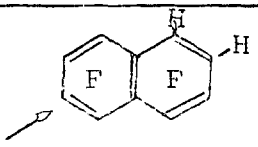
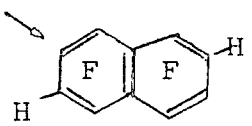
The second-order rate constants for the substrates under investigation are shown in Table 5.1. Monosubstitution by methoxide ion in (68), 70) and (71) was observed at the positions arrowed in Table 5.1 in agreement with the literature.[168,170] In (72), where the orientation of nucleophilic substitution has not been reported, detailed investigation of the crude product by ^{19}F n.m.r. spectroscopy showed the presence of two isomers. The major product was 2-methoxy-3,7-dihydro-1,4,5,6,8-pentafluoronaphthalene (73). This assignment was based principally on the known[172] *peri*-couplings exhibited by this type of compound; the coupling constants are shown below.

J_{1-8} = 68Hz



J_{4-5} = 58Hz (73)

TABLE 5.1 Rate Constants for the Reaction of Sodium Methoxide in Methanol with some Polyfluoronaphthalenes at 25.0°C

Substrate	Position of Attack	k_{II} (l $mol^{-1}s^{-1}$)
 (a)	2-	$(1.12\pm0.01)\times10^{-3}$
	6-	$(1.38\pm0.01)\times10^{-3}$
	6-	$(4.55\pm0.03)\times10^{-5}$
 (a,b)	7-	*ca.* 1.50×10^{-6} (c)

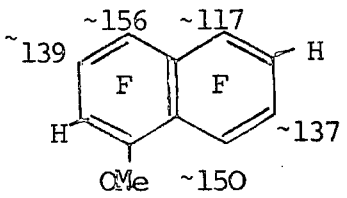
(a) Rate constant statistically adjusted.

(b) Minor product from attack at 5-position also found.

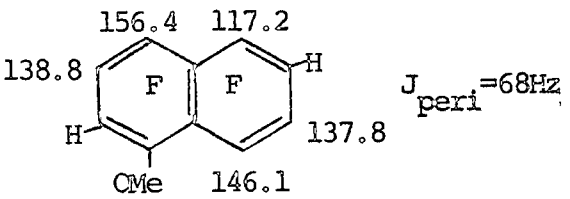
(c) Products inseparable by g.l.c.; approximate isomer ratio from ^{19}F n.m.r. investigations.

A second product (74) exhibited only one *peri*-coupling. The structure of (74) was established from the ^{19}F n.m.r. spectrum of (72) and the known *ortho*, *meta* and *para* effects

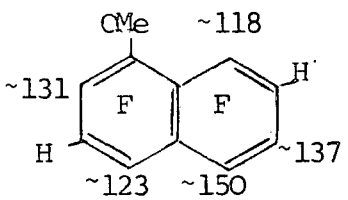
of MeO substituents on perfluoronaphthalenes.[17c] On this basis, (74) was identified as 1-methoxy-2,6-dihydro-3,4,5,7,8-pentafluoronaphthalene:



(Estimated shifts for 1-methoxy isomer)



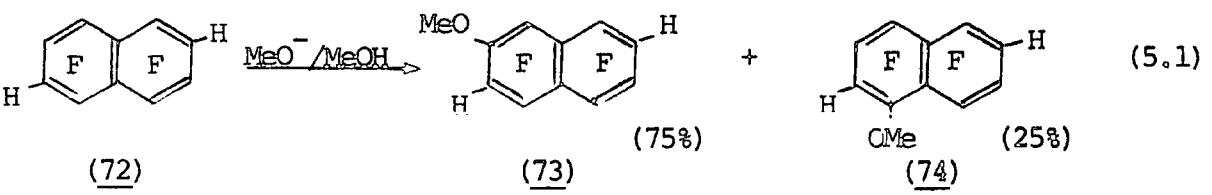
(Observed shifts)



(Estimated shifts for 4-methoxy isomer)

(all shifts in ppm relative to internal $CFCl_3$=0)

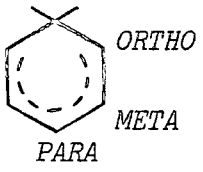
The reaction of (72) with sodium methoxide is shown in Equation 5.1:



(72) (73) (74) (5.1)

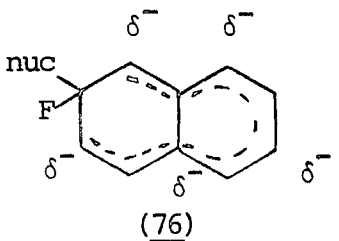
5.5 Discussion of Rate Data

In monocyclic systems, positions on the carbon framework with respect to the reaction site are defined as in (75).



(75)

However, for polycyclic systems, a slightly different nomenclature is required. If the Wheland intermediate-type representation of the transition state for nucleophilic substitution in a polyfluoronaphthalene (76) is considered, then the following definitions are now made:



(76)

(all unmarked bonds to F)

ORTHO positions: Adjacent to the site of Attack

"*PSEUDO-META*" positions: Adjacent to a carbon atom bearing localised anionic π-charge (δ-) in (76).

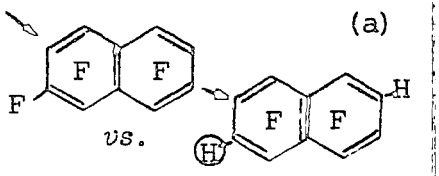
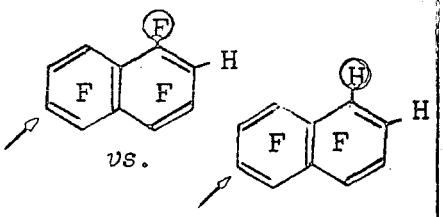
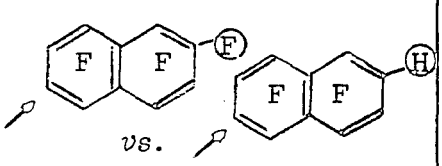
"*PSEUDO-PARA*" positions: At a carbon atom bearing localised anionic π-charge in (76) (and excluding *ortho*-positions).

By this definition, in (76) there are two *ortho*-fluorines, three "*psdueo-meta*" fluorines and two "*pseudo-para*" fluorines.

Having defined the *ortho*, "*pseudo-meta*" and "*pseudo-para*" positions in polycyclic systems, the activating influence of fluorine atoms at these sites in the naphthalene system may now be calculated from the rate constants quoted in Table 5.1. This is shown in Table 5.2.

According to this treatment, it is assumed that the effects of "*pseudo-meta*" and "*pseudo-para*" fluorines remain the same throughout the molecule, whereas in reality it is

TABLE 5.2 Activating Influence of Fluorine in the Naphthalene Ring System

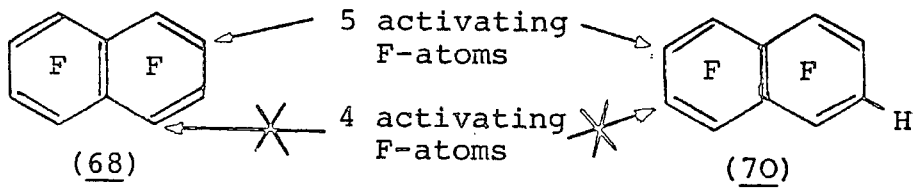
Comparison	Effect determined	k_F/k_H
 (a)	*ortho*-F / *ortho*-H	*ca.* 25
	"*pseudo-meta*" F / "*pseudo-meta*" H	30.3
	"*pseudo-para*" F / "*pseudo-para*" H	0.81

(a) Cannot determine effect directly as substitution always occurs in the fully fluorinated ring. This effect is calculated indirectly by making an allowance for the "*pseudo-meta*"-H in (72), so that

$$k_{F/k_H}\ (ortho) \approx \frac{k_{II}\ (68)}{k_{II}\ (72)} \times \frac{1}{30.3} = 25$$

probable that variations in the magnitudes of these effects occur. Nevertheless, despite the obvious limitations of this approach, the main observation from Table 5.2 is that fluorine atoms *ortho* and "*pseudo-meta*" to the reaction site have a large activating influence in the naphthalene system. The effect of a "*pseudo-para*" fluorine is seen to be much less significant, being comparable to a hydrogen atom at this position. These observations may be rationalised in a similar manner as previously discussed for the benzene system (Section 2.4.2.).

The separation of fluorine activating influences in this study reinforces the argument that, in the naphthalene system, nucleophilic attack occurs so as to maximise the number of activing *ortho* and "*pseudo-meta*" fluorine atoms. The observation of exclusive nucleophilic attack at the 2-position in octafluoronaphthalene (68) may therefore be rationalised, as may the exclusive 6-attack in 2H-heptafluoronaphthalene (70), in terms of a maximisation of fluorine activating effects at these positions.



(68) (70)

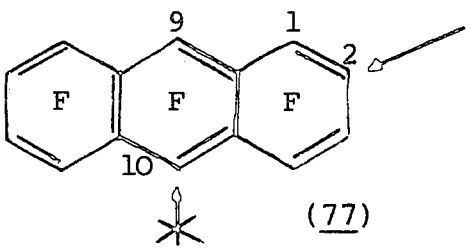
The application of this empirical approach to account for the orientation of nucleophilic substitution in more complex perfluoroaromatic systems will now be discussed.

5.6 Nucleophilic Substitution in Other Perfluoropolycyclic Systems

5.6.1 Decafluoroanthracene (77)

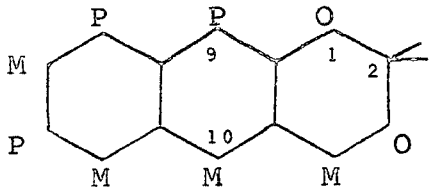
In a recent paper,[173] the orientation of nucleophilic attack in decafluoroanthracene (77) was predicted by an extension of the early, previously discussed (Section 2.4.1), I_π theory.[117] By this "amplified I_π repulsion" theory,[122] calculated[174] anionic charge densities in fluorine-bearing carbon atoms are summed for each possible Wheland-type intermediate, giving a parameter "θ" for each position of nucleo-

philic attack. The position of substitution predicted was that which gave the minimum value of θ *i.e.* which localised the least charge on fluorine-bearing carbons. In decafluoroanthracene (77) θ was found to be minimised for attack at the 9-/10-position.[173] However, nucleophilic substitution was subsequently shown[173] to take place at the 2-position:

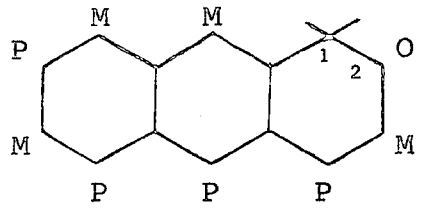


(77)

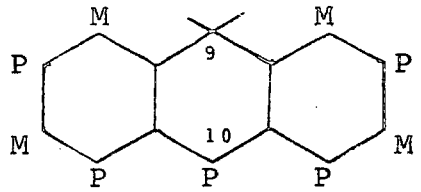
In the naphthalene system, it has been shown (Table 5.2) that the major orientating influence may be attributed to the need to maximise the number of activating *ortho*- and "*pseudo-meta*-" fluorine atoms. It is reasonable to assume that, in the anthracene system, the corresponding fluorine atoms will also be activating (although the magnitude of these effects may differ). Consequently the orientation of nucleophilic substitution in decafluoroanthracene (77) may be predicted in an analagous manner to that discussed in the previous Section for octafluoronaphthalene (68). Thus attack at the 2-position in (77) is observed because at this position the number of activating fluorine substituents is maximised. According to this approach, attack at the 9-/10-position is seen to be the least likely orientation:



≡ 6 activating F-atoms (attack at 2-position)



≡ 5 activating F-atoms (attack at 1-position)



≡ 4 activating F-atoms (attack at 9-position)

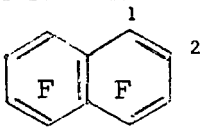
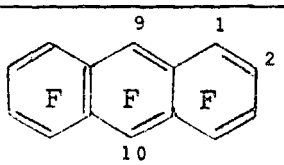
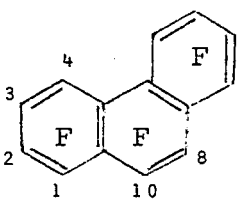
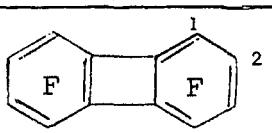
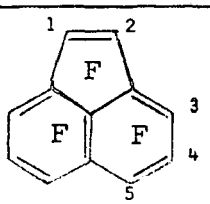
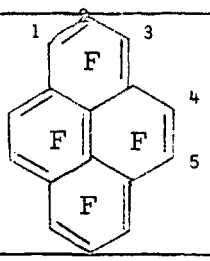
(all unmarked bonds to O = *ortho*, m = "*pseudo-meta*" and p = "*pseudo-para*" fluorines).

5.6.2 Other Systems

The orientation of nucleophilic substitution is known only for a limited number of perfluoropolycyclic compounds. In addition to octafluoronaphthalene[168] and decafluoroanthracene,[173] perfluoro-phenanthrene[175] (78), -biphenylene[176] (79), -acenaphthene[177] (80), -fluoranthene[178] and -pyrene[179] (81) have also been studied.

In Table 5.3, the predicted sites of nucleophilic substitution in (68) and (77)-(81) are compared with the known orientations in these compounds. It is reasonably assumed that, in each system, all *ortho* and "*pseudo-meta*" fluorine atoms (as defined in Section 5.6.1) are activating to nucleophilic attack. The position predicted is therefore that which is associated with the greatest number of activating fluorine substituents. All "*pseudo-para*" fluorines are assumed to have a negligible orientating effect. Thus

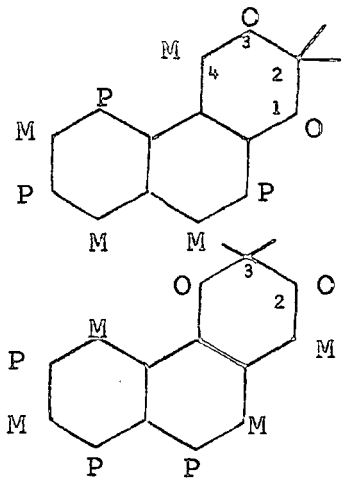
TABLE 5.3 Empirically-Predicted and Experimentally-Found Orientations of Nucleophilic Substitution in Some Perfluoropolycyclic Systems

System	Orientation of attack	
	Predicted	Found ref.
 (68)	2-	2- 168
 (77)	2-	2- 173
 (78)	2-, 3-	2- 175
 (79)	2-	2- 176
 (80)	3-, 5-	3- 177
 (81)	2-	1- 179

---

nucleophilic attack is correctly predicted at the 2-position in (79) and also in (68) and (77) as previously discussed.

In decafluorophenanthrene (78) the empirical approach does not distinguish between attack at the 2- and 3-positions, each of which is associated with the same number of activating fluorine atoms.



≡ 6 activating F-atoms (attack at 2-position)

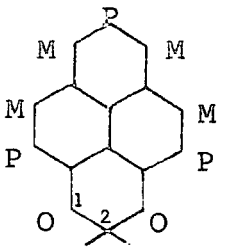
≡ 6 activating F-atoms (attack at 3-position)

(O = *ortho*, M = "*pseudo-meta*", p = "*pseudo-para*" -fluorine).

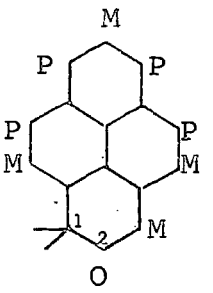
Nucleophilic replacement in (78) has been shown[175] to occur mainly at the 2-position. However, the possibility that a small amount of substitution may also occur at the 3-position can not be ruled out, as minor products in this study[175] were not investigated.

In octafluoroacenaphthene[177] (80) (and also in decafluorofluoranthene [178]) monosubstitution takes place at the 3-position. The empirical approach cannot readily account for this orientation as (80) is a non-alternant system. However, if (80) is treated as a disubstituted hexafluoronaphthalene, then nucleophilic attack would be predicted at both the 3- and 5-positions - a reasonable result bearing in mind the approximation made.

The approach fails to account for the orientation of substitution in decafluoropyrene (81); attack at the 2-position is predicted on the basis of fluorine activation whereas 1-substitution is actually found.[179] However, it is probable that in this system anionic charge in the transition state is so "spread out" that the localisation energy (L) for attack at each position becomes the dominant orient-

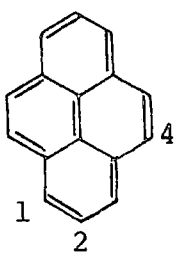


≡ 6 Activating F-atoms (attack at 2-position) ∴ predicted.



≡ 5 Activating F-atoms (attack at 1-position)

ating influence. Calculations[174] predict the following localisation energies for nucleophilic attack in this system:



Position	Localisation energy, L
1-	2.1899
2-	2.5489
4-	2.2743

The lower the L value, the more reactive the position;[174] hence, nucleophilic attack in decafluoropyrene is predicted at the 1-position.

5.7 Conclusions

(i) In the naphthalene system, fluorine atoms *ortho*- and "*pseudo-meta*" to the reaction site are activating to nucleophilic substitution relative to hydrogen by factors of *ca.* 25 and 30 respectively. A "*pseudo-para*" fluorine has a similar effect to hydrogen, with $^{k}F/k_{H}$ = 0.8 at this position.

(ii) Nucleophilic replacement by methoxide ion in 2,6-dihydrohexafluoronaphthalene (72) occurs mainly at the 7-position (75%) and also at the 5-position (25%).

(iii) The orientation of nucleophilic attack in polyfluoronaphthalene may be empirically predicted. Attack takes place so as to maximise the number of activating *ortho*- and "*pseudo-meta*" fluorine substituents.

(iv) This approach may be extended to account for the orientation of nucleophilic attack in other polycyclic systems.

(v) The approach does not distinguish between two possible sites of attack (one of which is observed experimentally) in the non-alternant systems discussed.

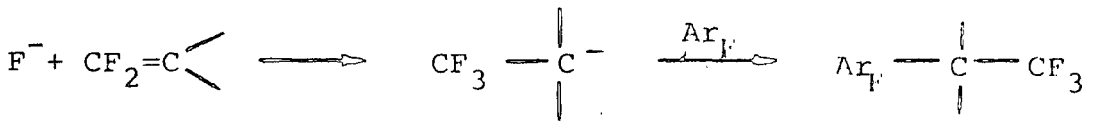
(vi) For pyrene and presumably for other large polycyclic systems, the orientation of substitution may be predicted from a consideration of localisation energy.

CHAPTER SIX

SOME REACTIONS OF 2H-PENTAFLUOROPROPENE

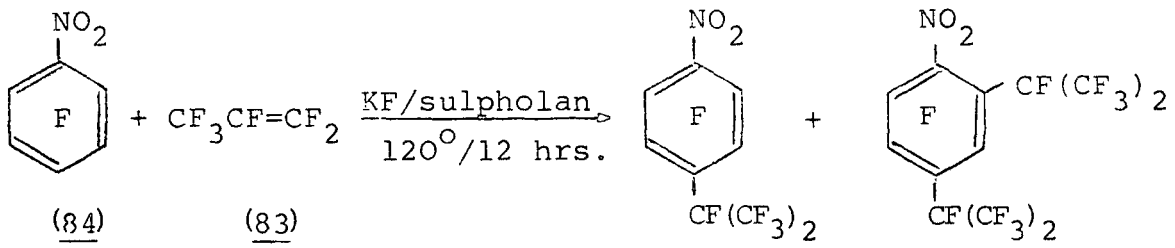
6.1 Introduction

The reactions of perfluoro-olefins with fluoride ion are synthetically very useful as they may be used in the preparation of perfluoroalkyl-substituted aromatic compounds. Reactions of this type proceed *via* the initial formation of a perfluorocarbanion (*e.g.*, (82); subsequent attack of this nucleophile on the substrate yields the perfluoroalkyl substituted product:



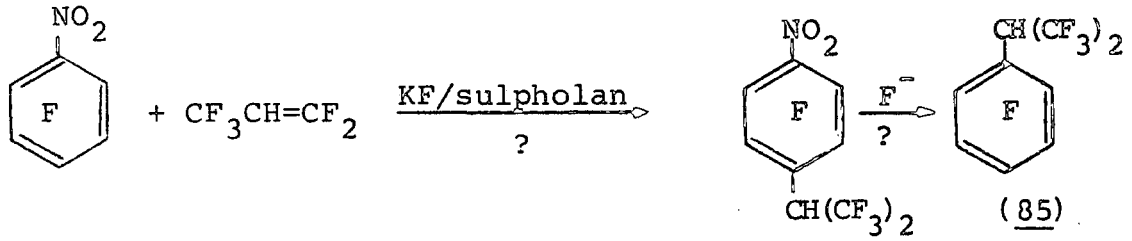
(80)

The substrate must usually be sufficiently activated; thus hexafluorobenzene does not normally react with perfluoro-olefins in the presence of fluoride ion.[180,181] However, the reaction of hexafluoropropene (83) with pentafluoronitro-benzene (84) and potassium fluoride is well known[180] (Equation 6.1):



(84) (83) + others (6.1)

It was originally intended to repeat this reaction in the presence of 2H-pentafluoropropene, $CF_3CH=CF_2$, with the aim being to synthesise perfluoro(2H-hexafluoroisopropyl)benzene (85) required for studies described in Chapter Seven (Equation 6.2):



(6.2)

However, this reaction yielded some most unusual products, and initiated further studies on the reactions of $CF_3CH=CF_2$ with aromatic substrates. These reactions are discussed in this Chapter.

6.2 Preparation of 2H-Pentafluoropropene (2H-PFP)

This was prepared according to the method of Sianesi and Fontanelli:[182]

$$CF_3\text{-}CF=CF_2 + MeOH \xrightarrow{(i)} CF_3CFHCF_2CH_2OH$$

$$CF_3CFHCF_2CH_2OH \xrightarrow{(ii)} CF_3CFHCF_2CO_2Na$$

$$CF_3CFHCF_2CO_2Na \xrightarrow{(iii)} CF_3CH=CF_2 + CO_2 + NaF$$

(i) benzoyl peroxide, 100°C, 5 hrs.

(ii) (a)- $K_2Cr_2O_7$/c. H_2SO_4, 80°C, 4 hrs.; (b)- NaOH aq.

(iii) Δ *ca.* 300°C.

2H-PFP may also be prepared by the following routes:

(a) $CF_3I + CF_2 = CH_2 \longrightarrow CF_3CH_2CF_2I \xrightarrow{KOH} CF_3CH = CF_2$[183]

(b) $(CF_3)_2CHCO_2K \xrightarrow{\Delta} CF_3CH = CF_2 + KF + CO_2$[184]

6.3 Some Known Reactions of 2H-Pentafluoropropene

The reaction of 2H-PFP with several nucleophiles has been reported.[185] Thus in moist TMS, 2H-PFP reacts with caesium fluoride to give 1,1,1,3,3,3-hexafluoropropane (87) *via* the carbanion (86):

$$CF_3\cdot CH{:}CF_2 \xrightarrow[TMS]{F^-} CF_3\text{-}\overline{C}H\text{-}CF_3 \xrightarrow{H_2O} CF_3CH_2CF_3$$

(86) (87)

The reaction of 2H-PFP with other nucleophiles is summarised below[185,186] (Equation 6.3):

$$nuc^- + CF_3CH{=}CF_2 \xrightarrow{ether} \underset{\text{(major)}}{\begin{matrix} CF_3 & & nuc \\ & C = C & \\ H & & F \end{matrix}} + \begin{matrix} CF_3 & & F \\ & C = C & \\ H & & nuc \end{matrix}$$

(nuc = NHR_2, SR^-, $HPMe_2$) (6.3)

Radical addition to 2H-PFP has also been investigated[187,188] and been found to be bidirectional; for example:

$$CF_3 + CF_3CH = CF_2 \begin{cases} \xrightarrow{} (CF_3)_2CH\text{-}\mathring{C}F_2 \xrightarrow{CF_3I} (CF_3)_2CHCF_2I \text{ (major)} \\ \xrightarrow{} CF_3\mathring{C}HCF_2CF_3 \xrightarrow{CF_3I} CF_3CHICF_2CF_3 \end{cases}$$

When 2H-PFP is treated with antimony pentafluoride, linear dimers are formed. The following mechanism has been proposed:[189]

$$CF_3CH{=}CF_2 \xrightarrow{SbF_5} \left[CF_2{=}{=}{=}\overset{+}{C}H{=}{=}{=}CF_2\right] \xrightarrow{CF_3CH=CF_2} CF_2{=}CHCF_2CH(CF_3)_2$$

The reaction of 2H-PFP with sulphur trioxide, yielding the β-sultone (88) has been reported.[184]

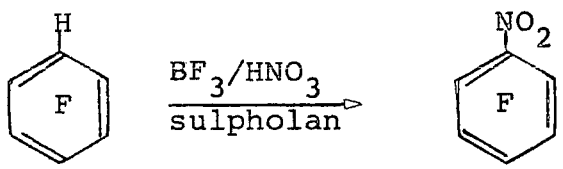
$$CF_3CH = CF_2 + SO_3 \longrightarrow CF_3CH\begin{cases} SO_2 \\ O \\ CF_2 \end{cases}$$

(88)

The polymerisation of 2H-PFP and its formation of copolymers with a number of fluorinated monomers has also been reported.[190]

6.4 Fluoride Ion-Induced Reaction of Pentafluoronitrobenzene with 2H-Pentafluoropropene

Pentafluoronitrobenzene (84) was first prepared from the reaction of pentafluorobenzene (89) with boron trifluoride and fuming nitric acid:[191]

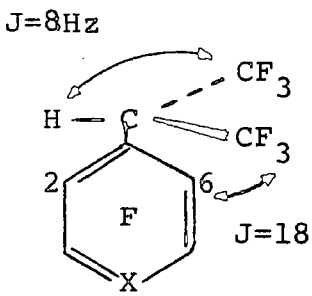


(89) (84)

The title reaction was carried out in an atmosphere of 2H-PFP with caesium fluoride as the source of F^- in tetraglyme at room temperature. The reaction afforded a complex mixture of products, separable only by careful gas chromotography, together with red-brown tar. Typically, total yields of 50-55% (excluding tar) were obtained; however, individual yields quoted for each product (isolated, pure, based on consumed olefin) are low due mainly to the repeated g.c.

necessary to effect complete separation. The products isolated from the title reaction, together with typical yields, are shown in Scheme 6.1.

The major product was perfluoro-1-nitro-4-(2H-hexafluoroisopropyl)benzene (90) as expected (Equation 6.2), presumably formed by the substitution of the *para*-fluorine in (84) by $\bar{C}H(CF_3)_2$. The ^{19}F n.m.r. spectra of (90) and of (85) (a minor product) illustrate the existence of restricted rotation of the $CH(CF_3)_2$ group; for example (91):



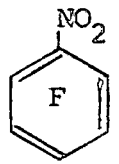
J=18-21 Hz (X = N=, ^{192} C-F, C-NO_2)

(91)

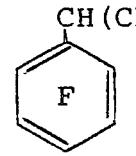
No oligomers of 2H-PFP were isolated from this reaction (although minor gaseous products were not identified) which is a contrast to the known reaction of hexafluoropropene under similar conditions, where appreciable oligomerisation takes place.[180]

However, a most unusual and unexpected product from the title reaction was perfluoro-3-methyl-2,1-benzisoxazole (92). The structure of this compound was determined principally by mass spectroscopy (M^+=259) and by its ^{19}F n.m.r., which showed the presence of one CF_3 group and four aromatic F-atoms (ABMX); assigned F-F coupling constants are shown below:

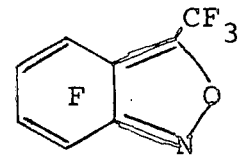
Scheme 6.1



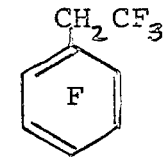
(84) + $CF_3CH=CF_2$ —CsF/tetraglyme, 25°C/14 hrs.→



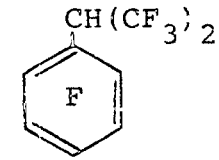
(90) (20%) +



(92) (14%) +

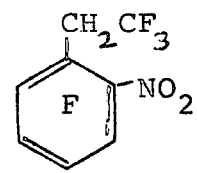


(93) (4%) +

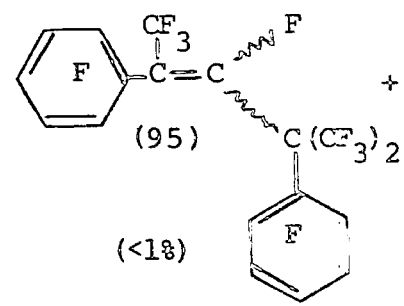


(85) (1%)

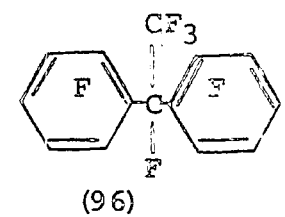
+



(94) (<1%)



(95) (<1%) +

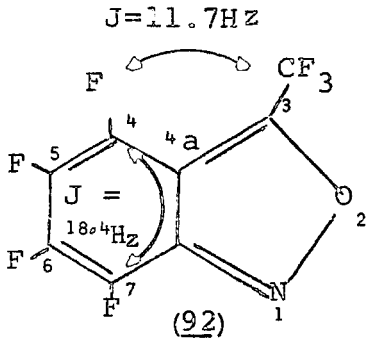


(96) (<1%)

+ unreacted (84) (17%) + $CF_3CH_2CF_3$ and other unidentified gaseous products

+ tar

+ other unidentified products.



(92)

J_{4-6} = 4.7 Hz

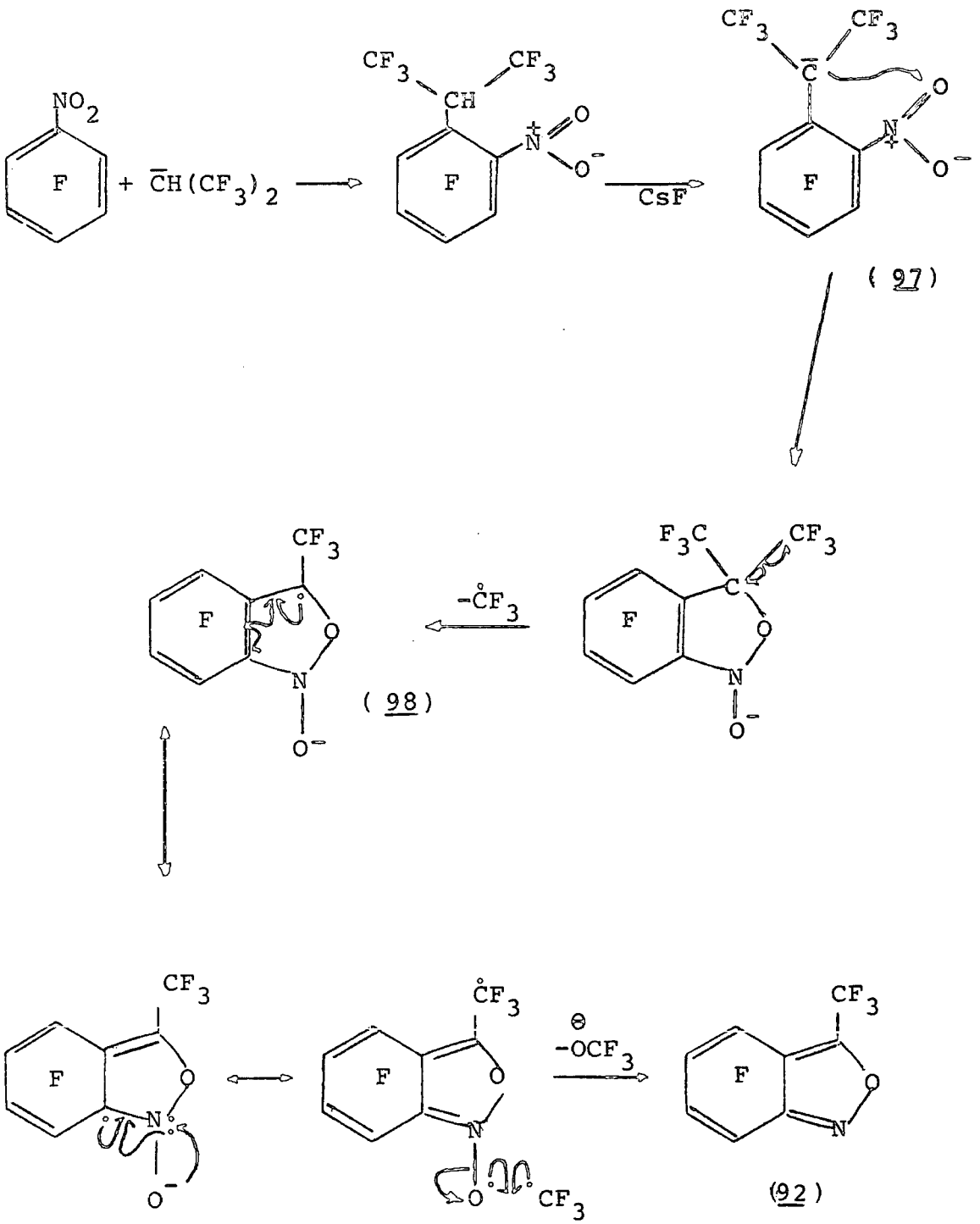
J_{5-7} = 4.5 Hz

Other couplings were visible but could not be unambiguously assigned. The structure of (92) was confirmed by its ^{13}C n.m.r., where four non-equivalent aromatic fluorine-bearing carbons, one CF_3 and an aromatic carbon adjacent to a nitrogen atom (C-7a) were observed; other assignments are shown in the Appendix. The UV spectrum of (92) showed three λ_{max} at 216 nm., 243 nm. (ε=4800) and 286 nm. (ε=1900).

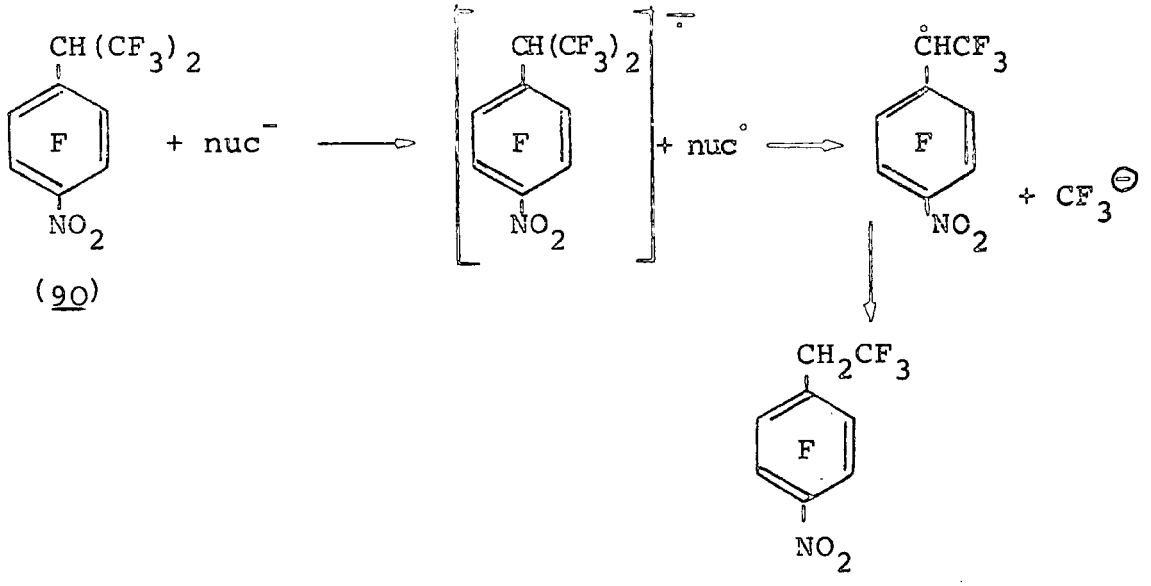
6.4.1 Mechanism for the Formation of Perfluoro-3-methyl-2,1-benzisoxazole

The nitro group is *ortho*- and *para*-directing in the nucleophilic aromatic substitution reactions of fluorocarbons. However, only *para*-perfluoronitro-(2H-hexafluoroisopropyl)benzene (90) was isolated from the title reaction (Scheme 6.1); *i.e.* no *ortho*-substituted derivative was detected. It therefore seems probable that the first step in the formation of (92) is attack of $\overline{C}H(CF_3)_2$ *ortho* to the NO_2 group in (84) as shown in Scheme 6.2. The acidic proton should easily be removed in the presence of caesium fluoride, forming the anion (97) which then cyclises and looses a $\mathring{C}F_3$ radical to form (98) which is resonance-stabilised as shown. Re-aromatisation of the isoxazole ring may then occur through elimination of trifluoromethoxide ion to form the product (92).

Scheme 6.2



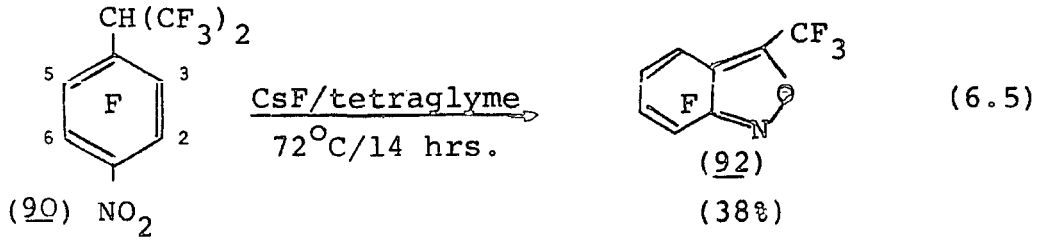
The formation of the minor adducts (93) and (94) (Scheme 6.1) may be explained by an electron-transfer process outlined below (Equation 6.4); a similar mechanism has been proposed for the substitution reactions of nitrobenzyl halides[193]:



(90) (93) (6.4)

6.4.2 Reaction of Perfluoro-1-Nitro-4-(2H-hexafluoroisopropyl)-benzene (90) with Caesium Fluoride

The aim of this experiment was to synthesise perfluoro(2H-hexafluoroisopropyl)benzene (85) by replacing the NO_2 group in (90) with F; the following was observed however (Equation 6.5):



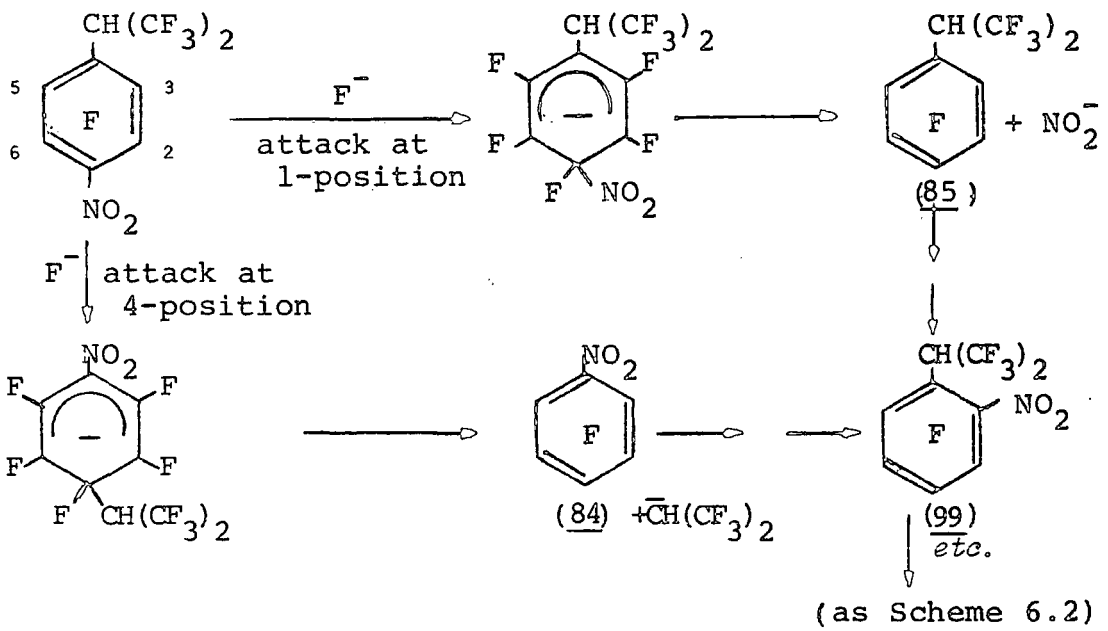
(90) (92) (38%) (6.5)

The structure of (90) was confirmed by observing the temperature dependence of the chemical shifts assigned to the 3- and 5-fluorine atoms. These signals became equivalent at about 120°C as the barrier to rotation of the $CH(CF_3)_2$ group decreased. This agrees with a previous study on some other

$CH(CF_3)_2$-substituted perfluoroaromatic systems,[192] and ruled out the possibility that (90) was the *ortho*-isomer.

The mechanism for this process may be explained in terms of an initial *ipso*-attack of fluoride ion at either the 1- or 4-positions in (90) (the reaction was carried out in a 4-fold molar excess of caesium fluoride) as shown in Scheme 6.3. Subsequent attack of the displaced group *ortho*

Scheme 6.3

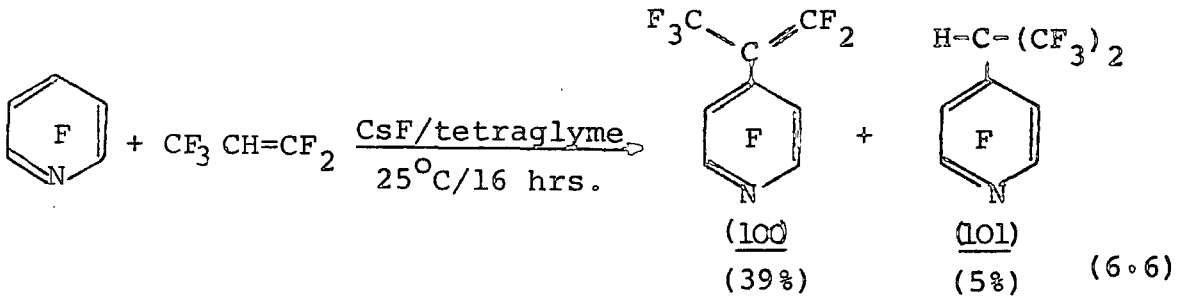


to the remaining substituent generates the intermediate (99) which then reacts according to Scheme 6.2. Small quantities of (85) were isolated from this reaction whereas no (84) was found, suggesting that displacement of the NO_2 group is the predominant process in the above Scheme.

6.5 Fluoride Ion-Induced Reaction of Pentafluoropyridine with 2H-Pentafluoropropene

This reaction was carried out under the same conditions discussed in Section 6.4. In addition to starting materials,

the products perfluoro-4-(prop-2-enyl)pyridine (100) and perfluoro-4-(2H-hexafluoroisopropyl)pyridine (101) were isolated (Equation 6.6). Typically, total recoveries of 75-85% were obtained; yields quoted refer to the isolated, pure compound after preparative-scale gas chromatography:

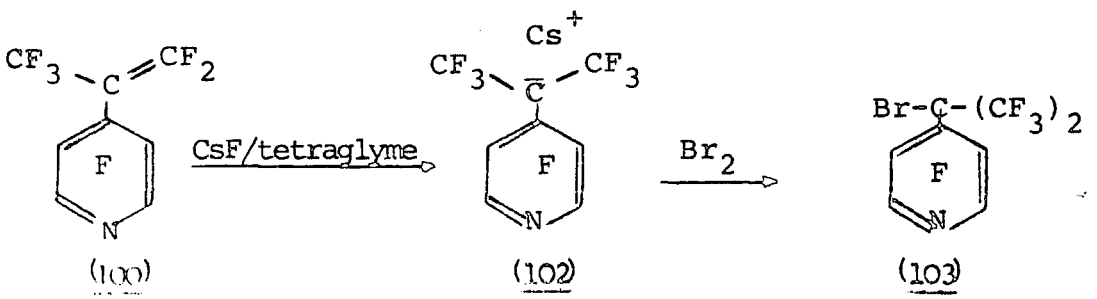


(100) (39%) (101) (5%) (6.6)

Compound (101) is formed by the nucleophilic attack of $\bar{C}H(CF_3)_2$ at the 4-position in pentafluoropyridine; subsequent elimination of HF from (101) gives the major product (100). Both compounds were identified from their ^{19}F n.m.r. spectra.[192,194]

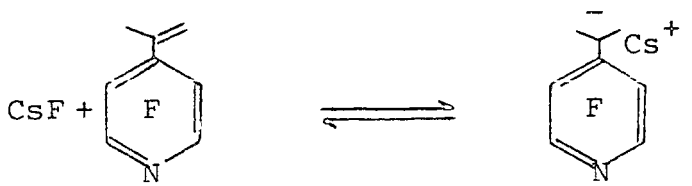
6.6 Reaction of Perfluoro-4-(prop-2-enyl)pyridine with Caesium Fluoride; Formation of a Stable Anion

Addition of dry caesium fluoride to a solution of (100) in dry tetraglyme under nitrogen resulted in the rapid formation of a strongly coloured homogeneous solution. This is due to the formation of an anion (102) which is directly observable by ^{19}F and ^{13}C n.m.r. and may be trapped with bromine giving the corresponding bromo-derivative (103):



(100) (102) (103)

The ^{19}F n.m.r. spectrum of (102) is characterised by the resonance corresponding to the CF_3 groups (adjacent to the charge centre) which occurs significantly downfield of the corresponding resonance in (100), (101) and (103). This is paralleled by the ^{13}C n.m.r. spectrum of (102). The fact that the ^{19}F n.m.r. spectrum of (102) remained effectively unchanged over a large temperature range (-40 to + 110°C) confirmed that the system was wholly in the form of the anion; there was no evidence for the presence of dimers or other systems. The anion is remarkably stable; the ^{19}F n.m.r. spectrum of (102) remained effectively unchanged over a period of weeks. Attempts to generate the anion using potassium fluoride in tetraglyme were generally less successful, resulting in incomplete conversion to the anion; addition of 18-crown-6-polyether improved this conversion somewhat. Generation of the anion in either sulpholan or acetonitrile with caesium fluoride resulted in a very broad ^{19}F n.m.r. spectrum in which peaks due to both (100) and (102) could be assigned. This observation is consistent with the occurrence of an exchange process in these solvents as shown by the following equilibrium (Equation 6.7):



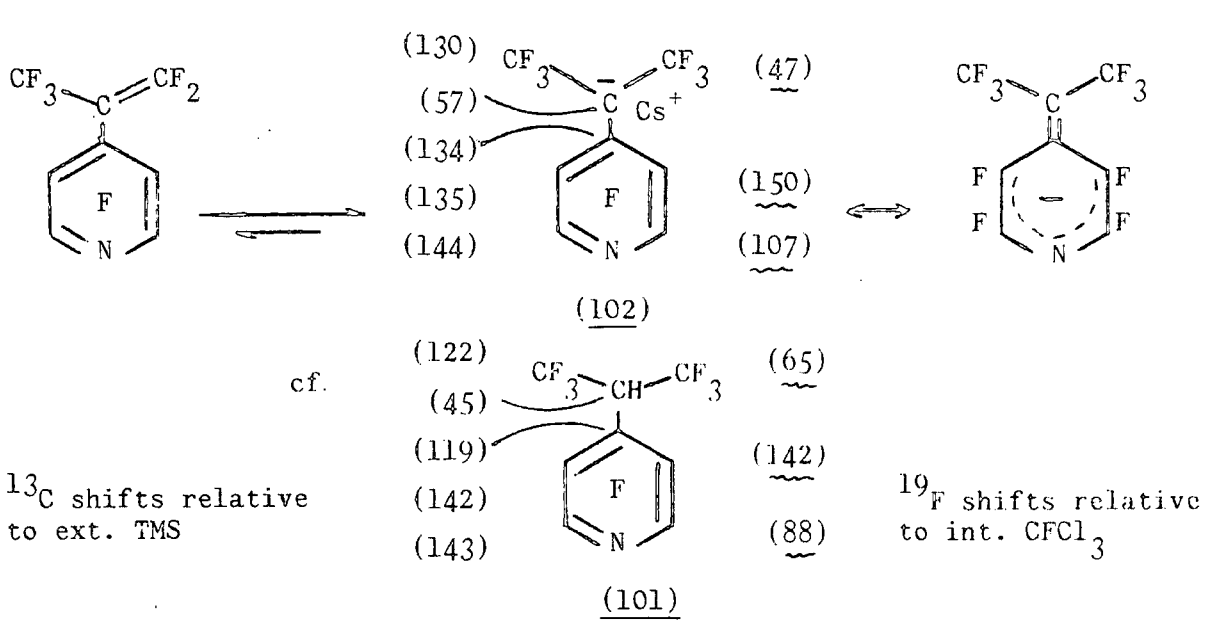
(100) (102) (6.7)

The generation of other carbanions by the addition of fluoride ion to a variety of fluoro-olefins has been discussed.[195]

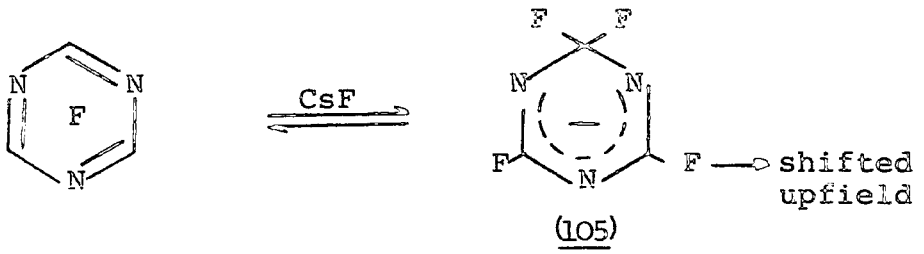
6.6.1 An Analysis of the ^{13}C and ^{19}F n.m.r. Spectra of the Anion (102)

It is well recognised that both the ^{13}C and ^{19}F chemical shifts reflect the π-electron density in a given system.[165,196,197] In Scheme 6.4, the ^{13}C and ^{19}F chemical shifts of the anion (102) are compared with those of a model compound, perfluoro-4-(2H-hexafluoroisopropyl)pyridine (101):

Scheme 6.4.



Direct correlations between the anion chemical shifts and local electron densities are difficult to make. However, from the above data it would appear that a considerable amount of charge is delocalised into the ring (104) as shown by the upfield ^{13}C, ^{19}F resonances at the 3,5-position in (102) compared to (101). Similarly, the ^{19}F resonance at the 2,6-position shows an upfield shift in (102) compared to (101). This may reflect the localisation of charge on the ring nitrogen, as a similar upfield shift has been observed in the σ-complex generated from trifluoro-1,3,5-triazine and caesium fluoride (105):[198]



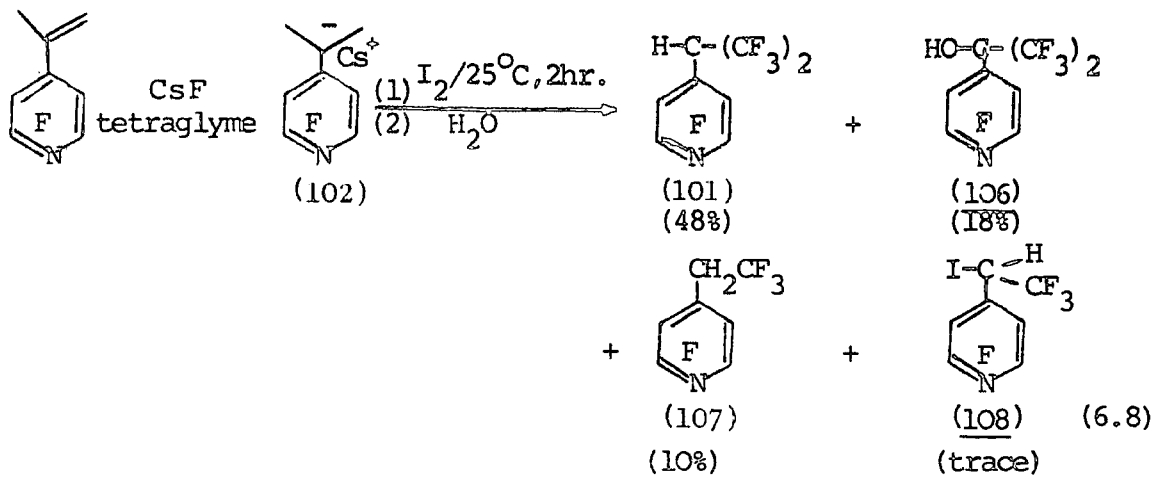
(105)

A feature of the ^{13}C and ^{19}F n.m.r. spectra of (102) is the marked downfield shift of the CF_3 resonances compared to the model system. This has been observed in a number of perfluorinated anions,[108,199] although an explanation for this effect is lacking.

Comparisons between the shifts corresponding to C-4 and $\overline{C}$ (closely associated with the Cs^+ counter ion) in (102) with the same shifts in (101) are of little value, since it is probable that a change in hybridisation takes place at these positions. Overall, however, and in the absence of other data, the chemical shifts quoted in Scheme 6.4 are consistent with a resonance stabilisation of the anion as represented by the canonical forms (102) ⟷ (104).

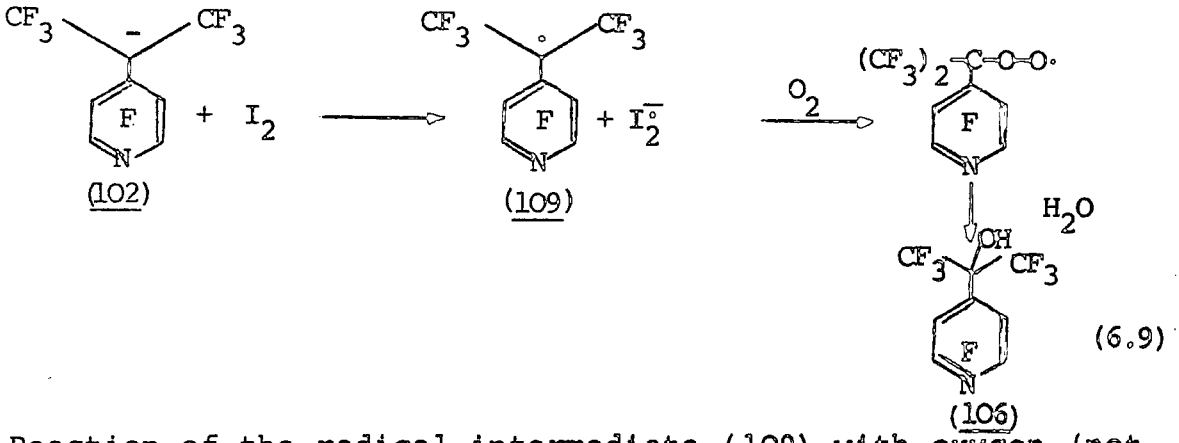
6.6.2 Trapping of the Anion (102) with Iodine

Addition of iodine to a stirred solution of (100) and caesium fluoride in tetraglyme, followed by quenching with water, caused the following reaction (Equation 6.8):



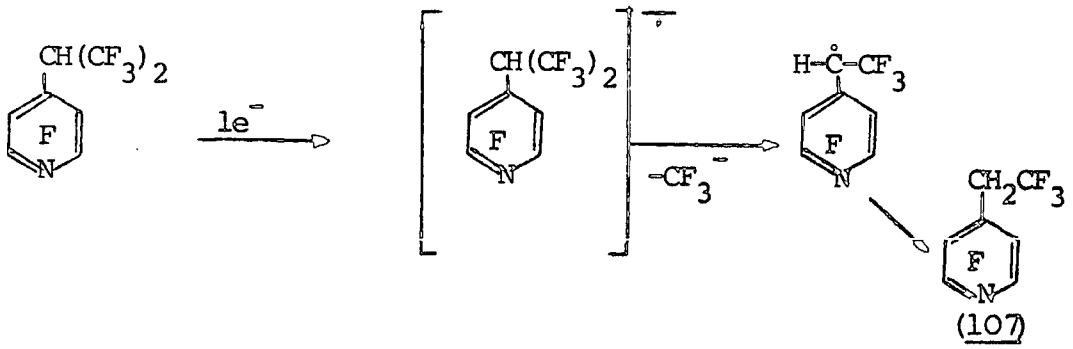
(6.8)

The major product from this reaction is perfluoro-4-(2H-hexafluoroisopropyl)pyridine (101), presumably formed by reaction of the anion (102) with water. The formation of perfluoro-4-(2-hydroxyhexafluoroisopropyl)pyridine (106) may be explained by an initial one-electron transfer from the anion (102) to iodine (Equation 6.9):



(6.9)

Reaction of the radical intermediate (109) with oxygen (not excluded from the reaction), followed by hydrolysis of the peroxide formed, would then yield the desired product (106). The formation of perfluoro-4-(2,2,2,-trifluoroethyl)pyridine (107) may be explained by a similar process to that shown in Equation 6.4:



In comparison to the trapping of (102) with bromine (where the expected bromo-derviative (103) is readily formed), the reaction of (102) with iodine gives markedly different products. Steric factors may be invoked to account for these observations.

CHAPTER SEVEN

NEGATIVE HYPERCONJUGATION IN SOME POLYFLUOROBENZENE DERIVATIVES

7.1 Introduction

The concept of carbon-fluorine hyperconjugation was first suggested as an important contributor to the electronic effect of perfluoroalkyl groups by Roberts *et al* in 1950.[200] This "negative hyperconjugation" has been defined[201] as the stabilising interaction between a filled carbanion lone pair orbital and a π^* (antibonding) C-X orbital (where X=F, CF_3). In resonance terms, a consequence of this interaction is the significant contribution of a "no-bond" structure in which charge is localised on fluorine;[202] an example is the β-fluoroethyl anion (110, 110a):

(110) (110a)

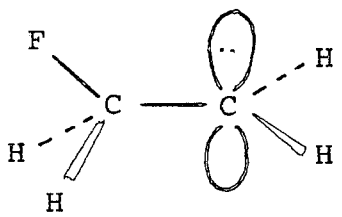
Recent molecular orbital (M.O.) calculations have argued that hyperconjugation involving the C-CF_3 bond may also be important.[203]

However, the general occurrence of negative hyperconjugation remains a controversial subject and it has been argued that inductive effects may equally well account for the observed effects.[204,205] The aim of the current investigation was to observe the effects of the CH_3, CH_2CF_3 $CH(CF_3)_2$ and $C(CF_3)_3$ groups on the reactivities of their perfluorobenzene derivatives and to determine whether there was any evidence for the occurrence of trifluoromethyl ion hyperconjugation.

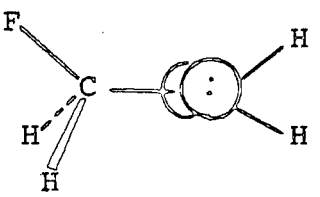
7.2 Recent Evidence For and Against the Occurrence of Negative Hyperconjugation

7.2.1 Aliphatic Systems

The β-fluoroethyl anion (110) has been studied using *ab initio* techniques. Both resonance and M.O. descriptions of negative hyperconjugation imply a dependence on the relative orientation of carbanion (2p) and C-F (σ^*) orbitals on the degree of stabilisation observed. This is reflected in the large calculated energy barriers to internal rotation in the β-fluoroethyl anion (E(110b) - E(110c)).[206]



(110b)



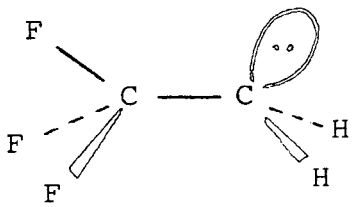
(110c)

Negative hyperconjugation (*i.e.* orbital overlap) is at a maximum in (110b) and zero in (110c) where the interacting orbitals are perpendicular. A similar model has also been used to account for the stereochemistry of nucleophilic vinylic substitution.[207] Energy barriers to internal rotation have also been found in the β-trifluoromethyl ethyl anion (111),[203] though these were not as large as in (110), which has been interpreted in terms of the poorer hyperconjugation of CF_3 compared to F in this system.

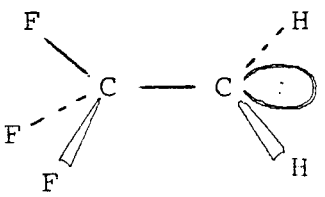
Streitwieser has also found barriers to internal rotation in $FCH_2\bar{C}H_2$ (110) and also in $CF_3\bar{C}H_2$ (112).[202] However these observations were accounted for by a Coulombic interaction between the carbanionic centre and the C-F bond dipole, resulting in a polarisation of the electrons surround-

ing the "hyperconjugating" fluorine atom. This polar effect was differentiated from hyperconjugation by the fact that charge transfer to fluorine was not found. This interpretation has been challenged by Schleyer *et al*, who argue[201] that as the definition of hyperconjugation involves orbital interactions, then both charge transfer and polarisation are possible consequences.

Recently, more sophisticated calculations on the trifluoroethyl anion (112) have shown much reduced barriers to internal rotation[201] (112a), 112b). However, changes in the geometry of (112a) (shorter C-C bond length and longer C-hyperconjugating F bond length) compared to the parent



(112a)



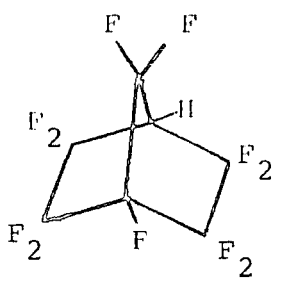
(112b)

compound (*i.e.* CF_3CH_3) were attributed[201] to the occurrence of negative hyperconjugation.

The significance of fluoride ion hyperconjugation has been investigated kinetically by the measurement of the relative rates of hydrogen-tritium exchange in tris-(trifluoromethyl)methane (113) and the bicyclic compound (114). Inductive stabilisation of the anions of (113) and (114)

$(CF_3)_3CH$

(113)



(114)

should be similar, so that enhanced reactivity of (113) (which in theory may have many resonance contributors) would indicate the occurrence of fluoride ion hyperconjugation. Stabilisation of the anion of (114) by this method is unlikely however (Bredt's Rule[208]) as the formation of a double bond at the bridgehead position is required. In basic conditions, both (113) and (114) have similar pKas.[209] In neutral conditions however, (113) was found to exchange more rapidly than (114) (which dehydrofluorinates in basic media) and so to the concept of fluoride ion hyperconjugation was again invoked.[210,211] It could be argued, however, that the difference in acidity between (113) and (114) is due to the greater number of β-fluorine atoms in (113) (inductive effect).

7.2.2 Aromatic Systems

Evidence for and against the occurrence of fluoride- and trifluoromethyl ion hyperconjugation in aromatic systems has been comprehensively reviewed.[204,205,212] The following is a summary of the more important points.

(i) Dipole Moment Measurements

Enhanced dipole moments in some para-CF_3 and para-$CF(CF_3)_2$-substituted anilines suggested the operation of fluoride and trifluoromethyl ion hyperconjugation.[200] However, similar enhancement was subsequently found in meta-substituted perfluoroalkyl anilines.[213] It was concluded that the effect observed was explicable by a π-inductive polarisation of the π-system by the perfluoroalkyl substituent.[213]

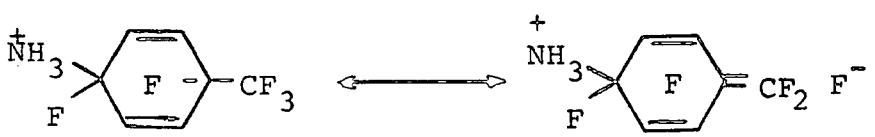
(ii) N.m.r. Measurements

The observation that the ^{19}F chemical shifts of some para-substituted monofluorobenzenes are solvent-dependent when the substituent is capable of resonance interaction with the para fluorine has been used as evidence for negative hyperconjugation. It has since been suggested however that dipolar interactions between the substituent and the π-system cause the observed effects.[215]

More recently, the ^{13}C n.m.r. spectra of a number of model benzyl fluoride systems have been reported.[216] The long range ($^5J_{C,F}$) coupling constants of these systems have been examined and it was suggested[216] that these parameters were primarily a manifestation of hyperconjugation of the C-F bond.

(iii) Studies of Chemical Reactivity

The rate constants for the attack by ammonia on a series of perfluoroalkyl-substituted benzene derivatives (where R_F = CF_3, CF_2CF_3, $CF(CF_3)_2$ and $C(CF_3)_3$) have been reported.[217] Stabilisation of the transition state for nucleophilic substitution by fluoride ion hyperconjugation (*e.g.* (115a), (115b)) should be at a maximum when R_F = CF_3 and should be reflected



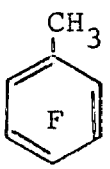
(115a) (115b)

in a decrease in the observed rate constant with successive replacement of F by CF_3. The series of compounds studied

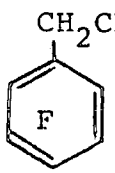
were found to be of comparable reactivity however and this was interpreted solely in terms of the (known[218]) similar inductive effects of the perfluoroalkyl substituents. The results may be reconciled in terms of negative hyperconjugation only if no-bond resonance involving the C-CF_3 and C-F bonds are equally as important. The Hammett σ_R^- constants (see Section 2.3) for the above perfluoroalkyl groups have also been calculated[218,219] and found to be comparable. If hyperconjugation is responsible for these apparent resonance effects, then again C-CF_3 no-bond resonance must be postulated.

7.3 Current Studies on Negative Hyperconjugation

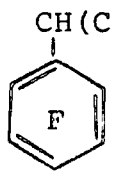
In the previous Section it was suggested that negative hyperconjugation involving the C-CF_3 bond may be an important factor affecting reactivity. This is a surprising result when it is considered that the acidity of HF is about 10^{30} times greater than that of HCF_3. The aim of the current study was to examine the substituent effect of the CF_3 group by successive replacement of the hydrogen atoms of the methyl group in pentafluorotoluene by CF_3 groups. This was to be achieved by determination of the rate constants for the nucleophilic substitution reactions of pentafluorotoluene (116), pentafluoro(2,2,2-trifluoroethyl)benzene (117), pentafluoro-(2H-hexafluoroisopropyl)benzene (85) and perfluoro-t-butyl benzene (118).



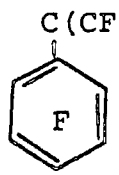
(116)



(117)



(85)



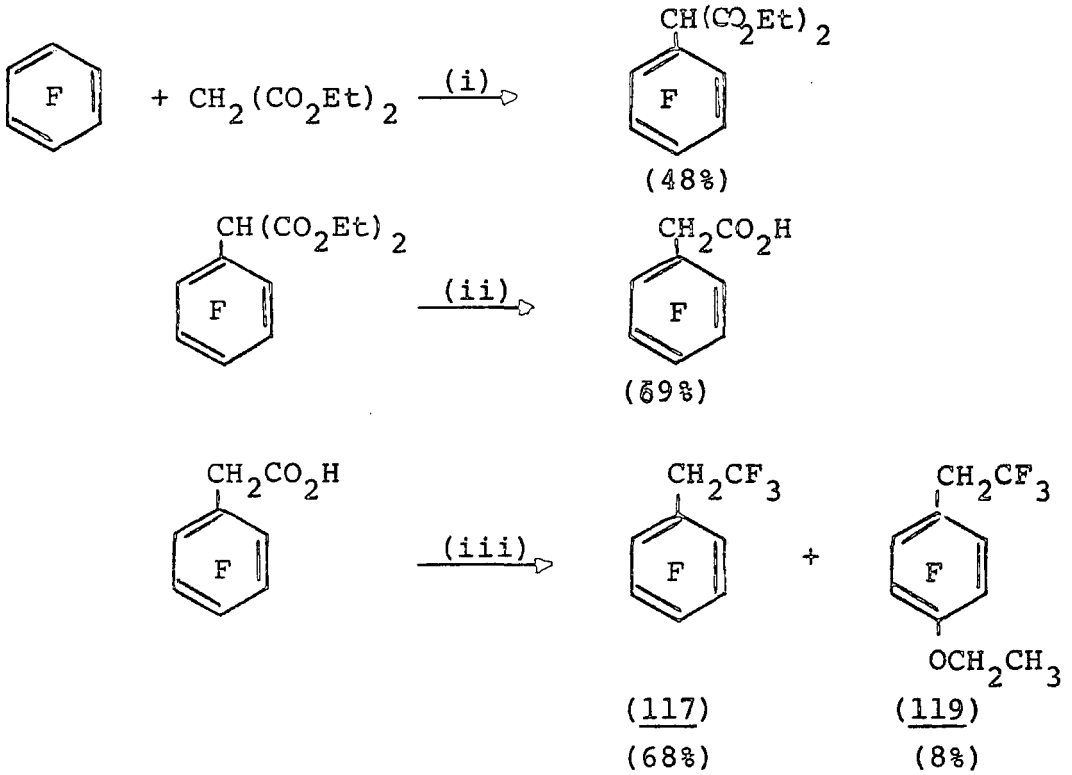
(118)

7.4 Preparation of Substrates

It was necessary to prepare pentafluoro-(2,2,2-trifluoroethyl)benzene (117) and pentafluoro-(2H-hexafluoroisopropyl)-benzene (85). Both pentafluorotoluene (116) and perfluoro-t-butylbenzene[226] (118) were provided and were purified before use as discussed in Section 12.1.

(a) Pentafluoro-(2,2,2-trifluoroethyl)benzene (117)

This was prepared *via* the following three-step procedure:



(i) NaH/DMF, Δ, 4-5 hrs.

(ii) (a) - c. NaOH, 100°C, 30 min.; (b) - c. HCl.

(iii) xs. SF_4, 170°C, 18 hrs.[221]

The isolation of 8% 1-ethoxy-4-(2,2,2-trifluoroethyl)tetrafluorobenzene (119) from step (iii) was attributed to the presence of a diethyl ether impurity in the reaction vessel.

(b) Pentafluoro-(2H-hexafluoroisopropyl)benzene (85)

This was isolated in very low yield from the fluoride-ion induced reaction of 2H-pentafluoropropene with penta-

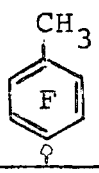
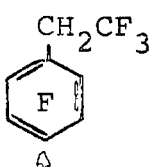
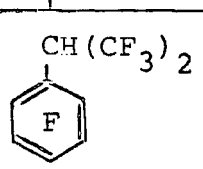
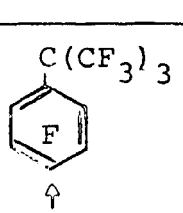
fluoronitrobenzene (84) as discussed in Sections 6.4 and 11.2.2.

7.5 Rate Measurements for the Reactions of Substrates with Sodium Methoxide

Rate measurements for all reactions discussed in this Chapter were carried out at 40.0°C with sodium methoxide as the nucleophile in methanol. Details of experimental methods and rate constant calculations are given in Section 12.2.

Rate constants for the reactions of the substrates with methoxide ion are shown in Table 7.1.

TABLE 7.1 Rate Constants for the Reaction of Sodium Methoxide with Some Pentafluorobenzene Derivatives in Methanol at 40.0°C.

Substrate (a)	Rate Constant, k_{II} ($l\ mol^{-1}\ s^{-1}$)
	$(1.12 \pm 0.03) \times 10^{-6}$
	$(3.95 \pm 0.04) \times 10^{-4}$
	(c) ———
	2.91 ± 0.1

(a) Position of substitution arrowed.

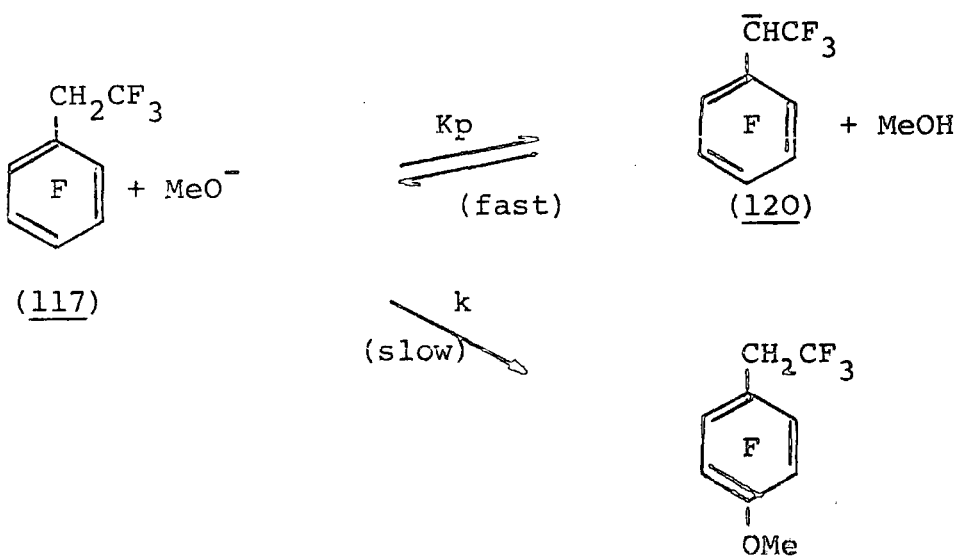
(b) Rate constant corrected for the basicity of sodium methoxide - see Section 12.2.a.

(c) No attack on ring.

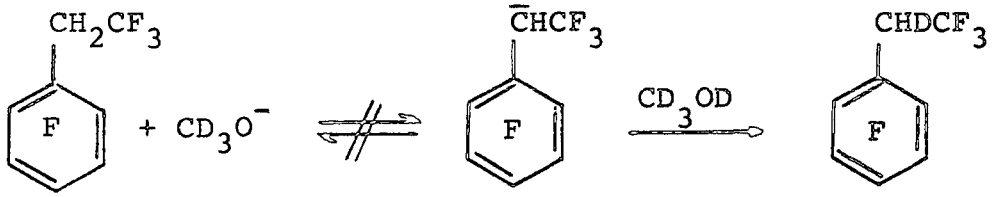
Under the experimental conditions used, exclusive nucleophilic attack *para* to the perfluoroalkyl substituent was observed in all cases except for the reaction of pentafluoro-(2H-hexafluoroisopropyl)benzene (85). This orientation has previously been observed for pentafluorotoluene (116)[170] and for perfluoro-t-butyl benzene (118) with ammonia as the nucleophile.[217] The observation of exclusive attack *para* to the substituent is explicable by the maximisation of the fluorine activating influences at this position (see Section 2.4.2). In the case of pentafluoro-(2H-hexafluoroisopropyl)-benzene (85), rapid loss of HF from the $-CH(CF_3)_2$ substituent occurred in preference to attack of methoxide ion on the aromatic ring.

The substitution product from the reaction of methoxide ions with pentafluoro-(2,2,2-trifluoroethyl)benzene (117) resulted from attack of the nucleophile *para* to the substituent. However, it was conceivable that the concentration of "free" substrate in this reaction may have been reduced by the setting up of the following equilibrium (Scheme 7.1):

Scheme 7.1



If pentafluoro(2,2,2-trifluoroethyl)benzene (117) is extensively ionised (*i.e.* if Kp is large) then the observed rate constant for the substitution process will be artificially low. The extent of ionisation was probed by attempting to trap (120) by reacting (117) with sodium d_3-methoxide/d_4-methanol (Equation 7.1).



(117) (120) (7.1)

However as no uptake of deuterium was observed it was concluded that pentafluoro-(2,2,2-trifluoroethyl)benzene (117) is essentially unionised under the experimental conditions used. This conclusion is supported by kinetic measurements, discussed in Section 12.3.

7.6 Interpretation of Rate Data

The rate constants quoted in Table 7.1 indicate that a marked increase in reactivity takes place upon successive replacement of H by CF_3 in these systems. This trend is also mirrored by the Hammett Substituent Parameters for the groups considered (Table 7.2). The magnitude of this effect may be gauged from comparisons between the rate constants quoted in Table 7.1. This is shown in Table 7.3.

TABLE 7.2 Substituent Parameters for Fluoroalkyl Groups

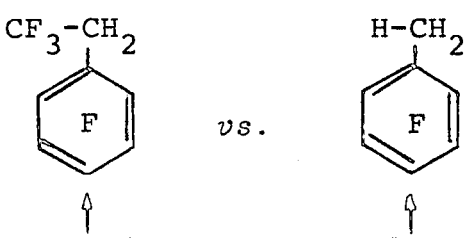
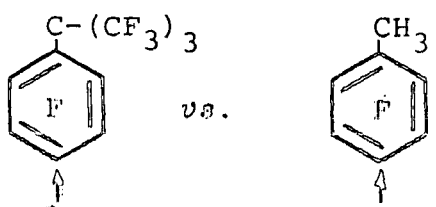
Substituent	σ_I (a)	σ_R^-
CH_3	-0.04	-0.11 b
CH_2CF_3	0.14	-0.04 b
$CH(CF_3)_2$	——	——
$C(CF_3)_3$	0.26	0.00 c 0.26 b

a. Ionisation of benzoic acid, 25°C. [113]

b. Ionisation of aniline, 25°C. [113]

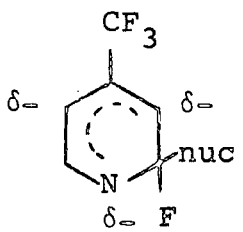
c. From ^{19}F n.m.r. studies. [219]

TABLE 7.3 Activating Influence of β-CF_3 Groups in Fluoroalkyl substituents in the Perfluorobenzene System

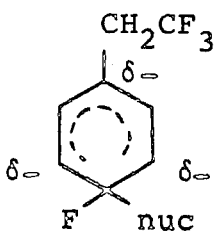
Comparison	k_{CF_3}/k_H
	*ca.* 350
	*ca.* 140 (a)

(a) $k_{CF_3}/k_H = \sqrt[3]{\frac{k_{II}\ (\underline{118})}{k_{II}\ (\underline{116})}}$ = 140 per CF_3 group.

Thus it can be seen that the activating effect of a β-CF_3 group in a fluoroalkyl substituent is quite substantial. The numerical values obtained for this effect may be compared with the "*meta*-effect" of the CF_3 group, determined earlier as described in Section 3.5.3; a value of *ca.* 350 was obtained. *Meta*-effects are primarily a measure of the ability of the substituent to stabilise the transition state (for which (121) is a model) by inductive means. Thus, if allowances are made



(121)



(122)

(all unmarked bonds to F)

for the differences between the two systems and the experimental conditions, the substituent effect of a β-CF_3 group determined in this study (Table 7.3) is seen to be very similar to the *meta*-effect of a CF_3 group. This observation suggests that the transition states for the series of substrates studied in this Chapter (*e.g.*, (122)) are stabilised primarily by inductive means.

The activating effect of each individual CF_3 group in perfluoro-t-butylbenzene (118) (assuming each group to have a similar effect) is seen to be rather less than the value obtained from pentafluoro-(2,2,2-trifluoroethyl)benzene (117) (Table 7.3). This may be explained in terms of a saturation effect as the number of CF_3 substituents is increased.

On first sight, the rate constants quoted in Table 7.1 appear to substantiate claims for the occurrence of CF_3^--ion hyperconjugation, as there is a substantial (>10^6 fold) increase in reactivity between pentafluorotoluene (116) and perfluoro-t-butylbenzene (118). However, the inductive effect of the CF_3 group is substantial (see Section 3.5.3) and so successive replacement of hydrogen in CH_3 by CF_3 groups will appreciably increase the inductive effect of the substituent group as a whole. Although the experimentally determined rate constants may be considered to follow equally well both σ_I and σ_R^- values quoted in Table 7.2, there is no need to invoke CF_3^--ion hyperconjugation as a possible mechanism for rate enhancement in these systems. The reactivity of the substrates under investigation may be explained simply in terms of the π- and σ-inductive effects of the fluoroalkyl substituents.

EXPERIMENTAL

Instrumentation

(i) Preparative Work

Infrared spectra were recorded on a Perkin-Elmer 457 Grating Infrared Spectrophotometer. Solid samples were recorded as KBr discs, liquid or low melting point solids as contact films between KBr plates and gaseous or low boiling point liquids in a cylindrical cell with KBr windows.

Proton (^{1}H) and fluorine (^{19}F) n.m.r. spectra were recorded on a Varian A56/60D spectrometer operating at 60 and 56.4 MHz respectively at the ambient probe temperature (40°C) and on a Brüker HK 90 with Fourier Transform facility at temperatures ranging from -40°C to +110°C. Chemical shifts are quoted in p.p.m. relative to TMS and $CFCl_3$. Carbon (^{13}C) n.m.r. spectra were recorded on a Brüker WH-360 instrument operating at 90.6 MHz; chemical shifts are quoted in p.p.m. relative to TMS.

Untraviolet spectra were recorded on a Pye-Unicam SP8-100 or Beckman Model 25 Spectrophotometer using acetonitrile, cyclohexane or methanol as the solvents.

Mass spectra were recorded on an A.E.I. M.S.9 Spectrometer or on a V.G. Micromass 12B Spectrometer fitted with a Pye 104 Gas Chromatograph.

Gas liquid chromatographic (g.l.c.) analyses were carried out on a Varian Aerograph Model 920 or Pye 104 Gas Chromatograph. Columns used were packed with 20% krytox (perfluoropolyoxypropylene) on chromosorb P (Column "K"), 20% diisodecylphthalate on chromosorb P (Column "A"), 20% polyethylene glycol (20M) on Celite (Column "Carbowax") and

30%, 10%, 5% and 1.5% silicone elastomer on Celite (Column "O"). Preparative scale g.l.c. was performed on a Varian Aerograph Model 920 using the above columns.

Fractional distillations of product mixtures were carried out using a Fischer-Spaltrohr MMM202 system.

Carbon, hydrogen and nitrogen analyses were obtained using a Perkin-Elmer 240 Elemental Analyser. Analysis for halogens were performed as described in the literature.[222]

Boiling points and melting points were determined at atmospheric pressure unless stated otherwise and are uncorrected.

(ii) Rate Measurements.

Thermostat baths were of conventional design. Temperature control was to ±0.01°C by contact thermometer, and heating achieved by thermostatted aquarium heaters. Thermometers standardised to ±0.02°C by the National Physics Laboratory were used for temperature measurement. The bath was filled with distilled water and was thermostated at 25.0° and 40.0°C.

When reaction rates were determined spectrophotometrically, absorbances were measured on a Pye Unicam SP8-100, a Beckman Model 25, or a Hi-Tech SF-3 Series Stopped-Flow Spectrophotometer, the cell compartments of which were thermostatted at 25°C.

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°C prior to use.

Ether or methylene chloride extracted solutions were dried over anhydrous magnesium sulphate and the solvent subsequently removed on a rotary evaporator.

Determination of Product Isomer Ratios

In a number of reactions two or more products were formed and the isomer ratios had to be accurately measured. Product mixtures were subjected to analytical g.l.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%. In the reaction of 2,6-dihydrohexafluoronaphthalene with methoxide ion, products were inseparable by g.l.c. In this case approximate isomer ratios were determined by ^{19}F n.m.r. integrations.

CHAPTER EIGHT

EXPERIMENTAL FOR CHAPTER THREE - ACTIVATING EFFECTS OF SUBSTITUENT GROUPS TO NUCLEOPHILIC SUBSTITUTION IN POLYFLUOROAROMATIC SYSTEMS

8.1 Preparation and Purification of Starting Materials

8.1.1 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 compound for its method of preparation.

(a) Pentafluoropyridine[223]

This was prepared by technical staff and was purified prior to use by preparative scale g.l.c. (Column 'A', 100°C).

(b) 4-Chlorotetrafluoropyridine (31)

This was obtained by a two-step preparation, the first stage being the synthesis of 4-hydrazinotetrafluoropyridine (30):

(i) Pentafluoropyridine (35.0g, 0.21 mole) was added dropwise to a stirred solution of hydrazine hydrate (25.0g, 0.5mole) in methanol (200 ml.). The solution was refluxed for 2 hrs., then poured into excess water (≈500 ml.) and ether extracted (4 x 50 ml.). The ethereal solution was washed several times with water and dried. Removal of the ether gave a buff-coloured solid shown to be 4-hydrazinotetrafluoropyridine (30) (33.9 g., 89%) by comparison of its i.r. spectrum with that of an authentic sample.[137] This was used without further treatment.

(ii) 4-Hydrazinotetrafluoropyridine (30) (16.0g, 0.088 mole) was added slowly to a stirred solution of copper (II) chloride (87.0g., 0.65 mole) in concentrated hydrochloric acid (600 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 colourless liquid product (11.0 g., 70%), which was shown to be 4-chlorotetrafluoropyridine (31) by comparison of its i.r. spectrum with an authentic sample.[137] Before use, this was purified by preparative scale g.l.c. (column 'O', 120°C).

(c) 4-Bromotetrafluoropyridine (32)

4-Hydrazinotetrafluoropyridine (30) (21.7 g., 0.12 mole) was added slowly to a stirred solution of copper(II) bromide (210 g., 0.94 mole) in 50% hydrobromic acid (580 ml.). The reaction was stirred at room temperature for 30 mins., then refluxed for 30 mins., after which time nitrogen had ceased to be evolved. The mixture was distilled and the organic layer separated from water in the distillate. The product was then worked up as described above to give a colourless liquid product (16.9 g., 61%). This was shown to be 4-bromotetrafluoropyridine (32), b.p. 137-139°C (lit.[138] 134-135°C), by comparison of its i.r. spectrum with that of an authentic sample. Before use, this was purified by preparative-scale g.l.c. (column 'O', 150°C).

(d) 4-Iodotetrafluoropyridine (33)

Sodium iodide (60.0 g., 0.4 mole), pentafluoropyridine (15.1 g., 89.4 mmoles) and dimethylformamide (15 ml.) were sealed in a 200 ml. Carius tube and heated, with agitation, at 130°C for 100 hrs. The violet-coloured product was extracted with 50:50 (v/v) ether-water (5x100 ml.). The ether extract was shaken with a saturated aqueous solution of sodium thiosulphate (50 ml.), then with water, dried ($MgSO_4$) and distilled, giving pentafluoropyridine (4.7 g., 31% recovery) and 4-iodotetrafluoropyridine (33) (7.8 g., 46% based on consumed pentafluoropyridine), b.p. 112°C/121 mm Hg (lit.[139] 84°C/40 mm Hg). This was purified before use by vacuum sublimation, m.p. 47-49°C (lit.[139] 47-48°C).

(e) 4-Cyanotetrafluoropyridine (34)

Sodium cyanide (2.5 g., 30 mmoles) was added slowly to a cold (0°C) stirred solution of pentafluoropyridine (10.0 g., 57.8 mmoles) in dimethylformamide (40 ml.). The resulting brown solution was stirred for 1 hr. at 0°C, then warmed to 25°C, treated with water (200 ml.) and extracted with ether (8x40 ml.). After drying ($MgSO_4$) the ether was driven off through a Vigreux column and the residue was distilled, giving pentafluoropyridine (2.1 g., 21% recovery) and a white solid (2.2 g., 27% based on consumed pentafluoropyridine). This was identified as 4-cyanotetrafluoropyridine (34) m.p. 66-68°C (lit.[140] 67°) b.p. 152-154°C (lit.[140] 154°/758 mm Hg).

(f) 4-Nitrotetrafluoropyridine (36)

This was a two-stage preparation, the first stage being the synthesis of 4-aminotetrafluoropyridine (35):

(i) Pentafluoropyridine (20.0 g., 0.118 mole), dioxan (25 ml.), and ammonia (40.0 ml.; 0.88 s.g.) were stirred under reflux for 2 hrs. On cooling, the organic layer became solid. Water (100 ml.) was added and the mixture ether extracted (4x50 ml.). After drying ($MgSO_4$) and removing the ether, a white solid remained (17.2 g., 88%) identified as 4-aminotetrafluoropyridine (35), m.p. 83-85°C (lit.[137] 85-86°C), by comparison of its i.r. spectrum with that of an authentic sample.[137] This was used without further treatment.

(ii) A mixture of methylene chloride (50 ml.), trifluoroacetic anhydride (14 ml.) and *ca.* 90% hydrogen peroxide (5 ml.) was stirred and heated under reflux for 15 mins.[224] A solution of 4-aminotetrafluoropyridine (35) (5.0 g., 30 mmoles) in methylene chloride (25 ml.) was then added to the refluxing solution; the mixture immediately became yellow and changed to bright green after 10 min. Hydrogen peroxide (2.5 ml.) was added after 20 mins. and again after 3 hrs., together with trifluoroacetic anhydride (2.5 ml.). After 10 hrs., the solution had become yellow. After a total reflux time of 24 hrs., water (150 ml.) was added. The methylene chloride layer was separated, washed several times with water and dried ($MgSO_4$). The solvent was driven off through a short Vigreux column, leaving an orange-coloured liquid. Distillation of the product (from P_2O_5) yielded pale yellow 4-nitrotetrafluoropyridine (36) (3.48 g., 57%) b.p. 99-102°C/140 mm Hg (Lit.[138] 154-156°C). This was purified before use by preparative-scale g.l.c. (column 'K', 110°C); the i.r. spectrum was identifical to an authentic specimen of the product.[138]

(g) Perfluoro-4-methylpyridine (38)

The first step in this two-stage synthesis was the preparation of tetrafluoropyridine-4-carboxylic acid (37):

(i) N-butyl lithium (19.6 mmoles) in hexane (13.5 ml.) was added (15 mins.) to a stirred solution of 4-bromotetrafluoropyridine (32) (4.5 g., 19.6 mmoles) in hexane (180 ml.) at -60°C and under an atmosphere of dry nitrogen. After 20 min. a dense white precipitate had formed. The temperature was maintained at -60°C whilst dry carbon dioxide was passed through the reaction mixture for 30 min. The mixture was then allowed to reach room temperature while the introduction of CO_2 continued. Water (100 ml.) was added, followed by dilute hydrochloric acid (20 ml. 36% HCl in 60 ml. H_2O). The mixture was then extracted with ether, dried ($MgSO_4$) and the solvent removed. A white solid (3.25 g., 85%) remained. This was vacuum sublimed, recrystallised (hexane) and identified as tetrafluoropyridine-4-carboxylic acid (37) m.p. 103-104°C (lit.[142] 102-103°C); the i.r. spectrum was identical with an authentic sample of the acid.[142]

(ii) Tetrafluoropyridine-4-carboxylic acid (37) (5.0 g., 25.6 mmoles) and sulphur tetrafluoride (18.0 g., 0.167 mole) were heated in a steel autoclave at 230°C for 24 hrs. The product consisted of one major component by g.l.c. and was purified by preparative scale g.l.c. (column 'K', 90°C) giving a colourless oil (2.8 g., 50%). This was identified as perfluoro-4-methylpyridine (38), b.p. 98-100°C (lit[144] 102-103°C) the ^{19}F n.m.r. spectrum of this compound was in agreement with the literature.[225]

(h) 3-Cyanotetrafluoropyridine (41)

3-Cyanotetrachloropyridine (39) (20.0 g., 82.6 mmoles), anhydrous potassium fluoride (30.0 g., 0.52 mole) and sulpholan (80 ml.) were stirred together at 220° for 7 days in a 250 ml. r.b. flask fitted with a reflux condenser and a calcium chloride drying tube. The crude product was removed under reduced pressure and shown by g.l.c. (column 'K', 150°C) to consist of two components. The major component (12.0 g., 74%) was identified as 3-chloro-5-cyanotrifluoropyridine (40) from its ^{19}F n.m.r. spectrum (authentic sample provided by I.C.I. Organics Division) and was not investigated further. The minor component, a colourless liquid (2.5 g., 17%), was identified as 3-cyanotetrafluoropyridine (41), b.p. 111-112°C/130 mm Hg. [Found: C, 40.87; F, 43.02; N, 15.61%: calculated for $C_6F_4N_2$; C, 40.9; F, 43.2; N, 15.9%]. N.m.r. spectrum No.1. I.r. spectrum No.1. Mass spectrum No.1.

(i) 2-Cyanotetrafluoropyridine (43)

The same technique was employed as in the previous preparation. 2-Cyanotetrachloropyridine (42) (17.0 g., 70.2 mmoles), anhydrous potassium fluoride (30.0g., 0.52 mole) and sulpholan (80 ml.) were stirred together at 150°C for 64 hrs. The product was removed under reduced pressure and shown by g.l.c. (column 'K', 150°C) to consist of one major component. This was distilled under reduced pressure to give 2-cyanotetrafluoropyridine (43) (8.0 g., 64.7%), a colourless liquid, b.p. 127-128°C/228 mm Hg (lit.[226] 97°C/64 mm Hg.). The ^{19}F n.m.r. spectrum of this compound was in agreement with the literature.[226]

(j) 2,4,6-Trichlorodifluoropyridine (44)[146]

This was prepared by technical staff and was purified prior to use by vacuum sublimation, m.p. 38-39°C (lit.[146] 38-39°C).

(k) 4-Hydrotetrafluorpyridine (45)

To a cold (-72°C), stirred solution of pentafluoropyridine (20.0g., 0.118 mole) in ether (100 ml.) and under an atmosphere of dry nitrogen was added (over 1 hr.) a suspension of lithium aluminium hydride (3.70 g., 97.4 mmoles) in ether (200 ml.). On completion of the addition, the reaction mixture was stirred at -72°C for a further hr. and then at room temperature for 42 hrs. Water (50 ml.) was then cautiously added to the reaction mixture, the ether layer was decanted and the aqueous layer ether extracted (2x25 ml.). The combined extracts were dried ($MgSO_4$), and the ether removed (Vigreux column). The crude product consisted of only one major component by g.l.c. (column 'K', 110°C). This was fractionated, yielding 4-Hydrotetrafluoropyridine (45) (11.4 g., 64%), a colourless liquid, b.p. 100-100.5°C (lit.[147] 102°C), identified by its ^{19}F n.m.r. spectrum.

(l) 2-Cyanotetrachloropyridine (42) and 3-cyanotetrachloropyridine (39)[145]

These were provided by I.C.I. Organics Division and were purified by vacuum sublimation before use.

(m) 1,2-Dicyanotetrafluorobenzene[227]

This was prepared by technical staff and was purified by vacuum sublimation before use, m.p. 87-88°C (lit.[227] 86-88°C).

8.1.2 Solvents

(a) Dioxan

The method adopted was that of Vogel.[228] 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 then left standing over fresh potassium hydroxide pellets for a further 20 hrs. The dioxan was refluxed with excess sodium metal 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°C was collected. The dioxan was stored under dry nitrogen under sodium wire in the dark.

(b) Water

Distilled water was used and its neutrality checked prior to use by universal indicator.

8.1.3 Ammonia

Analytical grade ammonia was used without further treatment.

8.2 Methods of Rate Measurements

(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, when the reaction was very slow (*e.g.* the reaction of 4-bromotetrafluoropyridine (32)) stock solutions of triple these concentrations were used.

Dioxan (60 ml.) and water (40 ml.) were pipetted into a stoppered conical flask and immersed in the thermostat bath (25.0°C). Then 5 ml. of stock ammonia solution was added and the contents of the flask mixed. Two 5 ml. aliquots of the solution were removed separately, quenched with distilled water (50 ml.) and titrated against standard hydrochloric acid (usually *ca.* 0.025 M, accurately known) 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; from this, the initial ammonia concentration was found.

The reaction was initiated by the addition of 5 ml. substrate solution, having been thermostatted at 25.0°C, to the reaction vessel; the resulting solution was thus a 60/40 (v/v) dioxan/water mixture. The reaction was followed, usually up to 75% of total reaction, by periodically quenching 5 ml. aliquots of the reaction solution in 50 ml. distilled water and titrating the residual ammonia with standard hydrochloric acid using methyl red as indicator. Infinity titres were taken after at least 10 half lives; in some cases the reaction was too slow for the infinity value to be measured.

The titrating acid was prepared by diluting commercial 0.1 M hydrochloric acid and standardising the resulting solution against standard borax ($Na_2B_4O_7.10H_2O$) solutions.

Second order rate constants were obtained as outlined in Section 3.3.

(b) Spectrophotometric Method

This method was used to follow the reaction of 3-cyano-tetrafluoropyridine (41). Comparison of the u.v. spectra of the starting material and the product showed that a wavelength of 290 nm gave the greatest range of optical density throughout the reaction (appearance of product).

Stock solutions of ammonia in water (7.97×10^{-3} moles ℓ^{-1}) and substrate in dioxan (*ca.* 10^{-4} moles ℓ^{-1}) 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°C thermostat bath, water from which passed through the cell compartment of the spectrophotometer (Pye Unicam SP8-100) which was used for absorbance measurements. 1.20 ml. of 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 (v/v) dioxan/water. The cell was immediately stoppered, shaken, and placed in the spectrophotometer. 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 every 30 secs. and the reaction was 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. First and second order rate constants were then calculated as described in Section 3.3.

8.3 Product Identifications

Unless otherwise stated, reaction products were isolated by pouring the remaining reaction solution, after completion of the kinetic measurements into excess water (100 ml.) and ether extracting (4x10 ml.). The combined ethereal solutions were washed with water and dried; removal of the ether left the product. Reaction products were usually identified from their ^{19}F n.m.r. spectra.

Each crude product was carefully examined by g.l.c. in order to determine the number of components present. In many of the reactions studied only one product was formed; however, in a few cases, attack occurred at two or more places in the molecule, giving rise to a product mixture. In these cases, isomer ratios were determined according to the Instrumentation Section and Section 3.3.

8.3.1 Reactions of Substrates with Ammonia in 60/40 Dioxan/Water

(a) With Pentafluoropyridine

The crude solid product was shown to consist of one component (apart from remaining solvent) by g.l.c. (column 'O', 220°C). This was shown to be 4-aminotetrafluoropyridine (35) by comparison of its i.r. spectrum with that of an authentic sample.

(b) With 4-Chlorotetrafluoropyridine (31)

The crude solid product was shown to consist of one component by g.l.c. (column 'O', 220°C). This was shown to be 2-amino-4-chlorotrifluoropyridine by comparison of its ^{19}F n.m.r. spectrum with that in the literature.[138]

(c) With 4-Bromotetrafluoropyridine (32)

A Carius tube containing 4-bromotetrafluoropyridine (32) (12.0 g., 52.2 mmoles) and aqueous ammonia (30.0 ml., 0.88 s.g.) was heated at 110°C for 1½ hrs.; on cooling, the organic layer became solid. Water was added to the mixture which was extracted with ether (3x50 ml.). Removal of the dried ether afforded an orange solid (9.3 g., 78.5%) which was recrystallised from pet. ether (40-60°)-benzene to give 2-amino-4-bromo-trifluoropyridine, m.p. 113-116°C (lit.[138] 116-117°C). The ^{19}F n.m.r. spectrum of the product was identical to that given in the literature.[138]

(d) With 4-Iodotetrafluoropyridine (33)

A Carius tube containing 4-iodotetrafluoropyridine (33) (0.91 g., 3.28 mmoles) and aqueous ammonia (12.0 ml., 0.88 s.g.) was heated at 110°C for 24 hrs. Water was added to the mixture which was extracted with ether (4x40 m l.), dried and evaporated. The solid product (0.63 g.) was shown by g.l.c. (column 'K', 200°C) to consist of one component in addition to unreacted starting material. This was identified as 2-amino-4-iodotrifluoropyridine by comparison of its ^{19}F n.m.r. spectrum with the literature value.[139] This compound was not isolated in the pure state.

(e) With 4-Cyanotetrafluoropyridine (34)

The crude, solid product was shown to be a mixture of two components in the ratio of 75.6:24.4 by g.l.c. integration (gas density balance, column 'O', 200°C). The ^{19}F n.m.r. spectrum of the product showed each component to have three fluorine atoms. The major component exhibited one downfield peak assignable to a fluorine atom *ortho* to ring nitrogen and two other peaks to high field; this is consistent with the major component being 2-amino-4-cyanotrifluoropyridine. The minor component exhibited two downfield peaks assignable to a fluorine atom *ortho* to ring nitrogen and one other peak to high field; this is consistent with the minor product being 3-amino-4-cyanotrifluoropyridine. A pure sample of each component was not obtained. However, the elemental analysis of the mixture, after vacuum sublimation, was consistent with the product being composed of two isomers. [Found: C, 41.48; H, 1.25; F, 32.44% $C_6H_2F_3N_3$ requires C, 41.6; H, 1.16; F, 32.9%]. Rate constants were calculated from the observed g.l.c. integrations.

N.m.r. spectra of 2-amino-4-cyanotrifluoropyridine (No.2) and 3-amino-4-cyanotrifluoropyridine (No.3) were obtained from that of the mixture. I.r. spectrum No.2.

(f) With 4-Nitrotetrafluoropyridine (36)

The crude, solid product was shown to be a mixture of three components in the molar ratio of 58.1:25.4:16.5 by g.l.c. integration (gas density balance, column 'K', 150°C). By comparison of the ^{19}F n.m.r. spectrum of the crude product with literature values from an earlier study of this reaction,[141]

the components were identified as 2-amino-4-nitrotrifluoropyridine, 4-aminotetrafluoropyridine (35) and 3-amino-4-nitrotrifluoropyridine respectively.

(g) With Perfluoro-4-methylpyridine (38)

The crude product was found to consist of one component in addition to starting material by gas chromatographic analysis (column 'K', 200°C). The ^{19}F n.m.r. spectrum of the adduct showed it to have one CF_3 group and three aromatic fluorine atoms, one of which was downfield and assignable to a fluorine atom *ortho* to ring nitrogen; the remaining ring fluorines were to high field. This is consistent with the product being 2-aminoperfluoro-4-methylpyridine, n.m.r. spectrum No.4. A pure sample of this compound was not obtained.

(h) With 3-Cyanotetrafluoropyridine (41)

3-Cyanotetrafluoropyridine (41) (0.82 g., 4.66 mmoles), aqueous ammonia (ml., 12 mmoles), dioxan (60 ml.) and water (32 ml.) were placed in a stoppered conical flask and allowed to react at 25°C for 25 mins. The resulting solution was poured onto water (50 ml.) and ether extracted (4x20 ml.). The combined ethereal solutions were washed with water and dried; removal of ether left a solid product (0.68 g., 84%). The crude product was found to consist of two components in the ratio of 65.6:34.4 by g.l.c. (gas density balance, column "carbowax", 160°C). The ^{19}F n.m.r. spectrum of the product showed each component to have three fluorine atoms. The major component exhibited two downfield peaks assignable to fluorine atoms *ortho* to ring nitrogen; this is consistent with

the major component being 4-amino-3-cyanotrifluoropyridine. The minor component exhibited one downfield peak and two high field peaks, consistent with it being 6-amino-3-cyano-trifluoropyridine. A pure sample of each component was not obtained. However elemental analysis of the vacuum-sublimed mixture was consistent with the product being composed of two isomers. [Found: C, 41.44; N, 24.10; F, 32.66%. $C_6H_2F_3N_3$ requires C, 41.6; N, 24.3; F, 32.9%]. Rate constants were calculated from the observed g.l.c. integrations.

N.m.r. spectra of 4-amino-3-cyanotrifluoropyridine (No.5) and 6-amino-3-cyanotrifluoropyridine (No.6) were obtained from that of the mixture. I.r. spectrum No.3.

(i) With 2-Cyanotetrafluorpyridine (43)

The crude product was found to consist of one component by g.l.c. analysis (column 'carbowax', 160°C). The ^{19}F n.m.r. spectrum of the product showed three fluorine atoms, one of which was downfield and assignable to a fluorine atom *ortho* to ring nitrogen. The remaining upfield shifts were assigned to fluorine atoms at the 3- and 5-positions, consistent with the product being 4-amino-2-cyanotrifluoropyridine. N.m.r. spectrum No.7. I.r. spectrum No.4. This compound was not obtained in the pure state.

(j) With 2,4,6-Trichlorodifluoropyridine (44)

2,4,6-Trichlorodifluoropyridine (44) (1.64g., 7.5 mmoles), aqueous ammonia (30 ml., 0.88 s.g.), dioxan (30 ml.) and water (20 ml.) were sealed in a Carius tube and heated at about 80°C for 3 weeks. The solution was poured into excess

water (50 ml.) and ether extracted (3x30 ml.). The combined ethereal solutions were washed with water and dried. Removal of the ether left a solid product (1.09 g., 73%). This was shown to be 4-amino-2,6-dichlorodifluoropyridine by comparison of its ^{19}F n.m.r. spectrum with an authentic sample.[153]

(k) With 4-Hydrotetrafluoropyridine (45)

4-Hydrotetrafluoropyridine (45) (3.0 g., 19.9 mmoles), aqueous ammonia (30 ml., 0.88 s.g.), dioxan (30 ml.) and water (20 ml.) were sealed in a Carius tube and heated at about 80°C for 3 weeks. The solution was poured into excess water (50 ml.) and ether extracted (4x50 ml.). The combined dried extracts were evaporated, leaving a white residue (2.46 g., 83%). This was identified as 2-amino-4-hydrotrifluoropyridine by comparison of its ^{19}F n.m.r. spectrum with that given in the literature.[229]

(l) With 1,2-Dicyanotetrafluorobenzene

The crude, solid product was found to consist of one component by g.l.c. analysis (column 'carbowax', 200°C). This was identified as 4-amino-1,2-dicyanotrifluorobenzene by comparison of its ^{19}F n.m.r. spectrum with that given in the literature.[230]

CHAPTER NINE

EXPERIMENTAL FOR CHAPTER FOUR - THE NATURE OF THE *ORTHO* EFFECT

9.1 Preparation and Purification of Starting Materials

9.1.1 Substrates

(a) 2H-Tetrafluoropyridine (52)

This was obtained from 4-chlorotetrafluoropyridine (31) *via* a three-step preparation:

(i) 4-Chlorotetrafluoropyridine (31) (7.2g., 38.8 mmoles) was added dropwise to a stirred solution of hydrazine hydrate (4.5 g., 90.0 mmoles) in ethanol (100 ml.). The solution was stirred at room temperature for 3 hrs. and then poured onto excess water (250 ml.) and ether extracted (5x30 ml.). The ethereal solution was washed with water and dried ($MgSO_4$); removal of the ether gave a buff-coloured solid shown to be 4-chloro-2-hydrazinotrifluoropyridine (7.0 g., 99%) by comparison of its i.r. spectrum with that of an authentic sample.[131] This was used without further treatment.

(ii) 4-Chloro-2-hydrazinotrifluoropyridine (6.2 g., 31.4 mmoles) was suspended in water (50 ml.) and a saturated solution of copper (II) sulphate (40 g. in 20 ml. water) added dropwise. The mixture was stirred at room temperature for 2 hrs., after which time the evolution of nitrogen was complete. The product was then steam distilled, 150 ml. of distillate being collected. This was extracted with ether (5x30 ml.); removal of the dry solvent left a crude product which was fractionated, giving 4-chloro-2-hydrotrifluoropyridine (2.7g., 51%), b.p. 125-126°C.

(iii) 4-Chloro-2-hydrotrifluoropyridine (2.5 g., 14.9 mmoles) was added to dry caesium fluoride (10.0g., 65.8 mmoles) in dry sulpholan (25 ml.) and the mixture stirred at 100°C for 6 hrs. The crude product was transferred under reduced pressure and shown to consist of one main component by g.l.c. (column 'O', 100°C). This was purified by preparative scale g.l.c. (column 'O', 130°C) giving a colourless liquid (1.70 g., 76%), identified as 2H-tetrafluoropyridine (52) by comparison of its ^{19}F n.m.r. spectrum with the literature value.[131]

(b) 3H-tetrafluoropyridine (27)[142]

This was prepared by technical staff and was purified by preparative scale g.l.c. before use (column 'O', 120°C).

(c) 4H-trifluoropyrimidine (54)

(i) Lithium aluminium hydride (2.42 g., 63.7 mmoles) in sodium-dried ether (200 ml.) was added during 1 hr. to a cold (-72°C), stirred solution of tetrafluoropyrimidine (20.90 g., 137.5 mmoles) in dry ether. The mixture was stirred at -72°C for 1 hr., allowed to warm to 20°C during 1 hr., then stirred at 20°C for 10 hrs. Water (50 ml.) was added cautiously to the product and the clear, orange-coloured, ether layer was removed. After removal of the dry ($MgSO_4$) ether the product (11.93 g.) was shown by g.l.c. to be a mixture of several components. This was separated by preparative scale g.l.c. (Column 'A', 100°C) to yield tetrafluoropyrimidine (6.59 g., 31.5% recovery), 4H-trifluoropyrimidine (54) (2.43 g., 19% based on tetrafluoropyrimidine consumed) and 4,6-dihydrodifluoropyrimidine (0.72 g., 7.3% based on tetrafluoropyrimidine consumed).

(ii) Attempted Preparation of (54) *via* 4-Hydrazino-trifluoropyrimidine

Tetrafluoropyrimidine (5.0 g., 32.9 mmoles) was added dropwise during 1 hr. to a cold (-5°C) stirred solution of hydrazine hydrate (1.65 g., 33.0 mmoles) in ethanol (35 ml.). The mixture was stirred at -5°C for 1 hr. and then poured onto water/ice (50 ml.) and extracted with ether (4x25 ml.). The combined extracts were dried, leaving a pale orange solid (4.65 g., 85%). Repeated recrystallisations from petroleum ether (b.p. 60-80°) gave N,N'-(bis-4,4'-perfluoropyrimidino) hydrazine (53) as pale yellow crystals, m.p.167-168°C(d). [Found: C, 32.43; N, 28.50 ; H, 0.36 ; F, 38.96 %. $C_8H_2F_6N_6$ requires C, 32.4; N, 28.4; H, 0.7; F, 38.5%]. N.m.r. spectrum No.8. I.r. spectrum No.5. Mass spectrum No.2.

(d) 5H-trifluoropyrimidine (55)[156]

This was prepared by technical staff and was purified before use by preparative scale g.l.c. (column 'O', 110°C).

(e) Pentafluoropyridine [223]

Provided; purified as described earlier (Section 8.1.1).

(f) Tetrafluoropyrimidine[157]

Provided in a pure state and not further treated.

9.1.2 Solvents and Reagents

(a) Reactions with Ammonia

Dioxan was purified as described earlier (Section 8.1.2). Distilled water and reagent grade ammonia were used.

(b) Reactions with Methoxide Ion

(i) Methanol

AnalaR grade, used as supplied.

(ii) Sodium Methoxide

Freshly cut pieces of sodium metal were cleaned in diethyl ether and methanol, weighed in sodium-dried diethyl ether and dissolved in AnalaR methanol under dry nitrogen. The resulting solution was centrifuged to remove any solid particles formed. Samples of the solution (usually around 0.75 moles ℓ^{-1}) were stored under dry nitrogen and were diluted with AnalaR methanol before use.

9.2 Methods of Rate Measurement

9.2.1 Reactions with Ammonia

Followed by the spectrophotometric method as described in Section 8.2.b. Comparison of the u.v. spectra of the starting materials and respective products showed that the wavelengths 272 nm (4H-trifluoropyrimidine (54)) and 265 nm (5H-trifluoropyrimidine (55)) gave a large range of optical density throughout the reaction. Stock solutions of ammonia in water (6.92×10^{-3} moles ℓ^{-1} for reaction with 4H-trifluoropyrimidine (54); 10.31×10^{-3} moles ℓ^{-1} for reaction with 5H-trifluoropyrimidine (55)) and substrate in dioxan (*ca.* 3×10^{-4} moles ℓ^{-1}) were prepared. First and second order rate constants were calculated as described in Section 3.3.

9.2.2 Reactions of Sodium Methoxide

(a) With Polyfluoropyridines

Followed spectrophotometrically as described earlier (Section 8.2.b). The wavelengths 221nm (pentafluoropyridine) and 220nm (3H-tetrafluoropyridine (27) and 2H-tetrafluoropyridine (52)) were used to monitor the progress of the reaction. Stock solutions of sodium methoxide in methanol (9.98×10^{-3} moles ℓ^{-1}) and substrate in methanol (*ca.* 4×10^{-4} moles ℓ^{-1}) were prepared. First and second order rate constants were calculated as discussed above.

(b) With Polyfluoropyrimidines

These reactions were extremely rapid and were followed by the stopped-flow technique. This method is a fixed-wavelength technique and has been described.[231]

The wavelengths 260nm (tetrafluoropyrimidine), 270nm (4H-trifluoropyrimidine (54)) and 250nm (5H-trifluoropyrimidine (55)) were used to follow the reactions. Stock solutions of sodium methoxide in methanol (6.79×10^{-3} moles ℓ^{-1} for reaction with 4H-trifluoropyrimidine (54); 9.64×10^{-3} moles ℓ^{-1} for reaction with tetrafluoropyrimidine and 5H-trifluoropyrimidine (55)) and substrate in methanol (*ca.* 4×10^{-4} moles ℓ^{-1}) were prepared.

Kinetic runs were carried out on a Canterbury Model SF-3L instrument, with the cell thermostated at 25.0°C. The stock solutions were stored in two, properly flushed, syringes. The syringes had a shared piston mechanism, so that samples leaving each syringe were of equal volume and flow rate before mixing. Mixed samples then passed into the cell of the instrument where

the absorbance of the solution was measured at the desired (fixed) wavelength. The absorbance was displayed, as a function of time, as a voltage (V) on an oscilloscope. First order rate constants were then calculated from the slope of a plot of ln (V_∞ - V_t) against time. The slopes and intercepts of all linear correlations were calculated *via* the principle of least squares. Duplicate kinetic runs (generally in good agreement) were repeated at least ten times and the mean value taken as the observed rate constant.

9.3 Product Identifications

9.3.1 Reactions of Ammonia in 60/40 (v/v) Dioxan/Water

(a) With Tetrafluoropyrimidine

Tetrafluoropyrimidine (2.56 g., 16.8 mmoles) was added to a stirred mixture of ammonia (1 ml., 0.88 s.g.), dioxan (24 ml.) and water (15 ml.) in a flask at room temperature. After stirring for 5 minutes, the solution was poured onto ice/water (100 ml.) and ether extracted (4x30 ml.). Removal of the dried ($MgSO_4$) ether gave a solid product (1.83 g., 73%) identified as 4-aminotrifluoropyrimidine from its ^{19}F n.m.r. spectrum.[157]

(b) With 4H-trifluoropyrimidine (54)

4H-trifluoropyrimidine (54) (0.1 g., 0.75 mmoles), dioxan (0.3 ml.) and aqueous ammonia (0.25 ml., 0.75 mmoles) were shaken in an n.m.r. tube and set aside for 1 hr. at room temperature. A white precipitate was produced; this was dissolved with a minimum amount of d_6-acetone. The ^{19}F n.m.r.

spectrum of the resulting solution showed the presence of only two fluorine atoms in the product, one of which was at low field and was assignable to a fluorine atom *ortho* to two ring nitrogens. The remaining peak was at high field and was assigned to fluorine at C-5. This is consistent with the product being 6-amino-2,5-difluoropyrimidine. N.m.r. spectrum No.9.

(c) With 5H-trifluoropyrimidine (55)

5H-trifluoropyrimidine (55) (0.52 g., 3.88 mmoles) was added to a mixture of aqueous ammonia (3.0 ml., 4.5 mmoles), dioxan (60 ml.) and water (37 ml.) in a conical flask thermostatted at 25.0°C. The reaction was allowed to proceed for 5 mins., after which time excess water (150 ml.) was added and the solution extracted with ether (4x50 ml.). Working up the ethereal layer as usual gave a solid product (0.30 g., 59%). This was shown to be a mixture of two components in the ratio of 74.1:25.9 by g.l.c. (gas density balance, column 'O', 200°C). The ^{19}F n.m.r. spectrum of the crude product showed each component to have two fluorine atoms. The major component was subsequently identified as 2-amino-4,6-difluoropyrimidine from a comparison of the ^{19}F n.m.r. spectrum of the mixture with the literature values obtained in an earlier study of this reaction.[158] Similarly,[158] the minor component was identified as 4-amino-2,6-difluoropyrimidine.

9.3.2 Reactions of Sodium Methoxide in Methanol

(a) With Pentafluoropyridine

Pentafluoropyridine (0.1 g., 0.59 mmoles) and sodium methoxide/methanol solution (0.8 ml., 0.75 M, 0.6 mmoles) were

shaken in an n.m.r. tube at room temperature. The ^{19}F n.m.r. spectrum of the product showed two fluorine resonances of equal intensity; this is consistent with the product being 4-methoxytetrafluoropyridine.[232]

(b) With 2H-tetrafluorcpyridine (52)

2H-tetrafluoropyridine (52) (0.1 g., 0.66 mmoles) and sodium methoxide/methanol solution (1 ml., 0.75 M, 0.75 mmoles) were shaken in an n.m.r. tube at room temperature. The ^{19}F n.m.r. spectrum of the product contained three fluorine resonances of equal intensity, one of which occurred downfield (*i.e. ortho* to ring nitrogen). This is consistent with the product being 4-methoxy-2,3,5-trifluoropyridine, in agreement with an earlier study of this reaction.[119]

(c) With 3H-tetrafluoropyridine (27)

3H-tetrafluoropyridine (0.36 g., 2.38 mmoles) in methanol (15 ml.) was added to a sodium methoxide/methanol solution (10 ml., 0.75 M, 7.5 mmoles) in methanol (75 ml.) in a conical flask thermostatted at 25.0°C. The reaction was allowed to proceed for 25 mins., after which time excess water (150 ml.) was added. The crude liquid product, isolated by ether extraction in the usual manner, was shown by g.l.c. (gas density balance, column 'O', 200°C) to contain, in addition to unremoved solvent, two components in the ratio 95.3:4.7. The ^{19}F n.m.r. spectrum of the major product (obtained from that of the mixture) showed two downfield peaks assignable to fluorine *ortho* to the ring nitrogen; this is consistent with the compound being 4-methoxy-2,5,6-trifluoropyridine, in agreement with an earlier report of this reaction.[119] Similarly,[119]

the ^{19}F n.m.r. spectrum of the minor component was consistent with it being 2-methoxy-3,4,6-trifluoropyridine.

(d) With Tetrafluoropyrimidine

Sodium methoxide/methanol solution (0.75 M) was added dropwise to a solution of tetrafluoropyrimidine (0.14 g., 0.92 mmoles) in methanol (1 ml.) in an n.m.r. tube at room temperature. After *ca.* 50% reaction of the substrate, the ^{19}F n.m.r. spectrum of the product showed the presence of one other component in addition to starting material. This was identified as 4-methoxy trifluoropyrimidine by comparison of its n.m.r. spectrum with that obtained from a previous study of this reaction.[157]

(e) With 4H-trifluoropyrimidine (54)

Sodium methoxide/methanol solution (0.75 M) was added to 4H-trifluoropyrimidine (54) (0.1 g., 0.75 mmoles) as described above. The ^{19}F n.m.r. spectrum of the product (after *ca.* 50% reaction) showed, in addition to starting material, the presence of two fluorine atoms in the methoxylated adduct. One resonance was found at low field and was assignable to a fluorine atom *ortho* to two ring nitrogens. The remaining peak was at high field and was assigned to a fluorine atom at C-5. Thus the product was identified as 6-methoxy-2,5-difluoropyrimidine. N.m.r. spectrum No. 10.

(f) With 5H-trifluoropyrimidine (55)

5H-trifluoropyrimidine (55) (0.72 g., 6.37 mmoles) in methanol (100 ml.) was thermostatted in a conical flask at 25.0°C. Sodium methoxide/methanol solution (5 ml., 0.75 M, 3.75 mmoles) was then added. After 30 secs. the reaction was quenched with

excess water (150 ml.) and extracted with methylene chloride (4x50 ml.). Working up the methylene chloride layer in the usual manner gave an oily liquid product (0.43 g., 55%). This was shown by g.l.c. (gas density balance, column 'O', 150°C) to contain, in addition to starting material and solvent, two other components in the ratio 64.2:35.8. The ^{19}F n.m.r. spectrum of the crude mixture showed that each adduct contained two fluorine atoms. The major product was identified as 4-methoxy-2,6-difluoropyrimidine by comparison of its ^{19}F n.m.r. spectrum with that given in the literature.[159] Similarly,[158] the minor product was identified as 2-methoxy-4,6-difluoropyrimidine.

CHAPTER TEN

EXPERIMENTAL FOR CHAPTER FIVE - NUCLEOPHILIC SUBSTITUTION IN THE POLYFLUORONAPHTHALENE SYSTEM

10.1 Preparation and Purification of Starting Materials

10.1.1 Substrates

(a) Octafluoronaphthalene (68)

The commercial product was purified by vacuum sublimation, m.p.88.5-89.5°C (lit.[168] 87-88°C).

(b) 2H-heptafluoronaphthalene (70)

The first step in the synthesis of this compound was the preparation of 2-hydrazinoheptafluoronaphthalene (69):

(i) Octafluoronaphthalene (68) (20.0 g., 73.5 mmoles) was dissolved in ethanol (100 ml.) and the solution warmed to reflux with stirring. Hydrazine hydrate (5.0 g., 0.1 mole) was then added and the mixture refluxed for 4 hrs. The mixture was then poured onto water (200 ml.) and extracted with methylene chloride (6x50 ml.). The extract was dried ($MgSO_4$), filtered and evaporated, to leave a buff-coloured solid (17.5g., 94%). This was identified as 2-hydrazinoheptafluoronaphthalene (69) and was used without further treatment.

(ii) 2-Hydrazinoheptafluoronaphthalene (69) (12.50 g., 44.0 mmoles) and Fehling's solution (500 ml. each of solutions 'A' and 'B') were refluxed together for 45 mins., during which time a red precipitate was formed. The product was steam distilled, filtered and vacuum sublimed giving a white crystalline solid (7.76 g., 69%). This was recrystallised from petroleum ether

(b.p. 60-80°) and vacuum sublimed again, giving 2H-heptafluoronaphthalene (70), m.p. 62-63°C (lit.[168] 63-64.5°C).

(c) 1,2-Dihydrohexafluoronaphthalene (71)

Cleaned sodium metal (0.90 g., 82.6 mmoles) was dissolved in AnalaR methanol (100 ml.). 2-Hydrazinoheptafluoronaphthalene (69) (6.0 g., 21.1 mmoles) was then added and the mixture stirred at room temperature for 1 hr., after which time nitrogen had ceased to be evolved. The mixture was then poured onto excess water (150 ml.) and ether extracted (4x50 ml.). After drying the combined extracts and removing the ether, a dark red oil (5.8 g.) remained. This was transferred under vacuum and then distilled, giving 1,2-dihydrohexafluoronaphthalene (71), a colourless low-melting solid (3.20 g., 64%), m.p. *ca.* 19°C, b.p. 124°C/40mm Hg.

(d) 2,6-Dihydrohexafluoronaphthalene (72)

Lithium aluminium hydride (3.42 g., 90.0 mmoles) in dry THF (125 ml.) was added dropwise during 2 hrs. to a stirred solution of octafluoronaphthalene (20.0g., 73.5 mmoles) in dry THF (50 ml.) under nitrogen. The reaction was then stirred at 76°C for 44 hrs. After cooling, water (200 ml.) was cautiously added and the mixture ether extracted (8 x 50 ml.). After removing the dried ($MgSO_4$) solvent and subliming the residue under vacuum a white solid (16.52 g.) was obtained. This was shown by g.l.c. (column "carbowax", 200°C) to be a mixture of one major and several minor components. The major component could only be separated by lengthy, repeated, preparative scale g.l.c. (column "O", 220°C), under which conditions the product had a retention time of *ca.* 45 mins. The separated major product was sublimed under reduced pressure,

giving 2,6-dihydrohexafluoronaphthalene (72) (6.38 g., 37%) as white crystals, m.p. 72-73°C. [Found: C, 50.56; H, 1.02; F, 48.52%. Calculated for $C_{10}H_2F_6$: C, 50.8; H, 0.85; F, 48.3%]. The ^{19}F n.m.r. spectrum of (72) (No.11) is characterised by its symmetrical AA'MM'XX' structure. I.r. spectrum No.6. Mass spectrum No. 3.

10.1.2 Solvents and Reagents

Sodium methoxide/methanol was prepared as described earlier (Section 9.1.2 (b)). AnalaR methanol was used.

10.2 Method of Rate Measurements

Stock solutions of sodium methoxide in methanol (*ca.* 0.75 moles ℓ^{-1}) and substrate in methanol (*ca.* 1.5 moles ℓ^{-1}) were prepared. The high substrate concentration was necessary if disubstitution by methoxide ion was to be avoided during each run. Methanol (100 ml.) and stock sodium methoxide/methanol (5 ml.) were pipetted into a stoppered conical flask, thermostatted at 25.0°C. After mixing, two 5 ml. aliquots were removed and titrated separately against standardised hydrochloric acid using methyl red as indicator; from this the initial methoxide ion concentration was found.

The reaction was initiated and followed in the usual way, as described in Section 8.2 (a). Rate constants were calculated from Equation 10.1:

$$k = \frac{1}{t} \cdot \frac{1}{a-b} \cdot \ln \left(\frac{b}{a} \frac{(a-x)}{(b-x)} \right) \qquad (10.1)$$

where,

a = initial concentration of substrate

b = initial concentration of nucleophile

x = concentration of nucleophile reacted at time t.

10.3 Identification of Products

(a) From Octafluoronaphthalene (68)

After completion of the kinetic run, the remaining reaction mixture was poured into excess water (150 ml.) and ether extracted (4x50 ml.). After removal of the dried ($MgSO_4$) solvent a solid product remained which was analysed by g.l.c. (column 'K', 205°C) and shown to consist of one other component in addition to unreacted starting material and solvent. This was identified as 2-methoxyheptafluoronaphthalene by its ^{19}F n.m.r. spectrum (which agreed with that given in the literature[170]) and by its mass spectrum (M^+=284).

(b) From 2H-heptafluoronaphthalene (70)

The reaction product was isolated in the usual manner. The crude product was found to contain one component in addition to unreacted starting material and solvent by g.l.c. (column 'K', 200°C). This was identified as 6-methoxy-1,3,4,5,7,8-hexafluoronaphthalene by comparison of its ^{19}F n.m.r. spectrum with that in the literature[170] and by its mass spectrum (M^+=266).

(c) From 2,6-Dihydrohexafluoronaphthalene (72)

2,6-Dihydrohexafluoronaphthalene (72) (1.50 g., 6.35 mmoles), methanol (5 ml.) and sodium methoxide/methanol (9 ml., 0.75 M, 6.75 mmoles) were sealed in a Carius tube and heated at 72°C for 19 hrs. The tube was then cooled, opened and the contents poured onto water (150 ml.) and ether extracted (4x50 ml.). After drying, removing the solvent left a white solid (1.63 g.). This was analysed by g.l.c. (column 'O', 180°C) and appeared to consist of one compound in addition to unreacted starting material and solvent. This was separated by preparative scale g.l.c. (column 'O', 240°C) and purified by small scale column chromatography (hexane eluant). However, analysis of this product by ^{19}F n.m.r. showed it to be a 75:25 mixture of two isomers. The major component was identified as 2-methoxy-1,4,5,6,8-pentafluoronaphthalene (73) (n.m.r. spectrum No.12), as discussed in Section 5.4. Similarly, the minor component was identified as 1-methoxy-3,4,5,7,8-pentafluoronaphthalene (74) (n.m.r. spectrum No.13).

It was not possible to obtain pure samples of each compound for chacterisation, but elemental analysis of the mixture was consistent with it being composed of isomers. [Found: C, 53.02; H, 1.79; F, 38.05%. Calculated for $C_{11}H_5F_5O$ C, 53.2; H, 2.0; F, 38.3%]. I.r. spectrum No.7. Mass spectrum No. 4.

(d) From 1,2-Dihydrohexafluoronaphthalene (71)

The crude product was found to consist of one component, apart from unreacted starting material and solvent, by chromatographic analysis (column 'K', 200°C). This was identified as 6-methoxy-3,4,5,7,8-pentafluoronaphthalene by comparison of its ^{19}F n.m.r. spectrum with that in the literature[170] and by its mass spectrum (M^+=248).

CHAPTER ELEVEN

EXPERIMENTAL FOR CHAPTER SIX - SOME REACTIONS OF 2H-PENTAFLUOROPROPENE

11.1 Preparation and Purification of Starting Materials

11.1.1 Substrates

(a) Pentafluoronitrobenzene (84)

Boron trifluoride was bubbled through a mixture of sulpholan (40 ml.) and fuming nitric acid (95%, 15 ml.) at 0°C until a saturated solution was formed (*ca.* 90 mins.). Pentafluorobenzene (89) (30.0 g., 0.179 mole) was added and the mixture stirred at 60-70°C for 2 hrs. During this time a homogeneous yellow-coloured solution was formed; this was poured onto ice/water (*ca.* 500 ml.) and steam distilled. The organic distillate was decanted and the aqueous layer extracted with methylene chloride (2x30 ml.). The combined extracts and organic layer were dried; removal of the methylene chloride (Vigreux column) and fractional distillation of the residue gave pentafluoronitrobenzene (84) (32.8 g., 86%), b.p. 114-114.5°C/142 mm Hg (lit.[191] 158-161°C).

(b) 2H-Pentafluoropropene

(i) 2,2,3,4,4,4-Hexafluorobutan-1-ol

Hexafluoropropene (83) (49.3 g., 0.329 mole), degassed AnalaR methanol (50.0 g., 1.56 mole) and benzoylperoxide (1.60 g., 6.61 mmole) were charged into a steel autoclave (165 ml. capacity) and heated at 100°C for 4½ hrs. After cooling, unreacted hexafluoropropene (83) (10.7 g., 71.3 mmoles) was removed, leaving a liquid product. This was fractionated,

giving 2,2,3,4,4,4-hexafluorobutan-1-ol (46.4 g., 99%), a colourless liquid, b.p. 113-114°C (lit.[182] 114-115°C).

(ii) Sodium 2,2,3,4,4,4-hexafluorobutanoate

2,2,3,4,4,4-Hexafluorobutan-1-ol (40.0 g., 0.22 mole) was added dropwise to a stirred solution of potassium dichromate (82.0 g., 0.279 mole) and concentrated sulphur acid (175 g.) in water (125 ml.) at 80°C. The reaction was stirred for 4 hrs. and then allowed to cool. An orange coloured organic layer separated, which was decanted. The aqueous layer was ether extracted (8x100 ml.) and the combined extracts and organic layer dried. Removal of the ether and fractional distillation of the product gave 2,2,3,4,4,4-hexafluorobutanoic acid (34.5 g., 73%), b.p. 142-144°C (lit.[182] 143-144°C). The acid (34.5 g., 0.176 mole) was then added to a solution of sodium hydroxide (7.05 g., 0.176 mole) in water (125 ml.). Evaporation of the water left sodium-2,2,3,4,4,4-hexafluorobutanoate (38.4 g., 100%), dried on a vacuum line.

(iii) 2H-Pentafluoropentene

Anhydrous sodium 2,2,3,4,4,4-hexafluorobutanoate (38.4 g., 0.176 mole) was deposited in a horizontal tubular glass vessel and slowly pyrolised with a bunsen flame. Gaseous products were first bubbled through a 20% sodium hydroxide solution and then collected in two cold traps (-40°C), connected in turn to a heavy white oil bubbler. The crude product (20.0 g.) was purified by trap-to-trap distillation and the fraction boiling between -20° and -23°C was collected. The product (17.0 g., 73%) was identified as 2H-pentafluoropropene, b.p. -21°C,[182] by comparison of its i.r. spectrum with an authentic sample. N.m.r. spectrum No.14.

(c) Hexafluoropropene (83) and Pentafluorobenzene (89)

The commercial products were used as supplied.

11.1.2 Solvents and Reagents

Tetraglyme (supplied by I.C.I.) was purified by stirring with sodium metal at 95°C for 3 hrs., followed by fractional distillation under vacuum. The middle fraction was collected over oven-dried molecular sieve (Type 4A) and stored under dry nitrogen.

Sulpholan and acetonitrile were purified by fractional vacuum distillation. The middle fractions were collected over dried molecular sieve (Type 4A) and stored under an atmosphere of dry nitrogen.

Potassium fluoride was dried by heating at *ca.* 180°C under high vacuum for several days and powdered in a glove bag filled with dry nitrogen. If necessary, it was reheated under vacuum and stored under a dry nitrogen atmosphere.

Caesium fluoride was flame-dried at high vacuum for 6 hrs. and then powdered and stored as described above.

11.2 Fluoride Ion-Induced Reactions of 2H-Pentafluoropropene

11.2.1 Standard Procedure

The required quantities of dry casesium fluoride, dry tetraglyme and substrate were rapidly introduced into a baked r.b. flask, fitted with a gas-tap and variable volume reservoir, against a flow of dry nitrogen. The apparatus was cooled, evacuated and then filled with the requisite amount

of gaseous 2H-pentafluoropropene to equilibrate it to atmospheric pressure. The mixture was vigorously stirred at the desired temperature and on completion of the reaction, *i.e.* collapse of the gas reservoir, the volatile product was vacuum transferred into a trap cooled by liquid air. The remaining product was poured onto excess water, the organic layer decanted, washed and combined with ethereal extracts of the remaining aqueous layer. After careful removal of the ether (Vigreux column), the crude products were combined and transferred under vacuum into a cold trap.

11.2.2 With Pentafluoronitrobenzene (84)

A typical experiment is described below, where all yields quoted refer to consumed olefin:

Pentafluoronitrobenzene (84) (13.0 g., 61.0 mmoles), dry caesium fluoride (14.14 g., 93.3 mmoles), dry tetraglyme (20 ml.) and 2H-pentafluoropropene (7.06 g., 53.4 mmoles) were rapidly stirred at room temperature for 14 hrs., during which time the gas reservoir collapsed. A volatile product (1.90 g.), isolated by vacuum transfer, was sealed in an n.m.r. tube and shown to consist mainly of unreacted 2H-pentafluoropropene and 1,1,1,3,3,3-hexafluoropropane (87). This was not investigated further. The remaining product (9.92 g.; total recovery 58%), a yellow liquid, was analysed by g.l.c. (column 'O', 170°C and 240°C) and shown to contain a complex misture of components. The product was separated into four main fractions, according to retention time, by preparative scale g.l.c. (column 'O', 180°C). The fraction of shortest retention time was further analysed (column 'A', 90°C) and shown to consist

of one major and several minor components. Separation by preparative g.l.c. (column 'A', 110°C) gave perfluoro(2H-hexafluoroisopropyl)benzene (85), a colourless liquid, (0.12 g., 1.0%). N.m.r. spectrum No. 15. I.r. spectrum No. 8. Mass spectrum No. 5, and an unresolved mixture of many components (0.08g.) which was not investigated further. The second fraction was further analysed (column 'K', 120°C) and found to consist of two main components. Separation by preparative scale g.l.c. (column 'K', 80°C) gave unreacted pentafluoronitrobenzene (84) (2.20 g., 17% recovery) and perfluoro-3-methyl-2,1-benzisoxazole (92) (1.43 g., 14.1%), a colourless liquid, b.p. 162-164°C [Found: C, 36.96; F, 51.60%; N, 5.67%; Calculated for C_8F_7NO; C, 37.06; F, 51.35; N, 5.41%]. Ultraviolet spectrum: λ_{max} 216nm (ε=5900), 243nm (ε=4800) and 286nm (ε=1900). N.m.r. spectra (^{19}F and ^{13}C) No.16. I.r. spectrum No.9. Mass spectrum No. 6 . The third fraction was found to contain one major component, purified by preparative g.l.c. (column 'O', 180°C). This was identified as perfluoro-1-nitro-4-(2H-hexafluoroisopropyl)benzene (90), a pale yellow liquid, (2.73g., 20.2%), b.p. 193-194°C [Found: C, 31.46; F, 55.36; N, 3.79%; calculated for $C_9F_{10}HNO$; C, 31.30; F, 55.07; N, 4.06%]. N.m.r. spectrum No. 17, I.r. spectrum No. 10. Mass spectrum No. 7. The fourth (longest retention time) fraction was analysed as usual (column 'O', 240°C) and shown to contain four components. These were separated (column 'O', 190°C) and identified as 1-nitro-2-(2,2,2-trifluoroethyl)tetrafluorobenzene (94), a yellow liquid, (0.09 g., 0.8%). N.m.r. spectrum No. 18. I.r. spectrum No. 11. Mass spectrum No. 8. 1-nitro-4-(2,2,2-trifluoroethyl)tetrafluorobenzene (93), a pale yellow

solid, (0.37 g., 3.4%), N.m.r. spectrum No.19. I.r. spectrum No.12. Mass spectrum No. 9 , perfluoro-2,4-diphenyl-4-methyl pent-2-ene (95), a yellow liquid (0.07g., 0.3%). N.m.r. spectrum No.20. I.r. spectrum No.13. Mass spectrum No. 10, and perfluoro-1,1-bis(phenyl)-ethane (96), a yellow liquid, (0.05 g., 0.3%). N.m.r. spectrum No.21. I.r. spectrum No.14, Mass spectrum No. 11.

11.2.3 With Pentafluoropyridine

Pentafluoropyridine (6.46 g., 38.2 mmoles), dry caesium fluoride (6.88 g., 45.3 mmoles), dry tetraglyme (10 ml.) and 2H-pentafluoropropene (2.78 g., 21.1 mmoles) were stirred at room temperature for 16 hrs. after which time the reservoir had collapsed. The crude product was poured into excess water (100 ml.) and the fluorocarbon layer which separated was decanted. The aqueous layer was ether-extracted (3x40 ml.), and the combined crude fluorocarbon and ethereal solutions were dried. Careful removal of the ether (Vigreux column), followed by vacuum transfer of the residue into a cold trap, gave a colourless liquid (8.53 g.). This was shown by g.l.c. (column 'K') to contain three components. Separation by preparative g.l.c. (column 'K', 80°C) gave pentafluoropyridine (2.89 g., 44.8% recovery), perfluoro-4-(prop-2-enyl)pyridine (100), a colourless liquid, (2.31 g., 39% based on pentafluoropyridine consumed), b.p. 130-132°C (lit.[192] 131-133°C). N.m.r. spectra (^{19}F and ^{13}C) No.22 and perfluoro-4-(2H-hexafluoroisopropyl)pyridine (101), a colourless liquid, (0.32g., 5.0%), b.p. 131-133°C (lit.[192] 133-134°C). N.m.r. spectra (^{19}F and ^{13}C) No.23.

11.3 Other Fluoride Ion-Induced Reactions

11.3.1 Reaction of Perfluoro-1-nitro-4-(2H-hexafluoroisopropyl)benzene (90) with Caesium Fluoride.

Perfluoro-1-nitro-4-(2H-hexafluoroisopropyl)-benzene (90) (4.60g., 13.3 mmoles), dry tetraglyme (2.5 ml.) and dry caesium fluoride (8.0 g., 53.3 mmoles) were stirred at 72°C for 14 hrs. under dry nitrogen and then poured onto water (500 ml.). A brown-coloured organic layer separated out and was decanted. The remaining aqueous solution was ether extracted (4x50 ml.), the combined extracts and organic layer dried ($MgSO_4$) and the solvent carefully removed. The residue was transferred under vacuum into a cold trap, giving a pale yellow liquid (1.97g.). The product was shown to consist of one major component and was purified by preparative g.l.c. (column 'K', 120°C) giving perfluoro-3-methyl-2,1-benzisoxazole (92) (1.22 g., 38%), identified by its ^{19}F n.m.r. and i.r. spectra.

11.3.2 Reaction of Perfluoro-4-(prop-2-enyl)pyridine (100) with Caesium Fluoride

(i) Perfluoro-4-(prop-2-enyl)pyridine (100) (0.1 g., 0.36 mmoles) dry tetraglyme (1 ml.) and dry caesium fluoride (0.1 g., 0.66 mmoles) were mixed in a baked n.m.r. tube under a stream of dry nitrogen. An orange-coloured solution was rapidly produced which was attributed to the formation of the anion (102), characterised by its ^{19}F and ^{13}C n.m.r. spectra (No.24) as discussed in Sections 6.6 and 6.6.1.

The same general technique as described above was used to examine the reaction of (100) with caesium and potassium fluorides in sulpholan and in acetonitrile.

(ii) Trapping of the Anion (102) with Bromine

Perfluoro-4-(prop-2-enyl)pyridine (100) (1.0 g., 3.56 mmoles), dry tetraglyme (7 ml.) and dry caesium fluoride (0.67 g., 4.47 mmoles) were rapidly stirred in a baked r.b. flask under dry nitrogen. After 30 mins., bromine (0.83 g., 5.19 mmoles) was added; a yellow precipitate formed immediately. The reaction product was poured onto water (100 ml.) and an orange lower layer was formed. This was decanted and the aqueous layer ether extracted. The combined extracts and fluorocarbon were dried; removal of the solvent left a liquid residue shown by g.l.c. (column 'K') to contain two components. Separation by preparative scale g.l.c. gave unreacted perfluoro-4-(prop-2-enyl)pyridine (100) (0.18 g., 18% recovery) and perfluoro-4-(2-bromohexafluoroisopropyl)pyridine (103), a white solid, (0.57 g., 51%), m.p. 36-37°C [Found: C, 25.18; N, 3.74; F, 50.36%; Calculated for $C_8BrF_{10}N$; C, 25.3; N, 3.68; F, 50.0%]. N.m.r. spectrum No.25. I.r. spectrum No.15. Mass spectrum No. 12.

(iii) Trapping of the Anion (102) with Iodine

Perfluoro-4-(prop-2-enyl)pyridine (100) (1.40 g., 4.98 mmoles), dry tetraglyme (6 ml.) and dry caesium fluoride (1.35 g., 8.88 mmoles) were rapidly stirred for 1 hr. as before. Iodine, (1.35 g., 5.31 mmoles) was then added and the mixture stirred for 2 hrs. The dark brown reaction product was poured onto water (100 ml.) and worked up as described above. A red-coloured liquid residue (1.32 g.) was produced, shown by g.l.c. (column 'O') to consist of one major and two minor components. These were separated by preparative g.l.c. (column 'O', 170°C) and identified as perfluoro-4-(2H-hexa-

fluoroisopropyl)pyridine (101) (0.72 g., 48%), perfluoro-4-(2-hydroxyhexafluoroisopropyl)pyridine (106), a colourless liquid (0.29 g., 18%). N.m.r. spectrum No.26. I.r. spectrum No.16. Mass spectrum No. 13 and tetrafluoro-4-(2,2,2-trifluoroethyl)pyridine (107), a colourless liquid, (0.12 g., 10%). N.m.r. spectrum No.27. I.r. spectrum No.17. Mass spectrum No.14 . A trace amount of another product could not be isolated pure but was identified as perfluoro-4-(1H-1-iodo-2,2,2-trifluoroethyl)pyridine (108) from its mass spectrum (M^+=359).

CHAPTER TWELVE

EXPERIMENTAL FOR CHAPTER SEVEN - NEGATIVE HYPERCONJUGATION IN SOME POLYFLUOROBENZENE DERIVATIVES

12.1 Preparation and Purification of Substrates

(a) Pentafluoro-(2,2,2-trifluoroethyl)benzene (117)

(i) Sodium hydride (5.44 g., 60% dispersion, 0.136 mole) was added during 1 hr. to a stirred solution of diethyl malonate (28.29 g., 0.177 mole) in dry DMF (100 ml.) in a baked r.b. flask under dry nitrogen. After the evolution of hydrogen had ceased, hexafluorobenzene (32.17 g., 0.178 mole) was added and the mixture refluxed for 5 hrs. The product was cooled, poured onto excess water (500 ml.) and extracted with methylene chloride (6x50 ml.). The combined extracts were dried ($MgSO_4$) and removal of the methylene chloride gave a red coloured residue which was transferred under vacuum to a cold trap (49.59 g. recovery). Fractional distillation of the product gave hexafluorobenzene (10.3 g., 32% recovery), diethyl malonate (13.6 g., 48% recovery) and pentafluorophenyl malonic ester, a viscous oil (13.4 g., 48% based on consumed diethyl malonate), b.p. 80-81°C/0.01mm Hg (lit.[233] 124°C/0.5mm Hg).

(ii) Pentafluorophenyl malonic ester (21.2 g., 65.0 mmoles) was added to a solution of sodium hydroxide (40.0 g., 1.0 mole) in water (100 ml.) and the mixture stirred under reflux for 35 mins. On cooling, the product was acidified (conc. HCl) and extracted with methylene chloride (5x50 ml.). The ex-

tracts were washed with dilute sodium carbonate, the aqueous layer decanted and acidified (conc. HCl) and extracted with diethyl ether (5x50 ml.). Removal of the solvent left a white solid which was recrystallised from petroleum ether (b.p. 40-60°) giving pentafluorophenylacetic acid, (10.1 g., 69%), m.p. 102-103°C (lit.[234] 103-105°C).

(iii) Pentafluorophenylacetic acid (11.81 g., 52.3 mmoles) and sulphur tetrafluoride (22.8g., 0.211 mole) were charged into a steel autoclave and heated at 170°C for 18 hrs. After cooling and venting the gaseous products, a brown liquid (11.90g.) remained. This was transferred under vacuum, giving a clear liquid (8.93 g.) shown to be a mixture of two components by g.l.c. (column 'O'). The mixture was separated by preparative g.l.c. (column 'O', 190°C) and the components identified as pentafluoro-(2,2,2-trifluoroethyl)benzene (117), a colourless liquid, (8.90 g., 68%) b.p. 130-131°C (lit.[221] 126-128°C) previously reported but incomplete spectral data given. N.m.r. spectrum No.28. I.r. spectrum No. 18. Mass spectrum No.15 and 1-ethoxy-4-(2,2,2-trifluoroethyl)tetrafluorobenzene (119), a colourless liquid, (1.15 g., 8%), b.p. 190-191°C. [Found: C, 43.75; H, 2.23; F, 48.46%. Calculated for $C_{10}H_7F_7O$: C, 43.5; H, 2.5; F, 48.2%]. N.m.r. spectrum No. 29. I.r. spectrum No.19. Mass spectrum No.16.

(b) Pentafluoro-(2H-hexafluoroisopropyl)benzene (85)

Prepared and purified as discussed in Sections 6.4 and 11.2.2. N.m.r. spectrum No.15. I.r. spectrum No.8. Mass spectrum No. 5.

(c) Perfluoro-t-butylbenzene (118)[226]

The sample used was prepared by a previous worker in this laboratory and was purified by preparative scale g.l.c. before use (column 'O', 120°C).

(d) Pentafluorotoluene (116)

The commercial product was used as supplied.

12.2 Method of Rate Measurements

(a) Compounds (85), (117) and (118)

The reactions of these compounds with sodium methoxide in methanol at 40.0°C were followed spectrophotometrically (see Section 8.2(b) for general method). Comparison of the u.v. spectra of the starting materials and respective products showed that the wavelengths 229nm (pentafluoro-(2,2,2-trifluoroethyl)benzene (117) and pentafluoro-(2H-hexafluoroisopropyl)benzene (85)) and 234nm (perfluoro-t-butylbenzene (118)) gave a large and easily measured range of optical density throughout the reaction. Stock solutions of sodium methoxide in methanol (5.84×10^{-2} moles ℓ^{-1} for reaction with (85) and (118); 0.721 moles ℓ^{-1} for reaction with (117)) and substrate in methanol (*ca.* 3.5×10^{-4} moles ℓ^{-1}) were prepared. First and second order rate constants were calculated as described in Section 3.3.

The rate constant for the reaction of pentafluoro-(2,2,2-trifluoroethyl)benzene (117) was determined at a relatively high methoxide ion concentration in order that an accurate infinity reading could be obtained. At methoxide ion concentrations greater than 0.1 moles ℓ^{-1}, the effective basicity

of the solution increases and is governed by a Hammett acidity function, H_m, defined[236] as (Equation 12.1),

$$H_m = pK_{MeOH} + \log_{10} \left(\frac{[MeO^-]}{[MeOH]} \right) \qquad (12.1)$$

Values of H_m solutions of sodium methoxide in methanol have been reported[236] and form an H_m acidity function scale. Using this scale, the "effective" concentration of methoxide ion in a given sodium methoxide solution may readily be obtained (Equation 12.),

$$\text{"Effective" methoxide ion concentration} = \frac{[MeO^-]}{[MeOH]} = \text{antilog } (H_m - pK_{MeOH}) \qquad (12.2)$$

where $pK_{MeOH} = 16.92$.

(b) Pentafluorotoluene (116)

The reaction of (116) with sodium methoxide at 40.0°C was too slow to be measured spectrophotometrically; consequently the titrimetric method was used. Stock solutions of sodium methoxide in methanol (*ca.* 2.6 moles ℓ^{-1}) and substrate in methanol (1.02 moles ℓ^{-1}) were prepared. AnalaR methanol (100 ml.) and stock sodium methoxide solution (5 ml.) were pipetted into a stoppered conical flask and the concentration of methoxide ion determined in the usual way by the separate removal of two 5 ml. aliquots of solution. The flask was then immersed in a water bath thermostatted at 40.0°C. The run was initiated by the addition of 5 ml. substrate solution and monitored as usual by the periodic removal of reaction mixture. Second order rate constants were then calculated as discussed in Section 10.2.

12.3 Other Kinetic Studies on Pentafluoro-(2,2,2-trifluoroethyl)benzene (117)

It was necessary to prove kinetically that (117) was essentially unionised in its reaction with sodium methoxide. It can readily be shown that the observed rate constant, k_{obs}, for a process such as Scheme 7.1 is obtained from (Equation 12.3),

$$k_{obs} = \frac{k\,[MeO^-]}{1 + kp[MeO^-]} \qquad (12.3)$$

$$\text{where} \quad Kp = \frac{[C_6F_5\bar{C}HCF_3]}{[C_6F_5CH_2CF_3]\,[MeO^-]}$$

There are two limiting cases. Firstly, if the substrate is extensively deprotonated (*i.e.* Kp is large) then Equation 12.3 reduces to $k_{obs} = {}^{k}/_{Kp}$, so that the observed rate constant is independent of methoxide ion concentration. However, if the substrate is essentially unionised, then Kp is small and Equation 12.3 reduces to $k_{obs} = k[MeO^-]$. Consequently, the extent of deprotonation of (117) may be gauged by examining the dependence on methoxide ion concentration of the first-order rate constant k_{obs}.

The rate constants for the reaction of (117) in this particular study was determined at 40.0°C over a range of sodium methoxide concentration using the spectrophotometric method. In very dilute concentrations of methoxide ion, accurate infinity readings could not be made owing to the slowness of the reaction. In these cases, first-order rate constants were determined by Guggenheim's method. This technique requires the measurement of optical density at

regular intervals so that the readings are separable into two groups corresponding to the times

$$t_1,\ t_2,\ t_3,\ \ldots\ldots\ldots\ (etc.)$$

and

$$(t_1+\Delta t),\ t_2+\Delta t),\ (t_3+\Delta t),\ \ldots\ldots\ldots\ (etc.)$$

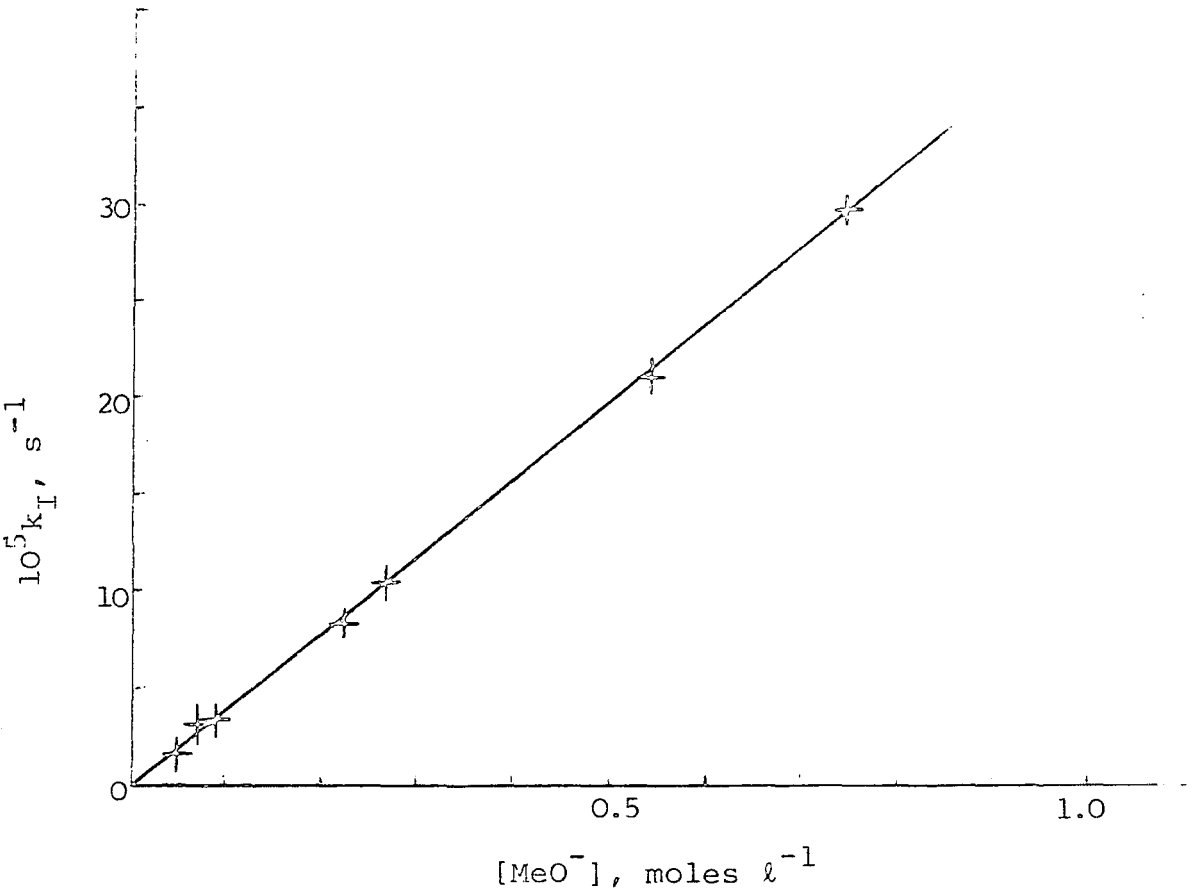
Accurate and reproducible values of k_I were obtained only if Δt was greater than at least two half-lives of the reaction. The slope of a plot of ln $(O.D._{t+\Delta t} - O.D_t)$ against time gave the desired rate constant $(-k_I)$. The experimentally determined rate constants are shown in Table 12.1 and are plotted in Graph 12.1.

TABLE 12.1 First-Order Rate Constants for the Reaction of Pentafluoro-(2,2,2-trifluoroethyl)benzene with Sodium Methoxide in Methanol at 40.0°C

Measured $[MeO^-]$, moles ℓ^{-1}	H_m	Effective $[MeO]$, moles ℓ^{-1}	$10^5 k_I$, s^{-1}
4.8×10^{-2}	——	4.8×10^{-2}	1.42
7.6×10^{-2}	——	7.6×10^{-2}	3.18
9.0×10^{-2}	——	9.0×10^{-2}	3.45
0.162	12.25	0.214	6.65
0.192	16.34	0.263	9.97
0.361	16.65	0.531	21.0
0.495	16.79	0.741	29.7

As the observed first-order rate constants for the reaction of (117) are linearly dependent (Graph 12.1, following) upon methoxide ion concentration, it is apparent that pentafluoro-(2,2,2-trifluoroethyl)benzene (117) is not extensively deprotonated in these reactions.

GRAPH 12.1 Effective Methoxide Ion Concentration *vs.* k_I for Pentafluoro-(2,2,2-trifluoroethyl)benzene



12.4 Product Identifications

(a) From Pentafluoro-(2,2,2-trifluoroethyl)benzene (117)

Pentafluoro-(2,2,2-trifluoroethyl)benzene (117) (0.1 g., 0.40 mmoles) and sodium methoxide/methanol solution (*ca.* 1 ml., 2.6 M) were mixed in an n.m.r. tube and set aside for 12 weeks at room temperature. The ^{19}F n.m.r. spectrum of the resulting solution showed the presence of one CF_3 group and two high-field aromatic fluorine resonances in the ratio 2:2. This is consistent with the product being 4-methoxy-1-(2,2,2-tri-

fluoroethyl)tetrafluorobenzene. N.m.r. spectrum No.30.

(b) From Pentafluoro-(2H-hexafluoroisopropyl)benzene (85)

Sodium methoxide/methanol solution (0.75 M) was added dropwise to a solution of pentafluoro-(2H-hexafluoroisopropyl)-benzene (85) (0.08g., 0.25 mmoles) in methanol (0.5 ml.) in an n.m.r. tube at room temperature. After *ca.* 90% reaction of the substrate, the ^{19}F n.m.r. spectrum of the product showed the presence of one other component apart from starting material. The product exhibited five aromatic fluorine atoms which integrated in the ratio 2:1:2 (three separate signals) indicating that, initially, methoxide ion did not attack the aromatic nucleus. Two other fluorine resonances, in the ratio of 2:2, were observed at low field and were attributable to two deshielded CF_2 groups. Thus in the absence of other data the initial product from the reaction of pentafluoro(2H-hexafluoroisopropyl)benzene (85) with methoxide ion was identified as 1,1,3,3-tetrafluoro-2-pentafluorophenyl-2-methoxyprop-1-ene. N.m.r. spectrum No.31.

(c) From Perfluoro-t-butylbenzene (118)

Sodium methoxide/methanol solution (0.75 M) was added dropwise to a solution of perfluoro-t-butylbenzene (118) (0.1 g., 0.26 mmoles) in methanol (0.5 ml.) in an n.m.r. tube at room temperature until complete conversion of the substrate was observed. The ^{19}F n.m.r. spectrum of the product showed, in addition to CF_3 resonances (nine fluorine atoms by integration), two upfield resonances attributable to four aromatic fluorine atoms in the ratio 2:2. Thus the product was identified as 4-methoxyperfluoro-1-t-butylbenzene. N.m.r. spectrum No.32.

(d) From Pentafluorotoluene (116)

Pentafluorotoluene (0.30 g., 1.65 mmoles) and sodium methoxide/methanol solution (1.5 ml., 2.6 M) were mixed in an n.m.r. tube and set aside for eight weeks at about 80°C. The ^{19}F n.m.r. spectrum of the product showed one other component in addition to unreacted starting material. This was identified as 4-methoxy-1-methyltetrafluorobenzene by comparison of its ^{19}F n.m.r. spectrum with that given in the literature[170] for this compound.

APPENDIX ONE

N.M.R. Spectra

1. 3-Cyanotetrafluoropyridine : (^{19}F).
2. 2-Amino-4-cyano-3,5,6-trifluoropyridine : (^{19}F).
3. 3-Amino-4-cyano-2,5,6-trifluoropyridine : (^{19}F).
4. 2-Aminoperfluoro-4-methylpyridine : (^{19}F).
5. 4-Amino-4-cyano-2,5,6-trifluoropyridine : (^{19}F).
6. 6-Amino-3-cyano-2,4,5-trifluoropyridine : (^{19}F).
7. 4-Amino-2-cyano-3,5,6-trifluoropyridine : (^{19}F).
8. N,N´-(bis-4,4´-perfluoropyrimidino)hydrazine : (^{19}F).
9. 6-Amino-2,5-difluoropyrimidine : (^{19}F).
10. 6-Methoxy-2,5-difluoropyrimidine : (^{19}F).
11. 2,6-Dihydrohexafluoronaphthalene : (^{19}F and ^{1}H).
12. 2-Methoxy-1,4,5,6,8-pentafluoronaphthalene : (^{19}F and ^{1}H).
13. 1-Methoxy-3,4,5,7,8-pentafluoronaphthalene : (^{19}F and ^{1}H).
14. 2H-Pentafluoropropene : (^{19}F and ^{1}H).
15. Pentafluoro-(2H-hexafluoroisopropyl)benzene : (^{19}F and ^{1}H).
16. Perfluoro-3-methyl-2,1-benzisoxazole : (^{19}F and ^{13}C).
17. 1-Nitro-4-(2H-hexafluoroisopropyl)tetrafluorobenzene : (^{19}F and ^{1}H).
18. 1-Nitro-2-(2,2,2-trifluoroethyl)tetrafluorobenzene : (^{19}F and ^{1}H).
19. 1-Nitro-4-(2,2,2-trifluoroethyl)tetrafluorobenzene : (^{19}F and ^{1}H).
20. Perfluoro-2,4-diphenyl-4-methylpent-2-ene : (^{19}F).
21. Perfluoro-1,1-bis(phenyl)ethane : (^{19}F).
22. Perfluoro-4-(prop-2-enyl)pyridine : (^{13}C).
23. Tetrafluoro-4-(2H-hexafluoroisopropyl)pyridine : (^{13}C).

24. Anion of Perfluoro-4-(prop-2-enyl)pyridine : (^{19}F and ^{13}C).

25. Perfluoro-4-(2-bromohexafluoroisopropyl)pyridine : (^{19}F).

26. Perfluoro-4-(2-hydroxyhexafluoroisopropyl)pyridine : (^{19}F).

27. Tetrafluoro-4-(2,2,2-trifluoroethyl)pyridine : (^{19}F and ^{1}H).

28. Pentafluoro-(2,2,2-trifluoroethyl)benzene : (^{19}F and ^{1}H).

29. 1-Ethoxy-4-(2,2,2-trifluoroethyl)tetrafluorobenzene : (^{19}F and ^{1}H).

30. 4-Methoxy-1-(2,2,2-trifluoroethyl)tetrafluorobenzene : (^{19}F).

31. 1,1,3,3-Tetrafluoro-2-pentafluorophenyl-3-methoxyprop-1-ene : (^{19}F).

32. 4-Methoxyperfluoro-1-t-butylbenzene : (^{19}F).

The following abbreviations are used in this appendix: S, singlet; D, doublet; T, triplet; Q, quartet; Sept., septet; M, multiplet.

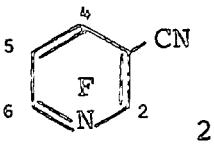
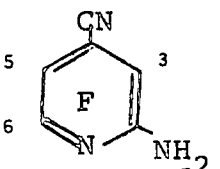
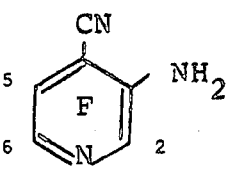
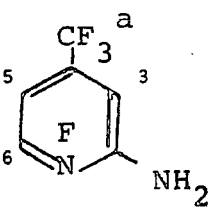
Unless otherwise stated, spectra were recorded at 40°C in $CDCl_3$.

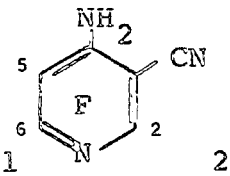
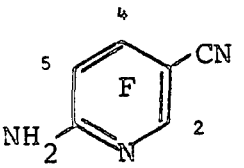
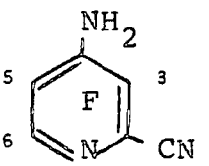
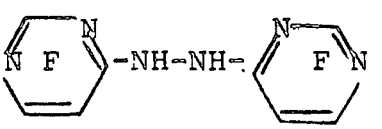
$CFCl_3$, TMS and TMS were used as references for ^{19}F, ^{1}H and ^{13}C spectra respectively.

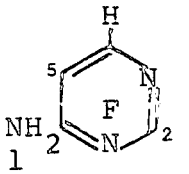
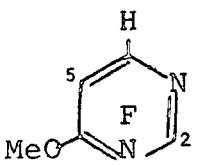
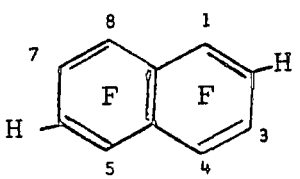
For ^{1}H spectra, downfield shifts are quoted as positive, whilst for ^{19}F spectra, upfield shifts are quoted as positive.

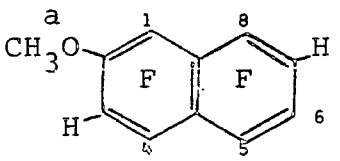
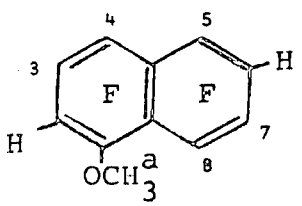
For ^{13}C spectra, "downfield" shifts are quoted as positive, where downfield is the direction of increasing the absolute values.

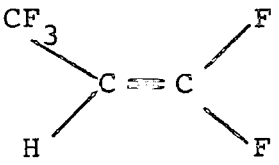
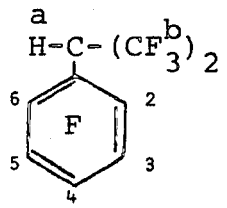
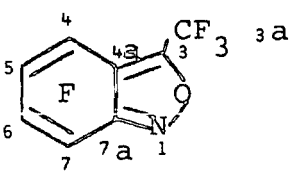
Relative intensities quoted for ^{13}C spectra are approximate values.

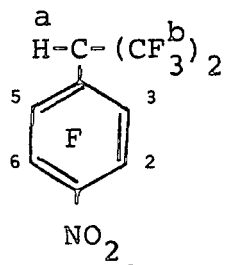
Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
1. 3-Cyanotetrafluoropyridine,			
60.8	M	1	2
72.8	M	1	6
106.5	M	1	4
163.6	M	1	5
2. 2-Amino-4-cyano-3,5,6-trifluoropyridine			
98.2	D(J=22.9Hz) of D(J=31.6Hz)	1	6
137.9	D(J=10Hz) of D(J=31.6Hz)	1	5
154.4	D(J=10Hz) of D(J=22.9Hz)	1	3
3. 3-Amino-4-cyano-2,5,6-trifluoropyridine			
86.0	D(J=11.7Hz) of D(J=30Hz)	1	6
109.2	D(J=11.7Hz) of D(J=19.7Hz)	1	2
143.4	D(J=19.7Hz) of D(J=30Hz)	1	5
4. 2-Aminoperfluoro-4-methylpyridine			
56.4	T (J = 22 Hz)	3	a
90.3	D (J = 26.6 Hz) of D (J = 31 Hz)	1	6
142.0	M	1	5
158.8	M	1	3

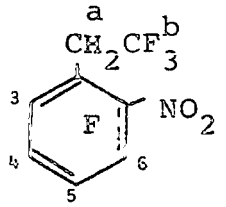
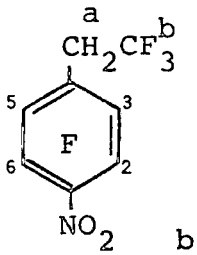
Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
5. 4-Amino-3-cyano-2,5,6-trifluoropyridine			
66.7	DD	1	2
88.5	DD	1	6
169.8	DD	1	5
6. 6-Amino-3-cyano-2,4,5-trifluoropyridine			
63.8	DD	1	2
122.8	DD	1	4
170.0	DD	1	5
7. 4-Amino-2-cyano-3,5,6-trifluoropyridine			
90.1	D (J = 19.5 Hz) of D (J = 29.3 Hz)	1	6
137.4	D (J = 10.5 Hz) of D (J = 19.5 Hz)	1	3
154.0	D (J = 10.5 Hz) of D (J = 29.3 Hz)	1	5
8. N,N'-(bis-4,4'-perfluoropyrimidino)-hydrazine			
47.7	D (J = 11 Hz) of D (J = 24.4 Hz)	1	2,2'
84.9	D (J = 11 Hz) of D (J = 16.9 Hz)	1	6,6'
178.1	D (J = 16.9 Hz) of D (J = 24.4 Hz)	1	5,5'

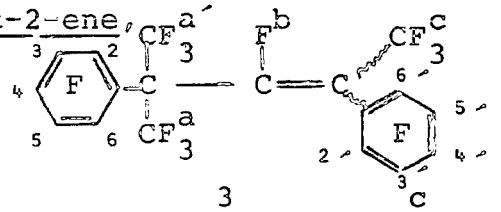
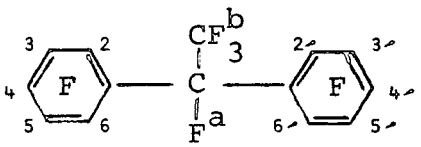
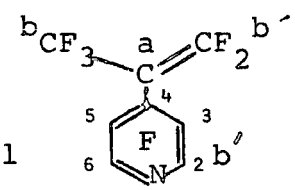
Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
9. 6-Amino-2,5-difluoropyrimidine, 			
52.6	D (J= 25.6 Hz)	1	2
160.3	D (J= 25.6 Hz)	1	5
10. 6-Methoxy-2,5-difluoropyrimidine, (solvent; $CDCl_3$/methanol) 			
49.6	D(J=27Hz)	1	2
159.3	D(J=27Hz)	1	5
11. 2,6-Dihydrohexafluoronaphthalene, 			
^{19}F spectrum			
116.8	D(J=62Hz) of M	2	1,5
136.3	M	2	3,7
149.3	D(J=62Hz) of M	2	4,8
^{1}H spectrum			
7.2	M broad	2	2 and 6.

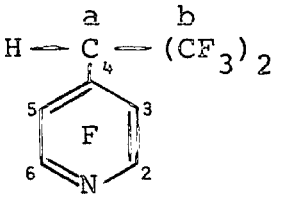
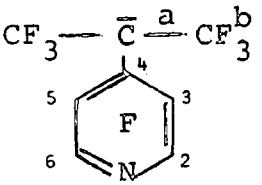
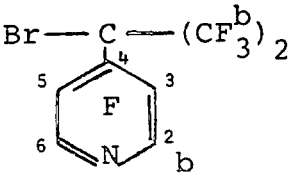
Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
12. 2-Methoxy-1,4,5,6,8-pentafluoronaphthalene,			
^{19}F spectrum			
118.1	M	1	8
119.7	M	1	4
139.9	M	1	6
146.6	D(J=68.3Hz) of M	1	1
150.5	D(J=58.6Hz) of M	1	5
^{1}H spectrum			
4.0	S	3	a
7.1	M broad	2	2 and 6
13. 1-Methoxy-3,4,5,7,8-pentafluoronaphthalene,			
^{19}F spectrum			
117.2	M	1	5
137.8	M	1	7
138.8	M	1	3
146.1	M	1	8
156.4	D(J=68.3Hz) of M	1	4
^{1}H spectrum			
3.9	S	3	a
7.1	M broad	2	2 and 6

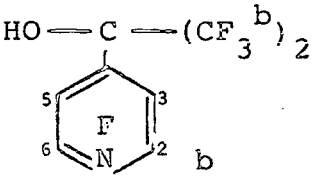
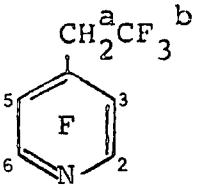
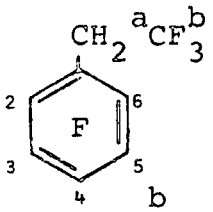
Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
14. 2H-Pentafluoropropene, (neat)			
^{19}F spectrum			
61.2		3	CF_3
75.8		1	a or b
80.8		1	a or b
^{1}H spectrum			
3.7	M	1	H
15. Pentafluoro-(2H-hexafluoroisopropyl)benzene,			
^{19}F spectrum			
64.4	D(J=8Hz) of D(J=18.8Hz)	6	b
134.7	M	1	6
140.9	D(J=19Hz) of M	1	2
149.2	M	1	4
159.9	M	2	3 and 5
^{1}H spectrum			
4.55	Sept. (J=8Hz)	1	a
16. Perfluoro-3-methyl-2,1-benzisoxazole,			
^{19}F spectrum			
63.2	D($J_{3a,4}$ = 11.7Hz)	3	3a
138.9	D(J=11.7Hz) of M	1	4
147.3	D(J=47Hz) of T (J=18.8Hz)	1	7
153.3		2	5,6

Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
16. Perfluoro-3-methyl-2,1-benzisoxazole, (contd.)			
^{13}C spectrum			
149.	Q (J=42.7Hz)	1	3
149.10	M	1	7a
143.8	D(J=261Hz) of T(J=12.8Hz)	1	5
139.0	D(J=253.9Hz) of T(J=14.9Hz)	1	6
138.5	D(J=265.4Hz) of D(J=13.5Hz) of D(J=3.7Hz)	1	4
132.9	D(J=258.3Hz) of D(J=14.6Hz) of D (J=5.3Hz)	1	7
119.0	Q (J=272.2Hz)	1	3a
105.2	D(J=19.1Hz)	1	4a
17. 1-Nitro-4-(2H-hexafluoroisopropyl)tetrafluorobenzene, 			
^{19}F spectrum : at 40°C			
64.3		6	b
131.3		1	
137.1		1	
145.2		2	
: at 80°C (solvent; d_6 DMSO)			
63.4		6	b
134.7		1	
135.2		1	
145.5		2	
^{1}H spectrum			
4.75	Sept. (J=8Hz)	1	a

Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
18. 1-Nitro-2-(2,2,2-trifluoroethyl)tetrafluorobenzene			
^{19}F spectrum			
65.8		3	b
136.2		1	
145.0		1	
147.9		1	
149.1		1	
^{1}H spectrum			
3.75	Q (J=9.2Hz)	2	a
19. 1-Nitro-4-(2,2,2-trifluoroethyl)tetrafluorobenzene			
^{19}F spectrum			
65.9		3	b
137.7		2	2,6 or 3,5
146.6		2	3,5 or 2,6
^{1}H spectrum			
3.63	Q (J=9.8Hz)	1	a

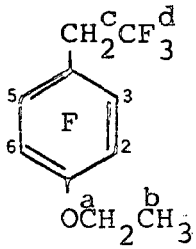
Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
20. Perfluoro-2,4-diphenyl-4-methylpent-2-ene, 			
68.3		3	c
71.7		1	b
71.9		6	a,a´
136.8		4	2,6 and 2´,6´
147.4		2	4,4´
159.4		4	3,5 and 3´,5´
21. Perfluoro-1,1-bis(phenyl)ethane, 			
78.7		3	b
137.2		4	2,6 and 2´, 6´
148.0		2	4,4´
157.2		1	a
158.5		4	3,5 and 3´,5´
22. Perfluoro-(prop-2-enyl)pyridine, ^{13}C spectrum 			
157.4	D (J = 305 Hz) of D (J = 301 Hz)	1	
143.9	D (J = 230 Hz) of D (J = 16 Hz)	2	2,6
142.0		1	4
140.4	D (J = 266 Hz) of D (J = 30 Hz)	2	3,5
121.5	Q (J=281Hz)	1	b
46.6	M	1	a

Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
23. Tetrafluoro-4-(2H-hexafluoroisopropyl) pyridine, 			
^{13}C spectrum (in CD_3CN, external TMS)			
143.8	D (J = 248 Hz) of M	2	2,6
141.2	D (J = 265 Hz) of M	2	3,5
121.8	Q (J = 281 Hz)	2	b
118.7	T (J = 16 Hz)	1	4
45.4	Sept. (J = 32.6 Hz)	1	a
24. Anion of Perfluoro-4-(prop-2-enyl)pyridine, 			
^{19}F spectrum (in tetraglyme)			
47.0	T (J = 17 Hz)	6	b
101.4	M	2	2,6
150.2	M	2	3,5
^{13}C spectrum (in tetraglyme, external TMS)			
144.7	D (J = 232 Hz) of M	1	2,6
134.5	D (J = 249 Hz) of M	2	3,5
133.9	T (J = 16 Hz)	1	4
128.9	Q (J=265Hz)	6	b
56.5	Sept. (J = 38.0 Hz)	1	9
25. Perfluoro-4-(2-bromohexafluoroisopropyl)-pyridine, 			
66.6	T (J = 20.1 Hz)	6	b
88.7	M	2	2,6
129.0	M	2	3,5

Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
26. Perfluoro-4-(2-hydroxyhexafluoroisopropyl)pyridine,			
75.5	T (J = 14.5 Hz)	6	b
79.0	M	2	2,6
136.3	M	2	3,5
27. Tetrafluoro-4-(2,2,2-trifluoroethyl)-pyridine,			
^{19}F spectrum			
65.4	T (J = 10 Hz) of M	3	b
89.9	M	2	2,6
143.3	M	2	3,5
^{1}H spectrum			
3.66	Q (J = 10Hz)	2	a
28. Pentafluoro-(2,2,2-trifluoroethyl)benzene,			
^{19}F spectrum			
66.7	T (J = 10 Hz) of M	3	b
142.0	M	2	2,6
153.7	M	1	4
162.3	M	2	3,5
^{1}H spectrum			
3.55	Q (J = 10Hz)	2	a

Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment

29. 1-Ethoxy-3-(2,2,2-trifluoroethyl)tetrafluorobenzene,



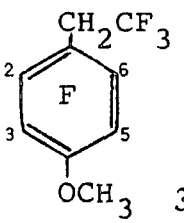
^{19}F spectrum

66.5	T (J = 10.4 Hz) of M	3	d
144.6	M	2	3,5
157.5	M	2	2,6

^{1}H spectrum

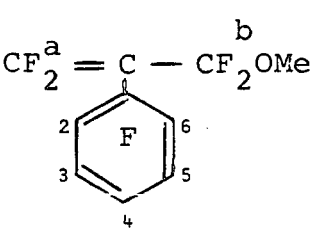
1.0	T (J = 7Hz)	3	b
3.1	Q (J = 10.4Hz)	2	c
3.9	Q (J = 7Hz)	2	a

30. 4-Methoxy-1-(2,2,2-trifluoroethyl)tetrafluorobenzene,

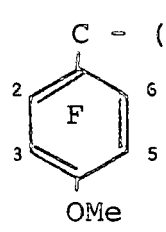


66.6	T (J = 10 Hz) of M	3	b
144.0	M	2	3,5
158.4	M	2	2,6

31. 1,1,3,3-Tetrafluoro-2-pentafluorophenyl-3-methoxyprop-1-ene,



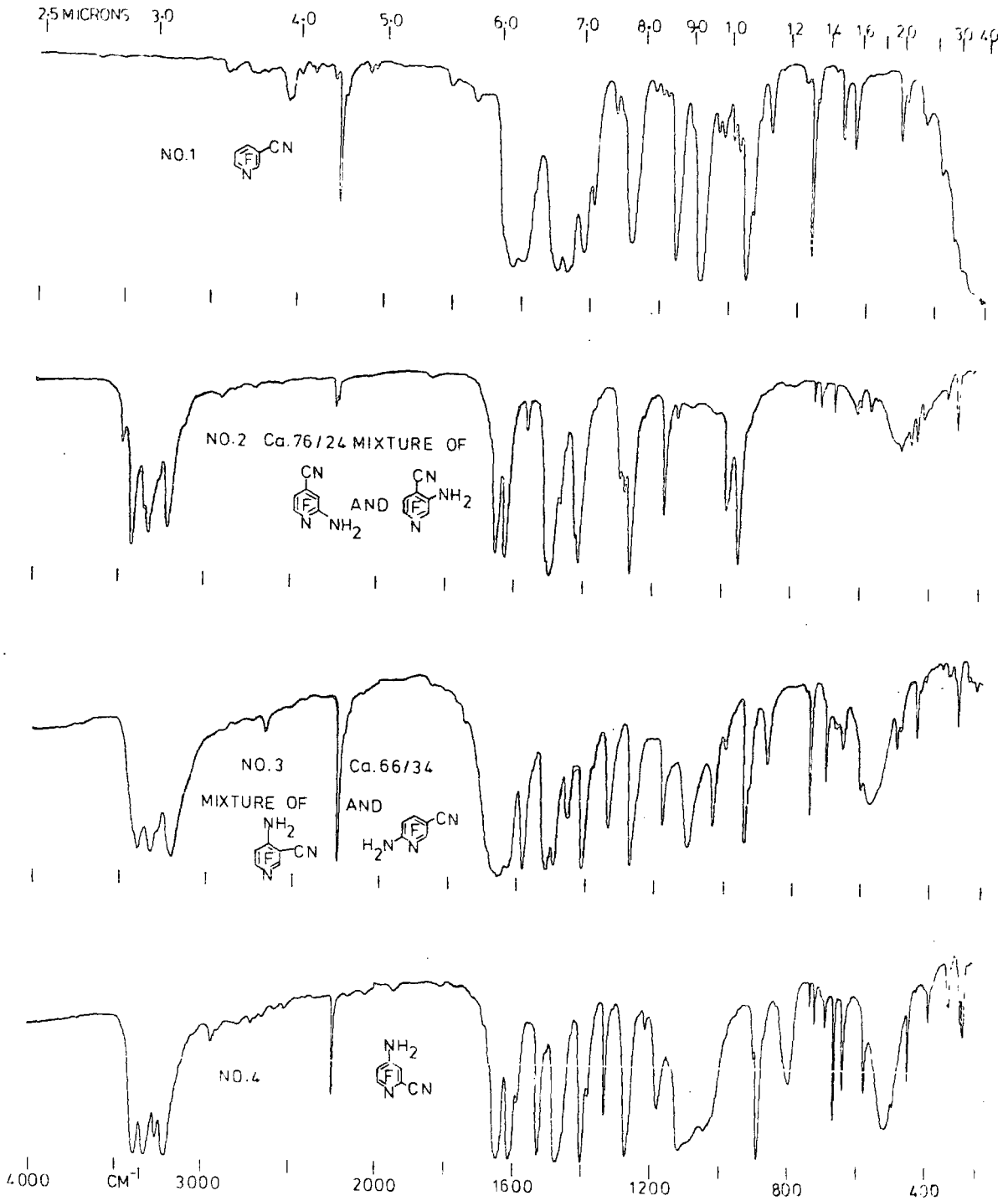
58.3		2	a
59.2		2	b
139.0	M	2	2,6
151.4	M	1	4
163.2	M	2	3,5

Shift (p.p.m.)	Fine Structure Coupling Constant (Hz)	Relative Intensity	Assignment
32. 4-Methoxyperfluoro-1-t-butylbenzene,			
61.1	T (J = 25.8 Hz)	9	b
129.7	M	2	2,6
156.6	M	2	3,5

APPENDIX TWO

I.R. Spectra

1. 3-Cyanotetrafluoropyridine.
2. *Ca.* 76/24 mixture of 2-amino-4-cyanotrifluoropyridine and 3-amino-4-cyanotrifluoropyridine.
3. *Ca.* 66/34 mixture of 4-amino-3-cyanotrifluoropyridine and 6-amino-3-cyanotrifluoropyridine.
4. 4-Amino-2-cyanotrifluoropyridine
5. N,N´-(bis-4,4´-perfluoropyrimidino)hydrazine.
6. 2,6-Di-hydrohexafluoronaphthalene.
7. *Ca.* 75/25 mixture of 2-methoxy-1,4,5,6,8-pentafluoronaphthalene and 1-methoxy-3,4,5,7,8-pentafluoronaphthalene.
8. Perfluoro-(2H-hexafluoroisopropyl)benzene.
9. Perfluoro-3-methyl-2,1-benzisoxazole.
10. 1-Nitro-4-(2H-hexafluoroisopropyl)tetrafluorobenzene.
11. 1-Nitro-2-(2,2,2-trifluoromethyl)tetrafluorobenzene.
12. 1-Nitro-4-(2,2,2-trifluoroethyl)tetrafluorobenzene.
13. Perfluoro-2,4-diphenyl-4-methylpent-2-ene.
14. Perfluoro-1,1-bis(phenyl)ethane.
15. Perfluoro-4-(2-bromohexafluoroisopropyl)pyridine.
16. Perfluoro-4-(2-hydroxyhexafluoroisopropyl)pyridine.
17. Tetrafluoro-4-(2,2,2-trifluoroethyl)pyridine.
18. Pentafluoro-(2,2,2-trifluoromethyl)benzene.
19. 1-Ethoxy-4-(2,2,2-trifluoroethyl)tetrafluorobenzene.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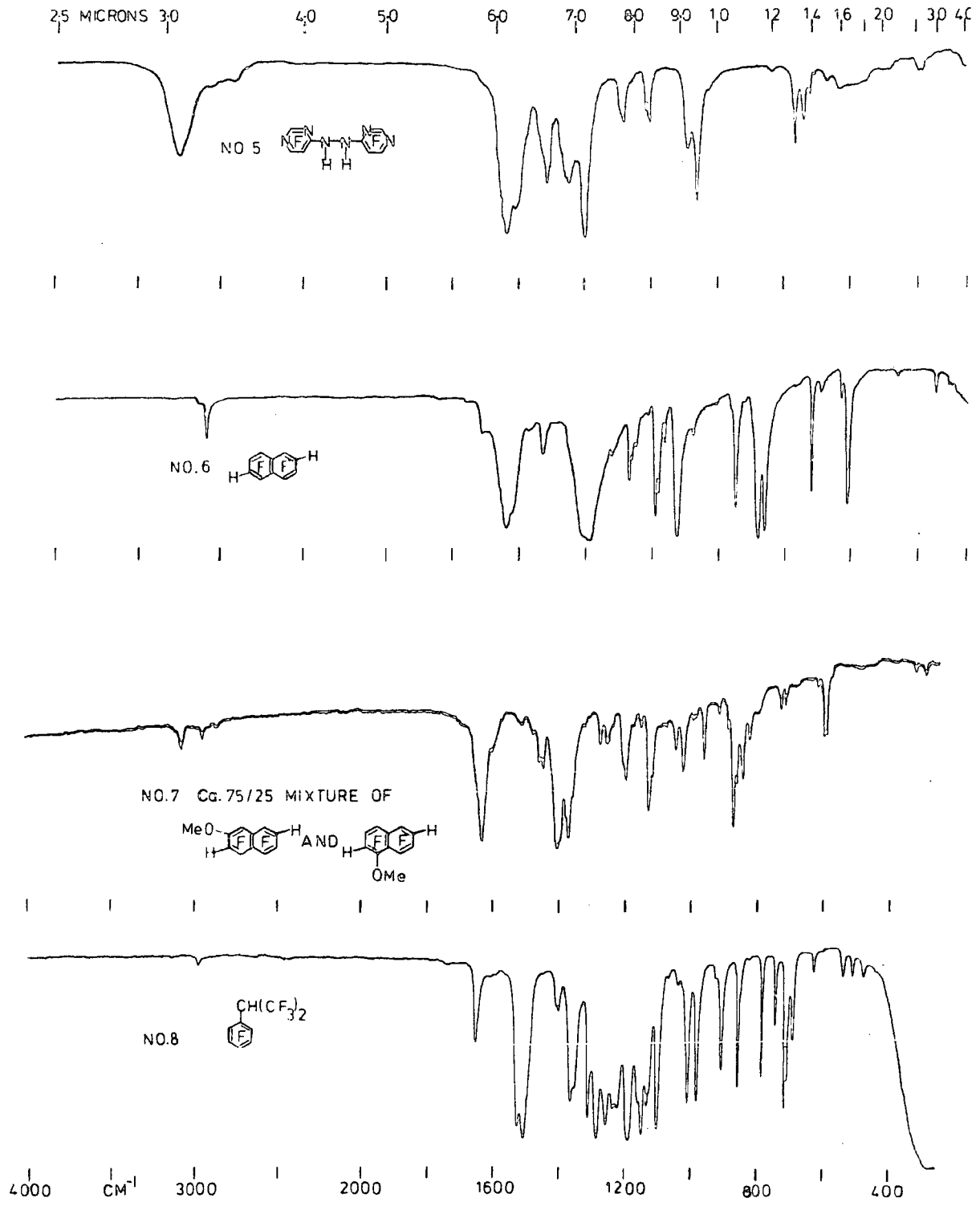
5·0
6·0
7·0
8·0
9·0
1·0
1·2
1·4
1·6
2·0
3·0
4·0
NO.1
NO.2 Ca.76/24 MIXTURE OF
AND
NO.3
Ca.66/34
MIXTURE OF
AND
NO.4
4000
CM⁻¹
3000
2000
1600
1200
800
400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7·0
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9·0
1·0
12
14
16
20
30
40
NO 5
NO.6
NO.7 Ca. 75/25 MIXTURE OF
MeO
AND
OMe
NO.8
CH(CF3)2
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CM-1
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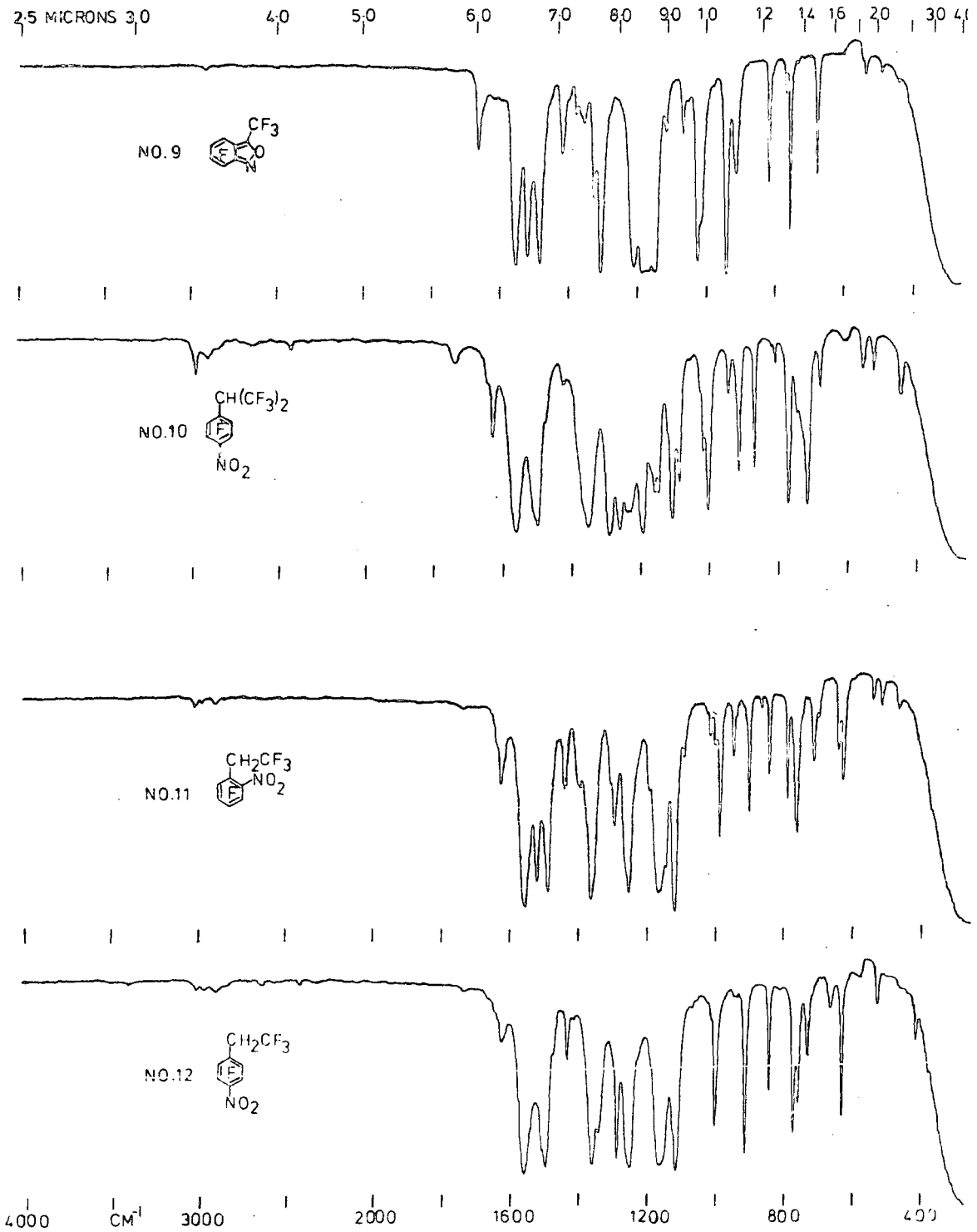
2000
1600
1200
800
400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5·0
6·0
7·0
8·0
9·0
1·0
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14
16
20
30
NO.9
CF3
NO.10
CH(CF3)2
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CH2CF3
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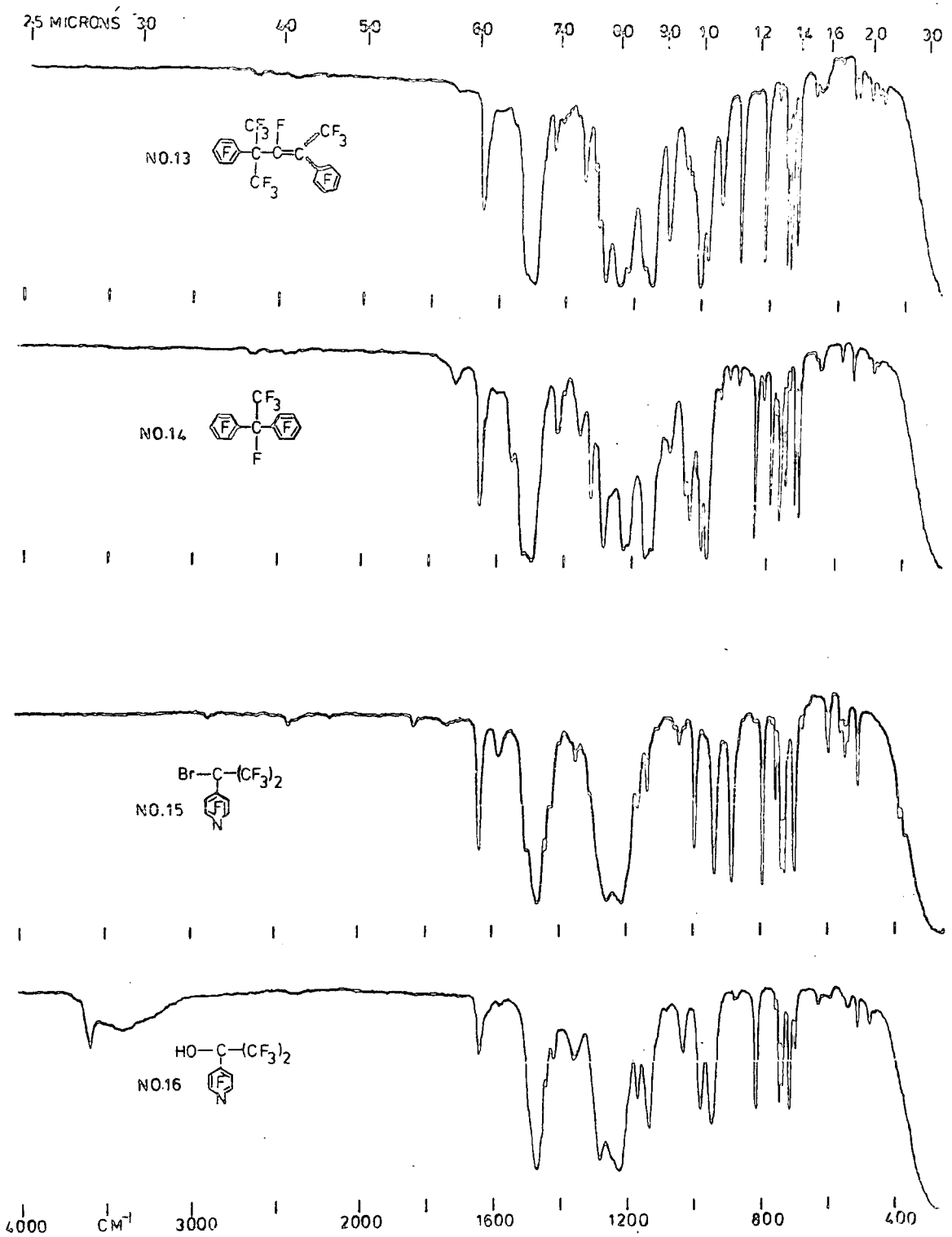
NO.12
CH2CF3
NO2
4000
CM-1
3000
2000
1600
1200
800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NO.14
NO.15
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CM⁻¹
3000
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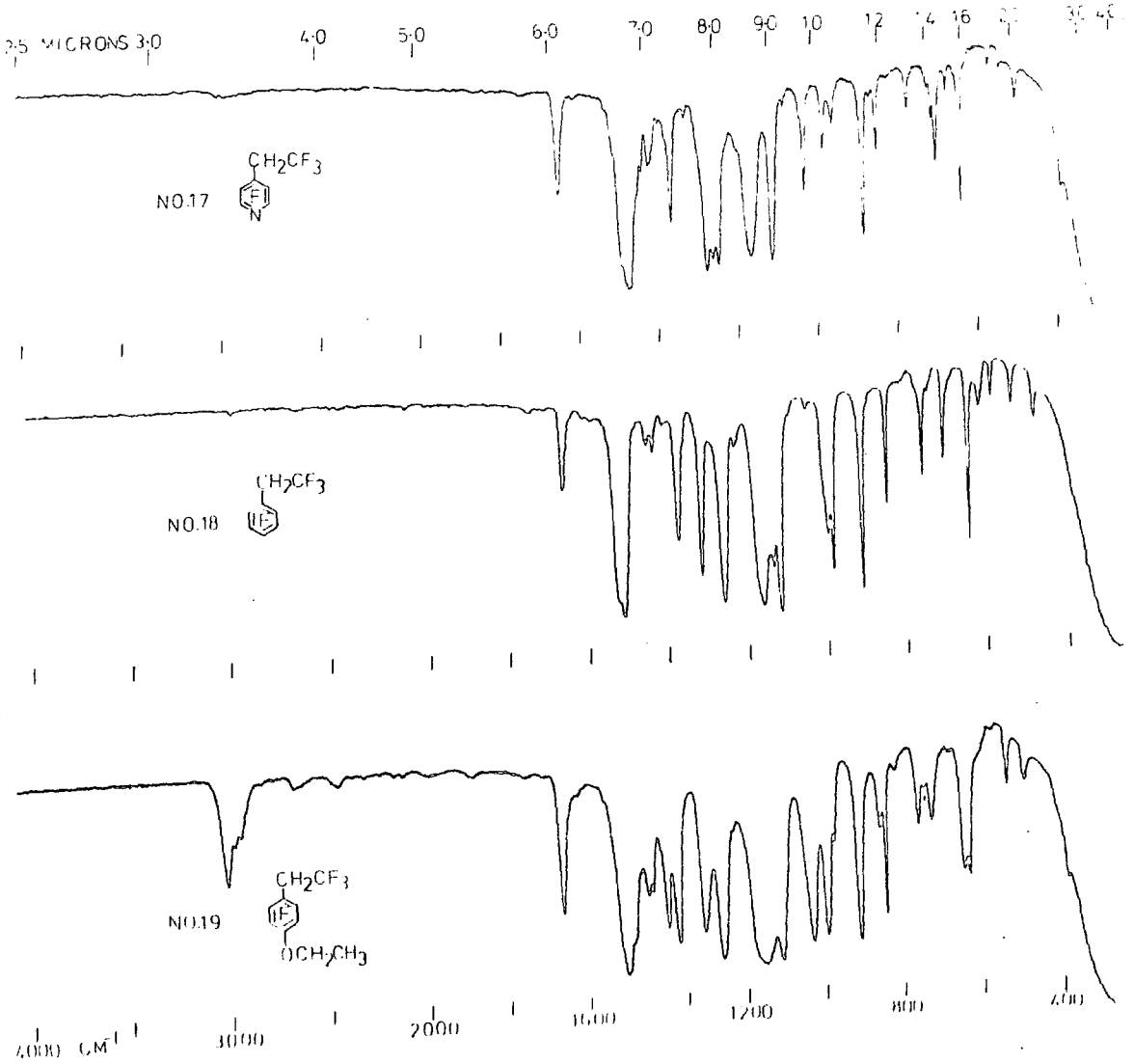
1600
1200
800
400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7·0
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9·0
10
12
14
16
NO.17
CH_2CF_3
NO.18
CH_2CF_3
NO.19
CH_2CF_3
OCH_2CH_3
4000 CM⁻¹
3000
2000
1600
1200
800
400

APPENDIX THREE

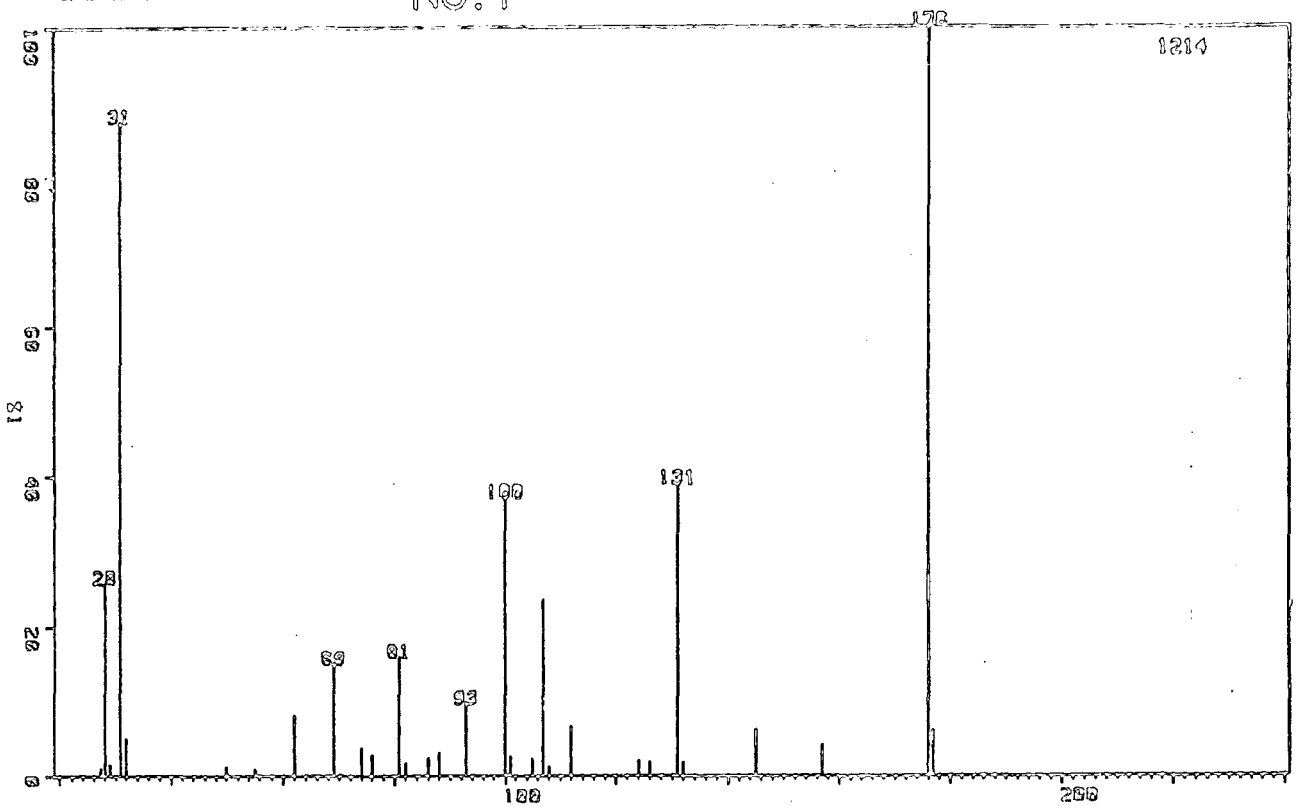
Mass Spectra

1. 3-Cyanotetrafluoropyridine.
2. N,N'-(bis-4,4'-perfluoropyrimidino)hydrazine.
3. 2,6-Dihydrohexafluoronaphthalene.
4. *Ca.* 75/25 Mixture of 2-methoxy-1,4,5,6,8-perfluoronaphthalene and 1-methoxy-3,4,5,7,8-pentafluoronaphthalene.
5. Pentafluoro-(2H-hexafluoroisopropyl)benzene.
6. Perfluoro-3-methyl-2,1-benzisoxazole.
7. 1-Nitro-4-(2H-hexafluoroisopropyl)tetrafluorobenzene.
8. 1-Nitro-2-(2,2,2-trifluoroethyl)tetrafluorobenzene.
9. 1-Nitro-4-(2,2,2-trifluoroethyl)tetrafluorobenzene.
10. Perfluoro-2,4-diphenyl-4-methyl pent-2-ene.
11. Perfluoro-1,1-bis(phenyl)ethane.
12. Pentafluoro-4-(2-bromohexafluoroisopropyl)pyridine.
13. Tetrafluoro-4-(2-hydroxyhexafluoroisopropyl)pyridine.
14. Tetrafluoro-4-(2,2,2-trifluoroethyl)pyridine.
15. Pentafluoro-(2,2,2-trifluoroethyl)benzene.
16. 1-Ethoxy-4-(2,2,2-trifluoroethyl)tetrafluorobenzene.

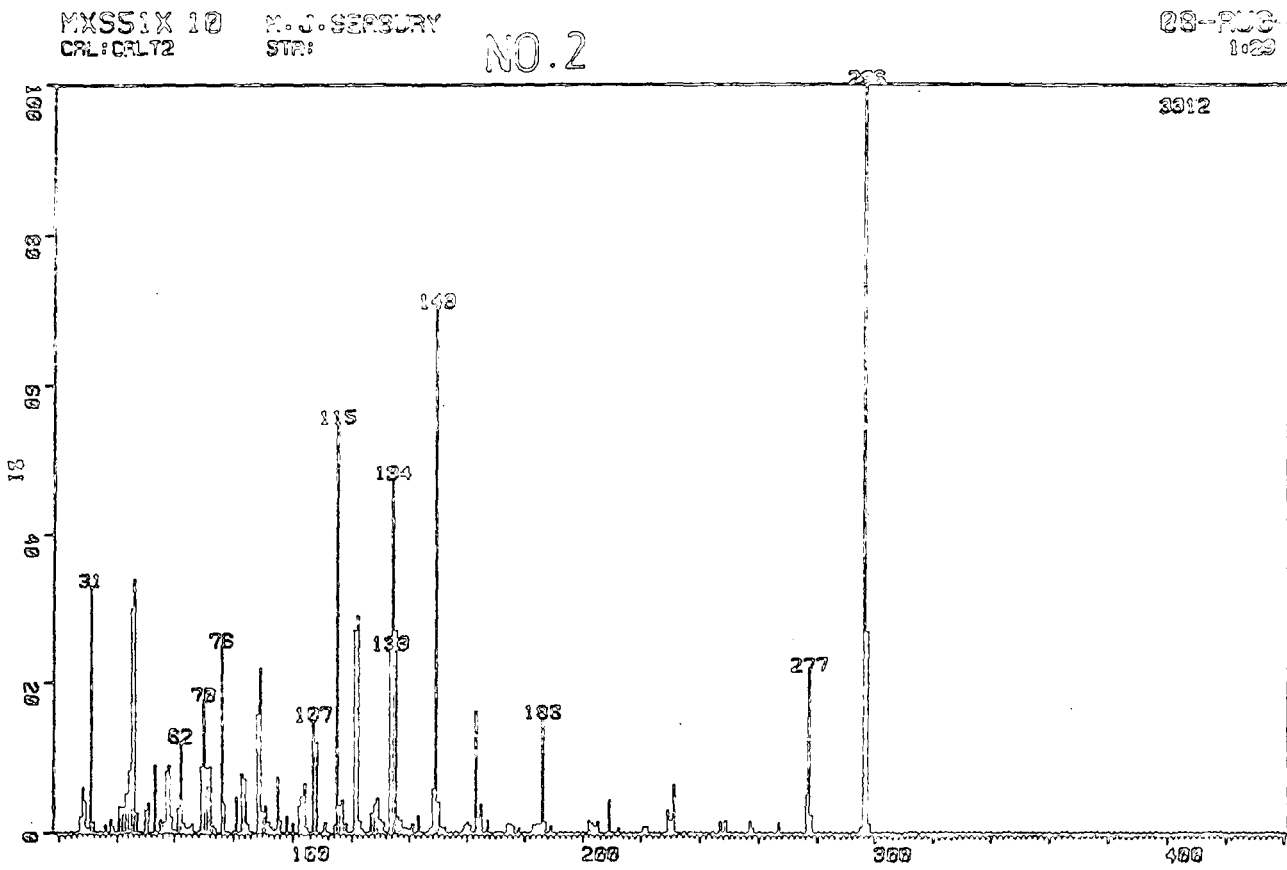
MXS40 5 M.J.SERBUAY
CRL1 CALM2S

NO.1

27-OCT-8



PEAK NO.	MASS	RLT. % BASE
1	27.23	1.07
2	29.13	25.78
3	30.07	1.57
4	30.90	87.40
5	31.09	5.09
6	41.08	1.24
7	57.14	0.91
8	67.01	8.07
9	69.96	14.99
10	71.02	3.71
11	76.01	2.60
12	80.87	15.98
13	81.95	1.73
14	86.92	2.39
15	98.00	3.13
16	98.01	9.64
17	99.94	37.15
18	100.99	2.64
19	105.03	2.31
20	106.99	23.56
21	107.98	1.24
22	111.96	6.59
23	124.03	2.06
24	126.03	1.89
25	130.95	72.13
26	131.93	1.89
27	145.01	6.18
28	156.97	4.12
29	175.98	100.00
30	176.98	6.01

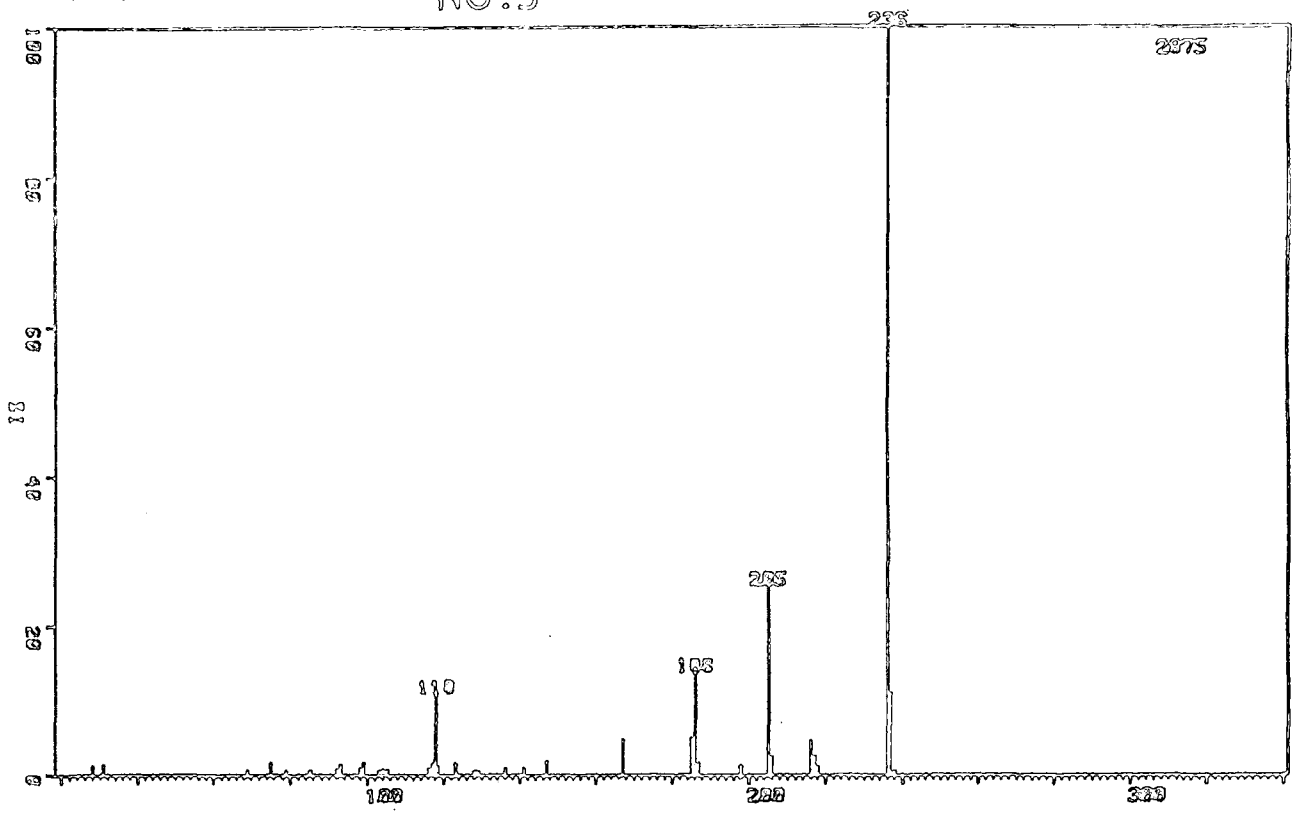


MASS	%HT. BASE	MASS	%HT. BASE	MASS	%HT. BASE	MASS	%HT. BASE
30.75	32.97	73.05	1.00	117.98	1.18	174.01	1.13
31.86	1.33	74.06	0.51	120.92	27.02	175.01	1.15
36.01	0.94	76.05	24.91	121.96	28.96	175.99	0.94
37.94	1.75	77.04	3.74	122.97	1.54	177.97	0.66
38.87	0.75	80.93	4.68	123.96	0.48	182.95	1.03
40.84	3.38	83.00	7.79	126.89	2.60	183.98	1.18
41.94	3.23	84.04	7.10	127.91	3.77	184.97	1.18
43.00	5.07	85.03	1.12	128.99	4.62	185.97	15.37
44.01	8.18	87.97	15.70	129.96	1.69	186.96	1.39
45.03	29.92	88.94	21.92	130.96	1.42	188.98	0.97
46.03	33.79	89.89	2.78	133.00	24.55	201.93	1.76
47.01	2.57	90.94	3.62	134.04	47.58	202.95	1.42
49.80	2.93	91.97	1.39	135.05	26.93	203.94	1.06
50.86	3.99	93.00	0.75	136.04	2.17	204.96	1.54
53.00	8.94	94.05	0.42	137.01	1.75	208.94	4.44
55.09	1.54	95.02	7.34	140.97	1.27	211.97	0.49
56.09	1.42	96.02	1.48	143.04	2.32	220.90	0.88
57.01	8.12	98.01	2.14	147.01	0.60	221.92	0.91
57.08	3.35	99.90	1.15	148.01	5.95	228.94	3.05
57.98	8.97	101.98	3.50	148.99	70.50	229.93	1.66
58.95	1.99	103.01	4.77	149.97	4.08	230.91	6.49
60.93	3.17	104.03	6.55	150.94	0.69	246.93	1.60
61.97	12.08	105.00	0.69	151.98	0.88	248.89	1.66
63.01	1.15	106.99	15.07	155.97	0.24	256.96	1.51
66.06	1.09	107.98	12.05	158.98	1.06	257.94	0.72
68.95	8.70	110.94	1.33	159.96	1.42	266.95	1.30
69.01	0.88	113.99	1.09	160.96	0.97	275.94	5.07
69.90	17.63	115.01	55.07	163.02	16.24	276.94	21.74
70.96	8.54	116.01	3.65	164.00	2.02	277.93	2.48
72.02	8.73	116.98	4.50	164.99	3.83	294.91	0.75
				166.98	1.69	295.92	100.00
						296.93	26.81

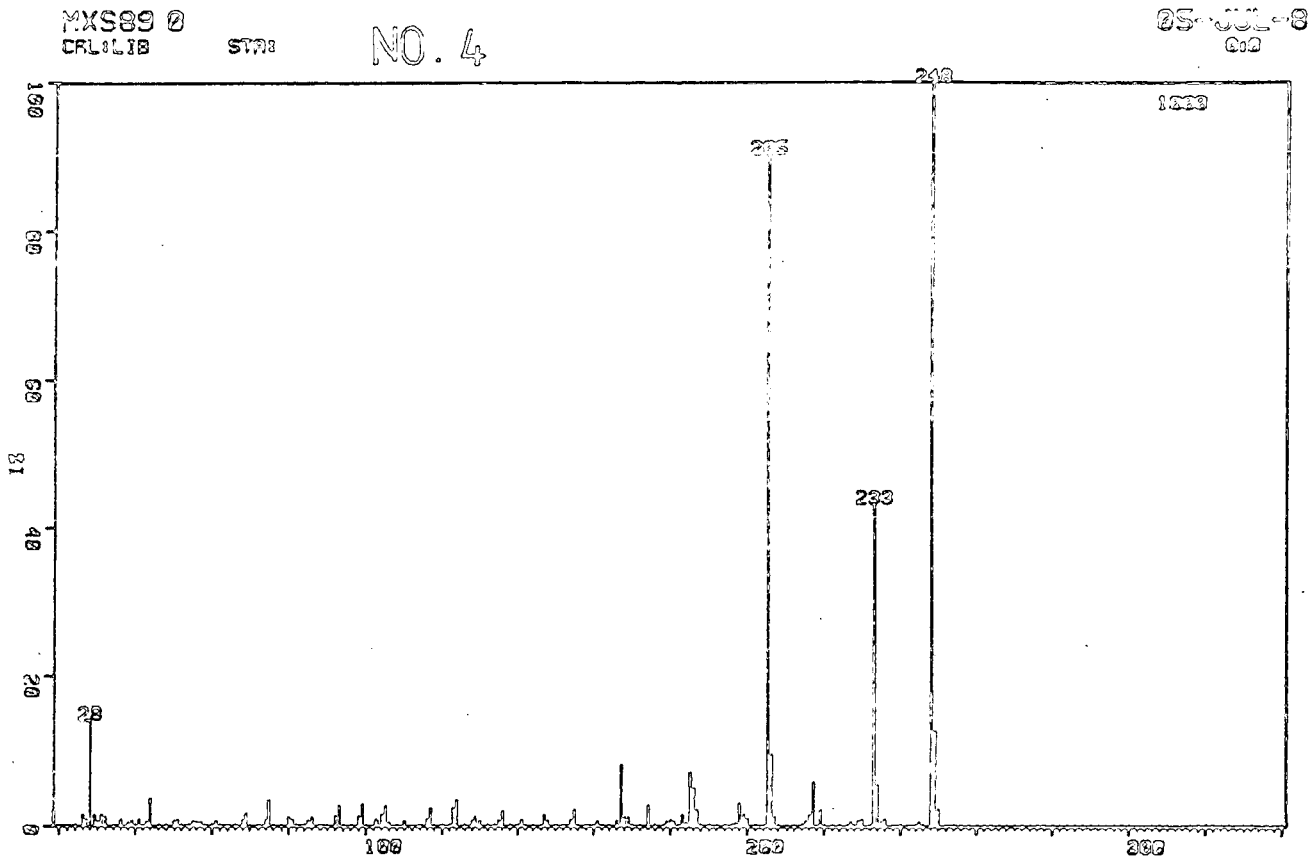
MXS90 6 M.J.SWINBURN
CAL:CAL15

NO.3

15-DEC-83



PEAK NO.	MASS	%HT. BASE
1	28.13	1.15
2	30.92	1.36
3	69.03	0.52
4	75.14	1.63
5	78.99	0.56
6	85.10	0.59
7	92.02	0.77
8	93.04	1.43
9	98.04	0.90
10	99.00	1.77
11	103.07	0.59
12	104.09	0.73
13	105.11	0.73
14	116.08	0.87
15	117.05	1.63
16	118.00	11.06
17	118.53	1.15
18	123.07	1.53
19	128.05	0.52
20	129.04	0.56
21	136.03	0.87
22	141.03	0.87
23	146.99	1.91
24	167.08	4.73
25	185.07	4.97
26	186.05	13.08
27	187.09	1.63
28	198.11	1.29
29	205.01	25.39
30	205.99	2.47
31	216.05	4.59
32	217.08	2.54
33	218.08	1.08
34	236.03	100.00
35	236.95	10.96
36	237.96	0.56



PEAK NO.	MASS	%HT. BASE
7	32.02	1.20
8	36.16	0.85
9	38.06	0.47
10	39.02	0.66
11	41.00	0.89
12	43.16	0.50
13	44.14	3.61
14	49.91	0.66
15	50.99	0.81
16	55.20	0.54
17	56.15	0.58
18	57.15	0.50
19	61.02	0.66
20	68.10	0.81
21	69.02	1.59
22	74.11	0.89
23	75.08	3.37
24	79.91	1.12
25	80.99	0.81
26	85.10	0.70
27	86.08	1.12
28	92.04	1.32
29	93.04	2.68
30	98.05	1.36
31	98.99	2.95
32	102.54	0.97
33	103.06	0.74
34	104.08	1.47
35	105.08	2.60

PEAK NO.	MASS	%HT. BASE
38	116.08	1.05
39	117.07	2.29
40	123.06	2.33
41	124.09	3.45
42	128.11	0.74
43	129.04	1.20
44	130.03	0.74
45	135.08	0.81
46	136.09	1.98
47	141.06	0.81
48	147.04	1.51
49	148.03	0.81
50	154.09	0.89
51	155.11	2.13
52	161.03	0.66
53	166.12	0.78
54	167.00	8.11
55	167.37	1.01
56	167.99	1.20
57	169.01	1.24
58	174.05	2.75
59	179.11	0.50
60	180.18	0.81
61	180.99	0.58
62	182.98	1.55
63	184.00	0.39
64	184.91	7.10
65	185.89	4.93
66	187.00	2.06

PEAK NO.	MASS	%HT. BASE
67	197.01	0.43
68	197.97	2.79
69	198.98	1.47
70	200.03	1.01
71	204.94	90.42
72	205.88	9.39
73	206.72	1.20
74	215.13	0.66
75	216.13	1.47
76	217.02	5.78
77	218.74	2.17
78	227.21	0.54
79	229.13	0.70
80	230.07	0.93
81	232.99	43.29
82	233.95	5.31
83	235.07	0.58
84	236.11	1.05
85	245.01	0.58
86	247.88	100.00
87	248.87	12.65
88	249.74	2.21

MXS871 0 M.J.SEABURY
CAL:CALM6

NO.5

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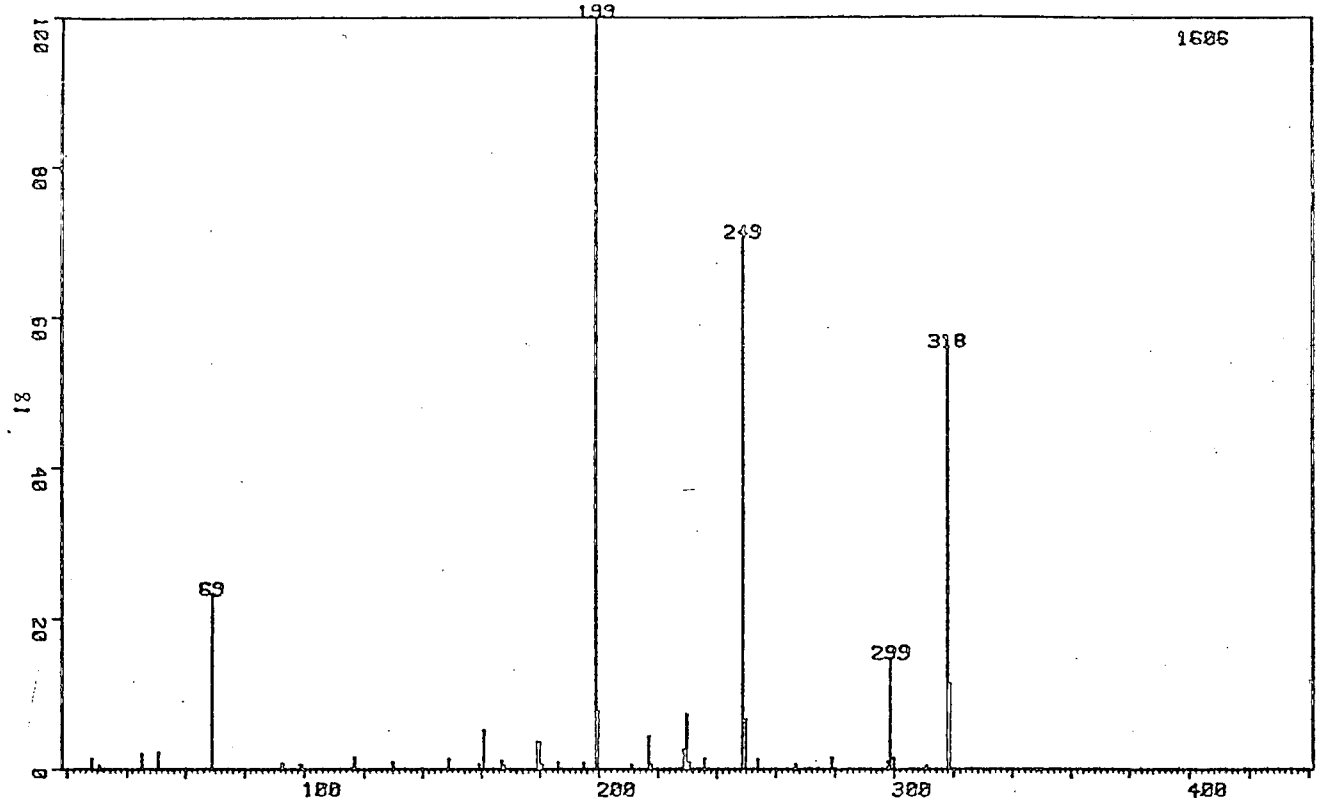
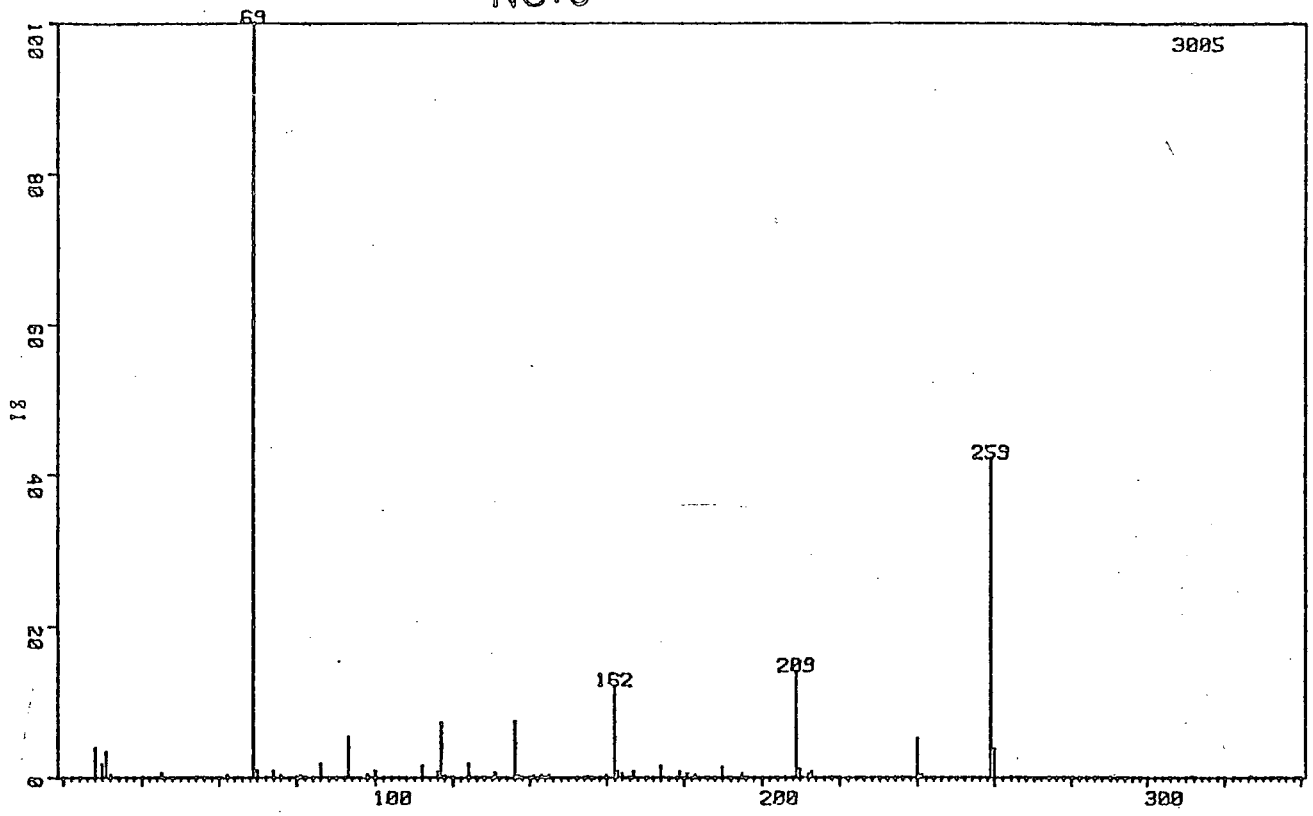


PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE
1	27.25	0.87	29	162.00	0.48
2	28.13	11.80	30	166.99	2.36
3	29.01	2.94	31	167.99	1.20
4	29.82	1.49	32	178.97	4.29
5	30.92	6.64	33	179.94	3.90
6	32.01	2.07	34	181.00	0.58
7	43.12	1.40	35	183.00	0.53
8	44.15	0.72	36	186.00	1.01
9	45.18	13.72	37	195.00	3.08
10	46.16	0.53	38	198.00	1.11
11	50.96	2.84	39	198.98	100.00
12	58.09	2.02	40	199.97	7.66
13	59.03	3.76	41	210.99	0.72
14	68.99	29.03	42	217.00	8.52
15	73.11	1.40	43	218.02	0.87
16	74.13	1.25	44	228.99	2.65
17	75.05	0.43	45	230.02	6.88
18	92.98	1.01	46	231.05	0.72
19	98.95	1.01	47	248.95	66.39
20	117.00	2.70	48	249.94	5.73
21	129.92	1.11	49	267.04	2.17
22	147.98	0.53	50	279.01	1.35
23	148.98	1.35	51	298.01	1.30
24	159.00	0.43	52	299.00	14.20
25	159.21	0.43	53	299.99	1.49
26	159.50	0.43	54	317.99	50.89
27	159.94	0.58	55	318.88	7.27
28	160.97	5.63			

MXS873 3 M.J.SEABURY
CAL:CALM6

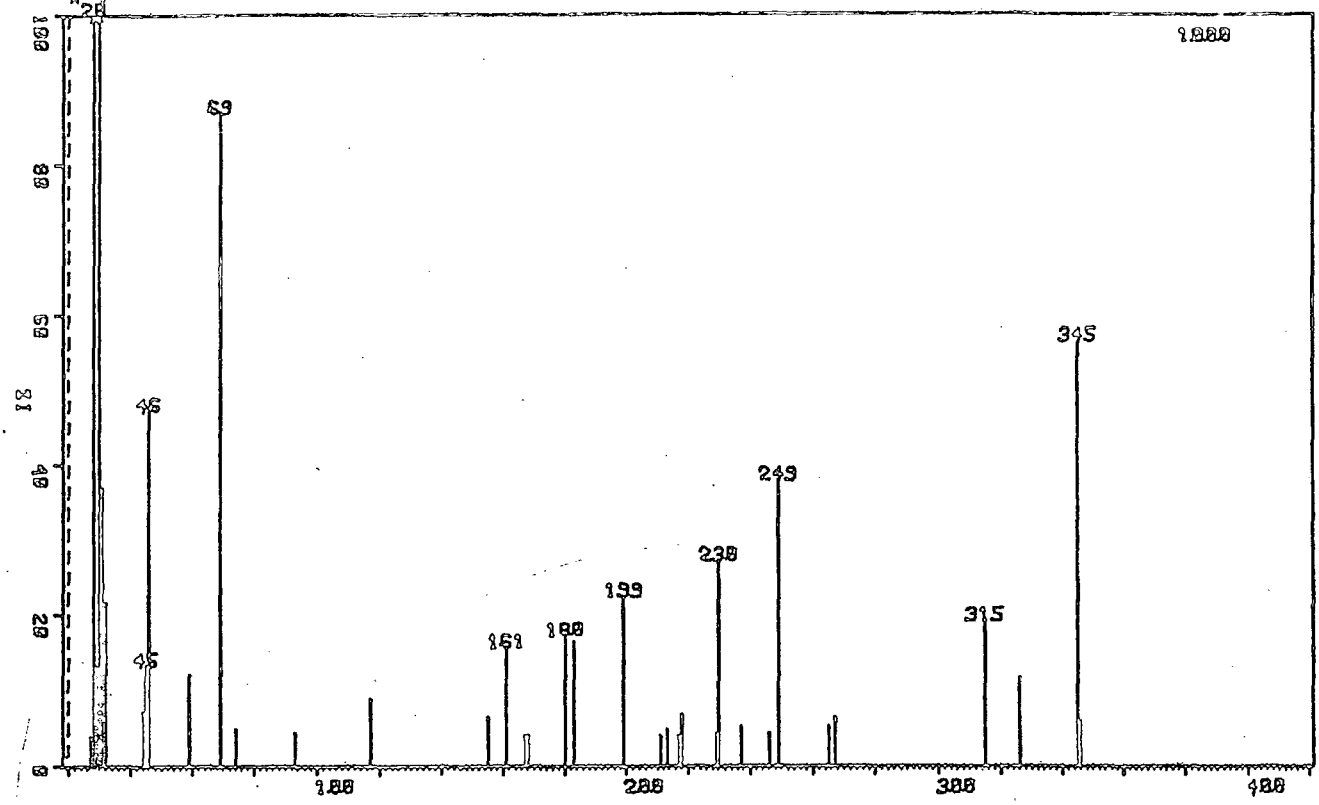
NO.6

06-FEB-84



PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE
1	28.07	3.86	24	140.91	0.33
2	29.77	1.83	25	142.96	0.50
3	30.83	3.36	26	144.97	0.37
4	31.95	0.50	27	154.92	0.33
5	45.14	0.60	28	159.85	0.40
6	62.00	0.37	29	161.90	12.15
7	68.94	100.00	30	162.91	0.87
8	69.88	1.06	31	163.91	0.63
9	74.05	0.93	32	166.93	0.83
10	76.05	0.37	33	173.90	1.63
11	80.90	0.37	34	178.87	0.83
12	86.00	1.86	35	180.90	0.60
13	92.98	5.36	36	182.96	0.43
14	97.98	0.43	37	189.89	1.43
15	99.92	1.00	38	194.96	0.60
16	111.95	1.63	39	208.89	14.08
17	115.98	0.83	40	209.92	1.20
18	116.97	7.29	41	211.95	0.57
19	117.95	0.37	42	212.93	0.90
20	123.97	1.90	43	239.81	5.26
21	130.89	0.70	44	240.92	0.50
22	135.98	7.49	45	258.92	42.26
23	136.96	0.40	46	259.83	3.83

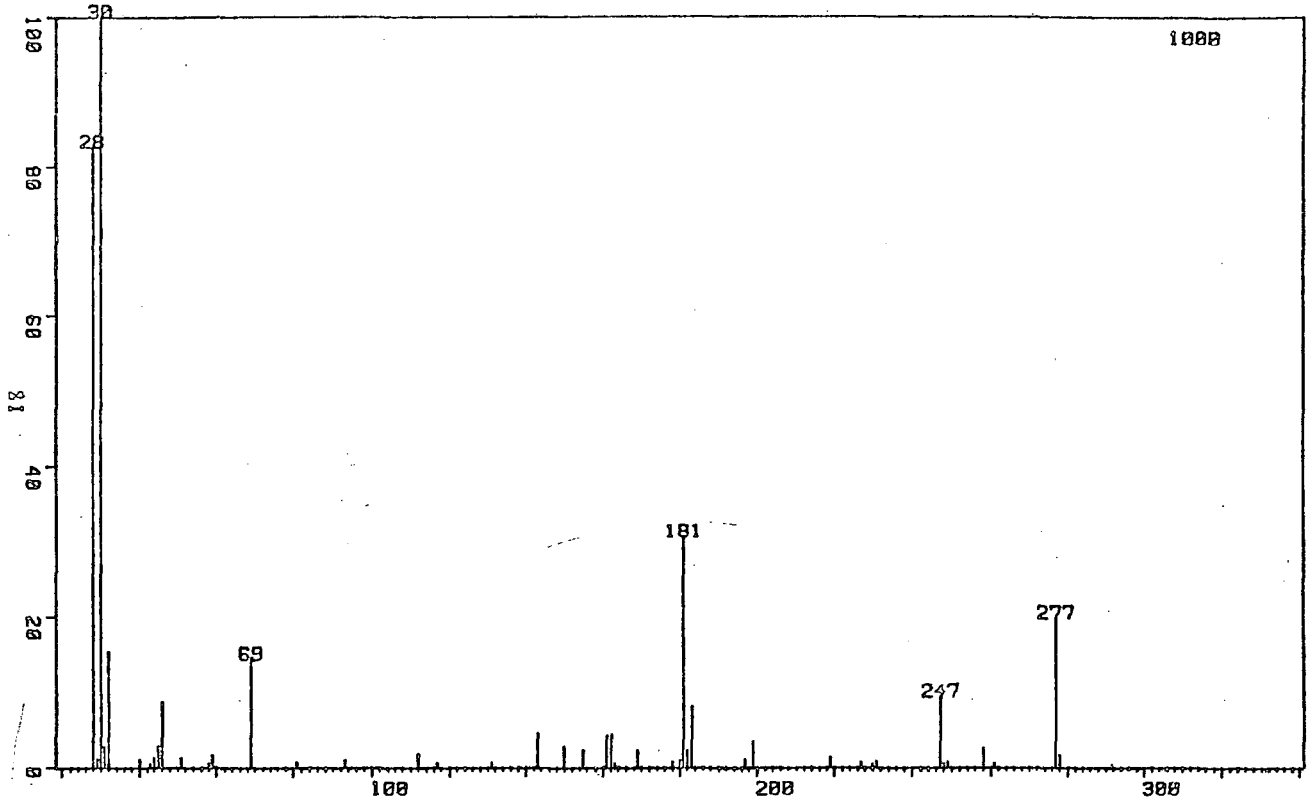
MXS870 0 NO.7 05-JUL-84



PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE
1	27.00	1.00%	22	168.00	1.00%
2	28.00	34.00%	24	180.00	4.30%
3	29.00	3.30%	26	183.00	4.10%
4	30.00	100.00%	27	199.00	5.60%
5	31.00	9.20%	29	211.00	1.00%
6	32.00	5.40%	30	213.00	1.20%
9	44.00	1.80%	31	217.00	1.00%
10	45.00	3.30%	32	219.00	1.70%
11	46.00	11.80%	34	229.00	1.10%
13	59.00	3.00%	35	230.00	6.80%
14	69.00	21.70%	37	237.00	1.30%
15	74.00	1.20%	39	246.00	1.10%
16	93.00	1.10%	40	249.00	9.50%
17	117.00	2.20%	42	265.00	1.30%
19	155.00	1.60%	43	267.00	1.60%
20	161.00	3.90%	46	315.00	4.80%
21	167.00	1.00%	48	326.00	2.90%
			49	345.00	14.10%

MXS872 0
CAL:LIB STA: NO.8

06-JUL-84
0:0

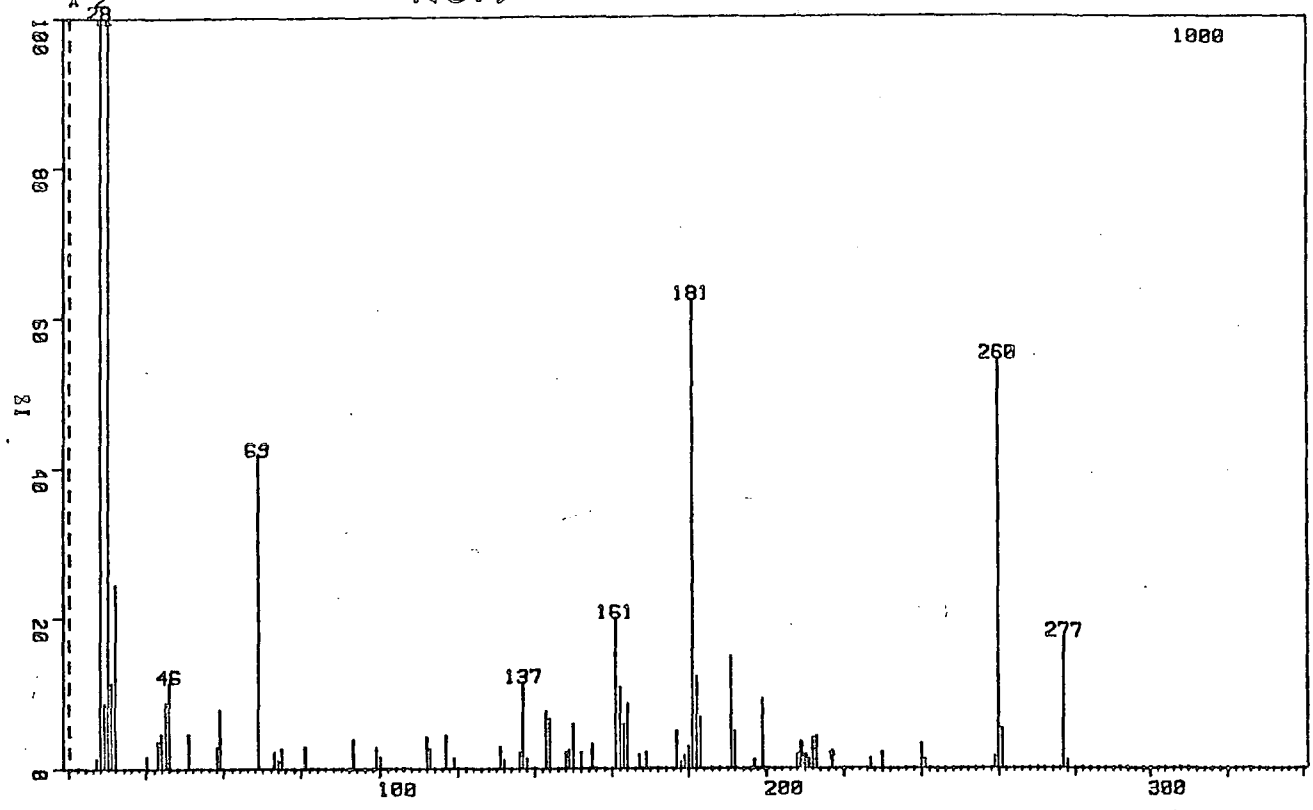


PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE
1	28.00	82.70%	23	161.00	4.30%
2	29.00	1.30%	24	162.00	4.50%
3	30.00	100.00%	25	163.00	0.60%
4	31.00	2.80%	26	169.00	2.30%
5	32.00	15.50%	27	178.00	0.90%
6	40.00	1.10%	28	180.00	1.10%
7	43.00	0.60%	29	181.00	30.70%
8	44.00	1.50%	30	182.00	2.40%
9	45.00	2.80%	31	183.00	8.10%
10	46.00	8.70%	32	197.00	1.20%
11	51.00	1.40%	33	199.00	3.40%
12	58.00	0.60%	34	219.00	1.50%
13	59.00	1.70%	35	227.00	0.80%
14	69.00	14.40%	36	230.00	0.50%
15	81.00	0.80%	37	231.00	1.00%
16	93.00	1.10%	38	247.00	9.40%
17	112.00	1.90%	39	248.00	0.60%
18	117.00	0.70%	40	249.00	0.90%
19	131.00	0.80%	41	259.00	2.60%
20	143.00	4.60%	42	261.00	0.60%
21	150.00	2.90%	43	277.00	19.80%
22	158.00	2.40%	44	278.00	1.90%

MXS871 0
CAL:LIB STA:

NO.9

05-JUL-84
0:0

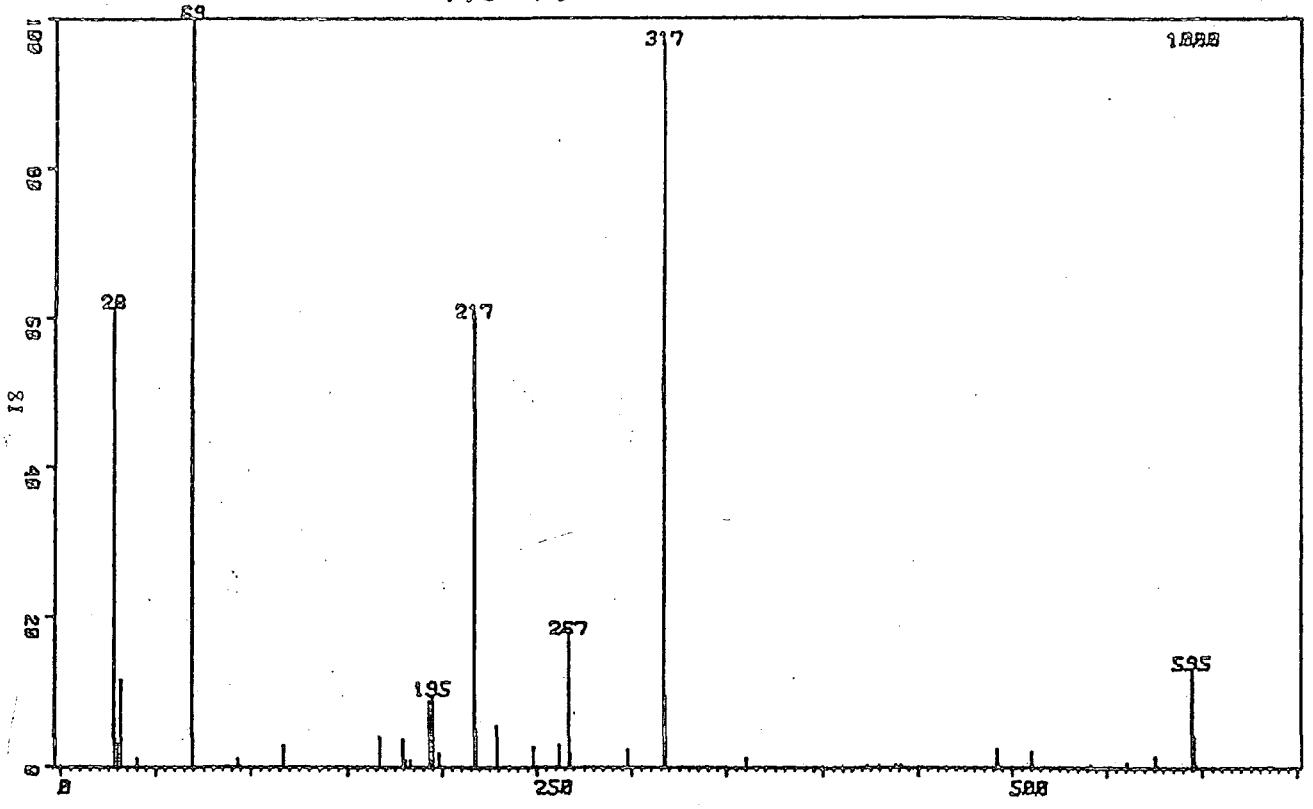


PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE
6	39.84	1.26	44	138.04	1.20	75	190.99	16.14
7	43.12	1.01	45	141.02	0.52	76	192.01	4.95
8	44.13	2.21	46	142.05	0.43	77	193.03	0.71
9	45.17	1.08	47	143.07	6.43	78	195.05	0.37
10	46.13	8.55	48	144.07	5.72	79	197.03	1.23
11	48.97	0.37	49	145.07	0.71	80	198.05	0.40
12	50.96	2.98	50	148.02	1.66	81	199.01	6.98
13	59.01	0.46	51	149.00	1.78	82	200.03	0.71
14	62.05	0.46	52	149.98	5.26	83	205.05	0.52
15	64.13	0.40	53	151.02	1.11	84	207.09	0.40
16	67.08	0.92	54	152.04	1.41	85	208.03	2.00
17	68.98	22.45	55	155.05	2.21	86	209.03	0.49
18	69.93	0.34	56	159.97	1.14	87	210.00	1.57
19	75.10	1.88	57	161.00	17.37	88	211.01	1.38
20	80.99	1.81	58	162.03	7.47	89	212.03	3.08
24	93.06	2.98	59	163.06	4.24	90	213.04	2.92
25	97.05	1.14	60	164.06	8.15	91	218.04	0.34
26	98.02	0.58	61	165.07	0.65	92	222.05	0.31
27	99.00	2.03	62	167.05	1.01	93	227.03	2.00
28	99.95	1.17	63	168.05	0.95	94	229.01	0.49
29	106.08	0.34	64	169.02	2.21	95	230.00	2.49
30	111.00	0.92	65	175.10	0.40	96	231.03	0.43
31	112.05	3.63	66	176.08	0.52	97	232.05	1.01
32	113.05	1.75	67	177.05	4.89	98	239.96	1.88
33	114.08	1.01	68	178.05	1.14	106	260.00	54.40
34	117.06	2.55	69	179.00	1.17	107	261.03	5.75
35	119.01	1.38	70	180.00	3.63	108	262.05	0.55
40	131.02	2.46	71	181.03	51.17	109	267.05	0.52
41	132.04	1.14	72	182.02	10.98	110	277.04	19.71
42	136.07	1.17	73	183.02	2.83	111	278.05	1.85
43	137.07	10.61	74	188.04	0.40			

MXS7F2 0
CAL:LIB STA:

NO.10

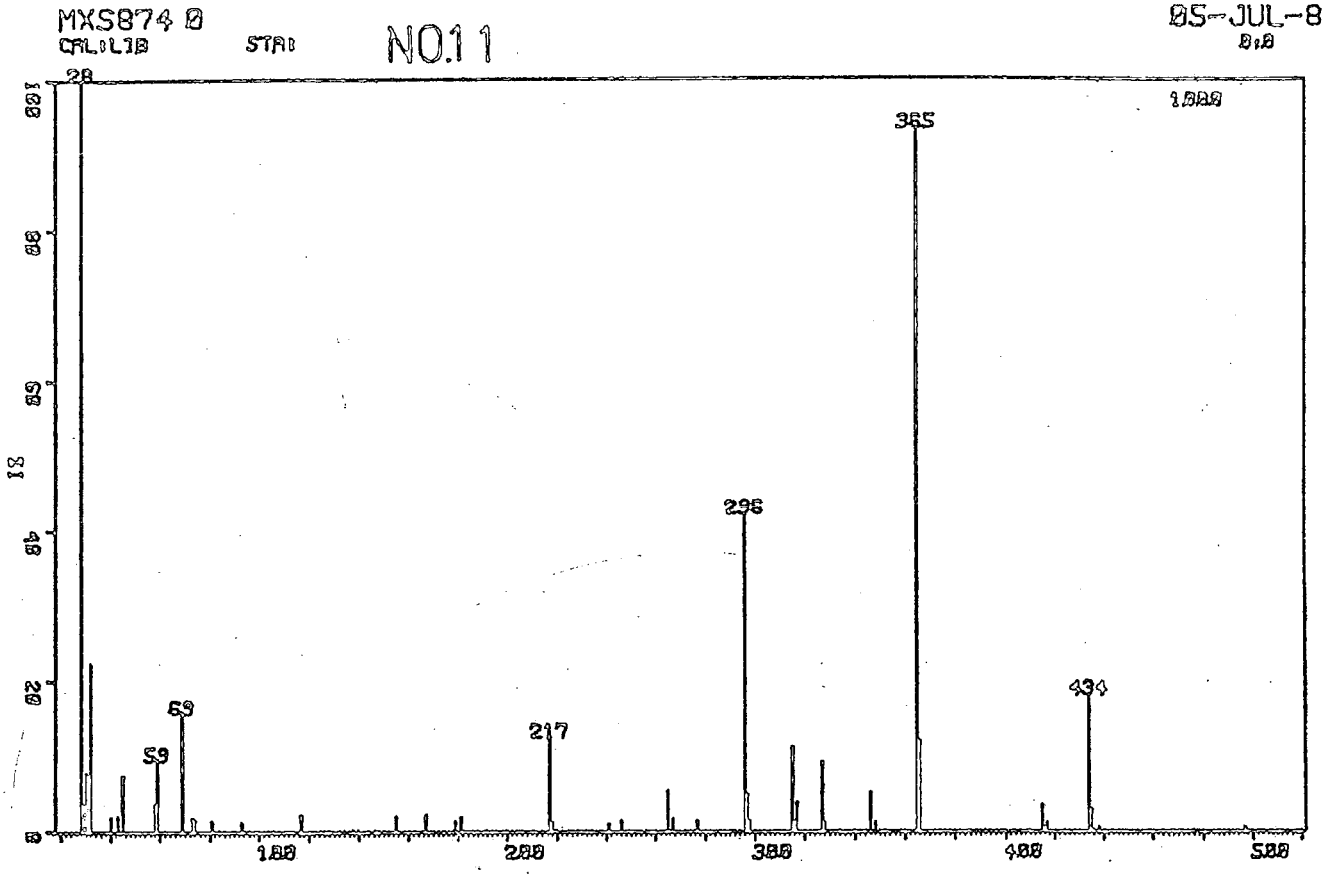
05-JUL-8



PEAK NO.	MASS	%HT. BASE
1	28.13	61.29
2	28.99	0.59
3	29.82	3.15
4	30.91	0.85
5	32.01	11.61
6	39.83	1.12
7	44.12	0.68
8	45.17	0.65
9	46.12	0.38
10	68.97	100.00
11	69.91	0.97
12	93.02	1.12
13	117.02	2.79
14	124.06	0.73
23	167.02	3.97
24	168.02	0.50
25	169.00	0.32
26	178.02	0.35
27	178.97	3.67
28	179.94	0.65
29	181.00	1.00
30	183.02	1.03
31	186.01	0.82
32	192.97	8.76
33	194.03	0.91
34	194.98	9.67
35	196.01	0.82

PEAK NO.	MASS	%HT. BASE
36	197.99	1.88
41	216.96	60.14
42	217.97	5.00
43	228.97	5.50
44	229.96	0.97
45	236.01	0.65
46	247.93	2.56
47	248.96	0.56
48	258.96	0.68
49	260.00	0.79
50	261.96	2.79
51	263.03	0.35
52	266.96	17.75
53	267.99	1.68
57	297.91	2.29
58	299.00	0.32
59	316.97	96.56
60	317.92	9.44
61	318.99	0.50
62	340.98	0.38
63	359.94	1.23
68	491.90	2.35
69	492.93	0.53
70	509.92	2.06

PEAK NO.	MASS	%HT. BASE
73	560.86	0.62
74	575.86	1.53
75	576.94	0.35
76	594.85	13.14
77	595.86	3.97
78	597.04	0.32



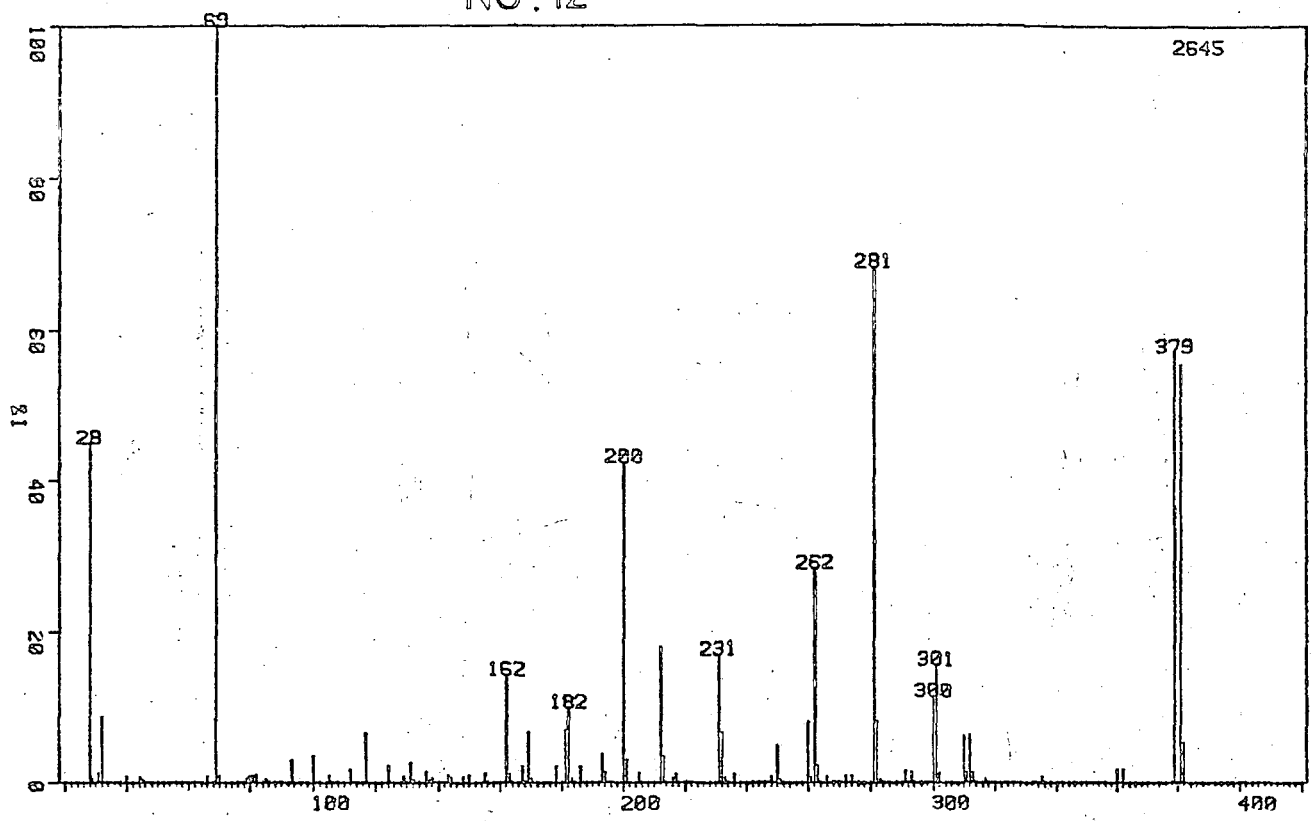
PEAK NO.	MASS	%HT. BASE
2	28.00	100.00%
3	29.00	3.60%
4	30.00	7.80%
5	31.00	7.30%
6	32.00	22.30%
7	40.00	1.90%
9	43.00	2.00%
11	45.00	7.30%
13	58.00	3.60%
14	59.00	9.50%
15	69.00	15.70%
16	73.00	1.70%
17	74.00	1.50%
18	91.00	1.40%
19	93.00	1.10%
21	117.00	2.20%
24	155.00	2.00%
26	167.00	2.20%
27	179.00	1.40%
28	181.00	1.90%
33	217.00	12.50%
34	218.00	1.20%
35	241.00	1.00%
36	246.00	1.40%

PEAK NO.	MASS	%HT. BASE
40	265.00	5.30%
42	267.00	1.70%
43	277.00	1.40%
44	296.00	42.30%
45	297.00	5.00%
46	298.00	1.40%
47	315.00	11.20%
48	316.00	1.40%
49	317.00	3.90%
50	327.00	9.10%
51	328.00	1.20%
52	346.00	5.10%
54	348.00	1.20%
56	365.00	93.40%
57	366.00	12.00%
60	415.00	3.40%
61	416.00	0.90%
62	417.00	1.50%
63	434.00	12.30%
64	435.00	2.10%
65	438.00	0.50%
66	497.00	0.50%
67	510.00	0.50%

MXS921 2 M.J.SEABURY
CAL:CALM13

NO.12

15-MAR-8



PEAK NO.	MASS	%HT. BASE
1	28.07	45.07
2	28.94	0.49
3	30.83	1.32
4	31.95	8.70
5	39.81	0.79
6	44.10	0.72
7	45.15	0.38
8	66.12	0.87
9	68.93	100.00
10	69.87	0.98
11	78.87	0.57
12	79.85	0.91
13	80.94	0.87
14	81.94	1.07
15	85.09	0.42
16	93.08	3.14
17	100.01	3.55
18	105.10	0.95
19	112.05	1.74
20	117.08	6.54
21	124.10	2.27
22	128.95	0.83
23	131.00	2.61
24	132.05	0.49
25	136.06	1.44
26	137.06	0.34
27	138.04	0.60
28	143.06	0.95
29	144.09	0.76
30	148.04	0.72
31	150.00	1.06
32	155.07	1.29
33	162.03	14.33
34	163.06	1.21
35	167.06	2.27
36	169.01	6.69
37	170.02	0.53
38	178.03	2.31
39	181.01	7.07
40	182.05	9.94
41	183.11	0.64
42	186.02	2.23
43	193.01	3.74
44	194.03	1.40
45	199.92	42.53
46	200.96	3.10
47	205.02	1.32
48	211.98	18.03
49	213.00	3.44
50	215.98	0.64
51	217.00	1.17
52	230.94	17.01
53	231.97	6.58
54	233.01	0.68
55	235.99	1.10
56	247.99	0.79
57	249.94	4.80
58	250.97	0.45
59	259.99	0.11
60	260.94	0.79
61	262.01	28.43
62	263.04	2.23
63	266.03	0.72
64	271.95	0.91
65	273.95	0.95
66	281.00	68.39
67	281.96	8.13
68	283.06	0.45
69	290.89	1.63
70	292.96	1.47
71	299.97	11.46
72	301.00	15.58
73	302.02	1.29
74	309.92	6.24
75	310.97	1.44
76	311.98	0.55
77	312.98	1.40
78	317.06	0.53
79	335.07	0.87
80	359.95	1.81
81	361.96	1.85
82	378.95	57.09
83	380.94	55.46
84	381.91	5.23

X93D2X 10 M.J.SERBURY 93D2 NO.13 01-AUG-8
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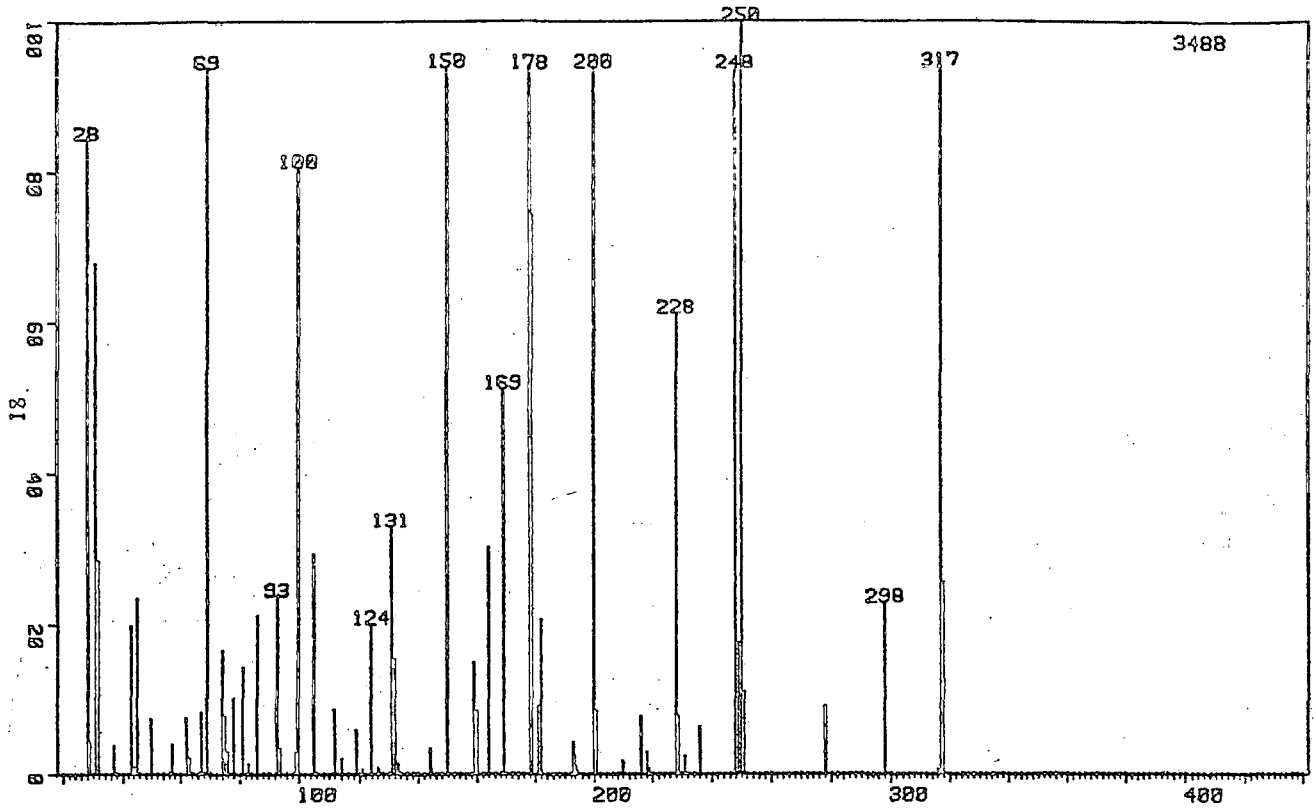
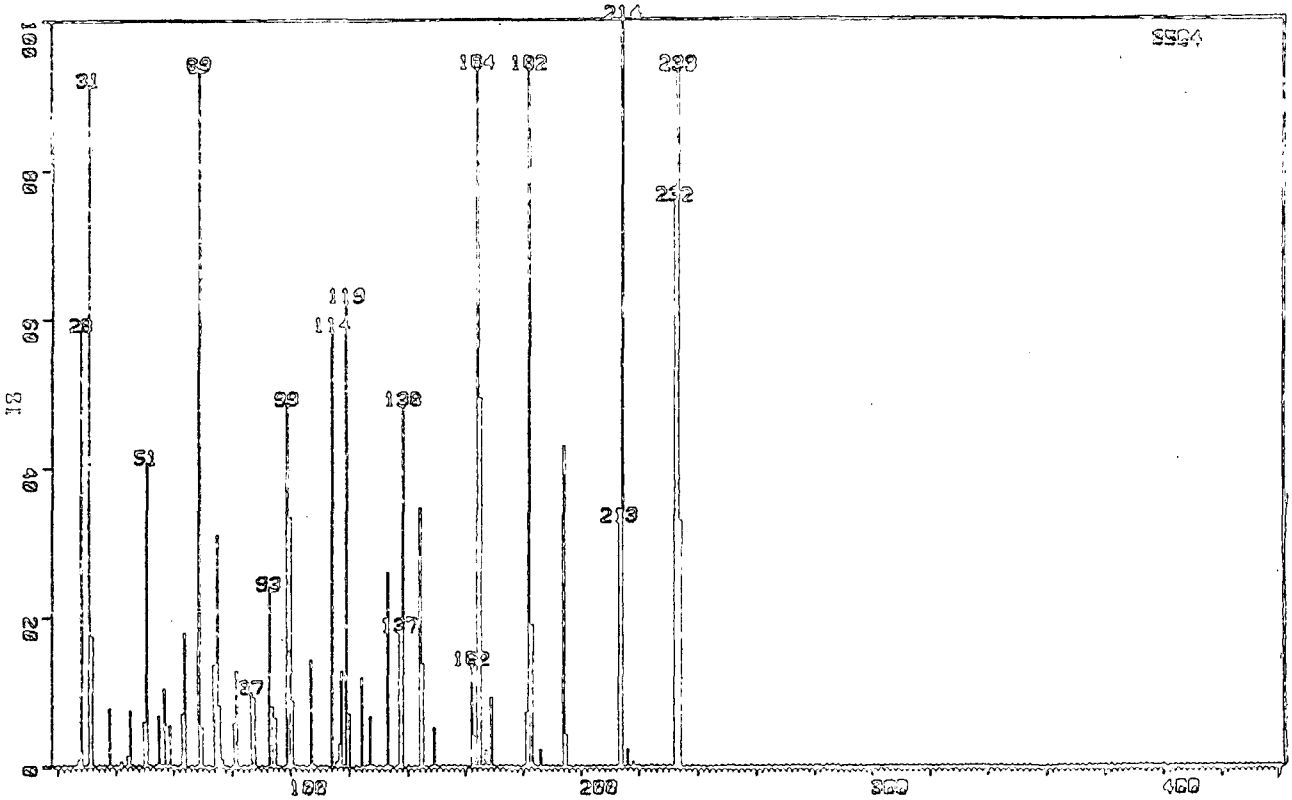
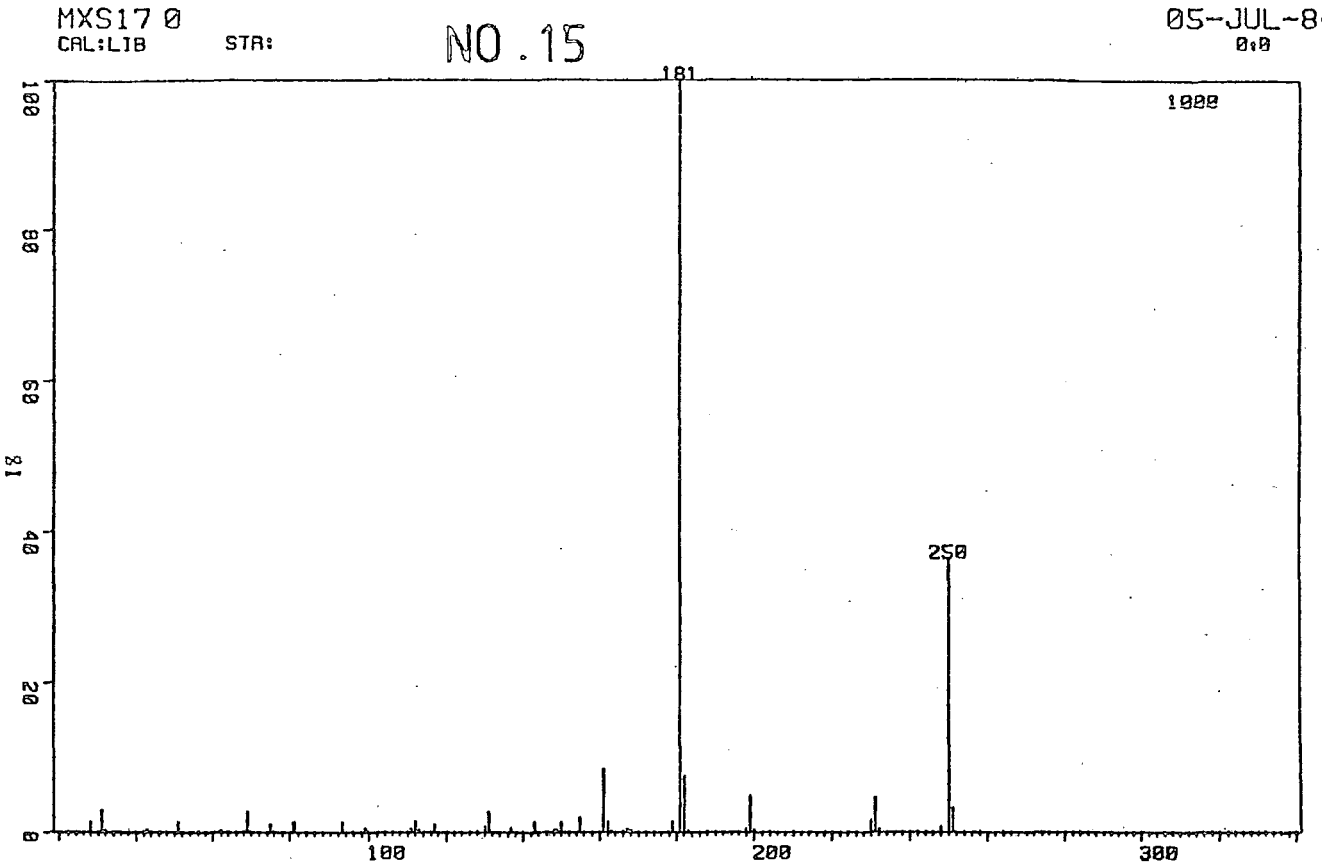


MASS	%HT. BASE	MASS	%HT. BASE	MASS	%HT. BASE
28.02	84.37	105.00	29.33	199.80	93.89
28.05	31.65	111.94	8.60	200.91	8.49
28.92	4.19	114.01	2.06	209.49	1.83
30.76	67.89	118.92	5.93	209.96	1.29
31.87	28.44	120.93	0.63	215.90	7.77
37.01	3.73	123.99	20.18	217.87	2.95
42.99	19.72	130.91	33.03	218.92	0.63
44.03	0.95	131.93	15.45	227.92	61.41
45.06	23.37	132.97	1.35	228.95	7.65
49.81	7.34	144.00	3.35	230.92	2.41
57.05	3.93	149.89	93.89	235.95	6.34
61.97	7.34	158.93	14.94	247.88	93.61
63.02	2.04	159.91	8.46	248.94	17.66
67.04	8.26	163.99	30.25	249.87	100.00
68.96	93.61	168.92	51.35	250.97	11.18
74.05	16.51	177.88	93.72	277.94	9.03
75.05	7.65	178.95	74.31	297.89	23.05
76.04	2.84	180.95	9.17	315.91	0.77
77.98	10.26	181.97	20.76	316.93	93.95
80.92	14.31	192.97	4.19	317.89	25.69
82.99	1.29	193.27	0.54		
86.00	21.07	193.72	2.38		
92.96	23.85	194.28	1.06		
93.99	3.38	194.43	0.46		
98.91	2.78	194.66	0.43		
99.87	80.71				

X93D1X 12 M.J.SERBURY 93D1 NO.14 01-AUG-8
CRL:CRLT2 STR: 1:48



MASS	ZHT. BASE	MASS	ZHT. BASE	MASS	ZHT. BASE
28.04	2.14	98.95	48.40	186.02	2.25
30.76	91.32	99.91	33.30	194.05	42.92
31.87	17.35	100.85	8.68	195.06	4.22
37.96	7.71	107.03	14.27	213.05	32.88
41.95	0.57	114.04	58.42	214.03	100.00
44.02	1.34	115.70	0.60	216.00	2.25
45.06	7.31	116.60	2.94	218.01	0.60
49.83	5.91	117.09	12.79	231.98	75.80
50.87	40.64	119.04	62.33	233.02	93.29
55.05	6.76	120.02	7.11	234.05	32.88
57.04	10.36	124.10	11.84		
58.97	5.34	126.99	6.62		
63.03	6.93	133.10	26.03		
64.08	17.92	137.09	18.24		
68.97	93.29	138.08	48.40		
69.91	5.14	144.11	34.67		
74.06	13.53	145.09	13.67		
75.06	31.02	149.02	5.11		
76.07	8.08	162.05	13.70		
77.06	1.00	163.06	4.00		
80.95	5.68	164.05	93.55		
81.99	12.76	165.09	49.32		
87.00	9.79	167.05	1.97		
87.99	9.13	169.01	9.10		
92.98	23.72	181.02	7.16		
94.01	7.99	182.01	93.46		
95.03	6.36	183.04	19.04		



PEAK NO.	MASS	%HT. BASE
1	28.07	1.40
2	30.82	3.01
3	31.94	0.37
4	43.07	0.49
5	50.91	1.40
6	62.00	0.29
7	68.92	2.75
8	75.00	1.12
9	80.87	1.46
10	92.96	1.40
11	98.94	0.63
12	110.92	0.54
13	111.95	1.55
14	112.96	0.49
15	116.97	1.15
16	129.86	0.83
17	130.93	2.72
18	136.97	0.60
19	142.95	1.40
20	147.94	0.26
21	148.89	0.43
22	149.89	1.37
23	154.94	1.93
24	160.88	8.45
25	161.94	1.52
26	162.98	0.29
27	166.97	0.54
28	167.98	0.29
29	178.92	1.52
30	180.88	100.00
31	181.91	7.48
32	182.97	0.32
33	197.95	0.57
34	198.94	4.84
35	199.93	0.49
36	229.89	1.60
37	230.90	4.55
38	231.95	0.49
39	247.89	0.83
40	249.91	35.38
41	250.93	3.21

MXS173 0
CAL:L7B STR1

NO.16

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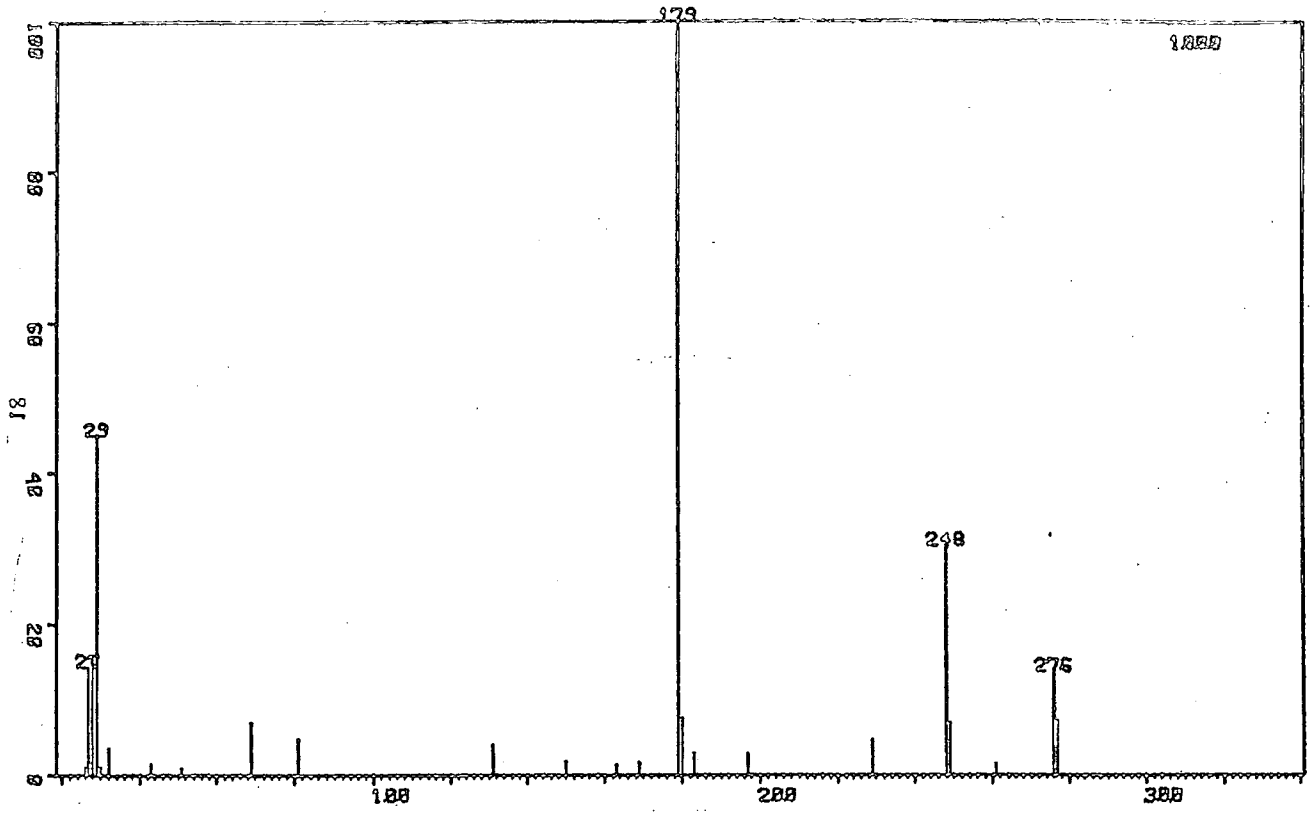
0:0



PEAK NO.	MASS	%HT. BASE	PEAK NO.	MASS	%HT. BASE
1	26.31	1.10	23	155.02	0.66
2	27.25	14.32	24	158.98	0.57
3	28.13	15.51	25	160.95	0.66
4	29.02	44.98	26	162.01	0.74
5	29.85	1.10	27	163.02	1.45
6	30.92	0.96	28	168.99	1.75
7	32.01	3.64	29	177.05	0.96
8	43.11	1.53	30	178.97	100.00
9	44.12	0.39	31	180.28	7.58
10	50.94	1.01	32	181.95	0.57
11	68.96	6.96	33	182.92	3.02
12	75.11	0.48	34	196.92	2.93
13	80.95	4.86	35	198.97	0.44
14	99.00	0.61	36	227.04	0.48
15	100.98	0.74	37	228.79	4.77
16	119.01	0.57	38	230.06	0.53
17	131.00	4.03	39	247.92	30.31
18	132.04	0.66	40	248.83	4.92
19	137.11	0.44	41	261.01	1.53
20	143.05	0.74	42	275.98	13.75
21	149.93	1.80	43	276.77	7.23
22	151.12	0.44			

APPENDIX FOUR

RATE DATA

Pentafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (min.)	Titre (ml.)	$10^4 k$ ($1 mol^{-1} s^{-1}$)
0	7.50	-
30	7.08	6.83
74	6.54	6.73
150	5.82	6.79
182	5.58	6.81
271	5.04	6.74
360	4.60	6.79
480	4.19	6.81

$[NH_3]_o$ = 7.23×10^{-2} moles l^{-1}

$[substrate]_o$ = 2.51×10^{-2} moles l^{-1}

k = $(6.79 \pm 0.03) \times 10^{-4}$ $l\ mol^{-1}\ s^{-1}$ (7 readings)

duplicate k = $(6.81 \pm 0.04) \times 10^{-4}$ $l\ mol^{-1}\ s^{-1}$ (7 readings)

mean k = $(6.80 \pm 0.03) \times 10^{-4}$ $l\ mol^{-1}\ s^{-1}$

4-Chlorotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	10^6 k (l mol^{-1} s^{-1})
0	32.33	-
1423	31.20	(2.44)
2872	30.00	3.02
4325	28.52	3.08
7177	26.37	3.14
8622	25.62	3.06
10059	24.67	3.14
11481	23.77	3.14
12927	23.03	3.16
18685	20.50	3.14

$[NH_3]_o$ = 0.191 moles l^{-1}

$[substrate]_o$ = 8.48×10^{-2} moles l^{-1}

k = $(3.12 \pm 0.02) \times 10^{-6}$ l mol^{-1} s^{-1} (8 readings)

duplicate k = $(3.12 \pm 0.02) \times 10^{-6}$ l mol^{-1} s^{-1} (7 readings)

mean k = $(3.12 \pm 0.02) \times 10^{-6}$ l mol^{-1} s^{-1}

4-Bromotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (min.)	Titre (ml.)	10^6 k (l mol^{-1} s^{-1})
0	33.86	-
4624	30.24	2.78
5418	29.32	2.82
7043	28.32	2.78
10049	26.62	2.74
11225	26.00	2.74
15657	24.05	2.72
17233	23.38	2.74
21147	21.95	2.72
27010	19.98	2.78

$[NH_3]_0$ = 0.219 moles l^{-1}

$[substrate]_0$ = 8.56×10^{-2} moles l^{-1}

k = $(2.76 \pm 0.01) \times 10^{-6}$ l mol^{-1} s^{-1} (9 readings)

duplicate k = $(2.76 \pm 0.01) \times 10^{-6}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(2.76 \pm 0.01) \times 10^{-6}$ l mol^{-1} s^{-1}

4-Iodotetrafluoropyridine * Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	10^6 k (l mol^{-1} s^{-1})
0	22.79	-
4434	21.04	2.02
5842	20.58	2.05
7162	20.05	2.08
8790	19.70	2.00
10097	19.42	2.03
12904	18.98	1.83
14315	18.60	1.78
17805	17.88	1.82

$[NH_3]_0$ = 0.206 moles l^{-1}

$[substrate]_0$ = 7.64×10^{-2} moles l^{-1}

k = $(1.98 \pm 0.04) \times 10^{-6}$ l mol^{-1} s^{-1} (8 readings)

duplicate k = $(2.02 \pm 0.03) \times 10^{-6}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(2.00 \pm 0.04) \times 10^{-6}$ l mol^{-1} s^{-1}

4H-tetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^7 k$ (l mol^{-1} s^{-1})
0	38.29	-
9741	37.88	1.27
21363	37.46	1.16
41610	36.55	1.26
66360	35.79	1.20
117200	34.25	1.19

$[NH_3]_0$ = 0.208 moles l^{-1}

$[substrate]_0$ = 7.49×10^{-2} moles l^{-1}

k = $(1.22 \pm 0.06) \times 10^{-7}$ l mol^{-1} s^{-1} (5 readings)

duplicate k = $(1.24 \pm 0.12) \times 10^{-7}$ l mol^{-1} s^{-1} (5 readings)

mean k = $(1.22 \pm 0.1) \times 10^{-7}$ l mol^{-1} s^{-1}

4-Nitrotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^3 k$ (l mol^{-1} s^{-1})
0	32.46	-
6.5	28.70	2.27
15	25.15	2.24
24.5	22.00	2.18
32.5	20.52	2.21
43.5	18.51	2.23
56	16.60	2.23
90.5	14.15	2.21
105	13.32	2.16
∞	9.38	-

$[NH_3]_o$ = 0.210 moles l^{-1}

$[substrate]_o$ = 7.62×10^{-2} moles l^{-1}

k = $(2.22 \pm 0.03) \times 10^{-3}$ l mol^{-1} s^{-1} (8 readings)

duplicate k = $(2.21 \pm 0.05) \times 10^{-3}$ l mol^{-1} s^{-1} (6 readings)

mean k = $(2.22 \pm 0.04) \times 10^{-3}$ l mol^{-1} s^{-1}

4-Cyanotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^4 k$ (l mol^{-1} s^{-1})
0	12.57	-
65	11.91	(2.61)
128	11.42	(2.60)
191	11.07	2.29
313	10.35	2.24
371	9.98	2.33
418	9.80	2.25
471	9.62	2.21
576	9.06	2.28
∞	3.12	-

$[NH_3]_o$ = 6.94×10^{-2} moles l^{-1}

$[substrate]_o$ = 2.62×10^{-2} moles l^{-1}

k = $(2.27 \pm 0.03) \times 10^{-4}$ l mol^{-1} s^{-1} (6 readings)

duplicate k = $(2.27 \pm 0.03) \times 10^{-4}$ l mol^{-1} s^{-1} (6 readings)

mean k = $(2.27 \pm 0.03) \times 10^{-4}$ l mol^{-1} s^{-1}

Perfluoro-4-methylpyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^5 k$ (l mol^{-1} s^{-1})
0	12.95	-
1260	11.12	4.26
1500	10.84	4.24
2679	9.68	4.27
3035	9.29	4.24
3336	9.17	4.21
4129	8.60	4.19
4273	8.52	4.22
5823	7.68	4.22

$[NH_3]_o$ = 6.98×10^{-2} moles l^{-1}

$[substrate]_o$ = 2.62×10^{-2} moles l^{-1}

k = $(4.23 \pm 0.02) \times 10^{-5}$ l mol^{-1} s^{-1} (8 readings)

duplicate k = $(4.21 \pm 0.02) \times 10^{-5}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(4.22 \pm 0.02) \times 10^{-5}$ l mol^{-1} s^{-1}

2,4,6-Trichlorodifluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^7 k$ (l mol^{-1} s^{-1})
0	32.49	-
4371	32.00	3.76
11516	31.25	3.67
29030	29.64	3.67
34531	29.13	3.72
29123	28.84	3.65
45089	28.32	3.68
49348	28.00	3.69
52190	27.78	3.68
54968	27.43	3.70
65244	26.88	3.66

$[NH_3]_o$ = 0.211 moles l^{-1}

$[substrate]_o$ = 7.62×10^{-2} moles l^{-1}

k = $(3.69 \pm 0.03) \times 10^{-7}$ l mol^{-1} s^{-1} (10 readings)

duplicate k = $(3.68 \pm 0.04) \times 10^{-7}$ l mol^{-1} s^{-1} (6 readings)

mean k = $(3.68 \pm 0.03) \times 10^{-7}$ l mol^{-1} s^{-1}

3-Cyanotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (secs.)	O.D.	10^3 k (s^{-1})
0	.233	-
30	.270	7.67
60	.298	7.46
90	.321	7.46
120	.342	7.45
150	.356	7.67
180	.367	7.58
210	.379	(7.93)
240	.383	7.45
∞	.413	-

$[NH_3]_O$ = 3.19×10^{-3} moles l^{-1}

k_I = $(7.53 \pm 0.06) \times 10^{-3}$ s^{-1} (7 readings)

k_{II} = (2.36 ± 0.02) l mol^{-1} s^{-1}

duplicate k_I = $(7.38 \pm 0.04) \times 10^{-3}$ s^{-1} (7 readings)

mean k_{II} = (2.33 ± 0.02) l mol^{-1} s^{-1}

2-Cyanotetrafluoropyridine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^3 k$ (1 mol^{-1} s^{-1})
0	18.91	-
9	15.45	8.24
23.5	12.18	8.26
37.5	11.30	8.15
42.8	10.42	8.12
48.1	9.84	8.11
59.8	8.55	8.16

$[NH_3]_0 = 6.29 \times 10^{-2}$ moles l^{-1}

$[substrate]_0 = 2.62 \times 10^{-2}$ moles l^{-1}

$k = (8.17 \pm 0.05) \times 10^{-3}$ l mol^{-1} s^{-1} (6 readings)

duplicate $k = (8.20 \pm 0.03) \times 10^{-3}$ l mol^{-1} s^{-1} (5 readings)

mean $k = (8.18 \pm 0.04) \times 10^{-3}$ x l mol^{-1} s^{-1}

1,2-Dicyanotetrafluorobenzene + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	Titre (ml.)	$10^3 k$ (l mol^{-1} s^{-1})
0	12.87	-
10	11.22	(3.80)
18.5	10.45	3.68
26	9.84	3.63
32.5	9.36	3.63
41	8.90	3.58
46.5	8.58	3.56
54	8.17	3.60
60	7.92	3.63
68.5	7.60	3.58
∞	3.43	-

$[NH_3]_o$ = 6.89×10^{-2} moles l^{-1}

$[substrate]_o$ = 2.50×10^{-2} moles l^{-1}

k = $(3.60 \pm 0.02) \times 10^{-3}$ l mol^{-1} s^{-1} (8 readings)

duplicate k = $(3.60 \pm 0.02) \times 10^{-3}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(3.60 \pm 0.02) \times 10^{-3}$ l mol^{-1} s^{-1}

5H-trifluoropyrimidine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	O.D.	$10^3 k$ (s^{-1})
0	.538	-
1	.569	2.87
2	.596	2.92
3	.618	2.91
4	.637	2.93
5	.652	2.90
6	.663	2.82
7	.676	2.90
8	.684	2.85
∞	.734	-

$[NH_3]_O$ = 1.15 x 10^{-2} moles l^{-1}

k_I = (2.89 , 0.03) x 10^{-3} s^{-1} (8 readings)

k_{II} = (2.51 ± 0.03) x 10^{-1} l mol^{-1} s^{-1}

duplicate k_I = (2.98 ± 0.05) x 10^{-3} s^{-1} (8 readings)

mean k_{II} = (2.56 ± 0.04) x 10^{-1} l mol^{-1} s^{-1}

4H-trifluoropyrimidine + Ammonia in 60/40 Dioxan/Water at 25.0°C

Time (mins.)	O.D.	$10^3 k$ (s^{-1})
0	.516	-
2	.572	3.06
4	.612	3.12
6	.640	3.18
8	.657	3.11
10	.670	3.12
12	.678	3.07
14	.683	3.05
16	.688	3.13
∞	.698	-

$[NH_3]_o$ = 6.90×10^{-3} moles l^{-1}

k_I = $(3.11 \pm 0.04) \times 10^{-3}$ s^{-1} (8 readings)

k_{II} = $(4.50 \pm 0.04) \times 10^{-1}$ l mol^{-1} s^{-1}

duplicate k_I = $(3.09 \pm 0.04) \times 10^{-3}$ s^{-1} (7 readings)

mean k_{II} = $(4.49 \pm 0.04) \times 10^{-1}$ l mol^{-1} s^{-1}

Pentafluoropyridine + Sodium Methoxide in Methanol at 25.0°C

Time (sec.)	O.D.	$10^2 k$ (s^{-1})
0	.241	-
2	.284	7.09
4	.322	7.12
6	.353	7.04
8	.382	7.11
10	.406	7.09
12	.428	7.14
14	.446	7.12
16	.462	7.12
∞	.566	-

$[MeO^-]_o$ = 4.99×10^{-3} moles l^{-1}

k_I = $(7.10 \pm 0.01) \times 10^{-2}$ s^{-1} (8 readings)

k_{II} = $(1.42 \pm 0.01) \times 10^{1}$ l mol^{-1} s^{-1}

duplicate k_I = $(7.09 \pm 0.01) \times 10^{-2}$ s^{-1} (6 readings)

mean k_{II} = $(1.42 \pm 0.01) \times 10^{1}$ l mol^{-1} s^{-1}

2H-tetrafluoropyridine + Sodium Methoxide in Methanol at 25.0°C

Time (sec.)	O.D.	$10^3 k$ (s^{-1})
0	.198	-
20	.220	4.65
40	.253	4.61
60	.279	4.65
80	.302	4.68
100	.322	4.66
120	.342	4.72
140	.357	4.64
∞	.531	-

$[MeO^-]_o$ = 4.99×10^{-3} moles l^{-1}

k_I = $(4.66 \pm 0.03) \times 10^{-3}$ s^{-1} (7 readings)

k_{II} = $(9.34 \pm 0.03) \times 10^{-1}$ l mol^{-1} s^{-1}

duplicate k_I = $(4.66 \pm 0.02) \times 10^{-3}$ s^{-1} (7 readings)

mean k_{II} = $(9.34 \pm 0.03) \times 10^{-1}$ l mol^{-1} s^{-1}

3H-tetrafluoropyridine + Sodium Methoxide in Methanol at 25.0°C

Time (sec.)	O.D.	$10^3 k$ (s^{-1})
0	.169	-
40	.204	2.93
80	.238	3.08
120	.268	3.13
160	.292	3.08
200	.315	3.10
240	.336	3.13
280	.352	3.09
∞	.485	-

$[MeO^-]_O$ = 4.99×10^{-3} moles l^{-1}

k_I = $(3.10 \pm 0.02) \times 10^{-3}$ s^{-1} (7 readings)

k_{II} = $(6.21 \pm 0.02) \times 10^{-1}$ l mol^{-1} s^{-1}

duplicate k_I = $(3.12 \pm 0.01) \times 10^{-3}$ s^{-1} (6 readings)

mean k_{II} = $(6.23 \pm 0.02) \times 10^{-1}$ l mol^{-1} s^{-1}

Tetrafluoropyrimidine + Sodium Methoxide in Methanol at 25.0°C

Time (msec.)	O.D.(V)
0	3.40
20	4.30
30	4.90
40	5.40
50	5.60
60	5.80
∞	6.00

k_I = 38.15 s^{-1} (6 readings)

duplicate k_I = 39.97, 37.46, 37.40, 37.67, 36.97, 37.72, 37.72 s^{-1}.

$[MeO^-]_O$ = 4.82 x 10^{-3} moles l^{-1}

mean k_I = (3.76 ± 0.03) x 10^1 s^{-1} (8 readings)

mean k_{II} = (7.80 ± 0.02) x 10^3 l mol^{-1} s^{-1}

4H-trifluoropyrimidine + Sodium Methoxide in Methanol at 25.0°C

Time (msec.)	O.D. (V)
0	2.15
50	3.25
100	4.15
150	4.80
200	5.25
250	5.65
300	5.90
350	6.15
∞	6.80

k_I = 5.57 s^{-1} (7 readings)

duplicate k_I = 5.46, 5.51, 5.51, 5.45, 5.48, 5.44, 5.47 s^{-1}

$[MeO^-]_o$ = 3.395 x 10^{-3} moles l^{-1}

mean k_I = (5.47 ± 0.03) s^{-1} (8 readings)

mean k_{II} = (1.61 ± 0.02) x 10^3 l mol^{-1} s^{-1}

5H-trifluoropyrimidine + Sodium Methoxide in Methanol at 25.0°C

Time (msec.)	O.D.(V)
200	1.20
400	2.70
600	3.70
800	4.35
1000	4.75
1200	5.05
1400	5.25
∞	5.70

k_I = 1.97 s^{-1} (7 readings)

duplicate k_I = 1.98, 1.95, 2.01, 2.03, 1.99, 1.97, 2.02, 1.98, 2.00 s^{-1}.

$[MeO^-]_O$ = 4.82 x 10^{-3} moles l^{-1}

mean k_I = (2.00 ± 0.02) s^{-1} (10 readings)

mean k_{II} = (4.15 ± 0.02) x 10^2 l mol^{-1} s^{-1}

Octafluoronaphthalene + Sodium Methoxide in Methanol at 25.0°C

Time (mins.)	Titre (ml.)	$10^3 k$ (l mol^{-1} s^{-1})
0	7.32	-
10	5.94	5.94
20.5	4.90	4.47
30	4.14	4.49
39.5	3.57	4.43
54	2.85	4.44
69	2.30	4.42
80	1.98	4.42
∞	0.0	-

$[MeO^-]_o$ = 3.96×10^{-2} moles l^{-1}

$[substrate]_o$ = 8.03×10^{-2} moles l^{-1}

k = $(4.46 \pm 0.01) \times 10^{-3}$ l mol^{-1} s^{-1} (7 readings)

duplicate k = $(4.46 \pm 0.01) \times 10^{-3}$ l mol^{-1} s^{-1} (7 readings)

mean k = $(4.46 \pm 0.01) \times 10^{-3}$ l mol^{-1} s^{-1}

2H-heptafluoronaphthalene + Sodium Methoxide in Methanol at 25.0°C

Time (mins.)	Titre (ml.)	$10^3 k$ (1 mol^{-1} s^{-1})
0	7.25	-
14	6.63	1.37
22.5	6.28	1.39
33.5	5.84	1.42
42.5	5.60	1.36
55.5	5.20	1.36
65.5	4.90	1.37
75	4.63	1.39
88	4.38	1.37
∞	0.0	-

$[MeO^-]_o$ = 3.93×10^{-2} moles l^{-1}

$[substrate]_o$ = 7.96×10^{-2} moles l^{-1}

k = $(0.38 \pm 0.01) \times 10^{-3}$ l mol^{-1} s^{-1} (8 readings)

duplicate k = $(1.38 \pm 0.01) \times 10^{-3}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(1.38 \pm 0.01) \times 10^{-3}$ l mol^{-1} s^{-1}

1,2-Dihydrohexafluoronaphthalene + Sodium Methoxide in Methanol at 25.0°C

Time (mins.)	Titre(ml.)	$10^5 k$ (l mol^{-1} s^{-1})
0	7.27	-
1320	5.45	(4.83)
1620	5.20	4.63
1759	5.08	4.61
3019	4.10	4.50
4430	3.22	4.53
4803	3.03	4.57
5631	2.66	4.56
6164	2.49	4.48
	0.0	-

$[MeO^-]_0$ = 3.94×10^{-2} moles l^{-1}

$[substrate]_0$ = 8.06×10^{-2} moles l^{-1}

k = $(4.55 \quad 0.04) \times 10^{-5}$ l mol^{-1} s^{-1} (7 readings)

duplicate k = $(4.56 \quad 0.03) \times 10^{-5}$ l mol^{-1} s^{-1} (7 readings)

mean k = $(4.55 \quad 0.03) \times 10^{-5}$ l mol^{-1} s^{-1}

2,6-Dihydrohexafluoronaphthalene + Sodium Methoxide in Methanol at 25.0°C

Time (mins.)	Titre (ml.)	$10^6 k$ (l mol^{-1} s^{-1})
0	6.90	-
8826	6.05	3.85
15628	5.50	3.85
19916	5.14	3.99
25691	4.76	4.03
31477	4.45	3.91
41567	3.90	3.88
46328	3.78	3.99
50584	3.62	3.77
56308	3.30	3.89
∞	0.0	-

$[MeO^-]_o$ = 3.26×10^{-2} moles l^{-1}

$[substrate]_o$ = 6.60×10^{-2} moles l^{-1}

k = $(3.91 \pm 0.03) \times 10^{-6}$ l mol^{-1} s^{-1} (9 readings)

duplicate k = $(3.93 \pm 0.04) \times 10^{-6}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(3.92 \pm 0.03) \times 10^{-6}$ l mol^{-1} s^{-1}

Pentafluorotoluene + Sodium Methoxide in Methanol at 40.0°C

Time (mins.)	Titre (ml.)	$10^6 k$ (l mol^{-1} s^{-1})
0	20.74	-
8497	20.20	1.11
15345	19.73	1.14
18342	19.60	1.08
24522	19.25	1.10
28480	18.96	1.15

$[MeO^-]_o$ = 0.126 moles l^{-1}

$[substrate]_o$ = 5.10×10^{-2} moles l^{-1}

k = $(1.12 \pm 0.02) \times 10^{-6}$ l mol^{-1} s^{-1} (5 readings)

duplicate k = $(1.13 \pm 0.04) \times 10^{-6}$ l mol^{-1} s^{-1} (8 readings)

mean k = $(1.12 \pm 0.03) \times 10^{-6}$ l mol^{-1} s^{-1}

Pentafluoro-(2,2,2-trifluoroethyl)benzene + Sodium Methoxide in Methanol at 40.0°C

Time (mins.)	O.D.	$10^4 k$ (s^{-1})
0	·514	-
10	·556	2.06
20	·594	2.09
30	·627	2.09
40	·657	2.10
50	·682	2.09
60	·708	2.14
70	·780	2.15
80	·748	2.15
∞	·877	-

$[MeO^-]_O$ = 0.361 moles l^{-1} (measured)

$[MeO^-]_O$ = 0.531 moles l^{-1} (effective)

k_I = (2.11 ± 0.02) x 10^{-4} s^{-1} (8 readings)

k_{II} = (3.97 ± 0.02) x 10^{-4} l mol^{-1} s^{-1}

duplicate k_I = (2.09 ± 0.03) x 10^{-4} s^{-1} (8 readings)

mean k_{II} = (3.95 ± 0.02) x 10^{-4} l mol^{-1} s^{-1}

Perfluoro-t-butylbenzene + Sodium Methoxide in Methanol at 40.0°C

Time (sec.)	O.D.	$10^2 k$ (s^{-1})
0	·410	-
3	·454	(8.14)
6	·492	8.62
9	·519	8.55
12	·539	8.41
15	·555	8.35
∞	·613	-

$[MeO^-]_o$ = 2.92 x 10^{-2} moles l^{-1}

k_I = (8.38 ± 0.1) x 10^{-2} s^{-1} (4 readings)

k_{II} = (2.90 ± 0.1) l mol^{-1} s^{-1}

duplicate k_I = (8.50 ± 0.12) x 10^{-2} s^{-1} (5 readings)

mean k_{II} = (2.91 ± 0.1) l mol^{-1} s^{-1}

COLLOQUIA AND CONFERENCES

The Board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing:

(A) all research colloquia, research seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

(B) all research conferences attended and papers presented by the author during the period when research for the thesis was carried out;

(C) details of the postgraduate induction course.

(A) RESEARCH COLLOQUIA, SEMINARS AND LECTURES

1. Durham University Chemistry Department Colloquia.

1981

14 October — Prof. E. Kluk (Katowice): "Chemoluminescence and photo-oxidation".

28 October — Dr. R.J.H. Clark (U.C.L.): "Resonance Raman Spectroscopy".

6 November — Dr. W. Moddeman (Monsanto): "High energy materials".

18 November — Prof. M.J. Perkins (London): "Spin-trapping and and nitroxide radicals".

25 November — Dr. M. Baird (Newcastle): "Intramolecular reactions of carbenes and carbenoids".

2 December — Dr. G. Beamson (Durham): "Photoelectron spectroscopy in a strong magnetic field".

1982

20 January — Dr. M.R. Bryce (University of Durham), "Organic metals".

27 January — Dr. D.L.H. Williams (University of Durham), "Nitrosation and nitrosoamines".

3 February — Dr. D. Parker (University of Durham), "Modern methods of determining enantiomeric purity".

10 February — Dr. D. Pethrick (University of Strathclyde), "Conformation of small and large molecules".

17 February — Prof. D.T. Clark (University of Durham), "Plasma Polymerization".

24 February — Prof. R.D. Chambers (University of Durham), "Recent reactions of fluorinated internal olefins".

2 March — Dr. L. Field (University of Oxford), "Applications of N.M.R. to biosynthetic studies on penicillin".

3 March	Dr. P. Bamfield (I.C.I. Organics Division), "Computer aided design in synthetic organic chemistry".
17 March	Prof. R.J. Haines (University of Natal), "Clustering around Ruthenium, Iron and Rhodium".
7 April	Dr. A. Pensak (DuPont, U.S.A.), "Computer aided synthesis".
5 May	Dr. G. Tennant (University of Edinburgh), "Exploitation of the aromatic nitro-group in the design of new heterocyclisation reactions".
7 May	Dr. C.D. Garner (University of Manchester), "The structure and function of Molybdenum centres in enzymes".
26 May	Dr. A. Welch, (University of Edinburgh), "Conformation patterns and distortion in carbometalloboranes".
14 June	Prof. C.M.J. Stirling (University College of Wales, Bangor), " How much does strain affect reactivity?".
28 June	Prof. D.J. Burton (University of Iowa, U.S.A.), "Some aspects of the chemistry of fluorinated phosphonium salts and their phosphonates".
2 July	Prof. H.F. Koch (Ithaca College, University of Cornell, U.S.A.), "Proton transfer to and elimination reactions from localized and declocalized carbanions".
13 September	Prof. R. Neidlein (University of Heidelberg, FRG), "New aspects and results of bridged annulene chemistry".
27 September	Dr. W.K. Ford (Xerox Research Center, Webster, N.Y.) "The dependence of the electron structure of polymers on their molecular architecture".

13 October — Dr. W.J. Feast (University of Durham), "Approaches to the synthesis of conjugated polymers".

14 October — Prof. H. Suhr (University of Tubingen, FRG), "Preparative Chemistry in Non-equilibrium plasmas".

27 October — Dr. C.E. Housecroft (Oxford High School/Notre Dame University", "Bonding capabilities of butterfly-shaped Fe_4 units implications for C-H bond activation in hydrocarbon complexes".

28 October — Prof. M.F. Lappert, F.R.S., (University of Sussex), "Approaches to asymmetric synthesis and catalyses using electron-rich olefins and some of their metal complexes".

15 November — Dr. G. Bertrand (University of Toulouse, France), "Crutius rearrangement in organometallic series. A route for hybridised species".

24 November — Prof. G.G. Roberts (Applied Physics, University of Durham), "Langmuir-Blodgett films: Solid state polymerisation of diacetylenes".

2 December — Dr. G.M. Brook (University of Durham), "The fate of the ortho-fluorine in 3,3-sigmatropic reactions involving polyfluoroaryl and -heteroaryl systems".

8 December — Dr. G. Wooley (Trent Polytechnic), "Bonds in transition metal-cluster compounds".

1983

12 January — Dr. D.C. Sherrington (University of Strathclyde), "Polymer-supported phase transfer catalysts".

9 February — Dr. P. Moore (University of Warwick), "Mechanistic studies in solution by stopped flow F.T.-N.M.R. and high pressure NMR line broadening".

21 February — Dr. R. Lynder-Bell (University of Cambridge", "Molecular motion in the cubic phase of NaCN".

2 March — Dr. D. Bloor (Queen Mary College, University of London), "The solid-state chemistry of diacetylene monomers and polymers".

8 March — Prof. D.C. Bradley, F.R.S. (Queen Mary College, University of London), "Recent developments in organo-imido-transition metal chemistry".

9 March — Dr. D.M.J. Lilley (University of Dundee), "DNA, Sequence, Symmetry, Structure and supercooling".

11 March — Prof. H.G. Viehe (University of Louvain, Belgium), "Oxidations on Sulphur", "Fluorine substitutions in radicals".
[The W.K.R. Musgrave Lecture].

16 March — Dr. I. Gosney (University of Edinburgh), "New extrustion reactions: Organic synthesis in a hot-tube"

25 March — Prof. F.G. Baglin (University of Nevada, U.S.A.), "Interaction induced Raman spectroscopy in supra-critical ethane".

21 April — Prof. J. Passmore (University of New Brunswick, U.S.A "Novel selenium-iodine cations".

4 May — Prof. P.H. Plesh (University of Keele), "Binary ionisation equilibria between two ions and two molecules. What Ostwald never thought of".

10 May — Prof. K. Burger (Technical University of Munich, FRG) "New reaction pathways from trifluoromethyl-substituted heterodienes to partially fluorinated heterocyclic compounds".

11 May — Dr. N. Isaacs (University of Reading), The Application of high pressures to the theory and practice of organic chemistry".

13 May — Dr. R. de Koch (Caloin College, Grand Rapids, Michigan/Free University, Amsterdam) "Electronic structural calculations in organometallic cobalt cluster molecules. Implications for metal surfaces".

16 May — Prof. R.J. Lagow (University of Texas, U.S.A.), "The chemistry of polylithium organic compounds. An unusual class of matter".

18 May — Dr. D.M. Adams (University of Leicester), "Spectroscopy at very high pressures".

25 May — Dr. J.M. Vernon (University of York), "New heterocyclic chemistry involving lead tetraacetate".

15 June — Dr. A. Pietrzykowski (Technical University of Warsaw/University of Strathclude), "Synthesis, structure and properties of Aluminoxanes".

22 June — Dr. D.W.H. Rankin (University of Edinburgh), "Floppy molecules - the influence of phase on structure".

5 July — Prof. J. Miller (University of Camfinas, Brazil), "Reactivity in nucleophilic substitution reactions".

5 October — Prof. J.P. Maier (University of Basel, Switzerland), "Recent approaches to spectroscopic characterization of cations".

12 October — Dr. C.W. McLeland (University of Port Elizabeth, Australia), Cyclization of aryl alcohols through the intermediacy of alkoxy radicals and aryl radical cations".

19 October — Dr. N.W. Alcock (University of Warwick), "Aryl tellurium (IV) compounds, patterns of primary and secondary bonding".

26 October — Dr. R.H. Friend (Cavendish Laboratory, University of Cambridge), "Electronic properties of conjugated polymrs".

30 November — Prof. I. Cowie (University of Stirling), "Molecular interpretation of non-relaxation processes in polymer glasses".

14 December — Prof. R.J. Donovan (University of Edinburgh), "Chemical and physical processes involving the ion-pair states of the halogen molecules".

1984

10 January — Prof. R. Hester (University of York), "Nanosecond laser spectroscopy of reaction intermediates".

18 January — Prof. R.K. Harris (University of East Anglia), Multi-nuclear solid state magnetic resonance".

8 February — Dr. B.T. Heaton (University of Kent), "Multi-nuclear n.m.r. studies".

15 February — Dr. R.M. Paton (University of Edinburgh), "Heterocyclic syntheses using nitrile sulphides".

7 March — Dr. R.T. Walker (University of Birmingham), "Synthesis and biological properties of some 5-substituted uracil derivatives; yet another example of serendipity in antiviral chemotherapy".

21 March — Dr. P. Sherwood (University of Newcastle), "X-ray photoelectron spectroscopic studies of electrode and other surfaces".

23 March — (Informal colloquium) Dr. A.Ceulemans (Catholic University of Leuven), "The Development of Field-Type Models of the Bonding in Molecular Clusters".

2 April — Professor K. O'Driscoll (University of Waterloo), "Chain Ending Reactions in Free Radical Polymerisation"

3 April — Professor C.H. Rochester (University of Dundee), "Infrared Studies of Adsorption at the Solid-Liquid Interface".

25 April — Dr. R.M. Acheson (Department of Biochemistry, University of Oxford), "Some Heterocyclic Detective Stories".

27 April — Dr. T. Albright (University of Houston), "Sigmatropic Rearrangements in Organometallic Chemistry".

14 May — Professor W.R. Dolbier, Jr., (University of Florida), "Cycloaddition Reactions of Fluorinated Allenes".

16 May — Dr. P.J. Garratt (University College, London), "Syntheses with Dilithiated Vicinal Diesters and Carboximides".

31 May — Dr. A. Haaland (University of Oslo), "Electron Diffraction Studies of some Organometallic Compounds".

11 June — Dr. G.B. Street (I.B.M. San José), "Conducting Polymers derived from Pyrroles".

2. DURHAM UNIVERSITY CHEMICAL SOCIETY LECTURES

1981

22 October — Dr. P.J. Corish (Dunlop): "What would life be like without rubber".

29 October — Miss J.M. Cronyn (Durham): "Chemistry in Archaeology".

12 November — Prof. A.I. Scott (Edinburgh): "An organic chemist's view of life through the n.m.r. tube".

19 November — Prof. B.L. Shaw (Leeds): "Big rings and metal-carbon bond formation".

3 December — Dr. W.O. Ord (Northumbria Water Authority): "The rôle of the scientist in a regional water authority".

1982

28 January — Prof. I. Fells (University of Newcastle upon Tyne), "Balancing the Energy Equations".

11 February — Dr. D.W. Turner (University of Oxford), "Photoelectrons in a Strong Magnetic Field".

18 February — Prof. R.K. Harris (University of East Anglia), "N.m.r. in the 1980s".

25 February — Prof. R.C.C. Norman, F.R.S. (University of York), "Turning Points and Challenges for the Organic Chemist".

4 March — Dr. R. Whyman (I.C.I. Ltd., Runcorn), "Making Metal Clusters Work".

14 October — Mr. F. Shenton (County Analyst, Durham), "There is death in the pot".

28 October — Prof. M.F. Lappert, F.R.S. (University of Sussex), "The Chemistry of Some Unusual Subvalent Compounds of the Main Group IV and V Elements".

4 November — Dr. D.H. Williams (University of Cambridge), Studies on the Structures and Modes of Action of Antibiotics".

11 November — Dr. J. Cramp (I.C.I. Ltd.), "Lasers in Industry".

25 November — Dr. D.H. Richards, P.E.R.M.E. (Ministry of Defence), "Terminally Functional Polymers, their Synthesis and Uses".

1983

27 January — Prof. D.W.A. Sharp (University of Glasgow), "Some Redox Reactions in Fluorine Chemistry".

3 February — Dr. R. Manning (Department of Zoology, University of Durham), "Molecular Mechanisms of Hormone Action"

10 February — Sir Geoffrey Allen, F.R.S. (Unilever Ltd.), "U.K. Research Ltd.".

17 February — [R.S.C. Centenary Lecture], Prof. A.G. MacDiarmid, (University of Pennsylvania), "Metallic Covalent Polymers: $(SN)_x$ and $(CH)_x$ and their derivatives".

3 March — Prof. A.C.T. North (University of Leeds), "The Use of a Computer Display System in Studying Molecular Structures and Interactions".

20 October — Prof. R.B. Cundall (University of Salford), "Explosives".

3 November — Dr. G. Richards (University of Oxford), "Quantum pharmacology".

10 November — Dr. J. Harrison (Sterling Organic), "Applied Chemistry and the Pharmaceutical Industry".

24 November — Prof. D.A. King (University of Liverpool), "Chemistry in two dimensions".

1 December — Dr. J.D. Coyle (The Open University), "The problem with sunshine".

1984

26 January — Prof. T.L. Blundell (Birkbeck College, London), "Biological recognition: Interactions of macromolecular surfaces".

2 February — Prof. N.B.H. Jonathan (University of Southampton), "Photoelectron spectroscopy - a radical approach".

16 February — Prof. D. Phillips (The Royal Institution), "Luminescence and photochemistry - a light entertainmentP.

23 February — Prof. F.G.A. Stone, F.R.S. (University of Bristol), "The use of carbene and carbyne groups to synthesise metal clusters".
[The Waddington Memorial Lecture].

1 March — Prof. A.J. Leadbetter (Rutherford Appleton Labs.), "Liquid Crystals".

8 March — Prof. D. Chapman (Royal Free Hospital School of Medicine, University of London), "Phospholipids and biomembranes: basic structure and future techniques"

28 March [R.S.C. Centenary Lecture]

Prof. H. Schmidbaur (Technical University of Munich, FRG), "Ylides in coordination sphere of metals: synthetic, structural and theoretical aspects".

(B) RESEARCH CONFERENCES ATTENDED

Graduate Symposium, Durham, April 1982.

Graduate Symposium, Durham, April 1983.

17th Sheffield Symposium on "Modern Aspects of Stereochemistry", Sheffield, 21 December 1983.

Graduate Symposium, Durham, April 1984.

A paper was presented by the author entitled "Effect of Fluorine in Nucleophilic Substitution".

International Symposium on "Chemistry of Carbanions", University of Durham, 16-20 July 1984.

(C) POSTGRADUATE INDUCTION COURSE

In each part of the course, the uses and limitations of the various services available were explained.

Departmental Organisation - Dr. E.J.F. Ross.

Electrical appliances and infrared spectroscopy - Mr. R.N. Brown.

Chromatography - Mr. J.A. Parkinson.

Microanalysis - Mr. T.F. Holmes and Mrs. M. Cocks.

Atomic absorption spectrometry and inorganic analysis - Mr.R. Coult.

Mass spectroscopy - Dr. M. Jones.

N.m.r. spectroscopy - Dr. R.S. Matthews.

Glassblowing techniques - Mr. R. Hart and Mr. G. Haswell.

Safety matters - Dr. M.R. Crampton.

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