

Kinetics of the Neutral Hydrolysis of Chloromethyl Chloroacetate

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As an example of neutral ester hydrolysis (mechanism $B_{AC}2$), the hydrolysis of chloromethyl chloroacetate in water has been investigated kinetically by an argentometric method at ten-degree intervals from 5°C to 85°C. The Arrhenius equation is not valid as the calculated activation energy decreases with increasing temperature. The value of the heat capacity of activation ΔC_p^\ddagger was found to be $-40 \text{ cal mole}^{-1} \text{ degree}^{-1}$. Neutral salts and acetone were found to retard the reaction strongly. The mechanism of neutral ester hydrolysis is discussed.

It has been found earlier that, besides the hydrogen-ion catalysed¹ and alkaline² hydrolyses, the α -halogenoalkyl esters of aliphatic acids have a neutral hydrolysis. The last-mentioned reaction usually takes place as a nucleophilic displacement of the α -halogen atom of the alkyl component¹, but in the case of chloromethyl formate¹, α,β -dichloroethyl formate³, and α,β,β,β -tetrachloroethyl acetate³, the reaction was found to be a neutral ester hydrolysis which evidently takes place by the same mechanism ($B_{AC}2$) as, e.g., the hydrolysis of alkyl halogenoacetates in neutral solution¹. To get more information on the kinetics of this reaction type, the hydrolysis of chloromethyl chloroacetate was studied because it could be assumed on the basis of structural effects that its hydrolysis in neutral aqueous solution is a neutral ester hydrolysis.

EXPERIMENTAL

Materials. Chloromethyl chloroacetate was prepared as described earlier². Perchloric acid solutions were prepared by diluting concentrated perchloric acid (*pro analysi*, d. 1.54, E. Merck AG.) with water; their molarities were determined by acid-base titration. The solutions of sodium perchlorate were prepared by dissolving in water weighed amounts of the water-free salt which was prepared by crystallising a commercial product (Laboratory Reagent, low in chloride, BDH) from water above 50°C⁴ and drying at 220°C. Acetone (*pro analysi*, E. Merck AG.) was used as received.

Kinetic measurements. The kinetic experiments were performed by the argentometric method described earlier⁵. The initial concentration of chloromethyl chloroacetate was

about 0.05 mole/l and the standard silver nitrate solutions were about 0.02 M. The titrations were performed potentiometrically using a Radiometer Titrator TTT1 and silver and mercury/mercurous sulphate electrodes.

Because the hydrogen ion exerts a slight accelerating influence on the reaction rate, the calculated first-order rate coefficients k_t increase during the reaction. The time-average of the hydrogen-ion concentration \bar{c}_t was calculated by means of the trapezoidal rule¹. The rate coefficients were either extrapolated to zero hydrogen-ion concentration as described below or, when the electrolyte or solvent effect was investigated without any acid present initially, interpolated to refer to an appropriate value of the hydrogen-ion concentration. In the latter case the necessary corrections were less than one per cent of the mean value \bar{k}_t of k_t . For illustration, the experimental data for the hydrolysis of chloromethyl chloroacetate in 0.1 M aqueous perchloric acid at 25°C (I), in water at 75°C (II), and in 0.3 M aqueous sodium perchlorate solution at 25°C (III) are given below.

I. t_{\min}	0	20.5	61.5	120	150	203	240.5	320	∞	
$10^5 x$	0	539	1449	2382	2723	3193	3421	3758	4210	
$10^4 c_t$	1061	1088	1136	1193	1218	1254	1275	1311		
$10^4 k_t$		1.113	1.143	1.159	1.156	1.166	1.160	1.162		
		$\bar{c}_t = 0.1211$ mole/l, $10^4 \bar{k}_t = 1.151$ s ⁻¹								
II. t_g	0	165	322	507	715	905	1116	1344	∞	
$10^5 x$	0	957	1649	2243	2700	2989	3190	3340	3611	
$10^4 c_t$	124	172	212	251	286	311	334	354		
$10^3 k_t$		1.866	1.894	1.915	1.926	1.943	1.926	1.926		
		$\bar{c}_t = 0.0274$ mole/l, $10^3 \bar{k}_t = 1.914$ s ⁻¹								
III. t_{\min}	0	41	65	90.5	122	150.2	220	260	320	∞
$10^5 x$	0	880	1303	1686	2160	2434	3064	3287	3584	4356
$10^4 c_t$	54	98	122	145	171	192	235	256	283	
$10^5 k_t$		9.17	9.11	9.02	9.36	9.08	9.21	9.00	9.01	
		$\bar{c}_t = 0.0188$ mole/l, $10^5 \bar{k}_t = 9.12$ s ⁻¹								

Random errors evidently have a pronounced effect at the higher temperatures, whereas the rate coefficients for the lower temperatures may be considered as reliable as those determined previously, *e.g.* in Ref.¹ (standard error of the mean less than 1 % of the mean value of the rate coefficient).

RESULTS

The experimental data are given in Tables 1 and 2 and the effect of hydrogen ion and added salts is illustrated in Fig. 1. The hydrogen ion is seen to increase the rate of the hydrolysis of chloromethyl chloroacetate, but the relationship is not linear. Therefore a parabolic equation

$$\bar{k}_t = k_o + k_{\text{HX}} \bar{c}_t + k_s \bar{c}_t^2 \quad (1)$$

was fitted to the data when calculating the effect of hydrogen ion at temperatures where measurements were performed over an extended concentration range. The calculations were performed by the method of least squares on a Wegematic 1000 electronic computer. The results are shown in Table 1. A linear equation, however, was applied when the measurements related to the reaction in dilute acid solutions (up to about 0.15 M) only.

Table 1. Kinetic data for the hydrolysis of chloromethyl chloroacetate in water and perchloric acid solutions.

Temperature °C	\bar{c}_t mole/l	$10^4 \bar{k}_t$ s ⁻¹	$10^4 k_o$ s ⁻¹	$10^4 k_{HX}$ l mole ⁻¹ s ⁻¹	$10^4 k_s$ l mole ⁻² s ⁻²	E_o kcal/ mole																																																																																																																																
5.00	0.0175	0.231	0.229	(0.08)		12.84																																																																																																																																
	0.0179	.230					15.00	0.0158	0.515	0.513	(0.24)		12.74	0.0176	.518	25.00	0.0141	1.084	1.082 ± 0.004	0.67 ± 0.04	-0.32 ± 0.08	12.30	0.0165	1.089	0.0178	1.097	0.0199	1.097	0.0266	1.107	0.1211	1.151	0.2158	1.207	0.2281	1.226	0.3189	1.261	0.5102	1.332	0.5391	1.352	35.00	0.0177	2.163	2.123 ± 0.009	1.73 ± 0.17	-0.69 ± 0.34	11.84	0.0180	2.131	0.0183	2.177	0.0185	2.159	0.0205	2.136	0.0237	2.162	0.1212	2.340	0.3231	2.598	0.5200	2.839	45.00	0.0175	3.931	3.900 ± 0.017	3.95 ± 0.31	-1.15 ± 0.62	11.47	0.0183	3.932	0.0189	4.022	0.0190	3.966	0.0217	4.026	0.0228	3.970	0.0229	4.015	0.1221	4.356	0.3169	5.041	0.5163	5.632	55.00	0.0212	6.96	6.78	(9.2)		11.07	0.0233	7.00	65.00	0.0215	11.57	11.2 ± 0.20	21.1 ± 0.8		11.4	0.0232	11.71	0.1239	13.78	75.00	0.0274	19.14	18.2	(41.8)		11.6	0.0309	19.68	85.00	0.0271	31.2	29.1 ± 2.2	59 ± 9			0.0325	30.5	0.1277	36.7				
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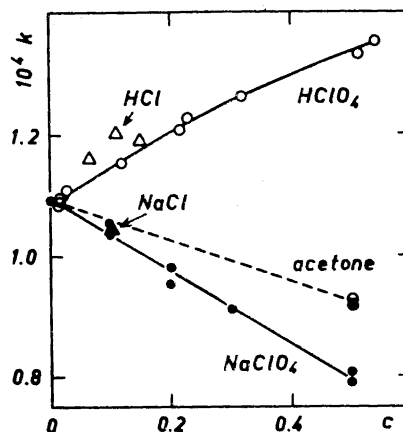


Fig. 1. The influence of acids (HClO_4 and HCl , \bar{k}_t versus \bar{c}_t), salts (NaClO_4 and NaCl , \bar{k}_t versus \bar{c}_{salt} , $c_t = 0.0180$ mole/l), and acetone (\bar{k}_t versus c_{acetone} , $c_t = 0.0200$ mole/l) on the rate of hydrolysis of chloromethyl chloroacetate in water at 25°C .

In those cases where only determinations without acid present initially were performed the values of k_o given in Table 1 were obtained by linear extrapolation from the experimental data using for k_{HX} the values (given in parentheses in Table 1) calculated by the aid of the Arrhenius equation.

The hydrogen-ion catalysed hydrolysis of chloromethyl chloroacetate will be discussed in a subsequent paper.

From Fig. 2 it is seen that $\log k_o$ is not a linear function of $1/T$. Values of the Arrhenius activation energy E_o for the neutral hydrolysis were calculated for ten-degree intervals and are shown in Table 1. Because E_o is clearly temperature-dependent the equation (cf. Ref.⁶)

$$\log k_o = \frac{A}{T} + B \log T + C \quad (2)$$

was fitted to the values of k_o for the temperature range from 5°C to 65°C by the method of least squares. The values of the parameters were found to be $A = -5179.9 \pm 124$, $B = -19.010 \pm 0.93$, and $C = 60.4466 \pm 2.54$.

The dependence of the rate on the concentration of sodium perchlorate (Table 2 and Fig. 1) is approximately linear at relatively low concentrations. The values of the coefficients k_o and k_{NaClO_4} in equation

$$k_t = k_o + k_{\text{NaClO}_4} c_{\text{NaClO}_4} \quad (3)$$

which were derived by the method of least squares for certain hydrogen-ion concentrations \bar{c}_t are given in Table 2. Potassium perchlorate and sodium perchlorate have a similar influence on the rate.

Hydrogen chloride and sodium chloride have approximately the same effect on the rate as perchloric acid and sodium perchlorate, respectively, although the method employed does not give accurate results for solutions of high chloride-ion concentration. This result shows that the nucleophilic displacement of the chlorine atom of the chloromethyl group by a perchlorate anion, which is included in the measured values, is insignificant.

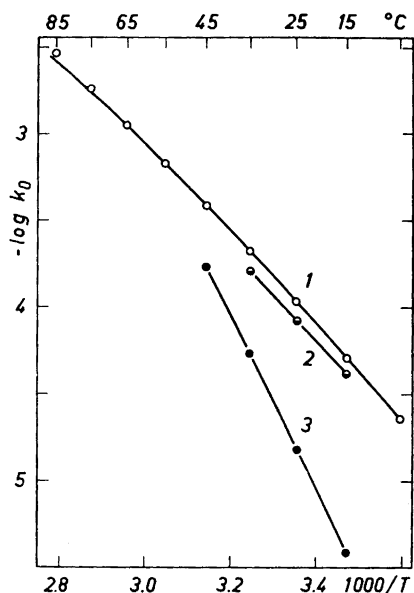


Fig. 2. Plots of $\log k_0$ versus $1/T$ for the neutral hydrolysis of chloromethyl chloroacetate (1), chloromethyl formate (2), and chloromethyl acetate (3) in water. The curves plot eqn. (2).

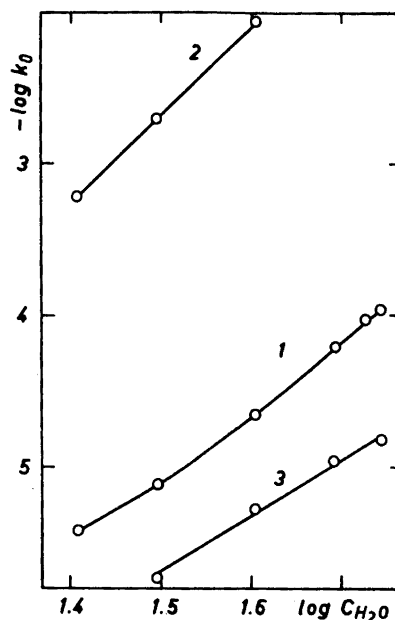


Fig. 3. Plots of $\log k_0$ versus $\log c_{H_2O}$ (the molar concentration of water in the solvent mixture) for the neutral hydrolysis of chloromethyl chloroacetate (1), α -chloroethyl acetate (2), and chloromethyl acetate (3) in acetone-water mixtures at 25°C.

The effect of added acetone (Table 2) is shown in Fig. 3 where $\log k_i$ (for $c_i = 0.0200$ mole/l) is plotted against $\log c_{H_2O}$. The resulting curve is concave upwards, the slope decreasing from the value 5.0 in water to the value 3.5 in 50% acetone-water. For comparison, the corresponding plots for chloromethyl acetate¹ (nucleophilic substitution by the S_N2 mechanism; slope 3.3) and for α -chloroethyl acetate¹ (solvolysis by the S_N1 mechanism; slope 5.9) are included in the figure.

DISCUSSION

The temperature dependence of the rate of hydrolysis. The low value of the activation energy E_0 (Table 1) shows that the reaction of chloromethyl chloroacetate is a neutral ester hydrolysis. The value of E_0 is close to that for chloromethyl formate (12.03 kcal/mole), the hydrolysis of which has been found to take place by the mechanism mentioned¹. It clearly differs from the values of E_0 for the reactions of, e.g., chloromethyl acetate (23.30 kcal/mole) and α -chloroethyl acetate (18.6 kcal/mole for the reaction in 40% acetone-water), which reactions take place as nucleophilic substitutions by the mechanisms S_N2 and S_N1 , respectively¹.

Table 2. Kinetic data for the hydrolysis of chloromethyl chloroacetate in aqueous solutions containing electrolytes or acetone.

Solute	Temperature °C	Conc. of solute mole/l	Experimental		Interpolated		$10^4 k_0$ s ⁻¹	$10^4 k_{\text{NaClO}_4}$ l mole ⁻¹ s ⁻¹
			c_t mole/l	$10^4 k_t$ s ⁻¹	c_t mole/l	$10^4 k_t$ s ⁻¹		
NaClO ₄	15.00	0.2	0.0185	0.462				
		0			0.0180	1.094		
	25.00	0.1	0.0171	1.033	0.0180	1.034		
			0.0190	1.053	0.0180	1.052		
		0.2	0.0167	0.977	0.0180	0.978	1.095	-0.602
			0.0171	0.953	0.0180	0.954	±0.012	±0.025
		0.3	0.0188	0.912	0.0180	0.911		
		0.5	0.0175	0.805	0.0180	0.805		
	35.00	0	0.0177	0.789	0.0180	0.789		
					0.0200	2.158		
		0.3	0.0209	1.861	0.0200	1.859	2.154	-0.948
	45.00	0.5	0.0202	1.686	0.0200	1.686	±0.018	±0.035
		0			0.0200	3.979		
		0.3	0.0216	3.353	0.0200	3.347	3.974	-2.05
0.5		0.0200	2.957	0.0200	2.957	±0.021	±0.05	
KClO ₄	25.00	0.1	0.0157	1.052	0.0180	1.054		
NaCl	25.00	0.1	0.0173	1.045	0.0180	1.045		
HCl	25.00	0.05	0.0635	1.161				
		0.10	0.1084	1.204				
		0.15	0.1470	1.192				
Acetone	25.00	0			0.0200	1.095		
		0.500	0.0201	0.925	0.0200	0.925		
			0.0256	0.921	0.0200	0.917		
		1.696	0.0190	0.606	0.0200	0.607		
		4.153	0.0166	0.217	0.0200	0.219		
		6.473	0.0193	0.075	0.0200	0.075		
		7.938	0.0209	0.039	0.0200	0.039		

The data do not obey the Arrhenius equation, but the values of k_0 for the temperature interval from 5°C to 65°C satisfy the more general eqn. (2) given in the preceding section. The rate coefficients for 75°C and 85°C are higher than eqn. (2) implies (Fig. 2), but because the experimental accuracy is low at these temperatures it is not possible to decide whether the difference is real. It would not, however, be unexpected to find that the activation energy increases at higher temperatures because the nucleophilic displacement of the chlorine atom of the chloromethyl group then begins to take place alongside the ester hydrolysis. The former reaction probably has an activation energy about ten kilocalories per mole higher than neutral ester hydrolysis (see preceding paragraph). The rate of the neutral hydrolysis in water at 25°C is only slightly lower for chloromethyl acetate¹ ($0.153 \times 10^{-4} \text{ s}^{-1}$) than for chloromethyl chloroacetate ($1.08 \times 10^{-4} \text{ s}^{-1}$) and the distant chlorine substituent in the acyl group can have no large effect on the rate of the S_N2 reaction.

According to the theory of absolute reaction rates, the heat capacity (ΔC_p^\ddagger), the heat (ΔH^\ddagger), and the entropy (ΔS^\ddagger) of activation are given by the equations (cf. Refs.^{7,8})

$$\Delta C_p^\ddagger = R(B - 1) \quad (4)$$

$$\Delta H^\ddagger = -RA \ln 10 + R(B - 1) T \quad (5)$$

$$\Delta S^\ddagger = R \left(\ln \frac{h}{k} + B - 1 + C \ln 10 \right) + R(B - 1) \ln T \quad (6)$$

where A , B , and C are the parameters of eqn. (2), R the gas constant, h Planck's constant, and k Boltzmann's constant. The values of the thermodynamic functions of activation for some compounds that hydrolyse by the mechanism of neutral ester hydrolysis ($B_{AC}2$) and, for comparison, for a few other compounds that solvolyse in water are given in Table 3 together with other kinetic data.

The data in Table 3 show that the values of the thermodynamic functions of activation, ΔC_p^\ddagger included, are of closely the same magnitude for both chloromethyl chloroacetate and chloromethyl formate, which react by the same mechanism. No data are available on the neutral hydrolysis of other carboxylic esters that would permit any conclusions about the temperature dependence of the activation energy. The rate data for the hydrolysis of esters catalysed by hydrogen ion¹⁶ and hydroxide ion¹⁷ have not been found to deviate from the Arrhenius equation. The values of ΔC_p^\ddagger (Table 3) derived for the solvolysis of esters of strong acids have generally been negative. A recalculation of the data for the displacement of chlorine in chloromethyl acetate¹ also yielded a negative value of ΔC_p^\ddagger (Table 3). The values of ΔC_p^\ddagger are approximately equal in all these solvolyses, evidently because ions are produced in the reactions¹². The values are also approximately equal to the values of ΔC_p in the ionisation of weak acids¹⁸. The reason has been assumed to be the different degrees of solvation of the initial and the transition states. As the value of ΔC_p for the freezing of water is -9.0 cal mole⁻¹ degree⁻¹, the values of ΔC_p^\ddagger for solvolytic reactions correspond to a "freezing" of 3 to 7 additional water molecules in the formation of the transition state (*cf.* Ref.¹⁵).

Medium effects. Palomaa, Salmi, and Korte¹⁹ already observed that dioxan lowers the rate of neutral hydrolysis of methyl trichloroacetate much more than the rates of catalysed ester hydrolyses. Ethanol was found by Jencks and Carriuolo¹⁰ to slow down the neutral hydrolysis of ethyl difluoroacetate greatly. Acetone decelerates the neutral hydrolysis of chloromethyl chloroacetate (Table 2 and Fig. 3) almost as much as it decelerates the solvolysis of α -chloroethyl acetate by the S_N1 mechanism.

Neutral salts also retard the rate of neutral hydrolysis of chloromethyl chloroacetate (Table 2); this retardation seems to be independent of the nature of the anion and is larger than the variable effects of neutral salts on the solvolyses of chloromethyl and α -chloroethyl acetates¹ (which effects are of opposite sign in many cases). A similar salt effect was noted by Jencks and Carriuolo¹⁰ in the neutral hydrolysis of ethyl difluoroacetate.

The neutral hydrolysis of esters proceeds at a much lower rate in deuterium oxide than in water (Table 3) according to the data of Jencks and Carriuolo¹⁰ and preliminary data collected by the present writers⁹.

Table 3. The thermodynamic parameters and other kinetic data for neutral solvolyses
 $RX + H_2O = ROH + HX$ in water at 25°C.

R	X	$10^3 k_0$ s ⁻¹	ΔH^\ddagger kcal/mole	ΔS^\ddagger E.U.	ΔC_p^\ddagger cal/mole degree	k_{H_2O}/k_{D_2O}	k_{OH}/k_{H_2O}	Supposed mechanism	Ref.
CH ₂ ClCO	OCH ₂ Cl	10.82	11.8	-37	-39.8 ± 1.8	3.5 ^a	1.2 × 10 ^{9b}	B _{AC} 2	1
HCO	OCH ₂ Cl	8.5	11.4 ^c	-39 ^c	-40.2 ^c		1.4 × 10 ^{9b}	B _{AC} 2	10
CHF ₂ CO	OC ₂ H ₅	5.7				2.1	4.4 × 10 ⁹	B _{AC} 2	10
CHCl ₂ CO	OC ₂ H ₅	0.50				5	10 × 10 ⁹	B _{AC} 2	10
CH ₂ ClCO	OC ₂ H ₅	0.011					19 × 10 ⁹	B _{AC} 2	10
CH ₃ COOCH ₂	Cl	1.53	22.8 ^c	-4 ^c	-62.4 ± 3.4 ^c		2.4 × 10 ^{7b}	S _N 2, I	1
CH ₃	Cl	0.00235	26.56	-4.3	-52.0	1.28	8600 ^d	S _N 2	8
CH ₃	OSO ₂ C ₆ H ₅	1.166	21.42	-9.3	-33.4 ± 1.1	1.10 ^e	2800 ^e	S _N 2, I	7
(CH ₃) ₂ CH	OSO ₂ C ₆ H ₅	26.27	21.81	-1.8	-41.2 ± 0.5		0	S _N 1	7
(CH ₃) ₃ C	Cl	3030	21.94 ^f	8.3 ^f	-45 ^f		0	S _N 1	15

^a According to preliminary experiments of the present authors.⁹

^b The rate coefficient of the alkaline hydrolysis, see Ref.²

^c The thermodynamic parameters have been recalculated from the earlier data¹ at three or four temperatures.

^d At 100°C according to Fells and Moelwyn-Hughes¹¹.

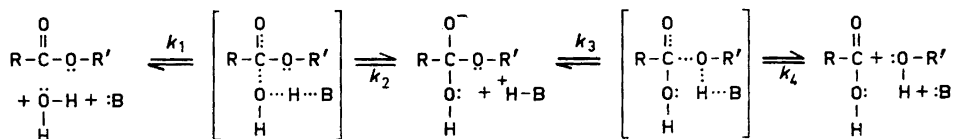
^e According to Robertson.¹²

^f At 50°C according to Robertson *et al.*,¹³ the data of Biorci and Moelwyn-Hughes¹⁴ for the methanolysis in methanol yield the value -45.5 cal mole⁻¹ degree⁻¹ for ΔC_p^\ddagger at 25°C.

Base catalysis. The hydroxide ion strongly catalyses the hydrolysis of esters as shown by the values of the ratio $k_{\text{OH}}/k_{\text{H}_2\text{O}}$ (Table 3), where k_{OH} and $k_{\text{H}_2\text{O}}$ ($= k_0/c_{\text{H}_2\text{O}}$) are the second-order rate coefficients of the alkaline and neutral hydrolyses, respectively. The exceptional value of this ratio for chloromethyl acetate is due to the change in mechanism from the nucleophilic displacement of chlorine in neutral water to alkaline ester hydrolysis. The values of this ratio are essentially smaller for bimolecular nucleophilic substitution reactions and zero for unimolecular solvolyses.

The hydrolysis of alkyl halogenoacetates¹⁰ and chloromethyl chloroacetate⁹ has been found to be subject to general base catalysis. The rate of the neutral hydrolysis is what would be expected from the base strength of water and the catalytic effect of other weak bases according to Brönsted catalysis law. The catalysis by hydroxide ion is, however, much stronger than expected from its base strength. On the other hand, the acceleration of the hydrolysis reactions of phenyl esters by weak bases has been shown to be due to nucleophilic, rather than general base catalysis²⁰.

Reaction mechanism. The neutral and general base-catalysed hydrolysis reactions of chloromethyl chloroacetate and chloromethyl formate are typical examples of similar reactions of esters with electronegative substituents. Other esters reacting by this mechanism are alkyl halogenoacetates. The data reported previously (see references in Refs.^{1,10}) and presented here are in accord with the following reaction mechanism (*cf.* Refs.^{10,20,27}), which is the $B_{\text{AC}}2$ mechanism of alkaline ester hydrolysis so modified that the attacking species is a water molecule rather than hydroxide ion. The addition of the water molecule to the carbonyl group is catalysed by a base B, which is a second water molecule in the neutral hydrolysis.



Bunton and Hadwick²¹ have shown that the neutral hydrolysis of methyl trifluoroacetate takes place by acyl-oxygen fission. In contrast to the case in base- and acid-catalysed ester hydrolyses²², the formation of a tetrahedral intermediate in neutral ester hydrolysis has not been confirmed by oxygen isotope exchange experiments but this is highly probable since sodium methoxide adds to the carbonyl group of ethyl fluoroacetates and the effect of successive substitution by fluorine in ethyl acetate displaces the position of equilibrium toward the addition compound²³. It is not possible by kinetic measurements to determine how the catalysing base B participates in the reaction¹⁰. There also may be a variety of pre-equilibria (*cf.* Ref.²⁰). For example, Butler and Gold²⁴ have proposed a mechanism for the base-catalysed hydrolysis of substituted phenyl acetates, in which the hydroxyl group of a water molecule adds to the carbonyl group of the ester in a rapid initial stage leading to a pre-equilibrium and the resulting negative ion reacts with the conjugate acid BH^+ of the catalysing base in the rate-determining stage.

The observed similarities between neutral and alkaline ester hydrolyses (*e.g.* the low activation energies and similar substituent effects) are explained by the proposed mechanism because it is only an extension of the generally accepted mechanism of alkaline ester hydrolysis. The low value of the activation entropy may be ascribed to the increase in order when the reactants pass from the initial state to the transition state (shown in brackets), which is evidently closely similar to the proposed intermediate in structure. The associated separation of charges is in agreement with the negative value of ΔC_p^\ddagger and explains also the strong solvent effect, which, on the other hand, is partly connected with the participation of at least two molecules of water in the formation of the transition state. The retarding effect of neutral salts may be explained, as Jencks and Carriuolo¹⁰ do, "in terms of a requirement for several moles of available water, which must be properly oriented in the polar transition state". The fact that the catalysis by the hydroxide ion is stronger than its base strength would imply in terms of the Brønsted catalysis law⁹ is readily understandable because the hydroxide ion can add to the carbonyl group directly and does not only promote the addition of water to this group as other bases do according to the proposed mechanism.

The mechanism leads to the expression $k = k_1/(1 + k_2/k_3)$ for the experimental rate coefficient. The rate is thus determined by both the rate coefficient k_1 of addition and the partitioning ratio k_2/k_3 , although the last two rate coefficients may be much larger than the first²⁰. A second chlorine atom has a greater accelerating effect on the rate of neutral ester hydrolysis when it is introduced into the alkyl than into the acyl group of methyl chloroacetate (Table 3 and Table 45 in Ref.¹). A possible explanation is that although the electronegative chlorine probably increases the value of k_1 less when it is a substituent of the alkyl group which is more distant from the reaction centre than the acyl group, it then decreases the ratio k_2/k_3 and increases k also that way. On the other hand, when the chlorine is a substituent of the acyl group the last-mentioned influence is just the opposite²⁰. The ratio k_2/k_3 , however, affects k appreciably only if it is not much smaller than unity; such a value of the ratio is not at variance with the results of oxygen isotope exchange experiments^{25,26}.

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