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MECHANISMS FOR REACTIONS OF HALOGENATED COMPOUNDS. PART 4.[1] ACTIVATING INFLUENCES OF RING-NITROGEN AND TRIFLUOROMETHYL IN NUCLEOPHILIC AROMATIC SUBSTITUTION

R.D. CHAMBERS, P.A. MARTIN, J.S. WATERHOUSE, D.L.H. WILLIAMS

Department of Chemistry, University Science Laboratories, South Road, Durham, DH1 3LE (U.K.)

and B. ANDERSON

I.C.I. Limited, Organics Division, P.O. Box No. 42, Hexagon House, Blackley, Manchester (U.K.)

SUMMARY

Rate constants have been measured for the reactions of ammonia with various fluorinated pyridines and diazines in aqueous dioxan at 25°. From the results the activating effects of ring-nitrogen (relative to C-H) and of trifluoromethyl (relative to -H) have been determined. Ring-nitrogen activates the system at points ortho-, meta- and para- to the point of substitution, in the ratios ortho- 6.2×10^4, meta- 8.5×10^2, and para- 2.3×10^5. Similarly a trifluoromethyl substituent is activating by a factor of 2.4×10^3 ortho- and 4.5×10^3 para- to the point of substitution.

RESULTS AND DISCUSSION

Highly fluorinated heterocyclic compounds are being actively developed as components for fibre-reactive dyes [2], the feature of special value being, of course, the particular ease of displacement of fluorine in nucleophilic aromatic substitution. It is of particular importance, therefore, to understand the factors influencing reactivity in these systems. Previously, we have been able to establish the relative activating influences of fluorine, relative to hydrogen, at different positions with respect to the site of nucleophilic attack (NH_3, aq. dioxan, 25°) as ortho-: meta-: para-, 31: 23: 0.26 and, in this paper, we describe for comparison the separation of activating influences of ring-nitrogen and of trifluoromethyl at different sites.

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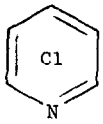
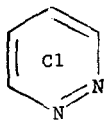
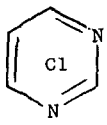
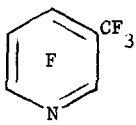
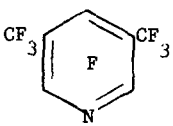
TABLE 1

Rate Constants[a] for attack by ammonia in dioxan-water (60:40 v/v) at 25°C and at 80°C (where indicated)

Substrate	Position of attack	$k/\ell\ mol^{-1}s^{-1}$	k_{rel} (relative to (1))
 (1)	4-	$(6.80 \pm 0.05) \times 10^{-4}$	1 (ref. 3)
(1) (at 80°C)	4-	$(2.80 \pm 0.07) \times 10^{-2}$	
 (2)	2-	$(1.55 \pm 0.02) \times 10^{-6}$	2.28×10^{3} (ref. 3)
 (3)	4-	1.35 ± 0.01	1.99×10^{3}
 (4)	-		ca. 10^{5} [b]
 (5)	4-	$(2.52 \pm 0.05) \times 10^{-2}$	3.70×10^{1}
 (6)	-	$(5.07 \pm 0.06) \times 10^{-5}$	7.46×10^{-2}

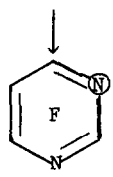
[a] All rate constants are corrected for statistical factors.

Substrate	Position of attack	$k/\ell\ mol^{-1}s^{-1}$	k_{rel} (relative to (1))
 (10)	4-	$\sim 1.67 \times 10^{-7}$	
 (11)	4-	$(1.08 \pm 0.01) \times 10^{-5}$	
 (12)	4-	$(3.08 \pm 0.03) \times 10^{-3}$	
 (13)	4- 6-	$(5.31 \pm 0.02) \times 10^{-2}$ $(2.66 \pm 0.01) \times 10^{-2}$	
 (14)	4- 6-	3.39 ± 0.02 1.31 ± 0.06	
 (15)	4- 6-	$(2.22 \pm 0.1) \times 10^{-5}$ $(5.87 \pm 0.3) \times 10^{-6}$	(ref. 4)
 (at 80°C) (16)	4-	$(6.7 \pm 0.1) \times 10^{-4}$	

[b] Too fast under these conditions to measure accurately.

Ring-nitrogen

Comparing the rate constants for substitution in (1), (3), and (4) there is an ca. 10^2 increase in reactivity associated with the introduction of each ring-nitrogen. More precisely, we can obtain an estimate of the effects of introducing nitrogen at the ortho-position as follows.



(3)

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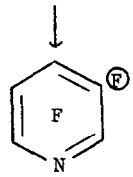


(1)

$$k_{(3)}/k_{(1)} = k_N/k_{CF}(\text{ortho-}) = 2.0 \times 10^3$$

$$\therefore k_N/k_{CH}(\text{ortho-}) = 2.0 \times 10^3 \times 31 = 6.2 \times 10^4$$

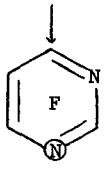
We are able to estimate the effect of nitrogen, relative to C-H, because we have already established that ortho-fluorine is activating by a factor of 31 in the pyridine system.

Similarly, comparing (5) with (1) we obtain a meta-effect.

$$k_{(5)}/k_{(1)} = k_N/k_{CF}(\text{meta}) = 37$$

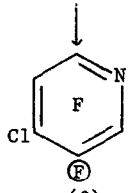
$$\therefore k_N/k_{CH}(\text{meta}) = 37 \times 23 = 850$$

To obtain the para-effect we compare (3) and (2), assuming that the value of (2) is very close to the value for attack at the 2-position, in pentafluoropyridine (1), if this could be measured. This is justified because we have established earlier that the effects of chlorine and of fluorine meta- to the site of nucleophilic attack are very similar [3]. Therefore para-effects are obtained as follows.



(3)

vs



(2)

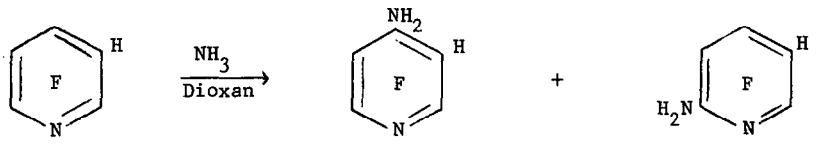
$$k_{(3)}/k_{(2)} = k_N/k_{CF}(\text{para-}) = 8.7 \times 10^5$$

$$\therefore k_N/k_{CH}(\text{para-}) = 8.7 \times 10^5 \times 0.26 = 2.3 \times 10^5$$

Overall, therefore, the activating influence of ring-nitrogen, may be compared for different sites:

ortho-	:	meta-	:	para-	
6.2×10^4	:	8.5×10^2	:	2.3×10^5	(Rel. to H)
[72	:	1	:	266]	(Rel. to the meta-position)

As we can see, even at the meta-position, nitrogen has a substantial activating influence and the ratio ortho-:para- = 1:3.7 fits surprisingly well with the observed distribution of isomers for nucleophilic attack in compound (7). Here, the activating effects of fluorine are closely similar for attack at both 4- and 6-positions in (7) (one ortho-F, two meta-F) and therefore the composition (8):(9) = 3.8:1, reflects the para-:ortho- influence of ring-nitrogen.



(7) (8) (9)

A comparison of the chloro compounds (10)-(12) allows us to determine the influence of ring nitrogen in ortho- and meta-positions, from the point of displacement of chlorine.

$$k_{(11)}/k_{(10)} = k_N/k_{C\text{-}Cl}(\text{meta-}) = 65$$

We are unable, however, to obtain reliable values for k_N/k_{CH} in these systems since we have not obtained activating effects for chlorine vs. hydrogen at positions ortho- and meta- to the site of displacement of chlorine. If, however, we use the values of the activating effects of a chlorine for diplacement of fluorine which have already been established [4] i.e. ortho-:meta-:para- = 86:24:6.9 then it is possible to obtain an estimate of k_N/k_{CH} for displacement of chlorine.

$$k_N/k_{CH}(\text{meta-}) = 65 \times 24 = 1.6 \times 10^3 \text{ (Cl displacement)}$$

$$k_{(12)}/k_{(10)} = k_N/k_{CCl}(\text{ortho-}) = 1.84 \times 10^4$$

$$\therefore k_N/k_{CH}(\text{ortho-}) = 1.84 \times 10^4 \times 86 = 1.6 \times 10^6 \text{ (Cl displacement)}$$

It appears, therefore, that the activating influence of ring-nitrogen is more pronounced for displacement of chlorine, than for fluorine, and this would be consistent with the later transition state which would be undoubtedly associated with the slower displacement of chlorine, than fluorine.

Trifluoromethyl

Using the same approach as described above, we may obtain corresponding values for the activating influence of trifluoromethyl groups ortho- and para- to the site of displacement of fluorine.

$k_{(13)}/k_{(1)} = k_{CF_3}/k_F = 78$

$\therefore k_{CF_3}/k_H(\text{ortho-}) = 78 \times 31 = 2.4 \times 10^3$

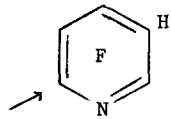
$k_{(14)}/k_{(1)} = 5.0 \times 10^3$

$\therefore k_{CF_3}/k_F(\text{ortho-}) = \sqrt{5.0 \times 10^3} = 71$

$\therefore k_{CF_3}/k_H(\text{ortho-}) = 71 \times 31 = 2.2 \times 10^3$

(13)

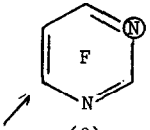
vs



(15)

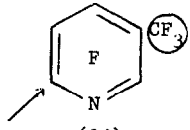
$k_{(13)}/k_{(15)} = k_{CF_3}/k_H(\text{para-}) = 4.5 \times 10^3$

The ortho-values may be obtained from different sources and good agreement is observed. It is clear that trifluoromethyl has an even smaller preference for para- over ortho- activation, than ring-nitrogen and we can now make direct comparisons of the activating influences of ring-nitrogen and trifluoromethyl.



(3)

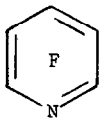
vs



(13)

$k_{(3)}/k_{(13)}(\text{6-position}) = k_N/k_{CCF_3}(\text{para-}) = 51$

$k_{(3)}/k_{(13)}(\text{4-position}) = k_N/k_{CCF_3}(\text{ortho-}) = 25$



(1)

vs

(16)

$k_{(1)}/k_{(16)} = k_N/k_{CCF_3}$ (para-) = 42 (80°C)

A comparison of (1) and (16) was only possible at 80°C but this gives k_N/k_{CCF_3} (para-) of roughly the same order as the value determined by comparison of (3) and (13) at 25°C. We hope to obtain corresponding meta-effects from future studies. Clearly, the effect of trifluoromethyl is substantial but is significantly less activating than that of ring-nitrogen.

EXPERIMENTAL

Materials. - All the compounds described in this paper have been described previously and were synthesised by known methods. Also, reactions of these systems with ammonia have been studied extensively [5] and, therefore, product isomer analysis was carried out by n.m.r. and by gas-density balance g.l.c.

Kinetics. - Rate measurements were carried out at 25°C except where stated, using 60:40 (v/v) dioxan-water. Samples were withdrawn at suitable intervals and quenched in a large excess of water, and the unchanged base was titrated against standard hydrochloric acid. The infinity value agreed well with that calculated from the weight of material used. Generally, reactions were followed for at least two half-lives and each run was carried out in duplicate. Second-order rate constants were calculated from equation (i), where a and b are the initial concentrations

$$k = \ln[b(a-2x)/a(b-x)]/(a-2b)t \qquad (i)$$

of ammonia and substrate respectively, since ammonia becomes protonated by the acid liberated in the reaction. The standard error of the mean in any individual run was ± 1% and duplicate runs agreed to within ± 1%. Where more than one product isomer was formed, the individual rate constants were calculated from the total rate constant and the yields of the isomeric products, as analysed both by n.m.r. and by gas-density balance g.l.c.

ACKNOWLEDGEMENTS

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2 See W. Harms, 'Organofluorine Chemicals and their Industrial Applications' (Ed. R.E. Banks), Ch. 9, Ellis Hoywood, Chichester, 1979.

3 R.D. Chambers, J.S. Waterhouse, and D.L.H. Williams, J. Chem. Soc. Perkin 2, (1977) 585.

4 R.D. Chambers, D. Close, W.K.R. Musgrave, J.S. Waterhouse, and D.L.H. Williams, J.C.S. Perkin 2, (1977) 1774.

5 See e.g. R.D. Chambers, W.K.R. Musgrave, and P. Urben, J.C.S Perkin I, (1974) 2580, and earlier parts of the series.