

The Effect of α -Fluoro-substituents on the S_N Reactivity of the C-Cl Linkage

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THE effect of α -fluoro-substituents on the rates of S_N reactions has hardly been studied.¹ Further information has now been sought from the hydrolysis of α -substituted benzyl chlorides (see Table 1) where the initial replacement of chlorine by a hydroxyl group determines the rate; the product is benzaldehyde or benzoic acid, depending on whether two or three halogens are attached to the reaction centre.

transition state. For (III) and (IV), $\Delta C^\ddagger/\Delta S^\ddagger$ has the value expected³ for entirely S_{N1} reaction, similar to the α -chloro-derivatives of (I).⁴ These mechanistic changes probably account for the absence of a logical pattern in Table 1.

A more useful comparison, based on data for reaction by the same mechanism for all the compounds, is given in Table 2 which shows the changes in the parameters for S_{N1} hydrolysis*

TABLE 1

Kinetic data for hydrolysis in 50% aqueous acetone at 50°
k in sec.⁻¹, E in kcal., ΔS^\ddagger and ΔC^\ddagger in cal. deg.⁻¹

Compound	$-\log k$	E	$-\Delta S^\ddagger$	$-\Delta C^\ddagger$
PhCH ₂ Cl (I)*	5.569	20.606	22.41	21.2
PhCHFCl (II)	4.876	20.603	19.25	(-2.5)
PhCFCl ₂ (III)	4.904†	22.141	14.62†	41.5
PhCF ₂ Cl (IV)	6.300†	23.141	17.91	51.3

* From earlier results. (Ref. 2).

† Per replacable Cl.

§ In good agreement with previous findings. (Ref. 1.)

TABLE 2

The effect of α -fluorination and α -chlorination on S_{N1} hydrolysis in 50% aqueous acetone at 50°.

	PhCH ₂ Cl (I)	PhCHCl ₂ (V)	PhCHFCl (II)
$\{ k_F/k_H$	13.5	0.66*	0.27
α -Fluorination $\left\{ \begin{array}{l} E_F - E_H \\ \Delta S^\ddagger_F - \Delta S^\ddagger_H \end{array} \right.$	$\left. \begin{array}{l} -2.0 \\ -1.0 \end{array} \right\}$	$\left. \begin{array}{l} -0.8 \\ -3.3^* \end{array} \right.$	$\left. \begin{array}{l} -1.4 \\ -6.9 \end{array} \right.$
α -Chlorination $\left\{ \begin{array}{l} k_{Cl}/k_H \\ E_{Cl} - E_H \\ \Delta S^\ddagger_{Cl} - \Delta S^\ddagger_H \end{array} \right.$	$\left. \begin{array}{l} 141^* \\ -3.6 \\ -1.3^* \end{array} \right\}$	$\left. \begin{array}{l} 22.9^* \\ -3.6 \\ -4.9^* \end{array} \right.$	$\left. \begin{array}{l} 6.9^* \\ -2.4 \\ -3.3^* \end{array} \right.$

Data for PhCHCl₂ and PhCCl₃ from earlier work (Ref. 4); E in kcal., ΔS^\ddagger in cal. deg.⁻¹.

* Per replacable Cl.

The hydrolysis of (I) occurs mainly, if not entirely, by mechanism S_{N2} ,² and an increased entropy of activation (ΔS^\ddagger) is responsible for the greater reactivity of (II) where the heat capacity of activation (ΔC^\ddagger) is almost zero. Both these observations suggest³ that the hydrolysis of (II) occurs either by concurrent S_{N1} and S_{N2} processes, or by mechanism S_{N2} via a temperature-dependent

when an α -hydrogen atom is replaced by fluorine or chlorine. Both substitutions reduce the activation energy (E), suggesting that the two halogens stabilise the transition state by electron release. Although the available evidence shows that fluorine generally responds more efficiently than chlorine to an electron-demanding situation, the converse appears to be indicated by the present

* Activation parameters (E_1 and ΔS_1^\ddagger) for the S_{N1} reactions of (I) and (II) were either calculated from the observed results by assuming concurrent S_{N1} and S_{N2} hydrolysis (cf. ref. 3), or by obtaining E_1 from data for more highly halogenated compounds (cf. ref. 2) and ΔS_1^\ddagger by analogy with structurally similar substrates. Both methods gave very similar results.

values of $E_X - E_H$. However, the systems now involve substituents close to the site of reaction and electron-attraction by the inductive effect ($F > Cl$) may therefore play an unusually large part in modifying the overall electron release. On the other hand, the activation energies in Table 2 are also consistent with the view that fluorine is the better electron-donor if the initial state is stabilised by bond-no-bond resonance⁵ (*i.e.*, by contributions from structures like $F^- C=X^+$) when fluorine and at least one other halogen are attached to the reaction centre.

Table 2 shows that the introduction of α -halogens decreases ΔS^\ddagger , particularly when the parent compound already contains two such atoms, and that entropy effects are responsible for the rate decrease caused by the α -fluorination of (II) and (V). The

abnormally negative values of ΔS^\ddagger for the S_N1 hydrolysis of benzotrihalides (see Table 1, ref. 1) can be interpreted in terms of reduced steric hindrance to the solvation of the transition state when structures like $+X=C Cl^-$ make a significant contribution. This is equivalent to postulating substantial electron-release by both α -fluoro- and α -chloro-groups.

The present results therefore suggest that an α -fluoro-substituent acts as an overall electron-donor in S_N1 reactions, and that the expected effect on the rate is obscured by unfavourable entropy effects and, possibly, by an accompanying stabilisation of the initial state.

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¹ J. Hine and D. E. Lee, *J. Amer. Chem. Soc.*, 1952, **74**, 3182.

² B. Bensley and G. Kohnstam, *J. Chem. Soc.*, 1957, 4747.

³ G. Kohnstam, "The Transition State", Chem. Soc. Special Publ. No. 16, 1962, p. 179.

⁴ B. Bensley and G. Kohnstam, *J. Chem. Soc.*, 1956, 286.

⁵ J. Hine, *J. Amer. Chem. Soc.*, 1963, **85**, 3239.