Kinetics and Mechanism of Trifluoroacetylation of Aromatic Compounds

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The trifluoroacetylation of 2-methylfuran in dichloroethane at 25° was found to obey third-order kinetics according to the equation $v = k_{obs}^{III}$ [substrate][anhydride][acid]. A mechanism involving the formation of an ion pair between the protonated anhydride and the trifluoroacetate anion as the acylating agent is suggested.

THE trifluoroacetylation of aromatic compounds by trifluoroacetic anhydride is an electrophilic substitution which allows the introduction of a $COCF_3$ group into an activated substrate,[1] and has already been used in our laboratories to determine the relative reactivities of some five-membered heteroaromatic compounds by a competitive procedure.[2,3]

Since it seems to be an aromatic acylation which does not need the presence of any catalyst, the kinetic study of this reaction appeared interesting and easier than typical Friedel–Crafts acylations, the mechanism of which has not yet been clearly elucidated despite many studies,[4,10] because of many equilibria and, therefore, several competing reactions.[9,10]

The kinetics of the substitution of 2-methylfuran in dichloroethane were studied at 25°. The reaction was complete in 90 min. We now describe the kinetic equation and suggest a mechanism for this reaction.

RESULTS

Determination of the initial concentrations of the reagents was somewhat difficult, because of high volatility and ready hydrolysis of trifluoroacetic anhydride. Because of this it was impossible to avoid the presence of trifluoroacetic acid, due to traces of water still present in the purified solvent. Furthermore, the amount of acid increases during the reaction since it is formed as a product.

The progress of the reaction was followed volumetrically, by measuring the total acidity of the water-quenched mixtures. G.l.c. analysis at the end of the reaction was performed to determine the initial percentage of the hydrolysed anhydride.

The reaction was found to obey third-order kinetics according to the equation $v = k^{III}$ [substrate] [anhydride] [acid].

Since the first-order participation of the anhydride and of the aromatic substrate was established by isolation methods,[11] the validity of this rate equation was tested for several initial concentrations of the acid, by further addition of this reagent. Third-order plots were always straight lines with random deviations. A typical run is reported in the Experimental section.

The observed rate constants of individual runs are listed

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[1] W. D. Cooper, *J. Org. Chem.*, 1958, **23**, 1382.

[2] S. Clementi and G. Marino, *Tetrahedron*, 1969, **25**, 4599.

[3] S. Clementi and G. Marino, *J.C.S. Perkin II*, 1972, 71.

[4] F. R. Jensen and G. Goldman, 'Mechanism of Acylations,' in G. A. Olah, 'Friedel–Crafts and Related Reactions,' Interscience, New York, 1964, vol. III, p. 1003.

[5] D. Cassimatis, J. P. Bonnin, and T. Theophanides, *Canad. J. Chem.*, 1970, **48**, 3860.

[6] D. P. N. Satchell, *Quart. Rev.*, 1963, **17**, 160.

[7] G. Hoornaert and P. J. Slootmaekers, *Bull. Soc. chim. belges*, 1969, **78**, 257, and previous papers of the series.

[8] I. Hashimoto, A. Kawasaki, and Y. Ogata, *Tetrahedron*, 1972, **28**, 217.

[9] R. Corriu, C. Coste, and M. Guerin, *Bull. Soc. chim. France*, 1970, 2643, and previous papers of the series.

[10] R. Corriu and G. Dabosi, *Bull. Soc. chim. France*, 1971, 1670.

[11] S. W. Benson, 'The Foundations of Chemical Kinetics,' McGraw-Hill, New York, 1960, p. 81.

in Table 1. Some third-order values are compared with the corresponding fourth-order ones (which depend on the square of the acid concentration) the plots of which are also linear. The average value for the third-order rate constant is 0·104 ± 0·008 l^2 mol^{-2} s^{-1}. Although the standard deviation is rather large, owing to uncertainties involved in the initial concentrations, the individual values do not depend on the concentrations of the reagents. On the other hand the fourth-order constants appear to be inversely proportional to the acid concentration, indicating that this rate equation does not describe the reaction pattern.

The effect of some added compounds is shown in Table 2.

TABLE 1

Observed third-order rate constants for the trifluoroacetylation of 2-methylfuran in dichloroethane at 25°

Run	10^2[ArH]/M	10^2[$(CF_3{\cdot}CO)_2O$]/M	10^2[$CF_3{\cdot}CO_2H$]/M	$k_{obs}^{III}/l^2\ mol^{-2}\ s^{-1}$	$k_{obs}^{IV}\ l^3\ mol^{-3}\ s^{-1}$
1	4·84	3·70	11·17	0·100	0·78
2	5·52	4·51	7·19	0·096	0·98
3	5·50	5·10	7·05	0·104	
4	4·97	4·30	5·77	0·116	1·68
5	18·79	7·96	5·55	0·093	
6	10·89	4·43	5·39	0·108	
7	7·34	5·98	5·10	0·095	
8	4·94	4·23	2·61	0·120	3·83

TABLE 2

Dependence of the rate on the presence of some added compounds

Added compound	10^2[ArH]/M	10^2[$(CF_3{\cdot}CO)_2O$]/M	10^2[CF_3CO_2H]/M	10^2[Added cpd.]/M	$k_{obs}^{III}/l^2\ mol^{-2}\ s^{-1}$
None (Table 1)	~5	~5	~5		0·104
Acetic acid	5·10	1·63	8·10	4·68	0·061 [a]
Acetic acid	6·00	2·17	7·58	3·30	0·044 [a]
5-Acetyl-2-methylfuran	5·10	4·80	8·05	8·44	0·069
Tetra-n-butylammonium trifluoroacetate	6·47	3·73	6·95	5·00	0·022
Tetra-n-butylammonium trifluoroacetate	6·64	2·43	5·05	40·0	0·003

[a] For a complete discussion see text.

The addition of acetic acid, the product, or tetra-n-butylammonium trifluoroacetate decreases the reaction rate, although the observed plots always remain nearly linear. The greatest decrease of the rate is due to the quaternary salt, while the product causes only a slight effect. In the presence of acetic acid a smaller rate constant was found, but in this case the main feature is the formation of the corresponding acetyl derivative (20%), together with the trifluoroacetylated product.

DISCUSSION

Since the rate equation depends on the acid concentration, the mechanism of Scheme 1 would appear possible for the trifluoroacetylation. The Wheland complex, as ion pair (a), can be formed *via* two alternative pathways.

(A) An interaction between the anhydride and the trifluoroacetic acid (1), leading to a more powerful electrophile (C_1), and subsequent attack on the aromatic substrate (2). According to a third-order equation the rate-determining step would be either the attack on the substrate (2), or the bond breaking of the σ-complex (5). The acylating agent (C_1) could exist in equilibrium (7) with the covalent form (C_2), as recently suggested from the Raman spectra of similar compounds.[12]

(B) A direct attack of the neutral anhydride on the substrate (3) leading to a charge-separated σ-complex (b), and its subsequent protonation by the acid (4). If this is the case, third-order kinetics will be observed only if step (5) is rate controlling. Steps (4) and (5) might also occur at the same time, if the acid function involves the assistance of the leaving group, together with the protonation of the intermediate.

The decomposition of the Wheland intermediate yields the trifluoroacetyl derivative and two mol. equiv. of acid, probably through a step in which an ion pair (the protonated product is the cation) and one mol. equiv. of acid are formed (5). The presence of such an ion pair has been already suggested,[10] but it must quickly lead to the product and the second acid molecule (6), since the rate equation depends on the acid concentration.

Trifluoroacetic Acid Catalysis.—The acylation involving the protonated anhydride (as an ion pair, C_1) is supported by a similar mechanism reported for the $HClO_4$-catalysed benzoylation of anisole in the same solvent.[10] On the other hand, in the acylation of hydroxy-compounds the trifluoroacetic acid catalysis has been described as assisting the bond breaking of the intermediate.[13]

Both the catalytic functions cannot occur at the same time, since the rate equation does not depend on the square of the acid concentration. Third-order kinetics would still be observed, if path (A) is the reaction mode, provided a second acid molecule is involved in step (5), but step (2) remains rate determining.

In order to establish if step (5) is rate determining, and thus check the validity of path (B), an estimate of the kinetic isotope effect should be attempted. Unfortunately, this measurement cannot be carried out in this

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[12] R. Corriu and G. Dabosi, *Bull. Soc. chim. France*, 1971, 1666.

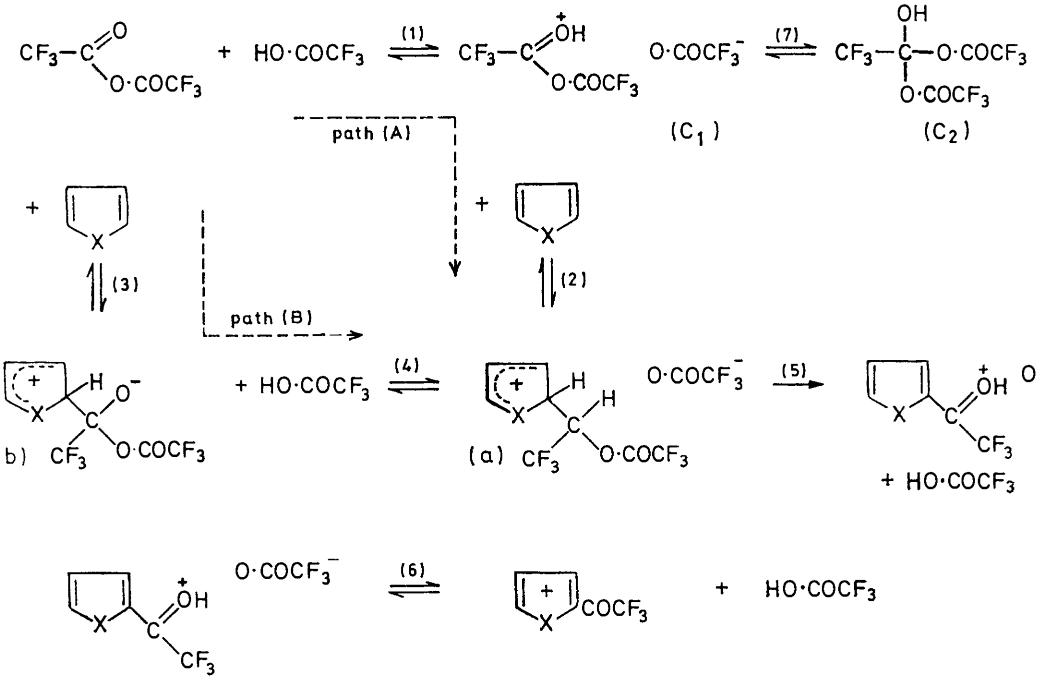
[13] T. G. Bonner, E. G. Gabb, and P. M. McNamara, *J. Chem. Soc.* (*B*), 1968, 72.

case, since the trifluoroacetic acid exchange is probably much faster than the substitution rate.

Effect of Added Tetra-n-butylammonium Trifluoroacetate.—The absence of free ions in a non-polar solvent such as dichloroethane was expected from previous results.[10,14] This is verified by the rate of reaction, since this should depend on the inverse of trifluoroacetate concentration if (C_1) gives rise to free ions. On the other hand, in this case the kinetic behaviour should be more complex, as the acid and the protonated product might also dissociate. Despite this, added tetra-n-butylammonium trifluoroacetate markedly decreases the reaction rate, without affecting the kinetic picture.

According to hypothesis (A), this decrease may be expected as a consequence of the reduction of the acylating agent concentration (C_1). As the salt also exists as an ion pair, its specific effect should not arise from a mass effect on the equilibrium (1). More likely the salt can give rise to a hydrogen-bonded complex with trifluoroacetic acid (which is then removed from the reaction medium), in which one or more acid molecules are involved.

If the reaction proceeds through path (B), the salt should affect the rate only if the suggested complex is formed, but it should cause two opposing effects. The removal of the acid from equilibrium (4) would lead to a lower rate, but its removal from equilibrium (1) would increase the amount of electrophile, *i.e.* the neutral anhydride. In this case the overall effect is hard to estimate.



Scheme 1

Accordingly, the observed rate lowering by the salt effect seems to support path (A).

Effect of Added Acetic Acid.—Further evidence in favour of path (A) arises from the effect of acetic acid. In fact in the presence of added acetic acid some acetylated product is obtained, which is not surprising, since the interaction of acetic acid with trifluoroacetic anhydride to give the mixed anhydride (ATFA) is well known,[15] and we have previously reported that the reaction of ATFA with heteroaromatic compounds gives a mixture of acetyl and trifluoroacetyl derivatives.[14,16] Hence the recovery of 2-acetyl-5-methylfuran as a product suggests that ATFA is actually present in the reaction medium. It follows that in the presence of added acetic acid a number of further equilibria are possible (Scheme 2).

According to the previously described mechanism (see above and ref. 15), ATFA is formed by an electrophilic addition of acetic acid to trifluoroacetic anhydride (steps 8 and 9), leading to the covalent form (C_4). Since the trifluoroacetate anion is a better leaving group than the acetate, decomposition of (C_4) gives the mixed anhydride rather than ' reverting to type '. Moreover, the acetylating agent would be the protonated ATFA ion pair (C_5), the formation of which could occur through either equilibria (10) and (11), or, alternatively, (12) and (13). The former path, involving a concerted elimination of an acid molecule, rather than the heterolysis of the C–O linkage with subsequent proton transfer to the more basic carbonyl group (α to methyl), appears to be the

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[14] S. Clementi and G. Marino, *Gazzetta*, 1970, **100**, 556.

[15] E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, *J. Chem. Soc.*, 1954, 2006.

[16] S. Clementi, F. Genel, and G. Marino, *Ricerca sci.*, 1967, **37**, 418.

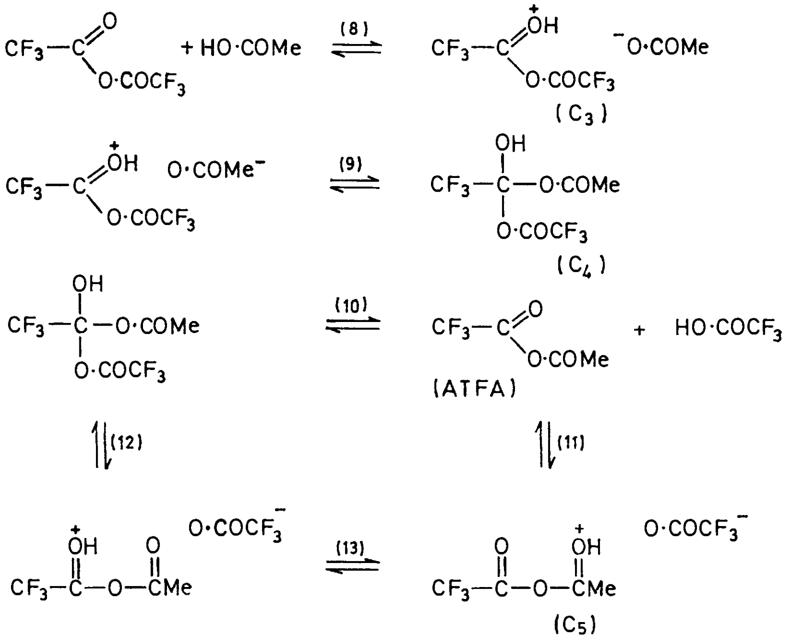
more probable, as an analogous result has been reported for benzoylation.[10]

The instantaneous concentration of AFTA, and of its protonated ion pair form (C_5), are given by equations (i) and (ii). Thus the competing acetylation reactions,

$$[\mathrm{ATFA}] = K_{\mathrm{eq}}\frac{[\mathrm{anhydride}]\,[\mathrm{AcOH}]}{[\mathrm{CF_3{\cdot}COOH}]} \qquad \text{(i)}$$

$$[\mathrm{C_5}] = K_{\mathrm{eq}}\,[\mathrm{anhydride}]\,[\mathrm{AcOH}] \qquad \text{(ii)}$$

involving either the neutral anhydride (path B) or its protonated ion pair form (path A), will show roughly third-order kinetics, as observed. An explanation of the smaller rate constant observed is somewhat difficult, since the whole system is very complex and an interaction between acetic and trifluoroacetic acid has been reported.[17]



SCHEME 2

However we have described [14] neutral ATFA as a trifluoroacetylating agent. Therefore path (B) could not lead to the presence of the acetyl derivative.

Moreover, the presence of ATFA indicates that trifluoroacetic anhydride is basic enough to be protonated by acetic acid. Of course if this acid leads to the addition compound, the stronger trifluoroacetic acid must behave in the same way.

Therefore equilibria (1) and (7) must be always involved in the reaction scheme, and (B) cannot be the only effective pathway. In addition, if path (B) is a competing reaction mode, the rate equation should not depend linearly on the acid concentration, since the amount of neutral anhydride varies inversely as that of the acid. Accordingly, path (B) is very unlikely.

Effect of Added Trifluoroacetyl Derivative.—The rate decrease due to added trifluoroacetyl derivative can be interpreted as evidence for the presence of equilibrium (6), assuming that the product affects the position of this equilibrium by a mass effect. Some acid is removed from the reaction medium and this decrease in concentration is responsible for the depressed rate. However, since this fast equilibrium follows the rate-determining step, this argument is consistent with both paths described above.

Nature of the Acylating Agent.—We suggest that the acylating agent responsible for path (A) (since we exclude the presence of free ions) is the protonated anhydride ion pair (C_1), since acylation by the covalent form (C_2) is very unlikely. Nevertheless the interaction between the acid and the anhydride could be less important, giving rise to a hydrogen-bonded complex, but such a species would not account for the acetic acid effect (formation of ATFA).

Conclusions.—The trifluoroacetylation involves catalysis by the corresponding acid, which is present at the beginning of the reaction because of the ready hydrolysis of the anhydride, and the amount of which increases, since it is formed as a product. Among various hypotheses the most likely catalytic function is the interaction with the anhydride, leading to the protonated anhydride ion pair, acting as the acylating species. The rate-determining step can be either attack on the aromatic substrate or decomposition of the intermediate.

EXPERIMENTAL

Materials.—Trifluoroacetic anhydride (Fluka) was distilled from P_2O_5 before each experiment. 2-Methylfuran

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[17] R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, 1961, **83**, 376.

(b.p. 62·5°), trifluoroacetic acid (b.p. 71°), and acetic acid (b.p. 118°) were commercial samples purified by distillation. 2-Methyl-5-trifluoroacetylfuran (b.p. 68° at 20 mmHg) was available from a previous study.[15] 1,2-Dichloroethane was treated with P_2O_5 and distilled through a Todd column; the medium fraction (b.p. 83·5°) was used.

Tetra-n-butylammonium trifluoroacetate was prepared by treating a 40% aqueous solution of the corresponding hydroxide with a slight excess of trifluoroacetic acid. A quantity of benzene was added to the crude precipitate formed, so that the residual water was distilled off as an azeotropic mixture.

Kinetic Procedure.—The kinetic runs were carried out at 25 ± 0·02° in a Haake thermostat, model F 4291, with initial reagents *ca.* 5×10^{-2}M. To prevent its hydrolysis the anhydride was always added last, and its amount was always less than that of the aromatic substrate.

The reaction was followed by titrating a portion (*ca.* 2 ml) of the reaction mixture quenched in water against a 0·05N-NaOH solution. Since the unchanged anhydride gives two mol. equiv. of acid, while only one mol. equiv. is formed from the reaction, the total acidity decreases as the reaction proceeds.

Because of the presence of an unknown amount of hydrolysed anhydride, the determination of the initial concentration of the reagents could not be obtained from the volumetric analysis only, but we can assume that the final amount of the trifluoroacetylated derivative must be equal to that of the unhydrolysed anhydride, since it is always less than that of the substrate and there was no trace of by-products. Quantitative analyses of the product were accomplished by g.l.c. on a Fractovap GI (Erba) apparatus, provided with a 2 m × 4 mm LAC 728 10% column at 100°, and using rectified iodobenzene as internal standard.

Kinetic Treatment of Rate Data.—The correct third-order rate equation, accounting for the increasing concentration of the acid, can be written as in equation (iii) (*a*, *b*, and *c* are the initial concentrations of the substrate, anhydride, and acid respectively):

$$\frac{dx}{dt} = k_{\text{obs}}^{\text{III}}\,(a - x)\,(b - x)\,(c + x) \qquad \text{(iii)}$$

$$\frac{1}{(a - b)\,(a + c)\,(b + c)}\left[(b + c)\ln\frac{a - x}{a} - (a + c)\ln\frac{b - x}{b} + (a - b)\ln\frac{c + x}{c}\right] = k_{\text{obs}}^{\text{III}}t \qquad \text{(iv)}$$

The definite integration of this equation leads to expression (iv) which was used to calculate graphically the observed rate constants. A typical run is reported in Table 3.

TABLE 3

A typical trifluoroacetylation run [a]

a = 0·0484M
b = 0·0370M
c = 0·1117M
$V_1 - V_\infty$ = 1·58 ml
N = 0·0477
v = 1·94 ml

Point	t/s	Volume (ml)	Reaction (%)	x	$f(x)$	$k_{\text{obs}}^{\text{III}}$/ $l^2\,mol^{-2}\,s^{-1}$
1	0	7·63	0·0	0·0000	0	
2	130	7·51	7·6	0·0028	15	112
3	440	7·33	19·0	0·0070	41	93
4	680	7·18	28·5	0·0105	67	98
5	1015	6·98	41·1	0·0152	112	110
6	1390	6·91	45·6	0·0169	131	94
7	1620	6·76	55·1	0·0204	178	110
8	1980	6·73	57·0	0·0211	192	97
9	2200	6·66	61·4	0·0227	222	101
10	1730	6·57	67·1	0·0248	270	99
11	2945	6·53	69·6	0·0258	297	101
12	3185	6·50	71·5	0·0265	318	100
	∞	6·05	100			

[a] For the explanation of symbols see text; $f(x)$ represent the first member of the integrated third-order equation.

We thank Professor G. Marino for having suggested this study, Professors E. Baciocchi, P. Linda, and G. Marino for discussion, and CNR for financial support.

[2/585 *Received*, 13*th March*, 1972]