Orientation and Reactivity in Nucleophilic Replacement in Polyfluoro-benzenes and -pyridines

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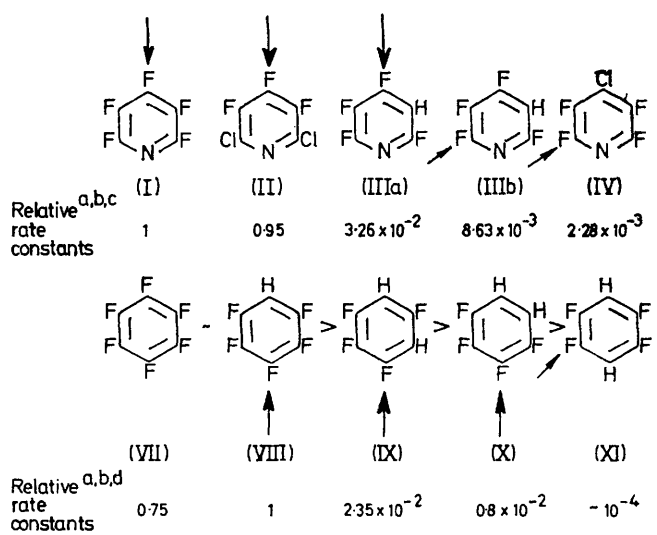
Summary Rate measurements for reactions of ammonia with polyfluoropyridines and methoxide with polyfluorobenzenes indicate that the activating influence of fluorine, with respect to the point of nucleophilic attack, is in the order: *meta* > *ortho* > *para*. This leads to a more complete explanation of the orientation of nucleophilic substitution in polyfluoro-benzenes and -pyridines than the generally accepted one.

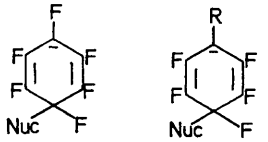
RATES of nucleophilic substitution in various polyfluoropyridines are being studied to compare the positional effects of fluorine relative to chlorine and hydrogen and the ratios of the measured rate constants for reactions of the pyridines (I)—(IV) with ammonia are shown.

Attack occurs in tetrafluoropyridine (III) at both the 2- and 4-positions and is deactivated at the 4-position (IIIa), with respect to (I), by a factor of 30. Since 2,6-dichlorotrifluoropyridine (II) reacts at a rate very close to that of (I), it may be deduced that fluorine and chlorine *meta* to the point of attack have a similar influence on reactivity. Therefore, we may take the rate constant for attack at the 2-position in (IV) as a reasonable estimate of the rate constant for reaction which would occur at the 2-position in pentafluoropyridine (I), if this could be measured. On this basis the 2-position in the tetrafluoropyridine (IIIb) is activated by a factor of *ca.* 3 with respect to (IV) and hence (I). These results imply then, that the effect of a fluorine *ortho* to the position of attack is significantly larger than the effect of a fluorine atom in a corresponding *para*-position although such a conclusion requires modification



[a] Arrows indicate position of attack [b] Corrected for the number of equivalent fluorines. [c] Ammonia in aqueous dioxan (60 : 40) at 25°. [d] Sodium methoxide in methanol at 50°.

of the currently-accepted theory[1] of attack in pentafluorobenzenes. In this theory, the major influence is generally attributed to a destabilising effect of fluorine when in a position *para* to the point of attack and, consequently, transition states, approximating to (V), are generally of higher energy than those involving attack *para* to the substituent, (VI) (*e.g.* R = H).

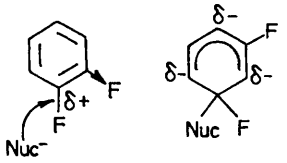


(V) (VI)

Hydrofluorobenzenes form a more simple series for examining substituent effects of fluorine than fluoropyridines and analysis of data obtained earlier for reaction of methoxide with tetrafluorobenzenes, leads to the reactivity sequence (VII)—(XI) shown in the Table. The comparable rates of (VII) and (VIII) indicate that the overall effect of a *para* fluorine is equivalent to that of hydrogen. This suggests that, in the transition state, inductive electron withdrawal by fluorine, $^{\delta-}C \rightarrow F$, is effectively balanced by electron-pair repulsions, $^{\delta-}C\text{–}\ddot{F}$.

Comparison of (VIII) and (IX) indicates a significant influence of a fluorine atom *ortho* to the point of attack even though it is unlikely that, in the transition state, the effect of *ortho* fluorines is significantly different from a *para* fluorine. Therefore, it is probable that this activation arises from an initial-state polarisation (XII) which allows easier approach of the nucleophile. A similar comparison of (VIII) and (X) reveals a large influence of fluorine *meta* to the point of attack which is quite consistent with the known stabilising effect of fluorine attached to carbon, which is adjacent to a carbanionic centre (XIII).

Therefore the apparent order of importance of fluorine in activating sites in an aromatic system is: *meta* > *ortho* ≫ *para*. The result of this is that attack would generally occur in C_6F_5X compounds so as to maximise the number of *ortho* and *meta* fluorine substituents, with the role of the *para* fluorine being much less significant. Compound (XI) is unreactive, not principally because nucleophilic attack has to occur *para* to a fluorine atom, but because we have, with respect to hexafluorobenzene, loss of a *meta* fluorine as well as an *ortho* fluorine and this amounts to a massive deactivation with respect to hexafluorobenzene.



(XII) (XIII)

However, when the substituent X, in C_6F_5X compounds, is a group which is a very effective electron-pair donor like NH_2, or OCH_3, then electron-pair repulsion appears to dominate, as argued previously.[1] Nucleophilic attack occurs mainly *meta* to the amino-group in pentafluoroaniline[2] and significant amounts of the corresponding *meta* product are obtained from pentafluoroanisole.[2b,3] Also, both systems are deactivated.

The explanations advanced above for the orientation of substitution in C_6F_5X compounds also account for the observed orientation of nucleophilic substitution in many polyfluoropyridines, even though the overall reactivity is undoubtedly dominated by the effect of ring nitrogen. In other nitrogen heterocyclic systems the situation is more complicated, however, and these will be discussed in later publications.

It must be emphasised that here we have been discussing the gross features which affect substitution but these effects are certainly modified by more subtle factors like solvation and steric effects in some systems.

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