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A KINETIC STUDY OF THE MECHANISM OF ESTERIFICATION OF 1-ARYLETHANOLS IN TRIFLUOROACETIC ACID

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Summary Aryl substituent effects upon the rate constants for the esterification of a series of 1-arylethanols in trifluoroacetic acid are in accordance with a reverse $A_{AL}1$ mechanism, for which the Hammett reaction constant $\rho = -3.69$ has been determined by correlation with σ^+ substituent constants. The rates of reaction are ca. 50-fold faster than those for corresponding benzyl alcohols which bear an electron-donating aryl substituent and which are also believed to undergo esterification in trifluoroacetic acid by the reverse $A_{AL}1$ mechanism; the reverse $A_{AC}2$ mechanism applies to benzyl alcohols which bear an electron-withdrawing aryl substituent.

While there have been numerous mechanistic studies of the acid-catalysed hydrolysis of esters, the reverse reaction has received little attention.[1] Furthermore, studies of esterification mechanisms have been designed in the main to reveal the rate-structure dependence for reactions of a range of carboxylic acids with a common alcohol. There have been very few studies of the kinetics and mechanism of reactions of alcohols with a common carboxylic acid, and these have generally been complicated by the necessary presence of a mineral acid catalyst.

We have already reported[2] that esterification of alcohols, of diverse structural types, can be achieved simply and quantitatively by dissolution of the alcohol in CF_3CO_2H (as solvent) whereupon the reaction proceeds spontaneously with no need for added catalyst. Our kinetic investigation established that the reaction mechanism changes from reverse $A_{AC}2$ for primary and secondary alcohols (RCH_2OH and R_2CHOH; R = alkyl) to reverse $A_{AL}1$ for t-butanol (Scheme). We also found[3] that, for substituted benzyl alcohols, the same change in mechanism occurs as the Hammett aryl substituent constant (σ) changes sign from positive to negative. Thus, the rates of trifluoroacetylation of substrates bearing an electron-withdrawing m- or p-substituent are correlated by the parameter $\rho = -0.79$, whereas rates of reaction of the m- and p-methyl derivatives are much faster than predicted by linear extrapolation; by correlation of the results for

Scheme. Mechanisms of trifluoroacetylation of alcohols

Reverse $A_{AL}1$ mechanism

$$ROH + H^+ \rightleftharpoons R\overset{+}{O}H_2 \xrightarrow[slow]{-H_2O} R^+ \xrightarrow[fast]{CF_3CO_2H} CF_3CO_2R + H^+$$

Reverse $A_{AC}2$ mechanism[a]

$$CF_3CO_2H + H^+ \rightleftharpoons CF_3\overset{+}{C}(OH)_2 \xrightarrow[slow]{ROH} CF_3\overset{R\overset{+}{O}H}{\overset{|}{C}}(OH)_2 \longrightarrow CF_3CO_2R + H_3O^+$$

[a] Pre-equilibrium self-protonation of CF_3CO_2H may not be a necessary requirement.

the latter compounds (and that for benzyl alcohol itself) with σ^+ parameters, an approximate value of $\rho = -5.1$ was estimated for the reverse $A_{AL}1$ mechanism.[3] Unfortunately, we were unable to determine rates of trifluoroacetylation of benzyl alcohols activated by alternative electron-donating aryl substituents; cf. amino-derivatives are completely protonated in CF_3CO_2H and the o- and p-methoxybenzyl alcohols behave anomalously.

In order to gain further evidence for the reverse $A_{AL}1$ mechanism of esterification of suitably activated alcohols, we have now studied the Hammett dependence for trifluoroacetylation of a series of 1-arylethanols which were readily prepared by hydride reduction of the corresponding methyl ketones. The reactions were conducted at 35°C in the thermostatted probe of a 90 MHz p.m.r. spectrometer and the progress of reaction was followed by integration of the methine quartet resonances of the alcohol and ester which were well separated ($\Delta\delta$ = ca. 1 p.p.m.) with the ester multiplet appearing at lower field. A large molar excess (> 15-fold) of CF_3CO_2H over alcohol was used and reactions were followed through at least four half-lives. Because of the high sensitivity of the reaction to substituent effects, it was not possible to determine the rate of reaction of each member of the series under the same conditions. We therefore chose to study the esterification of the m-chloro, m-nitro, and p-nitro derivatives in neat CF_3CO_2H but to moderate the rates of reaction of the parent 1-phenylethanol and its p-chloro and p-methyl derivatives by using as solvent $CDCl_3$ containing 7.5% v/v CF_3CO_2H. The rate of reaction of 1-(m-chlorophenyl)ethanol was also determined under the latter conditions, so that the relative effects (k_{rel}) upon rates of the full range of substituents could be determined. All reactions were pseudo-first-order (correlation coefficients > 0.999) and the rate constants (k) and (k_{rel}) values are in the Table.

Hammett correlation of $\log(k_{rel})$ values with the corresponding σ^+ values (Figure) gives, by least-squares best-fit analysis, the reaction constant $\rho = -3.69$ (correlation coefficient $r = 0.986$; cf. $r = 0.977$ and $\rho = -4.10$ for correlation with σ values). The correlation is remarkably good considering the nature

Table. Rate constants for the trifluoroacetylation of alcohols $XC_6H_4CHOHMe^a$

X	Condition^b	$10^4k/s^{-1}$	$k_{rel}{}^c$
p-NO_2	A	0.99	2.74×10^{-3}
m-NO_2	A	1.13	3.13×10^{-3}
m-Cl	A	46.6	1.29×10^{-1}
m-Cl	B	0.155	1.29×10^{-1}
p-Cl	B	0.233	1.94×10^{-1}
H	B	1.20	1.00
p-Me	B	53.0	44.2

[a] At 35°C. [b] A = neat CF_3CO_2H; B = $CDCl_3$ containing 7.5% v/v CF_3CO_2H (0.98M). [c] k_{rel} is the value k_X/k_H obtained by using the results for the m-chloro compound as reference for crossover between conditions A and B.

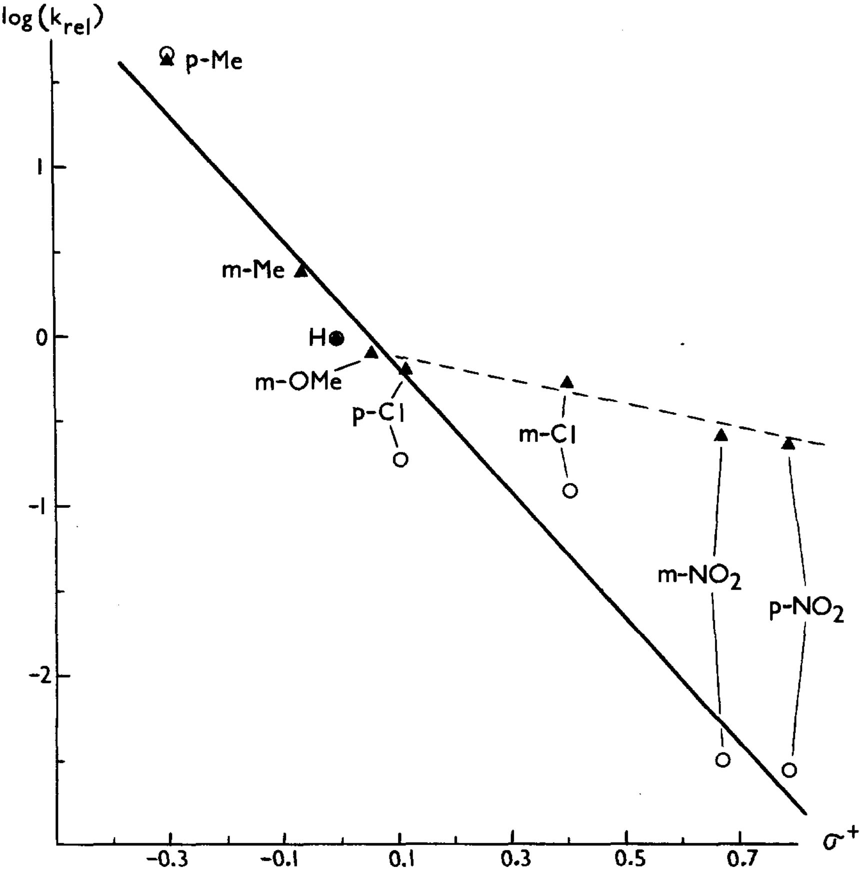

Figure. Hammett plot of log(k_{rel}) values for the trifluoroacetylation of 1-arylethanols (O) and benzyl alcohols (▲) against σ^+ substituent constants of the rate comparison, and the large negative ρ value is consistent with the development of substantial carbocation character at the benzylic site in the transition state of the rate-determining step of the reverse $A_{AL}1$ mechanism (Scheme); cf. ρ values of -4.0 to -4.5 are characteristic of S_N1-type solvolyses of benzylic and benzhydryl chlorides in hydroxylic media.[4] This value is in harmony with our interpretation of the behaviour of the series of benzyl alcohols towards trifluoroacetylation; indeed, the log(k_{rel}) values[3] for esterification of the m-methyl, p-methyl, m-methoxy, and p-chloro derivatives in neat trifluoroacetic acid are well correlated with σ^+ constants by the same ρ value (-3.69) as that for the 1-arylethanols (see Figure), whereas m-chloro-, m-nitro-, and p-nitro-benzyl alcohols are much more reactive than expected for esterification by the reverse $A_{AL}1$ mechanism but in accord with the reverse $A_{AC}2$ mechanism.[3]

An <u>approximate</u> estimate of the relative rates of the reverse $A_{AL}1$ trifluoroacetylation of corresponding alcohols of the 1-phenylethyl and benzyl series can be made by comparing the rates of reaction of 1-(p-tolyl)ethanol in $CDCl_3$ containing 7.5% v/v CF_3CO_2H and of p-methylbenzyl alcohol in neat CF_3CO_2H (see Table in ref. 3); when appropriate corrections are applied to take account of solvent and temperature differences, the rate ratio $k^{ArCHOHMe}/k^{ArCH_2OH}$ = ca. 50 is obtained for the reverse $A_{AL}1$ mechanism. This value falls within the range characteristic of the relative rates of S_N1 solvolyses of 1-phenylethyl chloride and benzyl chloride in protic media.[5]

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