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FLUORINATED HETEROCYCLIC COMPOUNDS

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SUMMARY

Fluorinated heterocyclic compounds have many features which distinguish them from other corresponding halogenated compounds. The reasons for the distinctive properties of fluorine are reviewed in relation to nucleophilic substitution reactions.

1. INTRODUCTION

It is probably fair to argue that one of the major preoccupations of chemists in industry and academic life is the search for 'new effects', i.e. compounds with novel chemistry and novel properties that can be exploited by industry. Introduction of fluorine into an organic system leads to a wide range of novel chemistry and effects[1,2] and the relevance of this contribution to a symposium on coloured compounds arises from the application of fluorinated heterocyclic compounds as components in fibre-reactive dyes.[3] Understanding the factors that affect nucleophilic aromatic substitution in those systems is clearly fundamental to their further development.

2. SYNTHESIS

Fluorine compounds are, of course, entirely synthetic and so we must ask how fluorine can be conveniently introduced into an organic compound. The sources of fluorine, available for synthetic procedures, may be outlined as follows:

$$\begin{tikzcd}
CaF_2 \arrow[r, "H_2SO_4"] & \text{HF (anhydrous)} \arrow[r, "\text{Electrolysis}", "\text{(KF.2HF)}"'] \arrow[d] & F_2 \arrow[d] \\
& \text{Metal fluorides (e.g. KF, } SbF_3\text{, etc.)} & \text{Transition metal fluorides (e.g. } CoF_3\text{, etc.)}
\end{tikzcd}$$

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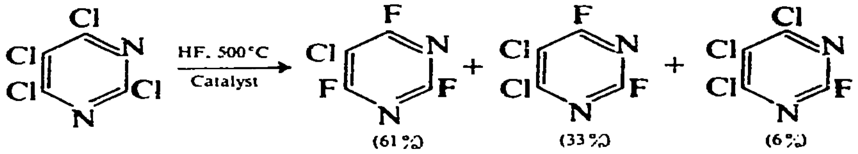
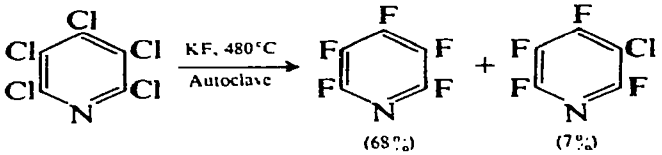
These can, of course, be used for the synthesis of other selective fluorinating agents, etc., but industry will prefer to use sources as close to fluorspar as possible. This, in effect, means hydrogen fluoride.



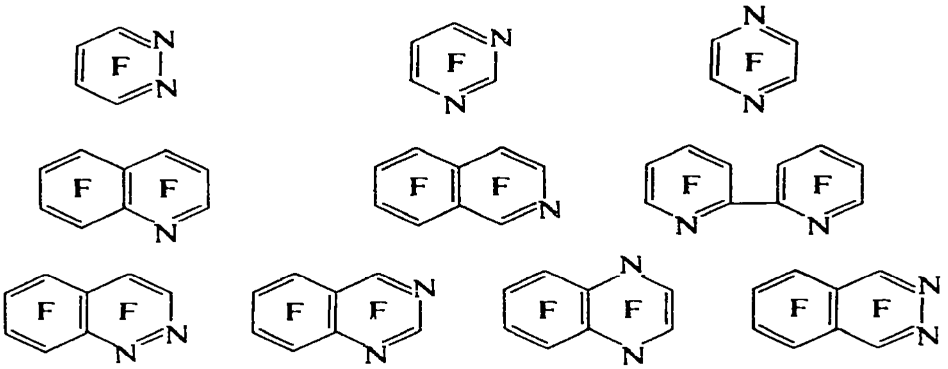
(Ref. 4)

In the laboratory, however, alkali-metal fluorides are very convenient sources of fluorine and we have pursued the synthesis of a range of heterocyclic compounds by this means, as illustrated for pentafluoropyridine.



(Refs. 5, 6)

Some other compounds that have been synthesised using this approach are shown below.

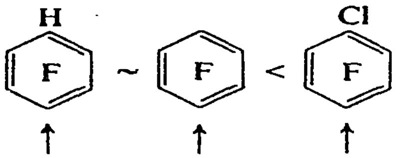


(Ref. 7)

(Ref. 8)

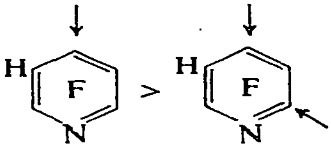
3. NUCLEOPHILIC SUBSTITUTION

The aspect of fluorinated aromatic compounds that makes them especially important to fibre-reactive dyes is their particular reactivity towards nucleophilic aromatic substitution. From an academic point of view, these fluorinated systems are of fundamental interest because they present reactivity and orientation problems for nucleophilic attack that are analogous to the classical problems in electrophilic aromatic substitution, as presented by hydrocarbon systems. For example, the qualitative order of reactivity in the benzene derivatives shown below



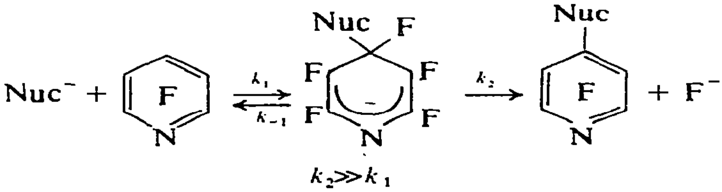
(F in the centre of a ring indicates that all unmarked bonds are to F)

(position of nucleophilic attack is arrowed) has been a source of controversy in the past. Also, the fact that nucleophilic attack occurs exclusively at the 4-position in pentafluoropyridine but attack occurs, with reduced rate constants, at both the 2- and 4-positions in tetrafluoropyridine has not been easy to explain.

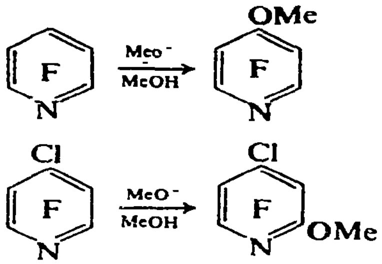


This discussion will be addressed especially at trying to answer the unusual activating and orientating influences of fluorine, and of chlorine, in comparison with other groups.

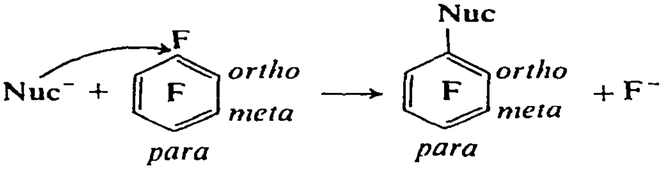
It is reasonable to assume the normal two-step mechanism of nucleophilic attack in these systems, with the first stage being rate-limiting. The type of evidence that



allows this assumption to be made is that pentafluoropyridine is much more reactive than pentachloropyridine and, whereas the 4-position in pentafluoropyridine is the most reactive site, displacement of fluorine from the 2-position is preferred in the corresponding 4-chloro derivative. These results are consistent only with a process that involves little or no carbon–halogen bond breaking in the rate-determined step.



In reality, halogen atoms at positions *ortho*, *meta* and *para* to the site of nucleophilic attack have different activating influences on the process of nucleophilic attack but the question is, how to separate these different effects?

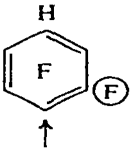
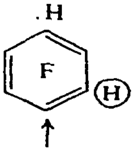
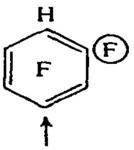
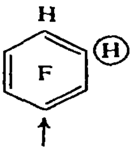


In collaboration with Dr D. L. H. Williams and our co-workers and, more recently, with B. Anderson from ICI Ltd, these separate effects have been determined by

TABLE 1

RATIOS OF MEASURED RATE CONSTANTS

(CH_3O^-/CH_3OH, 58 °C)

Benzene derivatives compared				k_F/k_H
	vs (i.e. $k/6$)[a]		*para*	0·43
	vs		*ortho*	57
	vs		*meta*	106

[a] Statistically corrected.

comparing various rate constants, as illustrated in Table 1 for benzene derivatives. These comparisons give the effects of fluorine vs hydrogen at positions *ortho*, *meta*, and *para* to the reaction site. We may conclude, therefore, that the activating influence of fluorine varies in the series *meta* > *ortho* ≫ *para*, for benzene derivatives, with *para*-fluorine being *deactivating*, with respect to hydrogen at the same position.

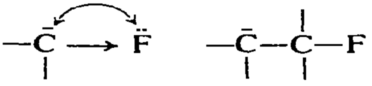
Separation of activating effects has also been achieved for pyridine systems,[10,11] by comparison of various systems, and the results are remarkably consistent for different pairs. The conclusions may be summarised as in Table 2. Before this work, great emphasis had been placed on an assumed deactivating effect of a *para*-fluorine but these results clearly indicate that this effect is relatively small in comparison with the significant activating effects of *ortho*- and *meta*-fluorine.

TABLE 2

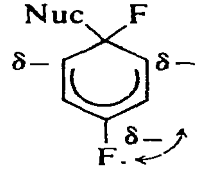
COMPARISONS OF k_F/k_H

	ortho-	*meta-*	*para-*
MeO⁻/MeOH, 58 °C			
Benzene derivatives	57	106	0·43
Pyridine derivatives	79	30	0·33
NH₃/dioxan, 25 °C			
Pyridine derivatives	31	23	0·26

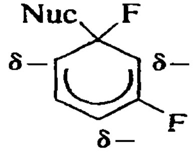
In advance of attempting to rationalise these conclusions, it is necessary to draw attention to what is already known of the effect of fluorine on carbanion stabilities.[1] Fluorine directly attached to a carbanionic site is in a state of conflict, where inductive electron withdrawal is offset by electron-pair repulsions, whereas fluorine attached at the adjacent site is strongly stabilising. If we first consider charge that is



strongly stabilising



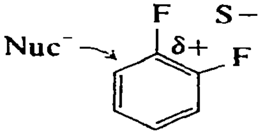
para-F < H (small)



meta-F≫H

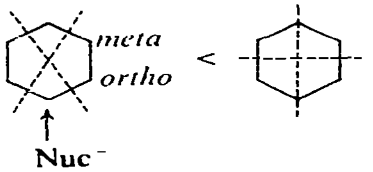
delocalised into the ring in the transition state for nucleophilic substitution, then we can reasonably account for the effect of *para*-F and *meta*-F vs H, on the basis of known effects on carbanion stabilities but, on the same basis, *ortho*-F should also be deactivating, which it is patently not.

Initial state effects can be important, e.g. the polarity of $\overset{\delta+}{C}\rightarrow\overset{\delta-}{F}$ is invoked to explain the normally much greater ease of nucleophilic displacement of fluorine than chlorine from an aromatic system. Consequently this idea has been extended to account for activation by *ortho*-F. A tempting possible alternative explanation is



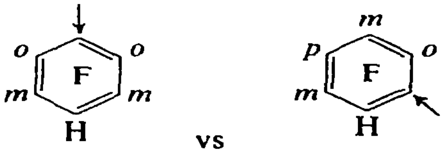
ortho-F (activating). Polar effect encourages approach of the nucleophile

based on a Frontier Orbital approach, e.g. if the LUMO of a highly fluorinated benzene derivative is no longer degenerate,[12] then it could be envisaged that *ortho*- and *meta*-fluorine atoms would have roughly the same activating influence. However, there is disagreement over calculations in this area.[12,13]



(Higher energy LUMO for a fluorinated derivative?)

Nevertheless, regardless of the problems of accounting for the puzzling difference in activation by *ortho*- and *para*-fluorine atoms, we now have a simple rationalisation for the observed orientating effects for nucleophilic substitution in many highly fluorinated aromatic systems, namely that attack occurs at the positions which maximise the number of available activating fluorine atoms. Considering pentafluorobenzene in detail (attack by MeO⁻/MeOH) the amount of 4- vs 2- attack may be compared, taking into account the statistical effect and using the experimentally determined activating influences of *ortho*-, *meta*-, and *para*-fluorine atoms.

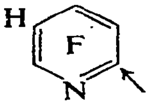


4-attack *2-attack*

$$\frac{4\text{-attack}}{2\text{-attack}} = \frac{1}{2} \times \frac{o.o.m.m}{o.m.m.p} = \frac{o}{2p} = \frac{106}{0{\cdot}86} = \frac{123{\cdot}3}{1}$$

$$\equiv 99{\cdot}2\,\%\ \text{4-attack}$$

In a pyridine system the orientating preference of ring nitrogen can be assessed from tetrafluoropyridine. Here attack at the 4- and 2-positions in each case involves one *ortho*- and two *meta*-fluorine atoms and therefore we see that only a small



Preference for 4- vs 2-attack = ca 4:1 (NH_3, dioxan)

preference arises from ring nitrogen in this system. The exclusive attack at the 4-position in pentafluoropyridine can be explained, therefore, in a similar way to that described for pentafluorobenzene, i.e. because this maximises the number of activating fluorines. Similar arguments account for orientation of substitution in other fluorinated heterocycles.

Returning to the puzzling *ortho*-activation by fluorine; if the explanation holds, a change with the reactivity of the system might be expected. Indeed, it has been seen earlier, that for pyridine derivatives ($MeO^-/MeOH$) $o > m$, whereas for the less reactive benzene derivatives, $m > o$. Likewise, a marked decrease in the *ortho* activation with decreasing reactivity of the nucleophile is seen (Table 3).

TABLE 3
ortho-ACTIVATION BY F RELATIVE TO H FOR PYRIDINE DERIVATIVES

Nucleophile	*o—F/o—H*
$MeO^-/MeOH$	79
NH_3/aq. dioxan	31
$PhNH_2$	1·3

(P. Martin, unpublished observations)

Activating effects of chlorine at different positions in a molecule, relative to the site of nucleophilic attack, may also be determined in ways similar to those already described.

Activation by Cl relative to H (pyridine systems, NH_3/aq. dioxan)

ortho-(86) > *meta*-(24) > *para*-(6·9)

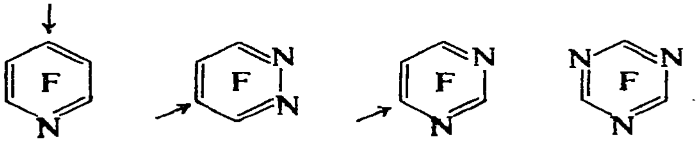
[cf. activation by F (31) > (23) > (0·26)]

These orders can be explained on the model described above, bearing in mind the effect of chlorine on carbanion stabilities.

$\bar{C}$—Cl stabilising $\bar{C}$—C—Cl probably strongly stabilising

The activating effects of ring nitrogen are, of course, quite substantial.

Ratio of rate constants for attack by NH_3/aq. dioxan, 25 °C



1 : 37·4 : 2,000 : > 10^5

(J. Waterhouse, unpublished results)

From various comparisons, we can obtain the relative activating influence of ring-N vs CH, and the ratios are as follows:

$$ortho = 6{\cdot}14 \times 10^4 \qquad meta = 851 \qquad para = 2{\cdot}3 \times 10^5$$

Thus, the relative order of activation by ring nitrogen, relative to the position of attack, is

$$ortho:meta:para = 72:1:266$$

$$\text{i.e. } ortho:para = 1:3{\cdot}7$$

Effects of other groups have also been determined,

e.g. *ortho*-CF_3 vs *ortho*-H = 2·4 × 10^3 (NH_3, dioxan, 25 °C)
para-CF_3 vs *para*-H = 4·5 × 10^3

Thus, CF_3 is not as activating as ring nitrogen.

Whatever the correct detailed explanations of the various activating effects described, the separated experimentally determined values allow discussion on a much sounder basis than was hitherto possible. My co-workers and myself believe that this is of significant value in the investigations relating to current fibre-reactive dye research.

ACKNOWLEDGEMENTS

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