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UNIVERSITY OF DURHAM

A THESIS

entitled

KINETICS AND MECHANISMS OF NUCLEOPHILIC SUBSTITUTION IN
POLYHALO-AROMATIC SYSTEMS

submitted by

DEBORAH CLOSE, B.Sc.

Submitted for the degree of Master of Science
1976

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Finally, thanks are due to the United States Air Force, for a maintenance grant.

MEMORANDUM

The work described in this thesis was carried out at the University of Durham between October 1975 and October 1976. This work has not been submitted for any other degree, and is the original work of the author, except where acknowledged by reference.

SUMMARY

The orientating effects of fluorine, chlorine and hydrogen in polyhaloaromatic systems undergoing nucleophilic attack, are compared by measuring the rates of substitution by ammonia in polyhalopyridines at 25^o, the solvent system being 60/40 dioxan/water.

Rate constant measurements indicate that the activating influence of fluorine, with respect to the point of nucleophilic attack, is in the order ortho > meta >> para:- 31:23:0.26 respectively, relative to hydrogen at the same position. These results, together with rate constants for the reactions of a series of hydrofluoropyridines with sodium methoxide in methanol at 50^o, which had been measured previously, lead to the conclusion that substitution in polyfluoroaromatic compounds occurs at a position where the number of ortho and meta fluorine atoms (the activating fluorines), is maximised. The activating effect of a meta fluorine is attributed to the inductive stabilising effect of the negative charge, by fluorine, in the transition state. That of an ortho fluorine is accounted for by the hard/soft acid/base theory.

The activating influence of chlorine with respect to the point of nucleophilic attack is found to be in the order ortho > meta > para:- 77:24:6.9 respectively, relative to hydrogen at the same position. The explanation for the high activating effects of the ortho and meta chlorines is similar to that given for fluorine in the same positions.

Relative to the para position, the activating influence of fluorine is thus determined as ortho:meta:para:- 199:88:1, while that of chlorine is determined as ortho:meta:para:- 13:3.5:1. Hence, for the chlorine series, the effects at each of the three positions are very similar, much more so than for the fluorine series.

Measurement of rate constants of various mono-substituted fluorobenzenes in the ammonia/dioxan/water system at 25° and at 90°, are in accordance with what was expected from considerations of charge distribution in the transition state. NO₂, CN, pentafluorophenyl, Cl, and Br are all activating with respect to fluorine in hexafluorobenzene and hydrogen in pentafluorobenzene.

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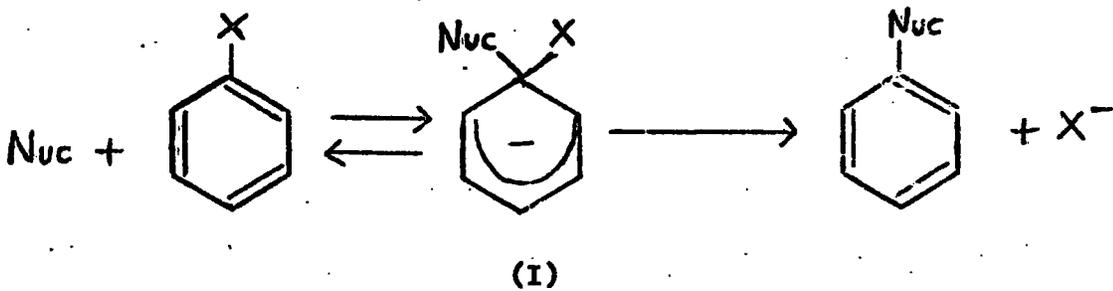
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INTRODUCTION

Mechanism of Nucleophilic Attack in Polyfluoroaromatic Compounds

Nucleophilic aromatic substitution reactions in 'activated' systems appear to occur most commonly by a bimolecular process. When the aromatic nucleus contains electron withdrawing groups, nucleophilic substitution reactions occur fairly readily, and frequently show second order kinetics, which is indicative of a bimolecular mechanism. The reaction probably proceeds as a two-step process, in which the attacking nucleophile forms a fully bonded intermediate with the aromatic system, the negative charge being delocalised in the ring, as in (I).



The central carbon atom is sp^3 hybridised, and hence structure (I) is an intermediate, not a transition state. Therefore, the mechanism is a two-step addition-elimination process, with two transition states (T.S.1 and T.S.2), one on each side of the intermediate complex. This can be represented by an energy profile diagram (Figure 1.1).

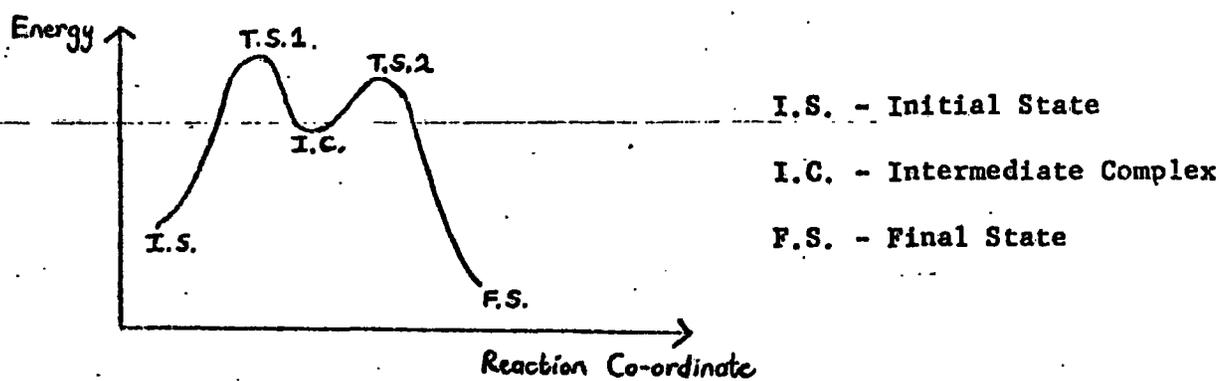
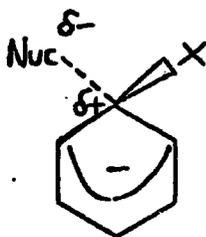


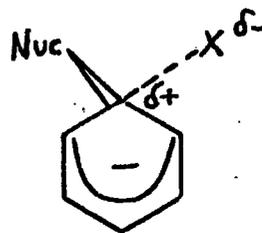
Figure 1.1.



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



(II)



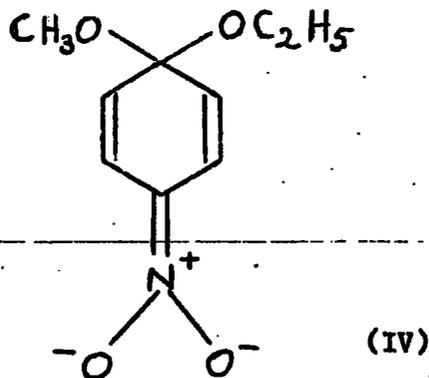
(III)

The relative energies of the two transition states depend upon the reaction. The rate-determining step is formation of the intermediate, if the energy of T.S.1 is greater than that of T.S.2. However, if the energy of T.S.2 is greater than that of T.S.1, then the dissociation of the intermediate is the rate-limiting step.

Evidence for the two-step addition-elimination mechanism

(i) Isolation of intermediates

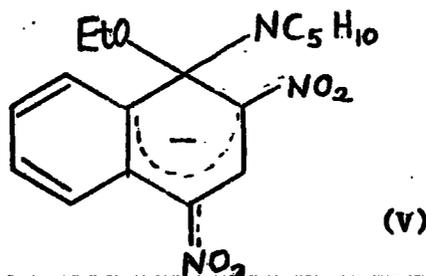
Intermediate complexes of similar structure to (I) have been isolated. Meisenheimer¹ isolated a red salt on the addition of potassium ethoxide to 2,4,6-trinitroanisole, and assigned the following structure to it (IV).



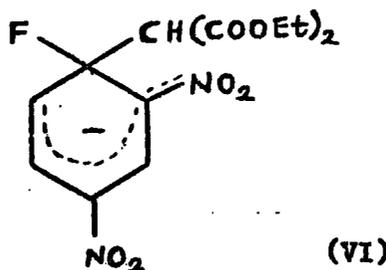
(IV)

In favourable cases, the intermediates in substitution reactions may be observed spectroscopically. Thus, in more recent work, the ¹H

nuclear magnetic resonance spectrum of a complex represented as (V), has been reported in the reaction of 2,4,-dinitro-1-naphthyl ethyl ether with piperidine in dimethyl sulphoxide.²



The visible spectra of 1-fluoro-2,4-dinitrobenzene in reaction with the sodium salt of diethyl malonate in dimethyl sulphoxide indicate initial fast formation of an intermediate, thought to have structure (VI), and slower formation of products; a kinetic analysis has been made.³



(ii) Leaving group mobilities

In nucleophilic aromatic substitution reactions, the observed ease of displacement of halide is in the order $F \gg Cl > Br > I$. This is the reverse order of the carbon-halogen bond strengths.⁴ Therefore, the reactions cannot be accounted for by a concerted one-step mechanism, as in aliphatic SN_2 substitution, in which bond breaking in the transition state results in the reaction rate being proportional to the carbon-halogen bond strength. The order of mobility in such a case is $I > Br > Cl > F$.⁵

If the rate determining step does not involve the breakage of any carbon-halogen bonds, the reaction must be occurring as an addition-elimination process, in which the rate of formation of the intermediate is the rate-limiting step.⁶

If the rate of formation of the intermediate is rate determining, the overall rate of reaction will depend upon the rate of formation of the carbon-nucleophile bond. This would be expected to be greater for fluoride than for the other halide compounds, as fluorine is more electronegative,⁷ and in the initial state of the molecule, it polarises the carbon-halogen bond to a greater extent than do the other halogens. The increased positive charge on the carbon atom will increase the rate of nucleophilic attack.^{8,9}

Position of Substitution by Nucleophiles in Polyfluoroaromatic

Compounds

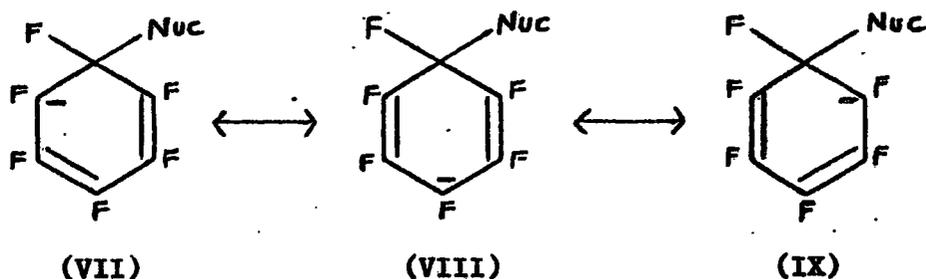
Nucleophilic substitution in hexafluorobenzene has been investigated, and monosubstituted products were obtained with methoxide ions,^{10,11} hydroxide ions,^{12,13} amines,¹⁴ and ammonia.¹⁵

In monosubstituted pentafluorobenzenes, (C_6F_5X), substitution has been found to occur almost exclusively at the position para to X when X was H ¹⁴, CH_3 ¹⁶, CF_3 ^{17,18}, CN ¹⁹, C_2F_5 ²⁰, C_6H_5 ²¹, SC_6H_5 ²², Cl, Br or I¹⁹. Attack occurred at the meta position, when X was NH_2 or O^- ²³. Ortho attack occurred when X was NO ²⁴ or NO_2 ^{25,26} and the nucleophile was ammonia or an amine.

Rationalisation of Position of Substitution in Terms of the π effect

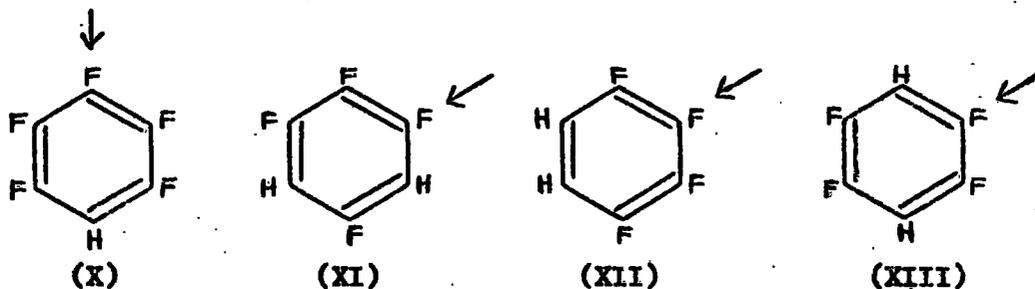
In order to explain the position of nucleophilic attack in polyfluoroaromatic compounds, the charge distribution in the transition

state, and the effects on that charge by substituents, have been considered.^{27,28} The transition state is represented by structures (VII), (VIII) and (IX).



It has been proposed that the transition state of the rate of limiting step in nucleophilic substitution, has a structure in which the charge is almost totally on the atom para to the position of attack. (VII) and (IX) contribute only a small part towards this structure, in which (VIII) is most significant.

The evidence for this charge distribution has been obtained from molecular orbital calculations,²⁹ and from the orientation of attack in pentafluorobenzene and the three tetrafluorobenzenes.²⁷ Nucleophilic attack in these four compounds occurs in the positions arrowed.



Attack occurs only para to a hydrogen atom, in compounds (X), (XI) and (XII). It has been suggested that fluorine is less capable of stabilising a negative charge on an α -carbon, than is hydrogen. Substitution does not occur at the ortho position, indicating that there is a non-equal distribution of charge in the transition state, at the positions ortho and para to the point of attack.

Effects of substituents

Substituents in polyfluoroaromatics, which are more effective than fluorine in stabilising negative charge, would be expected to direct the attacking nucleophile para to themselves, if the assumption is made that most of the charge in the transition state is on the carbon atom para to the position of substitution. This orientation is generally found.^{14,16,17,18,21,22} Ortho replacement occurs to a lesser extent, and diminishes in the order:- $C_6F_5Cl > C_6F_5Br > C_6F_5I \sim C_6F_5H$.¹⁹ This is rationalised in terms of the electronic effect which involves electron repulsion by halogens in π -electron systems. The fairly high percentage of ortho substitution for the reactions of pentafluoronitrobenzene with amines has been attributed to hydrogen bonding between the nitro group and the amine, when attack occurs at the ortho position.²⁶

Halogen substituents often destabilise a negative charge on an α carbon atom in the order:- $F > Cl > Br > I \sim H$,³⁰ especially when the geometry of the carbanion is planar. This order has been attributed to the $I\pi$ effect,³⁰ which occurs in a π system, and is a measure of the repulsion between the lone pair electrons of the halogens, and the negative charge on the carbon atom. The $I\pi$ effect for halogens is in the opposite direction to the $-I\sigma$ effect, which results from their electronegativities. It is, however, in the same direction as their $+M$ effects, but has not the same magnitude.

$I\pi$ repulsion occurs as a result of coulombic interaction between the electrons on an α carbon atom, and the non-bonded electron pairs on the halogen. This interaction occurs more readily for fluorine than for the other halogens, as the fluorine atom is small, and hence the

$I\pi$ effect is greater for fluorine than for the other halogens. As the halogen size increases, the interaction decreases, so therefore the $I\pi$ effect is diminished.

Figure 1.2 represents the $I\pi$ effect in the transition state for a nucleophilic substitution reaction. It is at a maximum in aromatic systems, as planar sp^2 geometry is enforced. The greater the amount of charge on the carbon, the greater is the $I\pi$ effect.

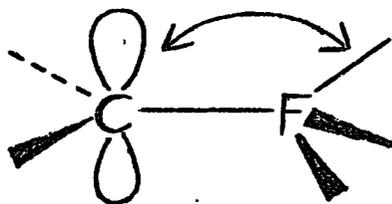
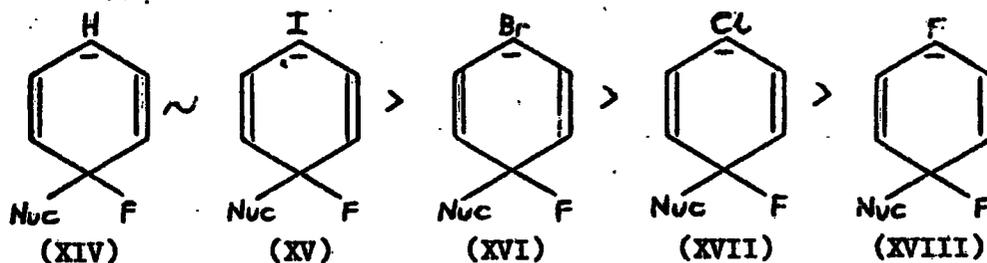


Figure 1.2.

The order of stability in the transition states, (XIV) to (XVIII) has been postulated from consideration of $I\pi$ interactions:-

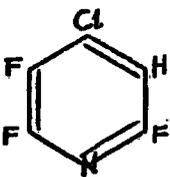
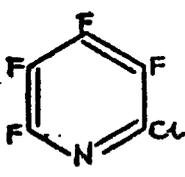
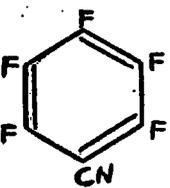
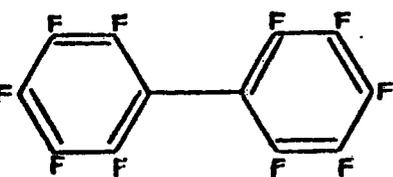
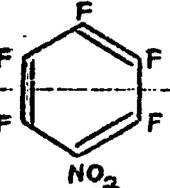
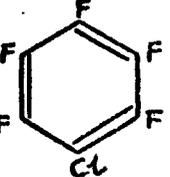


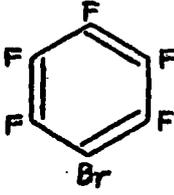
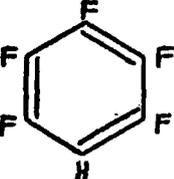
This explains why substitution in the compounds leading to the transition states shown, occurs at the para position.

PRESENT WORK

The rate constants of the compounds studied, considered together with work done earlier by J.S. Waterhouse at Durham University,³¹ and studies on fluorobenzenes at Birmingham University, allow an alternative rationalisation to be built up.³² This will be summarised later, but the following results have been obtained in the present study.

TABLE (1)

<u>Substrate</u>	<u>Position of Substitution</u>	<u>$k(1 \text{ mole}^{-1} \text{ min}^{-1})$</u>
	6 ^a	$(3.55 \pm 0.01) \times 10^{-4}$
	4 ^a	$(4.26 \pm 0.01) \times 10^{-2}$
	4	$(1.47 \pm 0.02) \times 10^{-2a}$ $(2.72 \pm 0.02) \times 10^{-2b}$
	4 ^b	$(5.09 \pm 0.09) \times 10^{-5}$
	4 ^a	$(1.19 \pm 0.04) \times 10^{-1}$
	4 ^c	$(1.25 \pm 0.01) \times 10^{-4}$

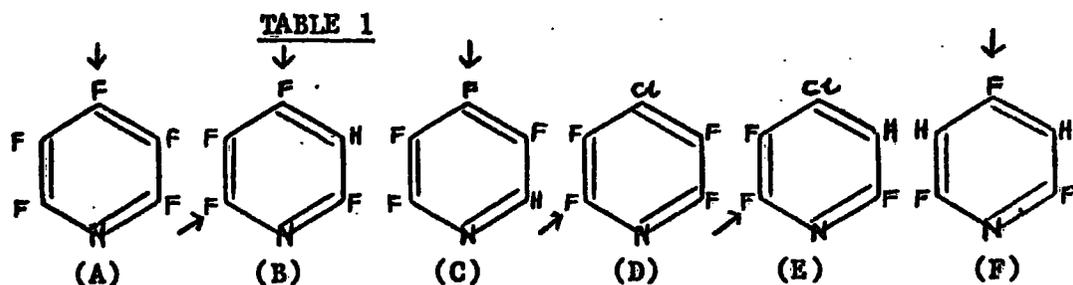
<u>Substrate</u>	<u>Position of Substitution</u>	<u>$k(1 \text{ mole}^{-1} \text{ min}^{-1})$</u>
	4 ^c	$(8.88 \pm 0.15) \times 10^{-5}$
	4 ^c	very slow

- a Reaction with ammonia in 60/40 dioxan/water at $\sim 25^{\circ}\text{C}$
 b Reaction with ammonia in 80/20 dioxan/water at $\sim 25^{\circ}\text{C}$
 c Reaction with ammonia in 80/20 dioxan/water at $\sim 90^{\circ}\text{C}$

Activating Influence of Fluorine in Polyfluoropyridines, in Nucleophilic Substitution Reactions with Ammonia

Rates of nucleophilic substitution in various polyfluoropyridines have been studied to compare the positional effects of fluorine relative to hydrogen.³³ Rate constant measurements for the reactions of various hydrofluoropyridines with ammonia in dioxan/water (60:40, v:v) at 25°C , indicate that the activating influence of fluorine, with respect to the position of nucleophilic attack, is in the order ortho > meta >> para: 31:23:0.26, respectively, relative to hydrogen at the same position.

Table 1 shows the ratios of the measured rate constants for reactions of some fluoropyridines with ammonia in aqueous dioxan (60:40) at 25° , the positions of attack being arrowed.



Rate constants relative to (A)	1	$3.26 \times 10^{-2}{}^a$	4.31×10^{-2}	2.28×10^{-3}	8.70×10^{-3}	$\sim 10^{-3}{}^c$
		$8.63 \times 10^{-3}{}^b$				

a = Rate constant for attack in 4-position

b = Rate constant for attack in 6-position

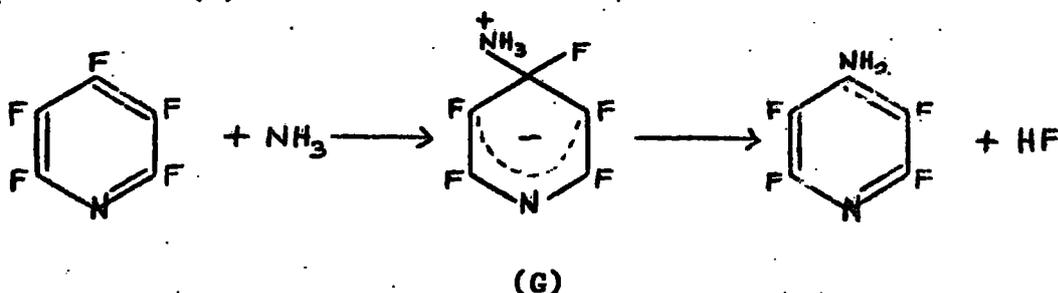
c = Approximate value due to slowness of the reaction

The effect of an ortho-fluorine, relative to the point of nucleophilic attack, in comparison with hydrogen at the same position, can be obtained by comparing the rate constants for attack at the 4-position in compounds (A) and (B). Similarly, the influence of a meta-fluorine is obtained by comparing the rate constants for attack at the 4-position in compounds (A) and (C), and comparison of rate constants for attack at the 6-position in compounds (D) and (E), gives the para-effect. The ratios of the three pairs of rate constants, and the overall ortho:meta:para ratio is shown below:-

$$\begin{aligned}
 k(A)/k(B) &= k_F/k_H \text{ (ortho)} &= 31 \\
 k(A)/k(C) &= k_F/k_H \text{ (meta)} &= 23 \\
 k(D)/k(E) &= k_F/k_H \text{ (para)} &= 0.26
 \end{aligned}$$

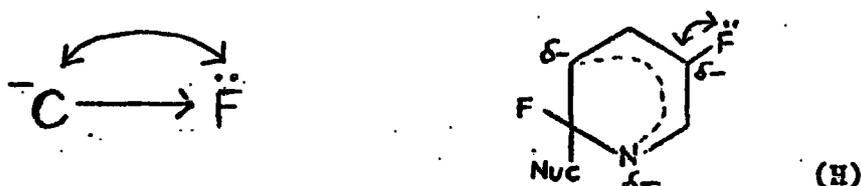
Rationalisation of Rate and Orientation of Substitution in
Hydrofluoropyridines

When the results given in Table 1 are interpreted, the assumption is made that reaction occurs in two stages, with the formation of the intermediate delocalised anion (9) as the rate-limiting step. This usually occurs when fluorine is displaced from aromatic systems and further evidence that addition is the rate determining stage, is the fact that attack in (D) occurs with displacement of fluorine, even though attack occurs exclusively at the 4-position in (A). If the second stage were rate-determining, chlorine would be expected to be displaced from (D)



Effect of fluorine para- to position of attack

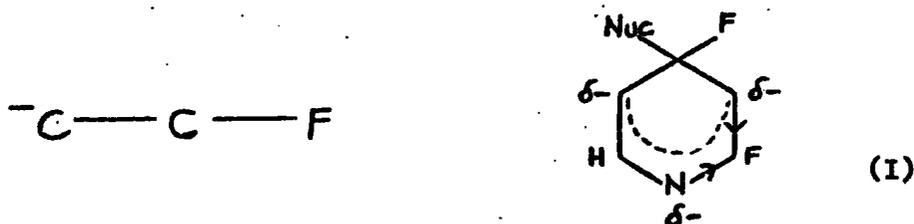
That a para-fluorine is slightly deactivating with respect to hydrogen at the same position, is attributed to the fact that in the transition state the inductive electron withdrawal by fluorine is strongly offset by electron-pair repulsion, as in (H).



Effect of fluorine meta- to position of attack

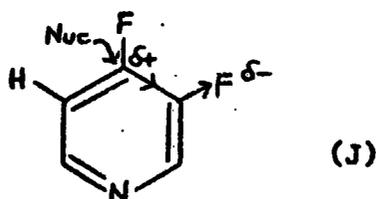
Fluorine in the position meta- to the point of substitution is

activating with respect to meta-hydrogen, because of the inductive stabilising effect of the negative charge, by fluorine, in the transition state (I).



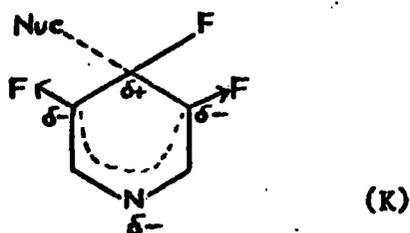
Effect of fluorine ortho- to position of attack

It would be expected that in the transition state, inductive electron withdrawal by an ortho- fluorine atom, would be balanced by electron pair repulsions, as in the case of a para-fluorine, and hence the effects of an ortho fluorine and a para-fluorine would be expected to be very similar. However, this is not the case, as ortho-fluorine is found to be more activating than meta-. Therefore, there must be some non-conjugative effect arising from fluorine at the ortho-position. An earlier explanation of the activating effect of an ortho-fluorine, was that it was due to an initial-state polarisation of the sigma electrons by fluorine, resulting in enhanced positive charge at the point of substitution, thereby allowing easier approach of the nucleophile.³²



However, the effect is probably accounted for by the hard/soft acid/base theory,³⁴ the carbon atom under attack being made harder, so

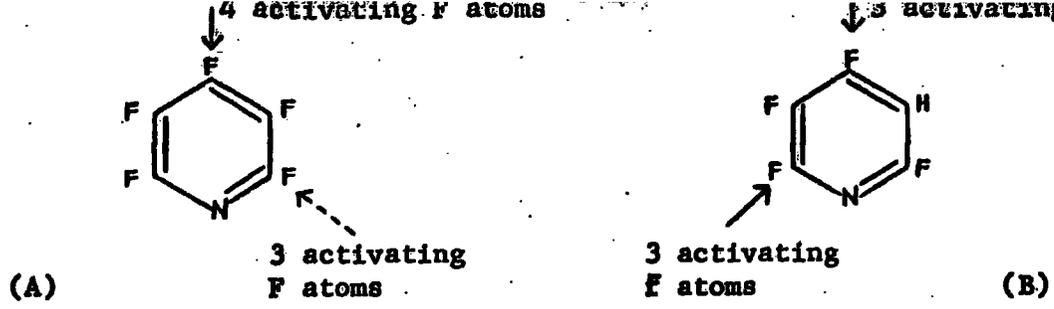
that attack by a relatively hard nucleophile, such as ammonia, is made easier. This could be described as a transition-state effect, as represented by (K).



The order of activating influence of substituent fluorine atoms with respect to the position of nucleophilic attack, ortho > meta >> para, leads to an explanation of the controlling influence of those substituents on the orientation of nucleophilic substitution in pentafluoropyridine. The ring nitrogen atom activates the system to a significant extent, and discriminates between the 2- and the 4- position. Evidence for this is provided from attack on 4-chloropyridine and 2-chloropyridine by methoxide ion. Although 4-chloropyridine is more reactive than 2-chloropyridine, the ratio of the rate constants at 50°C is 26.9.³⁵

Therefore, the effects both of the fluorine substituents, and of the ring nitrogen, govern the position of nucleophilic substitution in polyfluoropyridines, the number of activating fluorine atoms being maximised. Hence, attack by nucleophiles on pentafluoropyridine, (A), results in substitution exclusively at the 4-position, as the number of activating fluorine atoms, two ortho- and two meta-, is at a maximum.

Nucleophilic attack occurs at both the 4- and the 6- positions in 2,4,5,6-tetrafluoropyridine (B), as opposed to exclusive 4-attack in (A). The explanation for this divided attack is that there are the same number of activating fluorine atoms for each of the two positions.



Substituent effects of fluorine were examined earlier, at Birmingham University, by measuring rate constants of a series of hydrofluorobenzenes reacting with sodium methoxide in methanol at 50°C. Comparison of these rate constants, indicate that in this system, the activating influence of fluorine with respect to the point of nucleophilic attack, is meta > ortho >> para.³²

Table 2 shows the ratios of the rate constants for some fluorobenzenes, reacting with sodium methoxide in methanol at 50°C, arrows indicating the points of attack.

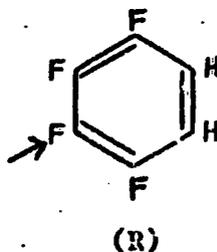
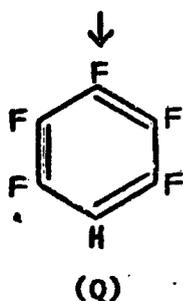
TABLE 2

	(L)	(M)	(N)	(O)	(P)
Relative rate constants	0.75	1	2.35×10^{-2}	0.8×10^{-2}	10^{-4}

The effect of fluorine ortho- to the position of attack, in comparison with hydrogen at the same position, can be obtained by comparing the rate constants for attack at the 4-position in (M) and (N). The comparison shows that ortho fluorine has a significant activating effect. A similar comparison of the rate constants for attack in compounds (M) and (O) indicate that fluorine is activating with respect to hydrogen, at the position meta- to the point of nucleophilic attack. The effect of a para-fluorine can be obtained by comparing the rate constants for attack in compounds (L) and (M). The results imply that a para fluorine is almost equivalent to a para hydrogen.

In this system, it can be concluded that the activating influence of fluorine atoms is meta > ortho >> para, the overall ratio being 167:56:1, respectively.

Therefore, the ortho/meta ratio differs for the methoxide/methanol and the ammonia/dioxan/water systems, the activating influence of fluorine atoms in the latter system being in the order ortho > meta >> para; 119:88:1, respectively. However, it is very important that in both systems the ortho-fluorine has a large activating effect, whereas the para-fluorine has an effect which differs little from that of hydrogen. Hence, it can be concluded that the positions of nucleophilic substitution in polyfluorobenzenes, are controlled by the necessity to maximise the number of activating fluorine atoms. This is exemplified in the compounds (Q) and (R) below, the positions of attack being arrowed.



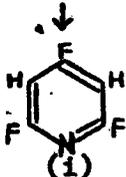
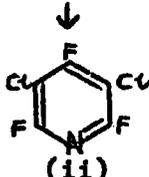
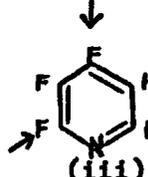
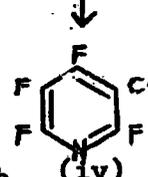
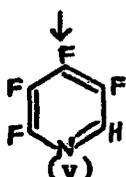
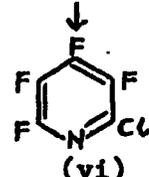
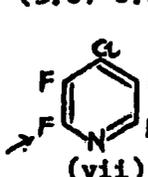
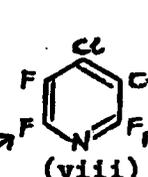
It was formerly postulated,²⁸ that para-fluorine had an important controlling effect, but the results from both the polyfluoropyridines and the polyfluorobenzenes indicate that this position is the least significant. Miller³⁶ anticipated the present results by extrapolation from σ^- values, although no value was available for fluorine in the ortho- position.

Orientating Influence of Chlorine Substituents in Nucleophilic Aromatic
Substitution Reactions

Rates of nucleophilic substitution in various polyfluoropyridines containing chlorine substituents, have been compared, in order to separate the orientating effects of chlorine atoms when ortho-, meta- and para- to the position of attack, relative to hydrogen in the same position.³⁷ Rate constant measurements for the reactions of various chlorine-containing polyfluoropyridines with ammonia in dioxan/water (60:40 v:v) at 25°C, indicate that the activating influence of chlorine with respect to the point of nucleophilic attack, is in the order ortho > meta > para; 77:24:6.9, respectively, relative to hydrogen at the same position.

Table 3 shows the measured rate constants for reactions of some chloro-fluoro-pyridines with ammonia in aqueous dioxan at 25°C, the positions of attack being arrowed.

TABLE 3

 (i)	 (ii)	 (iii)	 (iv)
$k(\text{l mole}^{-1}\text{s}^{-1}): \sim 1 \times 10^{-6}{}^a$	$(4.75 \pm 0.04) \times 10^{-3}$	$(2.22 \pm 0.1) \times 10^{-5}{}^b$ $(5.87 \pm 0.3) \times 10^{-5}{}^c$	$(1.92 \pm 0.02) \times 10^{-3}$
 (v)	 (vi)	 (vii)	 (viii)
$k(\text{l mole}^{-1}\text{s}^{-1}): (2.93 \pm 0.03) \times 10^{-5}$	$(7.12 \pm 0.04) \times 10^{-4}$	$(5.92 \pm 0.02) \times 10^{-6}$	$(4.87 \pm 0.2) \times 10^{-6}{}^d$ $(4.10 \pm 0.2) \times 10^{-5}{}^c$

a = approximate value for k, owing to the slowness of the reaction

b = Rate constant for attack in 4- position

c = Rate constant for attack in 6- position

d = Rate constant for attack in 2- position

The effect of an ortho-chlorine relative to the point of nucleophilic attack, in comparison with hydrogen at the same position, can be obtained by comparing the rate constants for attack at the 4-position in compounds (i) and (ii), and compounds (iii) and (iv). Similar comparison of the rates of attack at the 4-position in compounds (v) and (vi), leads to the effect of chlorine meta- to the point of attack, while the effect of chlorine para- to the position of attack is obtained by comparison of the rate constants for attack at the 6-position in compounds (vii) and (viii). The ratio of each pair of rate constants under consideration is given below:-

$$k(\text{ii})/k(\text{i}) = k_{\text{Cl}}/k_{\text{H}} (\text{ortho}) = 4.7 \times 10^3 \text{ ie. } 69 \text{ per ortho chlorine atom}$$

$$k(\text{iv})/k(\text{iii}) = k_{\text{Cl}}/k_{\text{H}} (\text{ortho}) = 86 \text{ per ortho chlorine atom}$$

$$k(\text{vi})/k(\text{v}) = k_{\text{Cl}}/k_{\text{H}} (\text{meta}) = 24 \text{ per meta chlorine atom}$$

$$k(\text{viii})/k(\text{vii}) = k_{\text{Cl}}/k_{\text{H}} (\text{para}) = 6.9 \text{ per para chlorine atom}$$

Therefore, the order of the activating influence of chlorine, relative to the position of nucleophilic attack is:- ortho:meta:para; ~ 77:24:6.9, relative to hydrogen at the same position. Relative to the para position, the ratio is ortho:meta:para; 13:3.5:1, respectively.

Comparison of the Activating Effects of Chlorine Relative to Fluorine in Nucleophilic Aromatic Substitution Reactions

The order of the activating influence of fluorine relative to the position of nucleophilic attack in the ammonia/dioxan/water system at 25°C, is:

F ortho : meta : para

 31 : 23 : 0.26 (relative to hydrogen)

 (119 : 88 : 1) (relative to the para- position)

The activating influence of chlorine for the same system is:

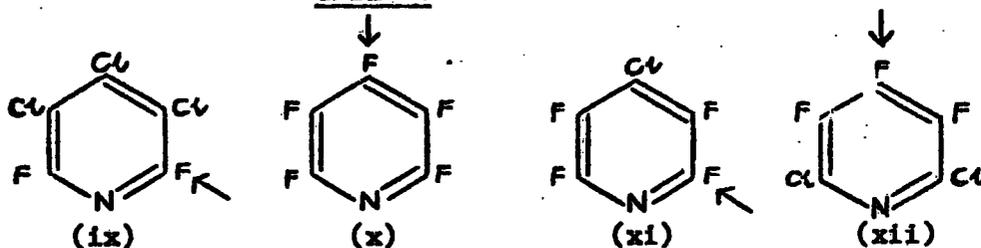
Cl ortho : meta : para

~77 : 24 : 6.9 (relative to hydrogen)

(13 : 3.5 : 1) (relative to the para- position)

For the chlorine series, the effects at each of the three positions are very similar, much more so than for the fluorine series. The rate constants shown in Table 4 were obtained under exactly the same conditions as those in Table 3, and comparison of some of the rate constants included in the two tables lead to direct chlorine/fluorine ratios.

TABLE 4



Rate Constants: $(1.30 \pm 0.01) \times 10^{-4}$ $(6.80 \pm 0.03) \times 10^{-4}$ $(1.55 \pm 0.01) \times 10^{-6}$ $(6.47 \pm 0.01) \times 10^{-4}$
($l \text{ mole}^{-1} \text{ s}^{-1}$)

Attack at the 4- position

$k(\text{ii})/k(\text{x}) = k_{\text{Cl}}/k_{\text{F}}$ (ortho) = 7.0 ie. 2.6 per ortho chlorine atom

$k(\text{iv})/k(\text{x}) = k_{\text{Cl}}/k_{\text{F}}$ (ortho) = 2.8 per ortho chlorine atom

$k(\text{vi})/k(\text{x}) = k_{\text{Cl}}/k_{\text{F}}$ (meta) = 1.05 per meta chlorine atom

$k(\text{vi})/k(\text{xii}) = k_{\text{Cl}}/k_{\text{F}}$ (meta) = 0.91 per meta chlorine atom

$k(\text{xii})/k(\text{x}) = k_{\text{Cl}}/k_{\text{F}}$ (meta) = 0.97 per meta chlorine atom

Attack at the 6- (or 2-) position

$k(\text{viii})$ (6-)/ $k(\text{xi}) = k_{\text{Cl}}/k_{\text{F}}$ (para) = 26.4 per para chlorine atom

$k(\text{ix})/k(\text{viii})$ (2-) = $k_{\text{Cl}}/k_{\text{F}}$ (para) = 26.7 per para chlorine atom

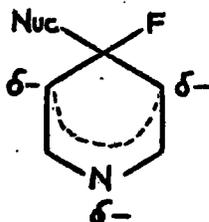
$k(\text{ix})/k(\text{viii})$ (6-) = $k_{\text{Cl}}/k_{\text{F}}$ (ortho) = 3.2 per ortho chlorine atom

$k(\text{viii})$ (2-)/ $k(\text{xi}) = k_{\text{Cl}}/k_{\text{F}}$ (ortho) = 3.1 per ortho chlorine atom

The ratios of pairs of rate constants for the ortho, meta and para positions, are very similar for any one position, leading to the conclusion that in the ammonia/dioxan/water system, steric effects are negligible, otherwise the ortho ratio determined from nucleophilic attack at the 4- position, where there are two adjacent halogenated positions, would be very different from the ratio determined by 2- or 6-attack, where nitrogen occupies one of the adjacent positions. The results also indicate that the effects of the halogens are additive, otherwise the values would not be in such close agreement.

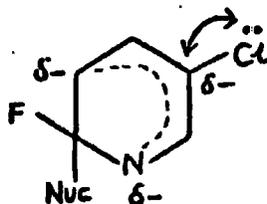
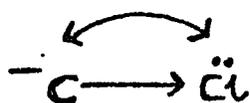
Rationalisation of Rate and Orientation of Substitution in Chloro-fluoropyridines

When interpreting the results given in Tables 3 and 4, it is assumed that the transition state has the structure previously shown, in the section where the results of Table 1 are rationalised. This structure is repeated below:-



Effect of chlorine para- to position of attack

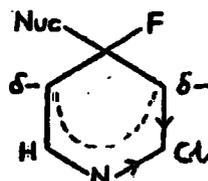
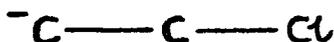
That a para- chlorine is only approximately 7 times more activating than hydrogen at the same position, is attributed to the fact that in the transition state the normal carbanion stabilisation by inductive electron withdrawal by chlorine, is offset by electron pair repulsion.



However, in the case of chlorine, the lone pair repulsion does not offset the inductive electron withdrawal to such a great extent as in the case of fluorine.

Effect of chlorine meta- to position of attack

Chlorine, in the position meta- to the point of nucleophilic attack, is activating with respect to meta- hydrogen, as the non-bonded electron repulsion is insignificant, so that the negative charge is stabilised by inductive electron withdrawal, as indicated below.

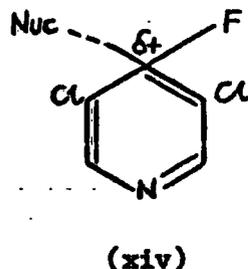
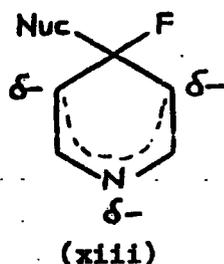


Chlorine and fluorine have a very similar activating effect at the meta- position, with respect to hydrogen. The stabilising influences of fluorine and chlorine on carbanions such as ${}^{-}\text{C}-\text{C}-\text{X}$ (where $\text{X}=\text{F}, \text{Cl}$) in a saturated system, cannot be effectively compared, as chlorine is eliminated readily, however, in an aromatic system such as ${}^{-}\text{C}=\text{C}-\text{X}$, it has been established that fluorine and chlorine have a similar acidifying influence on adjacent hydrogen.²⁸

Effect of chlorine ortho- to position of attack

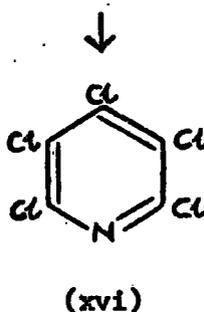
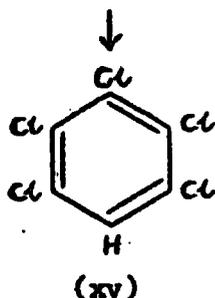
A chlorine atom in the position ortho to the position of nucleophilic attack is activating with respect to hydrogen, and is comparable with a fluorine in the same position. An explanation of this high ortho- effect has been proposed previously, in the section containing a rationalisation of the rate and orientation of

substitution in hydrofluoropyridines. In this case, the bond being formed between the substrate and the nucleophile would depend partly on the electrophilic nature of the carbon being attacked, this being increased by the presence of ortho-chlorine atoms. The transition state is somewhere between the two structures (xiii) and (xiv) shown below.



This explanation accounts for the fact that chlorine and fluorine in the ortho-position, have a similar effect. If the transition state was like (xiii) alone, ortho and para-halogens would have a similar effect, but the results in Tables 3 and 4, show that this is not so.

The effects described, lead to a rationalisation of the orientation of nucleophilic substitution in poly chloro-aromatic compounds. In pentachlorobenzene, (xv), nucleophilic substitution occurs para- to the hydrogen atom, as para- attack maximises the activating influence of the chlorine atoms, the order of activation being ortho > meta > para.

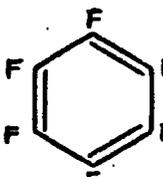
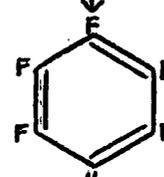
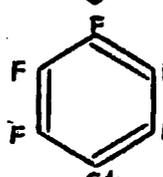
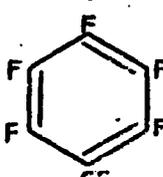
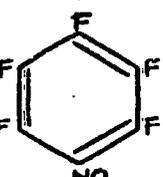


When pentachloropyridine, (xvi), undergoes nucleophilic attack, the activating influence of the chlorine atoms is maximised in a similar way, attack occurring at the 4- position.

Some Consequences of Orientating Influence of Fluorine in Nucleophilic Substitution of Polyfluoro Aromatic Compounds

Rate constants for the reactions of various mono-substituted pentafluorobenzenes, compounds of the type C_6F_5X , with methoxide ion in methanol at $60^\circ C$, were measured, at Birmingham,³⁸ Some of the results are shown in Table 5, below, the position of attack in each case, being arrowed.

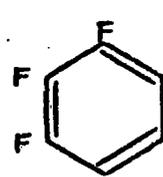
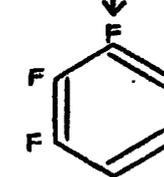
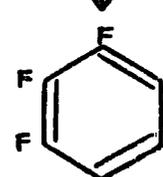
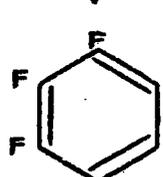
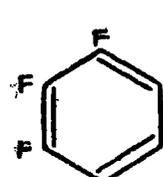
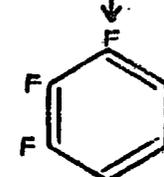
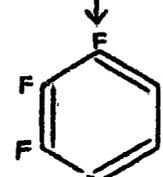
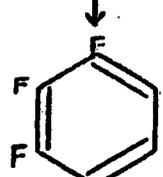
TABLE 5

					
Relative rate constants	0.90^a	1	4.6	4.5×10^3	2.3×10^6

a Actual relative value = 5.4

Reactions for a further set of C_6F_5X compounds have been performed,³⁹ and Table 6 below shows the observed rate constants, group I for the reaction with methoxide ion in dioxan/methanol (5:1V/V) at $50^\circ C$, and group II for the reaction with methoxide ion in methanol at $50^\circ C$.

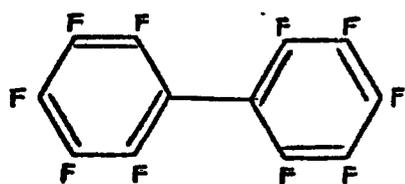
TABLE 6

<u>GROUP I</u>				
				
$k(\text{mole}^{-1}\text{s}^{-1}) 3.50 \times 10^{-3}^a$	4.00×10^{-3}	6.42×10^{-2}	3.85×10^{-2}	
<u>GROUP II</u>				
				
$k(\text{mole}^{-1}\text{s}^{-1}) 5.02 \times 10^{-5}^a$	8.66×10^{-5}	3.70	3.45×10^{-4}	

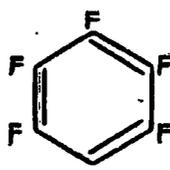
a = Actual value divided by 6

From the tables it can be seen that the substituents Cl, Br, I, CN, NO_2 and CF_3 , all of which are electrophilic, direct the position of nucleophilic attack, para to themselves. This is in agreement with the postulation in the previous sections, that in nucleophilic attack, the number of ortho and meta fluorines is maximised, as they have a significant activating effect, unlike para-fluorine. The tables show that the CF_3 , CN and NO_2 groups are much more activating than fluorine. The present work, involved reaction of the mono substituted pentafluorobenzenes with ammonia in 60/40 dioxan/water at 25°C . The results were given previously in Table (i). The NO_2 , CN and pentafluorophenyl groups are all activating with respect to hexafluorobenzene and pentafluorobenzene, which react in this system, at a rate which is too slow to measure. The NO_2 and CN groups were expected to be activating, from considerations of charge distribution in the transition state, and this is in agreement with the results in Tables 5 and 6.

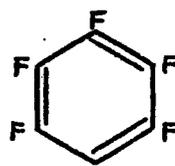
Decafluorobiphenyl, represented as (xvii), is observed to react more slowly than pentafluorobenzonitrile (xviii) by a factor of 534, and more slowly than pentafluoronitrobenzene (xix) by a factor of 2338.



(xvii)



(xviii)



(xix)

The rate constants observed for the reaction of (xvii), during each run, show no shift, so it seems likely that mono-substitution at the position para to one of the pentafluorophenyl groups is taking place, and that 4,4 di-substitution is unlikely.

Solvent effects

When the concentration of dioxan in the solvent was increased from 60% to 80%, the rate constant for the reaction of (xviii) with ammonia, was approximately doubled.

It has been proposed⁴⁰ that an increase in polarity of the medium makes possible an increase in reaction rates for those reactions in which a larger charge separation occurs in the transition state than in the initial state. This situation would be expected to occur in the nucleophilic substitution reactions with ammonia, but in fact, the reaction occurs faster in the less polar medium. This could be due to the initial protonation of ammonia in dioxan/water.

KINETIC METHODS AND RATE CONSTANT CALCULATIONS

Rate constants for the reactions were determined either at 25°C or 90°C, using ammonia as a nucleophile in 60/40 dioxan/water. The reactions at 25°C were followed by periodically removing a fixed volume from the reaction solution, 'freezing' the sample in 100 ml. of distilled water, and titrating this against standard hydrochloric acid, thus determining the concentration of nucleophile remaining. The reactions at 90°C were followed by sealing samples of the reaction solution in glass ampoules, which were plunged into ice/water to 'freeze' the reaction, and broken below the level of 100 ml. of distilled water. This was then titrated against standard hydrochloric acid, as for the reactions at 25°C.

The second order rate constants (k_{II}) were obtained from equation 1.

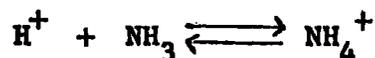
$$k_{II} t = \frac{1}{a-2b} \ln \frac{b}{a} \left(\frac{a-2x}{b-x} \right) \quad 1.$$

where a = initial concentration of nucleophile

b = initial concentration of substrate

x = concentration of substrate reacted at time t .

Equation 1 implies that ammonia is extensively protonated in 60/40 dioxan/water. Two molecules of ammonia are required for the reaction of one molecule of substrate, meaning that the equilibrium constant of the reaction below lies far to the right, resulting in the formation of the ammonium halide salt.



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

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

σ is obtained from the expression:-

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

where k_i = the i^{th} value of the rate constant for a run.

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

Values of k_i for which $(k_i - \bar{k}) > 2.5 \sigma$ are rejected, and new values of \bar{k} and σ are calculated.

EXPERIMENTAL

INSTRUMENTATION

(i) For preparative work

Infra-red spectra were recorded on a Grubb-Parsons 'Spectromaster' spectrometer. Liquid samples were in the form of thin contact films between potassium bromide plates, and solid samples were pressed into homogeneous thin discs with potassium bromide.

Proton (^1H) and fluorine (^{19}F) nuclear magnetic resonance spectra were recorded on either a Varian A56/60D spectrometer, or a Bruker at a temperature of about 40°C , the standard temperature of the probe.

Preparative scale vapour phase chromatography was achieved using a Varian 'Aerograph Autoprep instrument using column TXP. Analytical vapour phase chromatography was performed on either a Pye 104 Chromatograph, or a Griffin and George, D6, Gas Density Balance, using column 'O' in both, column 'TXP' on the Gas Density Balance, and column 'DNP' on the Pye 104.

Carbon, hydrogen and nitrogen analyses were obtained using a Perkin-Elmer 240 Elemental Analyser.

Mass spectra and molecular weights were obtained using an A.E.I. M.S.9 spectrometer.

(11) Rate measurements

All runs were carried out in thermostatted tanks, which were heated electrically by filament-type heaters, the temperature being controlled to $\pm 0.01^{\circ}\text{C}$ by contact thermometer. Water was used as liquid in the bath at 25°C , and lissapol was used for the bath at 90°C . The accurate temperature of each bath was measured by thermometers standardised to $\pm 0.02^{\circ}\text{C}$ by the National Physics Laboratory.

PREPARATION AND PURIFICATION OF STARTING MATERIALS

Solvents

(a) Dioxan. The method adopted was that of Vogel⁴¹. Commercial dioxan (2.1 l) was refluxed for 8 hours with concentrated hydrochloric acid (30 ml) and water (168 ml), with a steady stream of nitrogen bubbling through the solution to remove acetaldehyde as it was formed. Sodium hydroxide pellets were then added, with vigorous shaking, until no more dissolved, and the aqueous layer was separated off. The dioxan layer was left standing over fresh potassium hydroxide pellets for a further 20 hours. The aqueous layer was separated off, and the dioxan was refluxed with excess sodium for about 24 hours, until the surface of the sodium was bright. A small sample was tested for peroxide by adding potassium iodide solution, acidified with dilute hydrochloric acid. No iodine was detected, so peroxide was not present. The dioxan was distilled into an oven-dried flask under dry nitrogen. The fraction boiling between $101 - 102^{\circ}\text{C}$ was collected. The residue was destroyed by the addition of methylated spirit under nitrogen. When not in use, the dioxan was stored under nitrogen in a refrigerator at -5°C .

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

Substrates

Methods of preparation are given for compounds not previously synthesised. Those compounds which were commercially obtained, were checked for impurities by analytical v.p.c.

(a) 3-hydro-4-chlorotrifluoropyridine

This was obtained by a two stage preparation, the first stage being the preparation of 3-hydro-4-hydrazino-trifluoropyridine.

(i) 3-hydro-tetrafluoropyridine (16.6 g. 0.11 mole) was added dropwise to a stirred solution of hydrazine hydrate (9 g) in methanol (30 ml). The reaction was allowed to proceed at room temperature and was left overnight, resulting in the formation of an orange solid around the edges of the flask, and an orange liquid. This was poured into excess water (150 ml). Diethyl ether (150 ml) was added, dissolving the solid, and the two layers were separated. The aqueous layer was extracted with ether (5 x 30 ml), and the ether extracts were added together. The ethereal solution was washed several times with water, and dried over anhydrous magnesium sulphate. The ether was removed using a rotary evaporator, and the resulting yellow solid was dried using a vacuum line. The yield of 3-hydro-4-hydrazinotrifluoropyridine was 13.5 g (75%).

(ii) 3-hydro-4-hydrazinotrifluoropyridine (13 g. 0.08 mole) was added slowly to a stirred solution of copper(II) chloride (80.4 g. 0.60 mole) in concentrated hydrochloric acid (550 ml). The mixture was stirred at room temperature for two hours, then refluxed for 30 minutes, after which nitrogen ceased to be evolved. The mixture was distilled, and a pale yellow liquid came over. The organic layer, which was a deep yellow oil, was separated from the water in the distillate. The water layer was

47.

extracted with ether (3 x 15 ml). The ether extracts were added to the organic layer, and the resulting mixture was washed with water and dried over anhydrous magnesium sulphate. As the product was expected to be quite volatile, ether was not removed using a rotary evaporator, but was distilled off, using a Vigreux column, leaving a pale yellow liquid. Quantitative v.p.c. (Griffin Gas Density Balance. Column 'O'), showed that an impurity was present (~ 10%). An attempt was made to separate the impurity from the desired product using a concentric tube column, but complete separation was not achieved, as the two components had very similar boiling points. ^1H and ^{19}F n.m.r. spectra showed that the impurity was 6-chloro-3-hydro-trifluoropyridine, an isomer of the desired product. Separation was achieved by preparative v.p.c. (Aerograph, Column TXP, 140°C). The purity of the 3-hydro-4-chloro-trifluoropyridine was checked at intervals by analytical v.p.c. (Pye 104, Column DNP, 100°C). The yield of compound was 1.032 g (8%). It was shown to be 3-hydro-4-chloro-trifluoropyridine by ^1H and ^{19}F n.m.r. spectra. B. pt. 128°C . (Found: C 35.9%; N, 8.5%; H, 1%; M, 167. $\text{C}_5\text{ClHF}_3\text{N}$ requires C 35.9%; N, 8.4%; H .0.6%.

(b) 2-chlorotetrafluoropyridine

This was prepared in five stages, the first being the preparation of 4-hydrazinotetrafluoropyridine.

(i) Hydrazine hydrate (18 g) dissolved in ethanol (125 ml), was added to a quickfit flask, into which pentafluoropyridine (25 g) was added dropwise, at room temperature, with stirring, over a period of 30 minutes. Stirring was continued overnight, resulting in the formation of a white precipitate. The mixture was poured into ice-water, and ether extracted. The extracts were combined and dried over anhydrous magnesium sulphate, and ether was

removed, using a rotary evaporator, leaving 4-hydrazinotetrafluoropyridine.

(ii) 4-hydrazinotetrafluoropyridine (3 g) was added slowly to a stirred solution of copper(II) bromide (29 g) in aqueous (50%) hydrogen bromide (80 ml). After addition was complete, the mixture was stirred for 30 minutes, then steam distilled, and the aqueous distillate was ether extracted. The ether extracts were combined and dried, and ether was removed, leaving 4-bromotetrafluoropyridine (2.9 g 76%).

(iii) 2-hydrazino-4-bromo-trifluoropyridine was prepared by the same procedure as stage (i), 4-bromotetrafluoropyridine being added slowly to a mixture of hydrazine hydrate in ethanol.

(iv) Copper(II) chloride (70 g) was dissolved in concentrated hydrochloric acid (650 ml), and the solution was stirred at room temperature while 2-hydrazino-4-bromo-trifluoropyridine was added, batchwise, over a period of 30 minutes. After addition was complete, the mixture was refluxed for 2 hours, and distilled. The distillate was ether extracted, the combined extracts were dried and ether was removed. The product was analysed by v.p.c. (Pye 104; Column 'O', 150°C), and showed one major component with some lower boiling impurities. These lower-boiling components were removed using a concentric tube column. The residue was analysed by v.p.c. and found to be 95% 2-chloro-4-bromotrifluoropyridine.

(v) 2-chloro-4-bromotrifluoropyridine (5 g), sulpholan (30 ml), and caesium fluoride (10 g) were added to a quickfit flask fitted with a Teflon follower, and under nitrogen. The mixture was stirred at 100°C and checked hourly by v.p.c. (Pye 104, Column 'O', 200°C). After 5 hours the reaction was complete, and the product was transferred from the reaction flask. It was purified by preparative scale v.p.c. (Pye 105, Column 'O', 125°C). The yield of product was 1 g (27%). This was shown to be 2-chlorotetrafluoropyridine by comparison of its i.r. spectrum with that of an authentic sample³¹.

c) Pentafluorobenzonitrile

The purity of a commercial sample was checked by analytical v.p.c. (Pye 104, Column 'O', 122°C).

d) Decafluorobiphenyl

The purity of a commercial sample was checked by analytical v.p.c. (Pye 104, Column 'O', 200°C).

e) Pentafluoronitrobenzene

The purity was checked by analytical v.p.c. (Pye 104, Column 'O', 200°C).

f) Bromopentafluorobenzene

The purity of a commercial sample was checked by analytical v.p.c. (Pye 104, Column 'O', 200°C).

g) Chloropentafluorobenzene

The purity of a commercial sample was checked by analytical v.p.c. (Pye 104, Column 'O', 200°C)

h) Pentafluorobenzene

The purity of a sample was checked by analytical v.p.c. (Pye 104, Column 'O', 125°C).

Reagent

Ammonia. Analytical grade ammonia was used without further treatment.

METHODS OF RATE MEASUREMENT

(i) Reactions at 25°C.

Stock solutions of ammonia in water and substrate in dioxan were prepared, usually being approximately 3.0 moles ℓ^{-1} and 0.5 moles ℓ^{-1} respectively. 1.5 M ammonia did not react at a sufficiently fast rate to enable accurate rate constants to be determined, with such compounds

as 3-hydro-4-chloro-trifluoropyridine, and decafluorobiphenyl.

Dioxan and water (either 60 ml and 40 ml respectively, or 30 ml and 20 ml respectively), were pipetted into a conical flask which was stoppered and immersed in a thermostat bath at 24.98°C. The substrate solution was also placed in a stoppered flask in the thermostat bath. These solutions were allowed approximately 15 minutes to attain the temperature of the bath. 5 ml of stock ammonia solution were pipetted into the flask containing the dioxan/water mixture, and the contents of the flask were mixed. Two 5 ml aliquots of the solution were removed separately, quenched in distilled water (100 ml), and titrated against standard hydrochloric acid (usually approximately 0.05 M, but 0.025 M, if the concentration of the ammonia solution used was 1.5 M), using methyl red as indicator. Stock solutions of hydrochloric acid had been prepared by diluting commercial 0.1 M hydrochloric acid, and these were standardised against standard sodium hydroxide solution. The molarity of these stock solutions was checked periodically, by titration with standard sodium hydroxide solution.

From the two titrations of the samples removed from the reaction flask, 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 of substrate solution to the reaction flask, the reaction being timed from the first drop of substrate solution to enter the ammonia/dioxan/water mixture. The reaction was followed, by periodically removing 5 ml aliquots from the reaction solution, quenching in distilled water (100 ml), the time being noted as the last drop was added, as the water 'froze' the reaction. Titration of these solutions, against standard hydrochloric acid, using

methyl red indicator, enabled the amount of nucleophile still remaining to be calculated.

The initial substrate concentration was obtained from a knowledge of the weight dissolved in a certain volume of dioxan, 5 ml of which were diluted to a total volume of 100 ml or in some cases 50 ml, in the reaction flask. The second order rate constants were calculated as described previously.

Decafluorobiphenyl and bromopentafluorobenzene were insoluble in 60/40 dioxan/water, so in reactions where these compounds were used as substrates, the solvent was initially prepared from 40 ml of dioxan and 10 ml of water. The reaction of pentafluorobenzonitrile with ammonia was performed in both solvent systems in order to check if there was any significant change in rate constant in changing from one solvent system to the other.

In the reaction with pentafluoronitrobenzene the reaction solution was bright yellow and the end point in the titration of the residual ammonia against standard hydrochloric acid could not be distinguished using methyl red as indicator. Phenol red was found to be suitable, as indicator.

(ii) Reactions at 90°C

Stock solutions of ammonia in water and substrate in dioxan were prepared, the concentrations being approximately 6.0 moles l^{-1} and 2.0 moles l^{-1} respectively.

Dioxan (80 ml) and water (20 ml) were pipetted into a flask and 5 ml of stock ammonia solution were added. After mixing, two 5 ml aliquots were removed and were titrated against standard hydrochloric acid (approximately 0.1 M), using methyl red indicator.

5 ml of the substrate solution were pipetted into the flask, and

the solution was mixed. 5 ml aliquots of the reaction solution were sealed in glass ampoules and immersed simultaneously in the thermostat bath at 88.24°C. After 15 minutes an ampoule was removed, and plunged into an ice/water mixture to stop the reaction. Zero time for the reaction was taken as the instant of immersion in ice water. The ampoule was removed, washed, and broken using a thick glass rod, under the surface of 100 ml of water in a stout glass jar. The residual ammonia was titrated against standard hydrochloric acid, using methyl red as indicator. This titre was taken as the initial reading for the run and the initial ammonia concentration calculated from it. The reaction was followed by removing tubes periodically, plunging them into an ice/water mixture (this time being taken as the time of the reading), washing, then breaking them under the surface of 100 ml of water and titrating against standard hydrochloric acid. The initial substrate concentration was calculated, knowing the weight dissolved in a certain volume of dioxan, 5 ml of which were diluted to 100 ml in the reaction flask. The second order rate constants were calculated as previously described.

IDENTIFICATION OF PRODUCTS

After 'infinity time' the remainder of reaction solution for each run was added to excess water (150 ml) and this solution was ether extracted (3 x 20 ml). The ether extracts were combined, washed with water, dried over anhydrous magnesium sulphate and ether was removed using a rotary evaporator, leaving the product.

The melting point of the product was determined and its mass spectrum, infra-red and ¹⁹F n.m.r. spectra were obtained.

Products from reaction with Ammonia in Dioxan/Water

a) With 3-hydro-4-chloro-trifluoropyridine.

After recrystallisation from ethanol, the product was a white solid, shown to be 3-hydro-4-chloro-6-aminodifluoropyridine by its mass spectrum, ^{19}F N.M.R. spectrum, and by elemental analysis.

M.pt. 103-104°C (Found C, 37.2%; N, 17.2%; H, 2.2%; M (^{35}Cl), 164.

$\text{C}_5\text{H}_3\text{ClF}_2\text{N}_3$ requires C, 36.6%; N, 17.0%; H, 1.8%; M, 164). I.R. spectrum No. 3. N.M.R. spectrum No. 2.

b) With 2-chlorotetrafluoropyridine.

After recrystallisation from ethanol, the product was a white solid, shown to be 2-chloro-4-aminotrifluoropyridine by its mass spectrum, ^{19}F N.M.R. spectrum, and by elemental analysis.

M.pt. 118°C (Found C, 33.2%; N, 15.3%; H, 1.0%; M (^{35}Cl), 182. $\text{C}_5\text{H}_2\text{ClF}_3\text{N}_2$

requires C, 33.0%; N, 15.4%; H, 1.1%; M, 182). I.R. spectrum No. 5. N.M.R. spectrum No. 4.

c) With pentafluorobenzonitrile.

After recrystallisation from ethanol, cream crystals were obtained.

M.pt. 75°C (Found C, 44.1%; N, 14.6%; H, 1.1%; M, 190. $\text{C}_7\text{H}_2\text{F}_4\text{N}_2$ requires C, 44.2%; N, 14.7%; H, 1.1%; M, 190). I.R. spectrum No. 7. N.M.R. spectrum No. 5.

d) With pentafluoronitrobenzene.

After recrystallisation from ethanol, dull red crystals were obtained.

M.pt. 108-109°C (Found C, 34.1%; N, 13.2%; H, 1.2%; M, 210. $\text{C}_6\text{H}_2\text{O}_2\text{F}_4\text{N}$ requires C, 34.3%; N, 13.3%; H, 1.0%; M, 210). I.R. spectrum No. 9.

N.M.R. spectrum No. 6.

RATE DATA3-hydro-4-chlorotrifluoropyridine + ammonia in 60/40 dioxan/water at 24.98°C

<u>Run 1</u>			<u>Run 2</u>		
<u>Time (min)</u>	<u>Titre (ml)</u>	<u>$10^4 k (\text{l mole}^{-1} \text{min}^{-1})$</u>	<u>Time (min)</u>	<u>Titre (ml)</u>	<u>$10^4 k (\text{l mole}^{-1} \text{min}^{-1})$</u>
0	25.93		0	21.57	
1,408	24.75	3.51	1,391	20.57	3.54
2,953	23.66	3.52	5,640	18.30	3.53
5,735	22.10	3.54	7,075	17.72	3.51
7,158	21.49	3.50	8,512	17.12	3.61
8,606	20.92	3.50	9,956	16.69	3.56
10,064	20.40	3.54	11,477	16.23	3.58
15,799	18.86	3.61	15,716	15.22	3.60
20,124	18.15	3.57	17,173	15.00	3.53
			18,656	14.76	3.51

<u>Run 1</u>	$[\text{NH}_3]_0$	=	0.2593 M
	$[\text{Substrate}]_0$	=	0.05006 M
	k	=	$(3.54 \pm 0.01) \times 10^{-4} \text{ l mole}^{-1} \text{ min}^{-1}$
<u>Run 2</u>	$[\text{NH}_3]_0$	=	0.2168 M
	$[\text{Substrate}]_0$	=	0.05033 M
	k	=	$(3.55 \pm 0.01) \times 10^{-4} \text{ l mole}^{-1} \text{ min}^{-1}$
<u>Mean</u>	k	=	$(3.55 \pm 0.01) \times 10^{-4} \text{ l mole}^{-1} \text{ min}^{-1}$

2-chlorotetrafluoropyridine + ammonia in 60/40 dioxan/water at 25.00°C

Run 1			Run 2		
Time (min)	Titre (mℓ)	$10^2 k (\ell \text{ mole}^{-1} \text{ min}^{-1})$	Time (min)	Titre (mℓ)	$10^2 k (\ell \text{ mole}^{-1} \text{ min}^{-1})$
0	19.40		0	19.38	
17.38	18.10	4.29	16.5	18.14	4.32
44.72	16.54	4.26	44.58	16.55	4.25
74.08	15.33	4.21	70.5	15.40	4.28
101.23	14.44	4.22	95.83	14.57	4.24
136.25	13.54	4.26	125.1	13.83	4.18
167.5	12.94	4.25	148.67	13.25	4.28
194.23	12.50	4.29	233.67	11.99	4.29
220.03	12.21	4.21	264.45	11.70	4.26
270.97	11.68	4.22	307.42	11.38	4.22

Run 1 $[\text{NH}_3]_0 = 0.2070 \text{ M}$
 $[\text{Substrate}]_0 = 0.05003 \text{ M}$
 $k = (4.25 \pm 0.01) \times 10^{-2} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2068 \text{ M}$
 $[\text{Substrate}]_0 = 0.05004 \text{ M}$
 $k = (4.26 \pm 0.01) \times 10^{-2} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Mean $k = (4.26 \pm 0.01) \times 10^{-2} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Pentafluorobenzonitrile + Ammonia in 60/40 Dioxan/Water at 24.98°C

Run 1			Run 2			Run 3		
Time (min)	Titre (ml)	$10^2 k (\text{g mole}^{-1} \text{min}^{-1})$	Time	Titre	$10^2 k$	Time	Titre	$10^2 k$
0	11.27		0	21.93		0	21.92	
40.05	10.94	1.43	15.07	21.47	1.43	28.00	21.10	1.43
70.68	10.70	1.45	38.03	20.80	1.48	55.92	20.29	1.50
98.83	10.49	1.48	67.27	20.02	1.50	123.30	18.84	1.48
154.53	10.09	1.52	122.1	18.90	1.46	231.78	17.16	1.46
182.82	9.95	1.43	262.25	16.76	1.47	286.53	16.44	1.49
206.13	9.76	1.50	320.2	16.13	1.47	315.53	16.20	1.46
229.62	9.62	1.47	352.27	15.81	1.48	347.27	15.88	1.46
313.42	9.17	1.49	383.08	15.57	1.47	371.12	15.66	1.47
331.30	9.06	1.49	∞	12.67		∞	12.63	
357.05	8.94	1.47						
380.82	8.81	1.49						
1390.87	5.85	1.43						
1458.35	5.70	1.44						
1511.45	5.62	1.43						
1764.00	5.18	1.45						
∞	2.47							

Run 1 $[\text{NH}_3]_0 = 0.05670\text{M}$

$[\text{Substrate}]_0 = 0.02497\text{M}$

$k = (1.46 \pm 0.02) \times 10^{-2} \text{ g mole}^{-1} \text{ min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2198\text{M}$

$[\text{Substrate}]_0 = 0.04994\text{M}$

$k = (1.47 \pm 0.01) \times 10^{-2} \text{ g mole}^{-1} \text{ min}^{-1}$

Run 3 $[\text{NH}_3]_0 = 0.2196\text{M}$

$[\text{Substrate}]_0 = 0.04994\text{M}$

$k = (1.47 \pm 0.01) \times 10^{-2} \text{ g mole}^{-1} \text{ min}^{-1}$

Mean $k = (1.47 \pm 0.02) \times 10^{-2} \text{ g mole}^{-1} \text{ min}^{-1}$

Pentafluorobenzonitrile + Ammonia in 80/20 Dioxan/Water at 24.98°C

<u>Run 1</u>			<u>Run 2</u>		
<u>Time (min)</u>	<u>Titre (ml)</u>	<u>$10^2 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)</u>	<u>Time (min)</u>	<u>Titre (ml)</u>	<u>$10^2 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)</u>
0	21.74		0	20.85	
43.97	19.52	2.78	40.25	18.85	2.77
64.53	18.74	2.75	72.00	17.66	2.76
84.37	18.04	2.78	94.75	16.94	2.78
110.27	17.36	2.71	124.83	16.25	2.68
145.20	16.55	2.69	169.28	15.32	2.67
171.50	16.05	2.67	194.42	14.87	2.68
200.78	15.48	2.73	222.25	14.45	2.67
245.45	14.85	2.72	243.92	14.16	2.67
288.20	14.30	2.78	287.17	13.61	2.70

Run 1 $[\text{NH}_3]_0 = 0.2163\text{M}$

$[\text{Substrate}]_0 = 0.04994\text{M}$

$k = (2.73 \pm 0.01) \times 10^{-2} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2061\text{M}$

$[\text{Substrate}]_0 = 0.05020\text{M}$

$k = (2.71 \pm 0.02) \times 10^{-2} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Mean $k = (2.72 \pm 0.02) \times 10^{-2} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Decafluorobiphenyl + Ammonia in 80/20 Dioxan/Water at 24.98°C

Run 1			Run 2		
Time (min)	Titre (ml)	$10^5 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)	Time (min)	Titre (ml)	$10^5 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)
0	21.71		0	21.40	
1,284	21.57	4.72	2,747	21.10	4.87
2,769	21.43	4.67	4,257	20.93	5.25
5,079	21.15	5.09	8,501	20.58	4.69
7,037	20.95	5.13	10,007	20.44	4.76
8,463	20.83	4.96	11,477	20.25	5.04
9,930	20.68	4.96	13,010	20.05	5.30
11,345	20.49	5.30	14,506	19.92	5.27
15,690	20.03	5.43	20,009	19.40	5.42
17,125	19.92	5.34	21,554	19.27	5.41

Run 1 $[\text{NH}_3]_0 = 0.2171\text{M}$

$[\text{Substrate}]_0 = 0.05150\text{M}$

$k = (5.07 \pm 0.09) \times 10^{-5} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2110\text{M}$

$[\text{Substrate}]_0 = 0.05036\text{M}$

$k = (5.11 \pm 0.09) \times 10^{-5} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Mean $k = (5.09 \pm 0.09) \times 10^{-5} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Pentafluoronitrobenzene + Ammonia in 60/40 Dioxan/Water at 25.00°C

Run 1			Run 2		
Time (min)	Titre (ml)	10k ($\mu\text{mole}^{-1}\text{min}^{-1}$)	Time (min)	Titre (ml)	10k ($\mu\text{mole}^{-1}\text{min}^{-1}$)
0	20.28		0	20.30	
5.15	18.98	1.39	5.5	18.96	1.34
12.05	17.70	1.28	14.33	17.58	1.19
21.77	16.41	1.27	23.53	16.25	1.25
32.03	15.91	1.03	33.67	15.72	1.06
41.01	15.20	1.03	40.33	15.04	1.12
50.83	14.48	1.07	50.27	14.48	1.08
59.03	13.26	1.40	60.05	13.40	1.31
69.45	13.24	1.20	68.15	13.35	1.18
78.53	13.22	1.07	78.73	13.15	1.10

Run 1 $[\text{NH}_3]_0 = 0.2178\text{M}$

$[\text{Substrate}]_0 = 0.05005\text{M}$

$k = (1.19 \pm 0.05) \times 10^{-1} \text{ } \mu\text{mole}^{-1}\text{min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2180\text{M}$

$[\text{Substrate}]_0 = 0.05005\text{M}$

$k = (1.18 \pm 0.03) \times 10^{-1} \text{ } \mu\text{mole}^{-1}\text{min}^{-1}$

Mean $k = (1.19 \pm 0.04) \times 10^{-1} \text{ } \mu\text{mole}^{-1}\text{min}^{-1}$

Chloropentafluoropyridine + ammonia in 80/20 dioxan/water at 88.24°C

<u>Run 1</u>			<u>Run 2</u>		
<u>Time (min)</u>	<u>Titre (ml)</u>	<u>$10^4 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)</u>	<u>Time (min)</u>	<u>Titre (ml)</u>	<u>$10^4 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)</u>
0	10.58		0	10.60	
1,402	10.22	1.27	2,765	9.90	1.18
4,336	9.65	1.19	5,651	9.24	1.29
7,158	9.03	1.19	8,523	8.72	1.26
10,060	8.42	1.26	11,395	8.23	1.30
12,958	8.00	1.24	14,255	7.90	1.23
15,856	7.60	1.24	17,148	7.52	1.20
18,634	7.22	1.28	19,939	7.18	1.19
21,520	6.84	1.30	22,821	6.75	1.25
24,384	6.52	1.29	25,695	6.48	1.27

Run 1 $[\text{NH}_3]_0 = 0.2116\text{M}$

$[\text{Substrate}]_0 = 0.1000\text{M}$

$k = (1.25 \pm 0.01) \times 10^{-4} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2120\text{M}$

$[\text{Substrate}]_0 = 0.1000\text{M}$

$k = (1.24 \pm 0.01) \times 10^{-4} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Mean $k = (1.25 \pm 0.01) \times 10^{-4} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Bromopentafluoropyridine + ammonia in 80/20 dioxan/water at 88.24°C

Run 1			Run 2		
Time (min)	Titre (ml)	$10^5 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)	Time (min)	Titre (ml)	$10^5 k$ ($\ell \text{ mole}^{-1} \text{ min}^{-1}$)
0	10.70		0	10.66	
1,422	10.35	9.85	1,452	10.24	9.57
7,190	9.58	8.28	4,377	9.82	8.33
8,606	9.32	8.74	7,272	9.33	9.08
11,512	8.92	8.51	10,115	8.98	8.93
14,405	8.48	8.87	13,055	8.70	8.51
17,271	8.10	9.22	15,937	8.42	8.40
20,424	7.83	9.17	18,726	8.05	8.81
23,014	7.60	8.82	21,610	7.74	8.60
25,908	7.44	8.65	24,480	7.32	9.44

Run 1 $[\text{NH}_3]_0 = 0.2131\text{M}$

$[\text{Substrate}]_0 = 0.09997\text{M}$

$k = (8.90 \pm 0.15) \times 10^{-5} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Run 2 $[\text{NH}_3]_0 = 0.2132$

$[\text{Substrate}]_0 = 0.09997\text{M}$

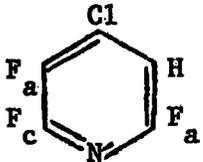
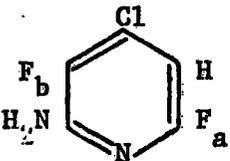
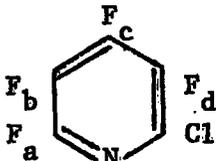
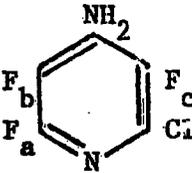
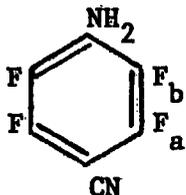
$k = (8.85 \pm 0.15) \times 10^{-5} \ell \text{ mole}^{-1} \text{ min}^{-1}$

Mean $k = (8.88 \pm 0.15) \times 10^{-5} \ell \text{ mole}^{-1} \text{ min}^{-1}$

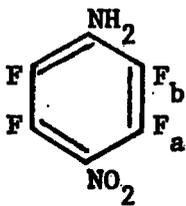
¹⁹F NUCLEAR MAGNETIC RESONANCE SPECTRA

<u>Spectrum Number</u>	<u>Compound</u>
1	3-hydro-4-chloro-trifluoropyridine
2	3-hydro-4-chloro-6-aminodifluoropyridine
3	2-chlorotetrafluoropyridine
4	2-chloro-4-amino-trifluoropyridine
5	Para-amino-tetrafluorobenzonitrile
6	Para-amino-tetrafluoronitrobenzene

Chemical shifts are in p.p.m. relative to internal CFCI_3 .

- | | | <u>Shift</u> | <u>Assignment</u> |
|----|---|--|-------------------|
| 1. |  | 72.1 (Broad S)
85.1 (Broad S)
149.1 (D.D.D.) | a
c
b |
| | $J_{ab} = 24$ $J_{bc} = 20$ | | |
| | Spectrum run as solution in CCl_4 | | |
| 2. |  | 74.6 (D)
150.7 (D) | a
b |
| | $J_{ab} = 24$ | | |
| | Spectrum run as solution in $CDCl_3$ | | |
| 3. |  | 84.8 (Broad S)
137.0 (T.D.)
140.1 (D.D.D.)
159.3 (D.D.D.) | a
c
d
b |
| | $J_{ab} = 23$ $J_{ac} = 16$ $J_{ad} = 26$ $J_{bc} = 16$ $J_{bd} = 4$ $J_{cd} = 18$ | | |
| | Spectrum run as pure liquid. | | |
| 4. |  | 91.0 (T.D.)
141.8 (D.D.)
162.3 (D.D.) | a
c
b |
| | $J_{ab} = 23$ $J_{ac} = 18$ $J_{bc} = 14$ | | |
| | Spectrum run as solution in $CDCl_3$ | | |
| 5. |  | 135.9
160.9 | a
b |
| | $J_{ab} = 12$ | | |
| | Spectrum run as solution in $CDCl_3$ | | |

6.

ShiftAssignment

98.7

a

112.7

b

$$J_{ab} = 14$$

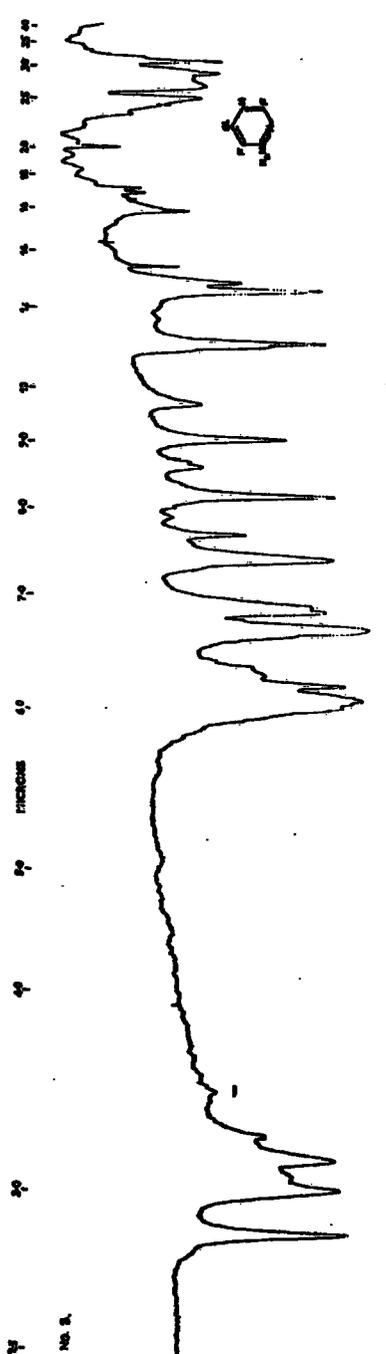
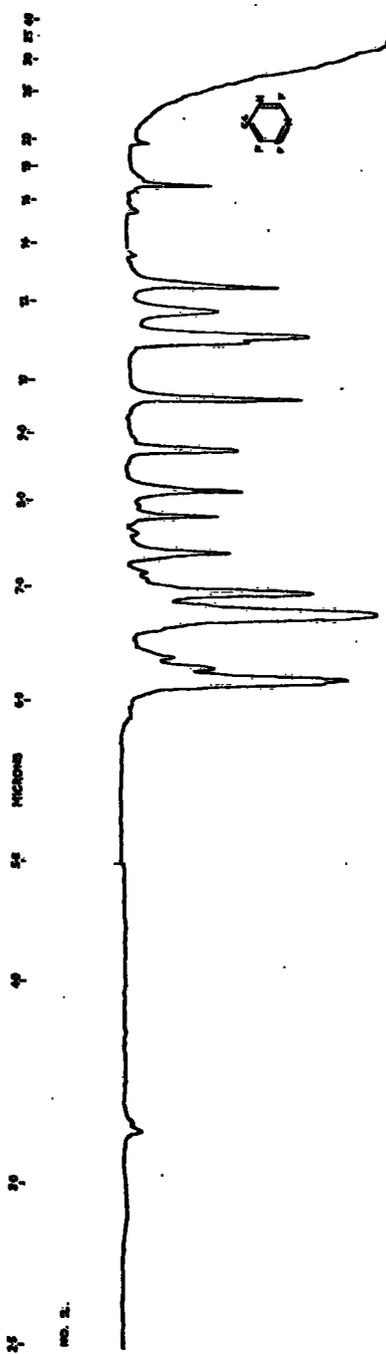
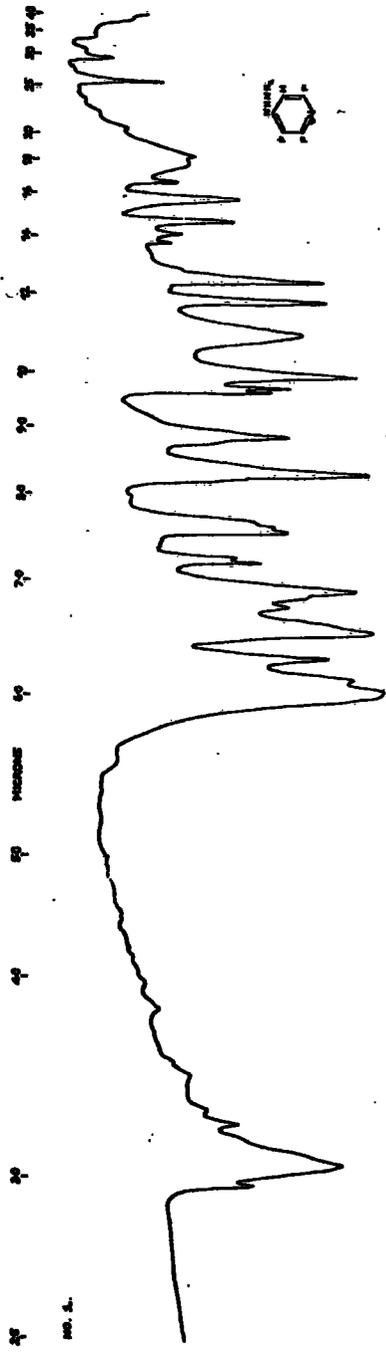
Spectrum run as solution in CDCl_3

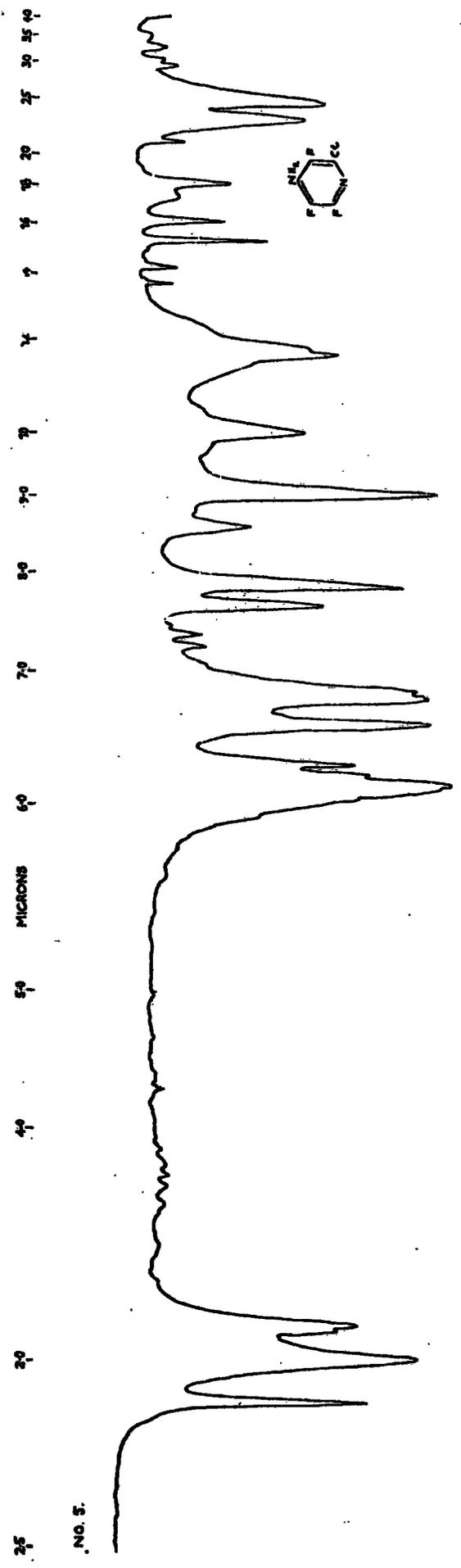
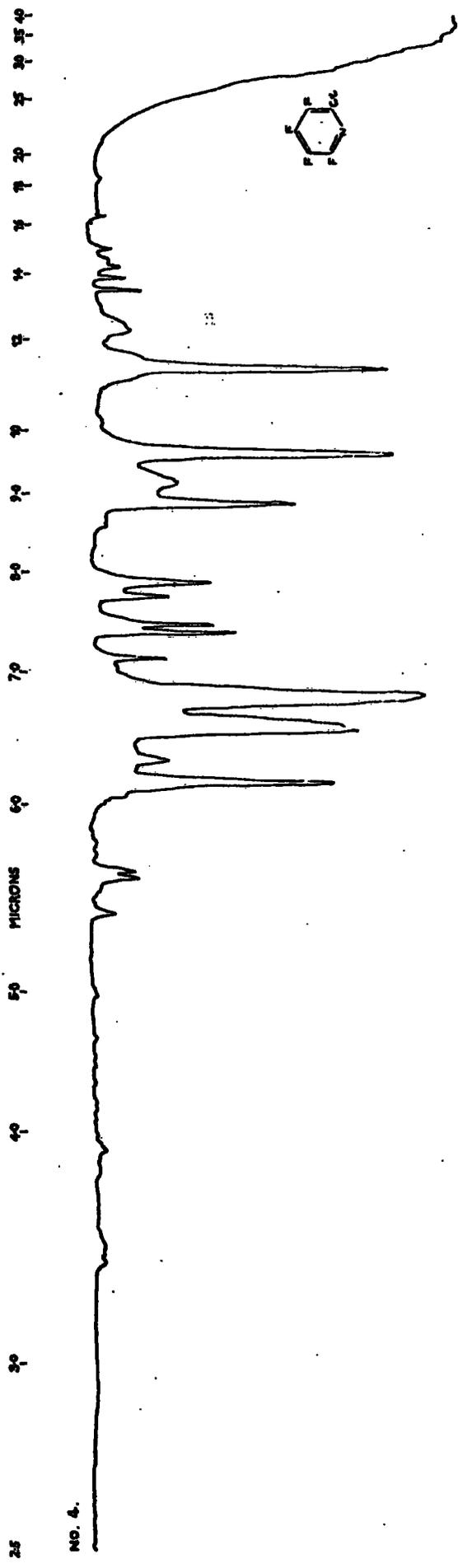
INFRA-RED SPECTRA

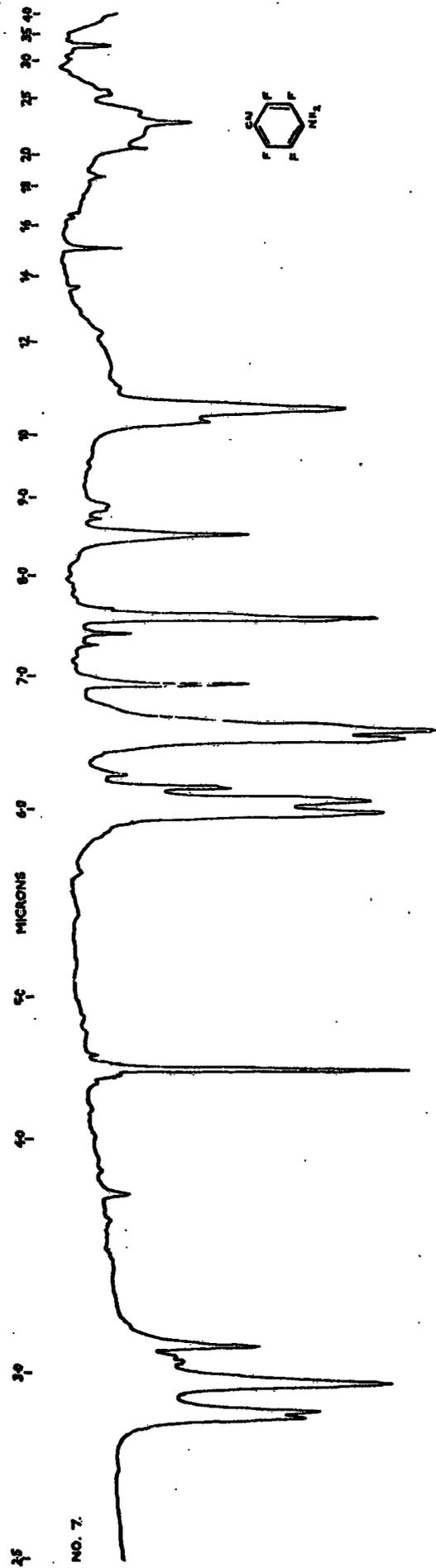
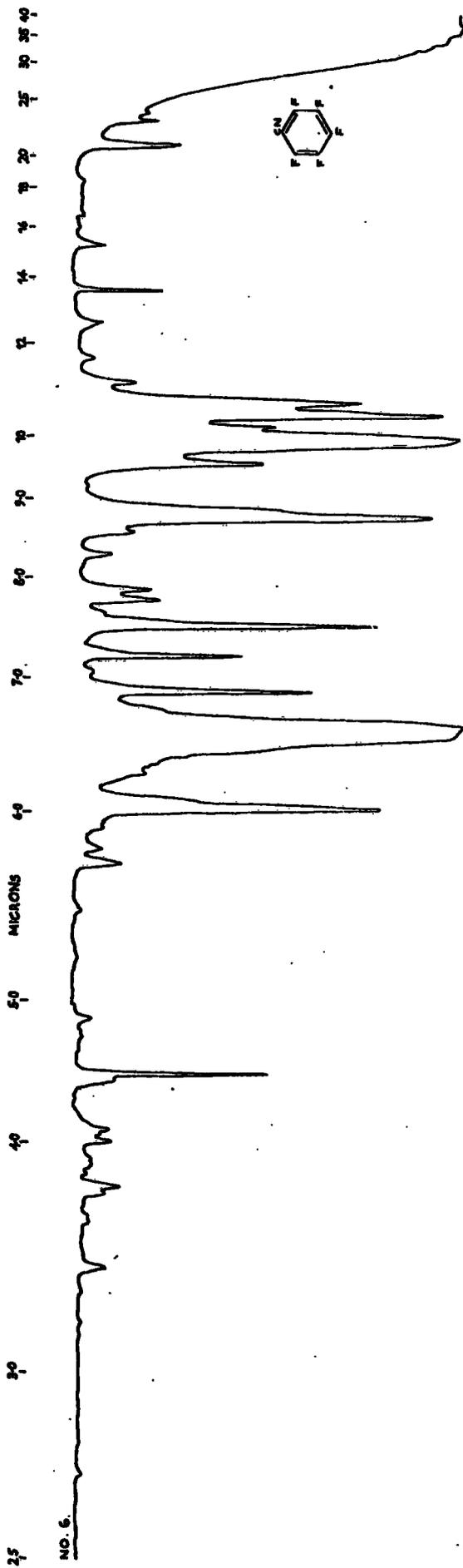
<u>Spectrum Number</u>	<u>Compound</u>	
1	3-hydro-4-hydrazinotrifluoropyridine	(solid)
2	3-hydro-4-chloro-trifluoropyridine	(liquid)
3	3-hydro-4-chloro-6-amino difluoropyridine	(solid)
4	2-chlorotetrafluoropyridine	(liquid)
5	2-chloro-4-amino-trifluoropyridine	(solid)
6	Pentafluorobenzonitrile	(liquid)
7	Para-amino-tetrafluorobenzonitrile	(solid)
8	Pentafluoronitrobenzene	(liquid)
9	Para-amino-tetrafluoronitrobenzene	(solid)

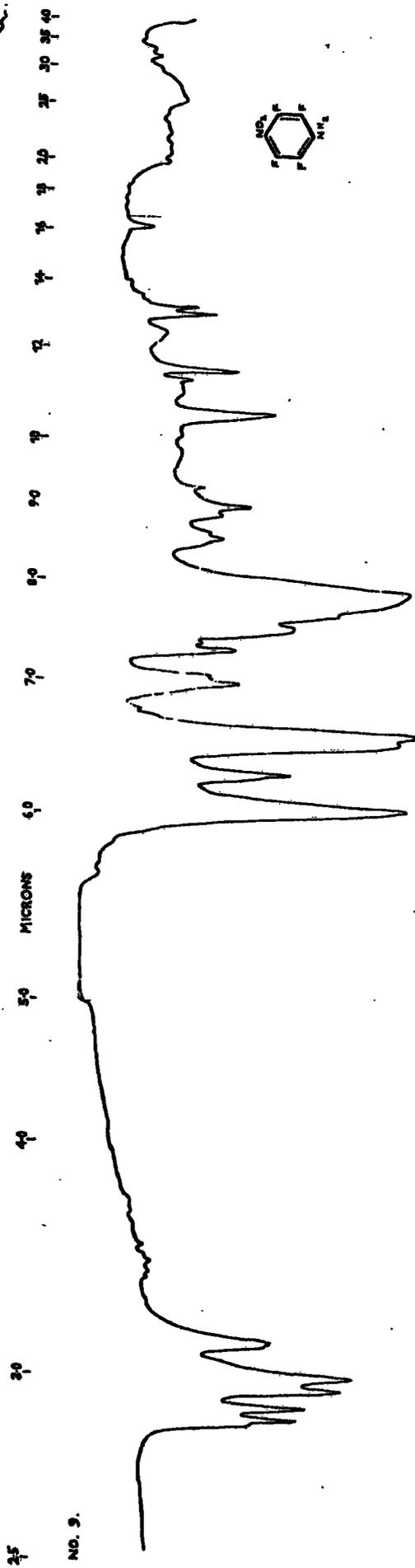
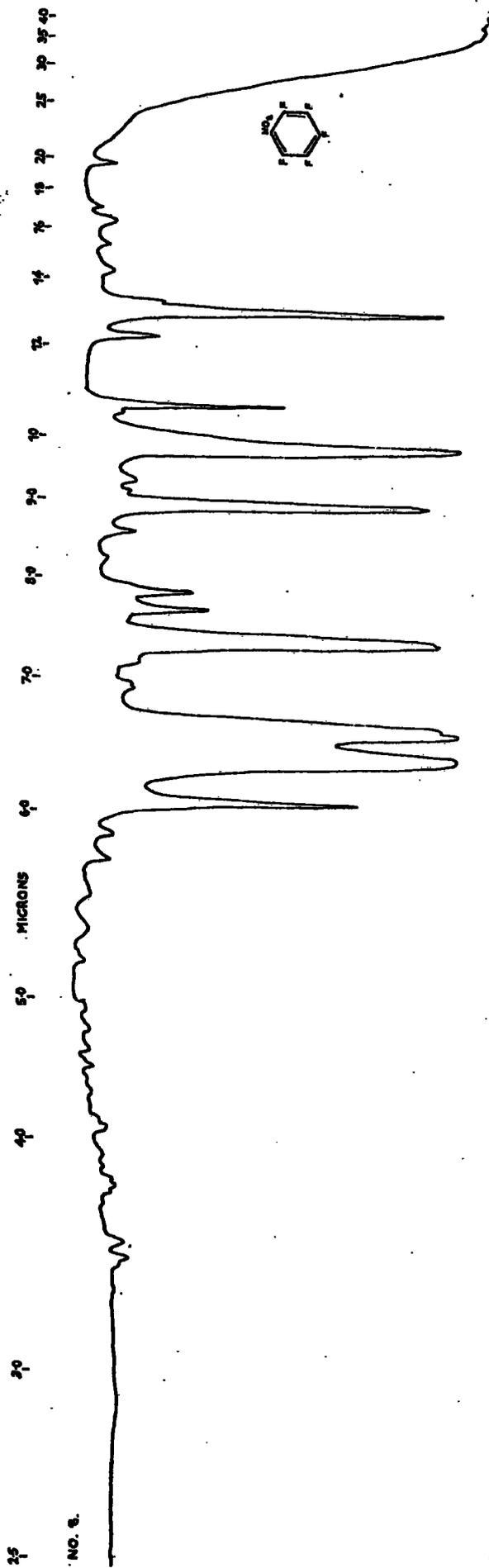
(liquid) - sample as contact film between potassium bromide discs.

(solid) - sample compressed into thin disc with potassium bromide.









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