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A KINETIC STUDY OF THE MECHANISMS OF ESTERIFICATION OF ALCOHOLS BY TRIFLUOROACETIC ACID

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Summary Rates of trifluoroacetylation of a structurally diverse range of aliphatic alcohols in neat trifluoroacetic acid at 35°C have been measured using ^{1}H n.m.r. spectroscopy. The reaction mechanism changes from reverse $A_{AC}2$ for primary and secondary alcohols (except Ph_2CHOH) to reverse $A_{AL}1$ for t-butanol.

There continues to be considerable interest in the mechanisms of formation and hydrolysis of esters of carboxylic acids, although studies of the latter process predominate.[1] For those examples where the kinetics of esterification of alcohols by carboxylic acids have been determined, the reactions have generally been limited to those promoted by dissolution of the acid in the alcohol (as solvent) containing a mineral acid catalyst. Very little attention has been paid to esterification of alcohols in CF_3CO_2H. We have now established that, for a wide range of structural types, this conversion 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.

In 1952, Traynham reported[2] that trifluoroacetylation of (-)-octan-2-ol in refluxing CF_3CO_2H proceeds without racemisation, indicating that the mechanism does not involve formation of an intermediate carbocation. There has been no later report of a mechanistic study of esterification of alcohols by CF_3CO_2H; this is particularly surprising since there are indications that the reverse reaction falls within a very limited class of ester hydrolyses which are insensitive to acid catalysis.[3] We now report some results of a kinetic study of the trifluoroacetylation of a range of simple alcohols dissolved in neat CF_3CO_2H.

$$ROH + CF_3CO_2H \rightarrow CF_3CO_2R + H_2O$$

For each reaction studied, a large molar excess of acid over alcohol (ca. 1M) was used and rates were determined by monitoring ^{1}H n.m.r. spectral changes with time.

Following the mechanistic classification introduced by Ingold[4] for acid-catalysed ester hydrolysis, four discrete mechanisms may be considered for these reactions: reverse $A_{AL}1$; reverse $A_{AL}2$; reverse $A_{AC}1$; and reverse $A_{AC}2$. The relative rates of esterification of the primary alcohols (1-3) reveal that replacement of a single methyl hydrogen of methanol by a methyl or even a t-butyl group has little effect on the reaction rate. Since it is well established[5] that S_N2 reactions of neopentyl substrates (Bu^tCH_2X) occur at rates very much slower than those of methyl analogues ($k_{MeX} : k_{Bu^tCH_2X}$ rate-constant ratios of $10^5 : 1$ are typical), it is clear that nucleophilic displacement of water by acid from the conjugate acid of the alcohol

Table. Rate constants (k) for trifluoroacetylation of alcohols (ROH) at 35°C

Substrate	R	$10^3 k/s^{-1}$	$k_{rel.}$
(1)	Me	1.52	1.00
(2)	Et	0.96	0.63
(3)	Bu^tCH_2	0.89	0.59
(4)	$PhCH_2$	0.78	0.51
(5)	$ClCH_2CH_2$	0.15	0.10
(6)	Pr^i	0.26	0.17
(7)	Bu^t	2.70	1.78

(i.e. the reverse $A_{AL}2$ mechanism) cannot be involved for these reactions.† For obvious reasons, the carbocation mechanism (reverse $A_{AL}1$) can be discounted for these primary alcohols,‡ and the reverse $A_{AC}1$ mechanism is also unsatisfactory (see later).

Benzyl alcohol (4) also reacts at a rate similar to those for the alcohols (1-3) and we recently reported[7] that, for derivatives containing electron-withdrawing ring substituents, the Hammett parameter $\rho = -0.79$ (correlation coefficient = 0.996 for six data points) is consistent with that expected for a reverse $A_{AC}2$ mechanism of esterification. We believe that this mechanism also best accounts for the relative reactivities of the alcohols (1-3) and is in harmony with the observed ca. sixfold reduction in the rate of trifluoroacetylation of ethanol caused by replacement of a β-alkyl hydrogen by chlorine (cf. 5). However, we also found that the rates of esterification of benzyl alcohols are very much more sensitive to the presence of electron-donating ring substituents, and we interpreted[7] the corresponding parameter ρ = ca. -5.1 (based on σ^+ substituent constants) in terms of the reverse $A_{AL}1$ mechanism.

It is apparent that such a mechanistic change can also be induced by trimethyl- (but not dimethyl-) substitution of methanol. Thus, while isopropanol (6) undergoes trifluoroacetylation at a rate sixfold slower than that of methanol, in accord with the reverse $A_{AC}2$ mechanism, the sterically more hindered t-butanol (7) reacts almost twice as fast as the primary alcohol. These results, and the earlier observation[2] of the behaviour of octan-2-ol, lead to the conclusion that primary and secondary alcohols react with CF_3CO_2H by the reverse $A_{AC}2$ mechanism, whereas tertiary alcohols (and other substrates capable of acid promoted conversion into stable carbocations) undergo trifluoroacetylation by the reverse $A_{AL}1$ process.§

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References

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2. J. G. Traynham, J. Amer. Chem. Soc., 74, 4277 (1952).
3. See ref.1, p.165.
4. C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca (New York), 1953, chap.XIV.
5. See J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", second edn., McGraw-Hill Kogakusha, Tokyo, 1977, p.315.
6. See ref.5, p.351.
7. P. Kavanagh, A. C. Knipe, and W. E. Watts, in press, Chem. Comm. 614.
8. See ref.4, pp.779-781.

† In this connection, it is noteworthy that no example of the $A_{AL}2$ mechanism of ester hydrolysis has ever been reported.[6]

‡ There was no evidence of skeletal rearrangement during the trifluoroacetylation of the alcohol (3) which cleanly afforded neopentyl trifluoroacetate.

§ There is good evidence that t-alkyl carboxylates undergo acid-catalysed hydrolysis by an $A_{AL}1$ mechanism.[8]

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