

665. *Tracer Studies in Ester Hydrolysis. Part VI.* The Hydrolysis of Methyl Trifluoroacetate.*

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The acyl-oxygen bond of methyl trifluoroacetate is broken during hydrolysis in acid, alkaline, or initially neutral solution. Substitution of fluorine in the acyl group of the ester increases the rate of hydrolysis in alkaline or initially neutral aqueous dioxan, but relatively decreases the rate in acid, and the extent of acid-catalysis is small compared with that for unfluorinated esters. Added salts decrease the rate of the neutral hydrolysis.

The dissociation constant of trifluoroacetic acid in aqueous dioxan has been estimated colorimetrically.

SUBSTITUTION of electron-attracting atoms or groups into the acyl group of a carboxylic ester is known to increase the rate of nucleophilic attack on the acyl-carbon atom.¹ It will also make it easier for the ester to ionise, giving carbonium and carboxylate ions, or for the nucleophilic reagent to displace the carboxylate ion from the alkyl group, and it has been suggested that the extent of alkyl-oxygen bond fission in the hydrolysis of an ester of a carboxylic or other acid can give a measure of the strength of the acid.² Such a method could be misleading if the mechanism and kinetic form of the hydrolysis were not known.

* Part V, *J.*, 1957, 3043.

¹ Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686.

² Anbar, Dostrovsky, Klein, and Samuel, *J.*, 1954, 3603.

Trifluoroacetic acid is very much stronger than other carboxylic acids, because of the powerful electron-attraction by the three fluorine atoms, and it is largely dissociated in dilute solution in water, but in concentrated aqueous solution it is considerably weaker than the strong mineral acids.³

Esters of trifluoroacetic acid have been known for some time,⁴ but the first work to give information on the mechanism of their formation and hydrolysis is that of Traynham.⁵ The esters of (—)-octan-2-ol with trifluoroacetic and perfluorobutyric acid were prepared by direct esterification, or by reaction between the alcohol and the acid chlorides. The optically active esters were then hydrolysed with alkali, to regenerate alcohol with no loss of activity. This suggests that both acid esterification and alkaline hydrolysis break the acyl-oxygen bond. It has also been shown spectroscopically that a stable entity is formed by reaction between ethyl trifluoroacetate and ethoxide ions, presumably by nucleophilic addition to the acyl-carbon atom.⁶

The rates of hydrolysis of esters of fluoro-carboxylic acids have been measured by several investigators. The rates of hydrolysis of ethyl esters in initially neutral aqueous acetone increase with increasing fluorination, and autocatalysis was observed for some reactions.⁷ It was also found that the rate of hydrolysis of ethyl trifluoroacetate was doubled by the addition of 0.05M-hydrochloric acid. More recently the hydrolyses (in initially neutral aqueous acetone) of *n*-alkyl trifluoroacetates have been followed conductimetrically.⁸ The rate decreased, with increasing chain length, to a limiting value; similar results have been found for the hydrolysis of *n*-alkyl benzoates.⁹ It was assumed that the conductivity varied linearly with concentration of trifluoroacetic acid. This is probably not correct, because the acid is only partially dissociated in this aqueous-acetone solvent.¹⁰

These kinetic and stereochemical experiments are consistent with acyl-oxygen fission for both esterification and hydrolysis, but they do not exclude the possibility that alkyl-oxygen bond fission might occur in some cases.

RESULTS

Bond Fission.—Methanol was isolated, by fractional distillation, from hydrolyses with the water enriched in ¹⁸O. Two sets of conditions were used: heterogeneous hydrolysis in water, and homogeneous hydrolysis in dioxan-water 60 : 40 (v/v). The results are given in Table 1. In all cases the acyl-oxygen bond was broken.

TABLE 1. *Position of bond fission.*

Reagent	Homogeneous		Heterogeneous	
	—	HClO ₄ (0.45M)	—	HClO ₄ (0.891M) NaOH (0.49M)
<i>N</i> _{MeOH} (atom % excess)	0.00	0.004	0.005	0.004 0.013

*N*_{H₂O} = 0.59 atom % excess; for the acid experiments this was diluted to a small extent by the water contained in 72% perchloric acid.

Kinetics.—The rates of hydrolysis in initially neutral aqueous dioxan were followed by three independent methods. The trifluoroacetic acid was estimated conductimetrically, or iodometrically; these methods gave consistent results, but dilatometry gave rate constants which were too high (see p. 3254). The conductimetric method was sufficiently sensitive to detect autocatalysis by trifluoroacetic acid. Results are in Table 2.

³ Long and Paul, *Chem. Rev.*, 1957, **57**, 1.

⁴ Swarts, *Bull. Acad. Roy. Belg., Classe Sci.*, 1922, **8**, 343; Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367.

⁵ Traynham, *J. Amer. Chem. Soc.*, 1952, **74**, 4277.

⁶ Bender, *ibid.*, 1953, **75**, 5986.

⁷ Gorin, Pierce, and McBee, *ibid.*, p. 5622.

⁸ Moffat and Hunt, *ibid.*, 1957, **79**, 54.

⁹ Tommila, *Ann. Acad. Sci. Fennicae*, 1942, *A*, **59**, No. 3.

¹⁰ Pierce and Gorin, *J. Amer. Chem. Soc.*, 1953, **75**, 1749.

TABLE 2. Rates of hydrolysis in aqueous dioxan. Initially neutral solution. Titrimetric and dilatometric methods.

Dioxan-water 70 : 30 (v/v).				
Temp.	0°	25.0°	44.6°	
$10^5 k_1$ (sec. ⁻¹)	1.80	10.0	24.0	
Dioxan-water, 60 : 40 (v/v).				
Temp.	0°	25.0°	34.8°	44.6°
$10^5 k_1$ (sec. ⁻¹)	5.47, 4.62 ^a	23.6, 25.0, 33.7 ^D	39.8	74.4
^a [LiClO ₄] 0.567M.				
Dioxan-water, 40 : 60 (v/v). Temp. 0°.				
Reagent	0.482M-LiClO ₄	0.567M-Et ₄ NBr	—	
$10^5 k_1$ (sec. ⁻¹)	21.8	20.9	33.2 ^D	

^D Values so marked were obtained dilatometrically, and are included to show the error of the method for neutral hydrolyses.

Conductimetric method, showing the autocatalysis.

Dioxan-water, 60 : 40 (v/v). Temp. 0°, unless otherwise specified.				
[CF ₃ ·CO ₂ Me] (initial) (M)	0.058	0.058 *	0.060 †	0.036 ‡
$10^5 k_1$ (sec. ⁻¹) (initial)	5.42	7.17	24.6	25.6
„ (final)	7.11	—	30.4	30.7

* CF₃·CO₂H added initially = 0.058M. † Temp. 25.0°. ‡ Dioxan-water, 40 : 60 (v/v).

The Arrhenius equations are (from titrimetric and conductimetric results):

Dioxan-water, 70 : 30 (v/v); $k_1 = 10^{8.9} \exp(-10,500/RT)$ (sec.⁻¹).
 „ 60 : 40 (v/v); $k_1 = 10^{8.4} \exp(-10,200/RT)$ (sec.⁻¹).

Acid solutions. Temp. 0°, and dilatometric results unless otherwise specified.

Dioxan-water, 70 : 30 (v/v).								
[HClO ₄] (M).....	0.27	0.50	0.92	0.98	1.47			
$10^6 k_1$ (sec. ⁻¹)	8.30	18.2	22.7	24.0	20.4			
Dioxan-water, 60 : 40 (v/v).								
[HClO ₄] (M).....	0.084	0.196	0.200	0.391	0.445	0.613	0.999	
$10^5 k_1$ (sec. ⁻¹)	8.50 ^a	76.1 ^b	14.0	19.5	16.8 ^c	28.4	37.3	
Dioxan-water, 40 : 60 (v/v).								
[HClO ₄] (M).....	0.144	0.157	0.258	0.350	0.371	0.372	0.536	0.675
$10^5 k_1$ (sec. ⁻¹)	40.6	43.4 ^a	45.8	39.8 ^e	36.9 ^d	51.8	56.2	57.1

^a Titrimetric method. ^b Temp. 25°. ^c [LiClO₄] = 0.567M. ^d [LiClO₄] = 0.585M. ^e [Et₄NBr] = 0.370M.

Iodometry was also used for hydrolyses in the presence of dilute perchloric acid, and dilatometry was satisfactory when the concentration of perchloric acid exceeded *ca.* 0.1M.

Alkaline hydrolysis by sodium hydroxide was too fast for conventional kinetic methods, but the reactions with sodium hydrogen carbonate or carbonate could be followed.

DISCUSSION

Consideration of the kinetic form and mechanism of these hydrolyses is simplified by the fact that only mechanisms of acyl-oxygen bond fission need to be considered (Table 1).

The marked effect of alkali on the hydrolysis shows that the mechanism here is *B*_{Ac}2. We can make no accurate comparison between the alkaline rates of this and other esters, because we do not know the concentrations of hydroxide ions in solutions of sodium carbonate or sodium hydrogen carbonate in aqueous dioxan. The rate is, as would be expected, greater with sodium carbonate. It is possible to make only a qualitative rate comparison between the alkaline hydrolyses of methyl acetate ¹¹ and trifluoroacetate. The latter is considerably faster.

Hydrolyses of alkyl trifluoroacetates in initially neutral solutions are much faster than of unsubstituted carboxylic esters. Our values (Table 2) are similar to those found for

¹¹ Fairclough and Hinshelwood, *J.*, 1937, 538.

hydrolysis in aqueous acetone,⁸ although the Arrhenius parameters differ for the two solvents. These parameters are in the range usually associated with bimolecular ester hydrolyses with acyl-oxygen fission,¹² and the rate increases with increasing water content of the solvent. All this evidence makes it most probable that here too the slow step of the reaction is nucleophilic attack of a water molecule on the acyl-carbon atom, by mechanism $B_{Ac}2$. We do not know whether bond-making and -breaking are synchronous, or whether an intermediate of finite life is formed by nucleophilic addition to the acyl-carbon atom of the ester molecule.⁶

The increase in rate observed during a run in initially neutral solution is an auto-catalysis by trifluoroacetic acid, and the rate towards the end of a reaction is very close to that observed initially with a comparable amount of added trifluoroacetic acid (Table 2).

Neutral salts (lithium perchlorate and tetraethylammonium bromide) decrease the rate of hydrolysis in initially neutral solution. Kinetic effects of non-common ion salts on nucleophilic displacements on alkyl halides, or 'onium salts, in hydroxylic solvents can be explained in terms of changes in the size or distribution of charge during formation of the transition state. This simple theory is less satisfactory in ester hydrolyses where the nucleophilic reagent attacks a multipolar molecule. From the Brönsted equation we can write for the bimolecular neutral hydrolysis of an ester, E:

$$\text{Rate} \propto [E] \cdot a_{H_2O} \cdot f_E/f_{T+}$$

(f_E and f_{T+} are the activity coefficients of the initial and transition state respectively, and a_{H_2O} is the activity of water.)

We know that many neutral salts "salt in" carboxylic esters,¹³ *i.e.*, decrease their activity coefficients, though because of the rapid hydrolysis of alkyl trifluoroacetates this point cannot be tested here. It is also likely that salts will decrease the activity of water, and it seems that these salt effects on the reactants are the controlling factors in the neutral hydrolyses.

The acid hydrolyses were in general followed dilatometrically, although two control runs were done by the rather less accurate titrimetric method (Table 2). In all solvents the extent of acid-catalysis was small, very much less than usual for carboxylic-ester hydrolyses. The rate constant for a specific hydrogen-ion-catalysed reaction is made up of an equilibrium constant for the protonation of the neutral ester molecule, and a rate constant for the slow decomposition of the conjugate acid so formed. There is no reason why the decomposition should be slowed by the electron-withdrawing fluorine atoms, because it almost certainly involves a bimolecular attack by water molecules, and so we suppose that the small acid rate (relative to the neutral rate) is caused by a decrease in the basicity of the neutral ester molecule.

With increasing concentration of perchloric acid the rates tend to level off (see Figure), and a maximum is observed for the least aqueous solvent (although this is hardly outside the experimental error, see p. 3254). This levelling off is almost certainly not caused by complete protonation of the neutral molecule, as is sometimes found,¹⁴ because a trifluoroacetate would be much too weak a base to be protonated fully in *ca.* *m*-perchloric acid in aqueous dioxan. It is a salt effect of the ions of perchloric acid, and decreases the rate of both acid-catalysed and neutral reactions.

This general behaviour is also found for the hydrolysis of phenyl trifluoroacetate (to be reported later). In this reaction a pronounced maximum is found and it also can be treated semi-quantitatively. It is here assumed that the "salt effects" of perchloric acid and lithium perchlorate are the same, and that the salt effect is proportional to concentration. These are oversimplifications. The relation between rate and ionic concentration usually follows an exponential equation, but use of this would make the

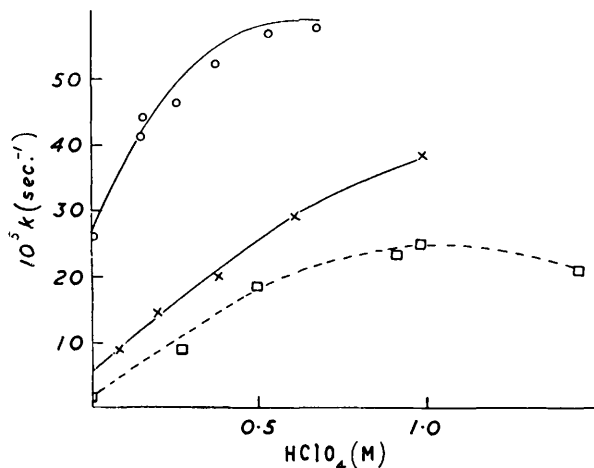
¹² Long and Pritchard, *J. Amer. Chem. Soc.*, 1957, **79**, 2365.

¹³ Waing, *J.*, 1954, 2879.

¹⁴ Evidence summarised by Long and Paul, *Chem. Rev.*, 1957, **57**, 954, 988.

calculation excessively complicated, and for low concentrations of salts or acid the linear and exponential forms do not differ much.

Acid hydrolysis of methyl trifluoroacetate at 0°.



Full lines are calculated. ○ 40 : 60, × 60 : 40, □ 70 : 30 v/v dioxan-water.

The observed first-order rate constant k^0 can be separated into two terms, e.g.,

$$k^0 = k_n^0 + k_a^0 \cdot C_a \quad (1)$$

where C_a and C_s are the concentrations of the fully dissociated mineral acid and salt respectively, and k_n^0 and k_a^0 are:

$$k_n^0 = k_n - p(C_s + C_a) \quad (2)$$

$$k_a^0 = k_a - q(C_s + C_a) \quad (3)$$

Here k_n and k_a are the rate constants for neutral and acid hydrolyses, respectively, at zero ionic concentration. When $C_s = 0$, equations 1, 2, and 3 give the quadratic equation:

$$k^0 = k_n + (k_a - p - qC_a)C_a \quad (4)$$

The rate constant k_n is known, p can be evaluated from the salt effect on the neutral rate, and $(k_a - p)$ is the initial slope of the plot of rate constant against acid concentration. The remaining parameter q is evaluated by taking a point on the experimental plot and solving equation (4). The quadratic form of this equation predicts a maximum in the rate, and the calculated position is:

$$C_a(\text{max.}) = (k_a - p)/2q$$

The values so calculated are given below in the units for k^0 and k_n of $10^{-5} \text{ sec.}^{-1}$; for k_a and p , $10^{-5} \text{ sec.}^{-1} \text{ mole}^{-1} \text{ l.}$; and for q , $10^{-5} \text{ sec.}^{-1} \text{ mole}^{-2} \text{ l.}^2$; with C_a in mole l.^{-1} .

Dioxan-water, 40 : 60 v/v. Temp. 0°. $k_n = 25.6$; $k_a = 127$; $p = 7.9$; $q = 107$ (from $k^0 = 57.1$ at $C_a = 0.675\text{M}$). Calc. $C_a \text{ max.} = 0.56\text{M}$.

Dioxan-water, 60 : 40 v/v. Temp. 0°. $k_n = 5.45$; $k_a = 47.1$; $p = 1.5$; $q = 13.6$ (from $k^0 = 37.5$ at $C_a = 1.0$). Calc. $C_a \text{ max.} = 1.7\text{M}$.

The rate constants for 70 : 30 v/v dioxan-water are not sufficiently accurate for evaluation of these constants, but here $10^5 k_a \approx 30 \text{ (sec.}^{-1} \text{ mole}^{-1} \text{ l.)}$.

The second-order rate constants, k_a , for the acid-catalysed reaction decrease with decreasing water content of the solvent. This is, in fact, the order of the relative acidities as determined by indicator measurements,^{15,16} suggesting that the determining factor for

¹⁵ Braude and Sterne, J., 1948, 1976.

¹⁶ Bunton, Ley, Rhind-Tutt, and Vernon, J., 1957, 2327.

the solvent effect on the acid reaction is the extent of protonation of the neutral ester molecule, rather than the rate of decomposition of the conjugate acid.

In formulating this picture of the kinetic form of acid hydrolysis we have assumed that the mechanism is $A_{Ac}2$. This is almost certainly correct, because we know the bond fission to be acyl-oxygen, and mechanism $A_{Ac}1$ is found only in highly ionising acidic solvents or with esters in which the acylium ion is stabilised by electron release.

EXPERIMENTAL

Materials.—Methyl trifluoroacetate was prepared by mixing trifluoroacetic acid with an excess of methanol at room temperature, and distilling off the ester through a 20 cm. helix-packed column. The ester, after refractionation, had b. p. 40°, and sap. equiv. 127.5. The purity was tested by passing the ester through a gas-phase chromatograph. The trace showed the presence of a minor peak of area *ca.* 1/1000 that of the main peak. A b. p. of 43° has been reported for this ester.^{8, 17}

Kinetic Measurements.—The solvent was aqueous dioxan, containing 40%, 60%, or 70% of purified dioxan (v/v).

The conventional method for following an ester hydrolysis, by acid-base titration, could not be used, because the ester reacts very rapidly with hydroxide ions. Three methods were used.

(1) *Titrimetric method.* Portions (5 c.c.) of the reaction mixture were added to ice-cold 70% acetone (30 c.c.) containing a solution (1—4 c.c.) of potassium iodide (0.03M) and potassium iodate (0.15M). The iodine liberated was titrated quickly with 0.01N-sodium thiosulphate; no indicator was used: $6H^+ + 5I^- + IO_3^- \longrightarrow 3I_2 + 3H_2O$. This method was not very accurate but could be used for runs in initially neutral or dilute acid solutions. An example is given:

Solvent, dioxan-water 60 : 40 v/v. Temp. 0°. The concentration units are in c.c. of 0.01N-sodium thiosulphate per 5 c.c. portions.

Time (min.)	0	15	20	30	40	60.5	75	∞	
[CF ₃ ·CO ₂ H]	3.30	3.70	8.20	9.50	12.30	14.70	18.75	20.40	29.25 29.70

$10^5k_1 = 23.6$ (sec.⁻¹) obtained graphically from the usual first-order integrated rate equation.

This iodometric method was not used for the runs with sodium carbonate or hydrogen carbonate. In these, portions (5 c.c.) were titrated rapidly with 0.05N-hydrochloric acid (methyl-orange). An example is given with values for the half-lives of other experiments:

Dioxan-water 40 : 60 v/v.

Initially [Na₂CO₃] = 0.076N, [CF₃·CO₂Me] = 0.047M, temp. 0°.

Time (min.)	0	1	3	5.5	6.75	10	15	20
Titre (c.c.)	7.55	3.72	3.35	3.30	3.22	3.08	2.87	2.83

Initially [NaHCO₃] = 0.070N, [CF₃·CO₂Me] = 0.047M, temp. 0°: $t_{\frac{1}{2}} = 7.25$ min.

Initially [NaHCO₃] = 0.093N, [CF₃·CO₂Me] = 0.071M, temp. 0°: $t_{\frac{1}{2}} = 7.5$ min.

Initially [NaHCO₃] = 0.089N, [CF₃·CO₂Me] = 0.058M, temp. 15°: $t_{\frac{1}{2}} \sim \frac{1}{2}$ min.

If sodium hydroxide is added to a solution of the ester at 0° the end-point drifts continuously. We tried to follow the reaction by mixing a solution of the ester with one of sodium hydroxide, and then quickly quenching the reaction by adding an excess of hydrochloric acid. This was unsuccessful; probably the rate of mixing was the limiting factor.

(2) *Conductance method.* This is very sensitive, but is suitable only for hydrolyses in initially neutral solution. The conductivity of trifluoroacetic acid in the kinetic solvents was first measured. A sample of the values so obtained is given below.

Dioxan-water 60 : 40 v/v, temp. 0°.

[CF ₃ ·CO ₂ H] (10 ⁻² M)	0.107	0.540	0.820	1.90	3.74	8.20	13.12	16.82
Λ (ohm ⁻¹ cm. ²)	50.5	47.2	43.7	37.6	32.6	27.3	23.6	21.5

Dioxan-water 60 : 40 v/v, temp. 25°.

[CF ₃ ·CO ₂ H] (10 ⁻² M)	0.73	1.90	3.94	5.36	6.84	8.32	9.95	11.53
Λ (ohm ⁻¹ cm. ²)	70.3	56.7	48.2	44.1	41.6	39.1	37.3	35.5

Dioxan-water 40 : 60 v/v, temp. 0°.

[CF ₃ ·CO ₂ H] (10 ⁻² M)	0.182	0.389	1.61	3.10	5.47	6.71	8.37	9.98
Λ (ohm ⁻¹ cm. ²)	99.4	97.0	87.6	77.8	65.5	59.6	52.7	47.2

¹⁷ Gryszkiewicz-Trochimowski, Sporzyński, and Wnuk, *Rec. Trav. chim.*, 1947, **66**, 413.

The changes in conductivity during reaction were converted into changes in the concentration of the trifluoroacetic acid. This was essential because the acid is only partially dissociated in aqueous dioxan, and the degree of dissociation varies with the concentration. The alternate points of a run followed by this method are given below:

Dioxan-water 60 : 40 v/v, temp. 25°.									
Time (min.)	10	20	30	40	56	79	92	110	∞
[CF ₃ ·CO ₂ H] (10 ⁻² M)	1.16	2.15	2.97	3.75	4.70	5.78	6.20	6.70	7.90
Initial 10 ⁵ k ₁ = 24.6 (sec. ⁻¹).									

(3) *Dilatometry*. This method was used for the neutral and acid hydrolyses. The results for the neutral hydrolyses were consistent among themselves, but not with those of the other methods. The rates were 30–40% higher (Table 2). This discrepancy comes from an inherent defect in the dilatometric method, which makes it unreliable for reactions such as these. It is assumed, in the use of the dilatometric method, that the percentage volume change during reaction is equal to the percentage reaction. This assumption is usually correct, but not in the hydrolysis of an alkyl trifluoroacetate in initially neutral solution. The volume change during reaction is caused by disappearance of ester and water and formation of alcohol and trifluoroacetic acid. The acid is only partially dissociated, and the greater part of the volume change caused by trifluoroacetic acid comes from interaction between its protons and solvent molecules. Therefore the volume change will depend upon the degree of dissociation of the acid, and this, and the volume change per unit of reaction, will change during the reaction. We should expect the volume change for a given amount of reaction to be greatest at the beginning of a run, when the concentration of trifluoroacetic acid is low and its degree of dissociation high. Thus the rates measured dilatometrically should be too high, as is found. The logarithmic plot, as used,¹⁸ would be too insensitive to detect trends during reaction. Although the method does not give correct results in initially neutral solution it is satisfactory in the presence of perchloric acid in concentration sufficient to buffer the hydrogen-ion concentration and so keep the degree of dissociation constant during a run. From the dissociation constants of trifluoroacetic acid determined during this work we can calculate the change in the degree of dissociation (α) during a kinetic run.

Dioxan-water 40 : 60 v/v.				Dioxan-water 60 : 40 v/v.			
[HClO ₄] (M)	[CF ₃ ·CO ₂ H] (M)	α	$\Delta\alpha$	[HClO ₄] (M)	[CF ₃ ·CO ₂ H] (M)	α	$\Delta\alpha$
0.0	0.01	0.05	0.12	0.0	0.01	0.05	0.26
0.2	0.95	0.83	0.03	0.1	0.79	0.53	0.02
0.3	0.50	0.47	0.01	0.2	0.23	0.21	0.00
0.4	0.40	0.39	0.00		0.13	0.13	
	0.33	0.33					

These calculations are approximate, because activity effects are neglected, but they show that the dilatometric method is likely to give the wrong answer in initially neutral solution. They also suggest that it is reliable when sufficient perchloric acid is present. Dilatometry should be satisfactory for reactions with acid products when the acid is either weak or very strong; the difficulties arise here because trifluoroacetic acid, in aqueous dioxan, is of intermediate strength. The suppression of the dissociation of trifluoroacetic acid imposes another limit on the method, because with increasing perchloric acidity the volume change (a contraction at all acidities in the two more aqueous solvents) becomes too small. Our experiments were taken to this limit with some loss of accuracy at the higher acidities. In 70 : 30 v/v dioxan-water the usual contraction, decreasing with acidity, is replaced by a small expansion at perchloric acidities >0.8M. This behaviour is real and independent of the dilatometer; presumably at higher acidities the contraction during reaction which comes from the interaction between protons and solvent molecules becomes less than the expansion caused by the formation of two product molecules from one ester molecule. We estimate that the accuracy of the dilatometric runs with [HClO₄] <0.5M is 2%. At higher perchloric acidities (*ca.* M) the accuracy is reduced to 5%.

Bond Fission.—*Homogeneous conditions*. The solvent was 60 : 40 v/v dioxan-water, with the water enriched in ¹⁸O. After complete reaction under kinetic conditions at 25° dry potassium carbonate was added, and the non-aqueous layer separated and dried over more potassium

¹⁸ Guggenheim, *Phil. Mag.*, 1926, 2, 538.

carbonate. It was then distilled and the first portion of the distillate fractionated through a 12" column packed with a metal spiral. The methanol so obtained had a high refractive index, n_D^{25} ca. 1.33, and was probably contaminated with a small amount (<4%) of dioxan.

Heterogeneous conditions. The ester was completely hydrolysed in isotopically enriched water, with vigorous stirring, at 25°. The final solution was neutralised with aqueous sodium hydroxide, and the methanol was distilled off and purified by fractionation as already described. The isotopic abundances of the methanol samples were determined by pyrolysis to carbon monoxide and mass-spectrometric analysis of this gas.

APPENDIX

Dissociation Constants in Aqueous Dioxan.—The usual method for determination of acid dissociation constants, that of conductivity,¹⁹ was not very suited to our system, because it requires a reliable value for Λ_0 , and it was difficult to determine this in aqueous dioxan. Therefore an indicator method was used; the values so obtained were in agreement with approximate values calculated from our conductivity data.

The dissociation constant of purified *m*-nitroaniline in perchloric acid in aqueous dioxan at 15° was first determined spectrophotometrically, at 370, 375, and 380 m μ in 60 : 40 v/v dioxan-water, and 365, 370, and 375 m μ in 40 : 60 v/v dioxan-water. The indicator ratio, $r = [\text{BH}^+]/[\text{B}]$, where B is *m*-nitroaniline, was determined for a series of perchloric acidities; the ratio $r/[\text{H}^+]$, extrapolated to zero concentration of perchloric acid, gave the thermodynamic dissociation constant K_b . All measurements were at room temperature:

In 40 : 60 v/v dioxan-water, $K_b = 38.7$ (mole⁻¹ l.).

In 60 : 40 v/v dioxan-water, $K_b = 12.5$ (mole⁻¹ l.).

The indicator ratios can then be determined in trifluoroacetic acid solutions, giving the apparent hydrogen-ion concentration, and so the dissociation constant. These classical dissociation constants, K_c , extrapolated to zero acid concentration, give the thermodynamic dissociation constants K_a .

Dioxan-water 40 : 60 v/v:

[CF ₃ ·CO ₂ H] (10 ⁻² M)	2.14	4.27	6.41	8.55	10.7
r (average)	0.727	1.39	1.94	2.45	2.68
[H ⁺] (10 ⁻² M)	1.95	3.66	5.10	6.38	6.95
Degree of dissoen.	0.912	0.857	0.795	0.746	0.650
K_c (10 ⁻¹ mole l. ⁻¹)	2.00	2.19	1.99	1.92	1.29

$$K_a = 0.21 \text{ (mole l.}^{-1}\text{)}$$

Dioxan-water 60 : 40 v/v.

[CF ₃ ·CO ₂ H] (10 ⁻² M)	2.13	4.26	6.38	8.51	10.64
r (average)	0.166	0.293	0.401	0.500	0.606
[H ⁺] (10 ⁻² M)	1.30	2.34	3.25	4.09	5.04
Degree of dissoen.	0.61	0.55	0.51	0.48	0.47
K_c (10 ⁻² mole l. ⁻¹)	2.04	2.85	3.37	3.78	4.54

$$10^2 K_a = 1.5 \text{ (mole l.}^{-1}\text{)}$$

These values show that the dissociation constant decreases sharply with decreasing water content, e.g., the values in water are 0.588 (mole l.⁻¹) at 25° and 0.533 at 35°. ²⁰

It is known that the dissociation constant of hydrochloric acid decreases with decreasing water content of an aqueous-dioxan solvent. Thus the dissociation ²¹ in 40% dioxan (by wt.) is ca. 1, in 70% it decreases to 7.7×10^{-3} (mole l.⁻¹), and in 82% to 2.02×10^{-4} at 25°. From an interpolation of these values it seems that in our aqueous dioxan solvents hydrochloric acid has a dissociation constant ca. 5 times that of trifluoroacetic acid.

Pierce and Gorin ¹⁰ measured the relative strengths of hydrochloric and trifluoroacetic acid in water and in 70 : 30 v/v acetone-water, from their catalytic effects on the hydrolysis rate of ethyl acetate. The rates for a given acid concentration are identical in water, but that with hydrochloric acid is ca. 2½ times greater in the mixed solvent. Thus the solvent

¹⁹ Harned and Owen, "Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950.

²⁰ Henne and Fox, *J. Amer. Chem. Soc.*, 1951, **73**, 2323.

²¹ Owen and Walters, *ibid.*, 1938, **60**, 2371.

“levelling” effect of water makes trifluoroacetic acid almost fully dissociated in dilute aqueous solution; this effect has disappeared in aqueous acetone, and in these aqueous-organic solvents trifluoroacetic acid is not a strong acid.

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