

Comparison of Structural Effects in the Hydrolysis of Carboxylic Acid Ortho-esters

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Structural effects in the hydrolysis of carboxylic acid ortho-esters have been discussed in only a few papers.^{1,2} The effect of the alcohol component in formic and benzoic acid esters has been recently investigated,^{3,4} but no systematic study has been made of the effect of the acid component. In contrast to the hydrolysis of the related acetals,^{1,5} it can be inferred from the few kinetic values available^{1,2,6} that the effect of the alkyl or aryl substituent at the reaction centre is relatively small. Thus, ethyl orthoacetate is hydrolyzed only 40 times faster than the corresponding orthoformate whereas, surprisingly, a similar substitution in acetals increases the rate by a factor of about 10^3 .⁵ However, it should be noted that with ethyl ortho-esters the mechanism of hydrolysis changes when the acid component is altered: ethyl orthoformate³ and ethyl orthobenzoate⁴ are hydrolyzed through a pre-equilibrium protonation (*A-1* mechanism), while the hydrolysis of the orthoacetates and orthopropionates involves a rate-determining proton transfer (*A-S_E2* mechanism).⁶

These complications are avoided with a series of compounds in which the hydrolysis mechanism does not change with the acid component. Diethyl 2,2,2-trichloroethyl derivatives were expected to be suitable model compounds, as it could be concluded^{7,8} that the hydrolysis proceeds exclusively with trichloroethoxy as the leaving group. Furthermore, the *A-S_E2* mechanism is greatly favoured here owing to the low basicity of the protonation site and the high stability of the diethoxy carbonium ion formed.

Materials. Two alternative methods were used in the preparation of the unsymmetrical ortho-esters. In most cases the ortho-ester was synthesized from the corresponding triethyl ortho-ester through acid-catalyzed transesterification. The most volatile component, ethanol, was distilled off from an equimolar mixture of the symmetrical ortho-ester and 2,2,2-trichloroethanol. A small amount of *p*-toluenesulfonic acid was present as catalyst. It has been shown previously⁸ that under mild con-

ditions only one of the ethoxy groups is replaced. Formation of more chlorinated derivatives is rendered difficult by the low stability of the dialkoxy-carbonium ions with one or two trichloroethoxy groups.

In the preparation of the monochloroacetic acid and dichloroacetic acid derivatives an alternative method was applied; a ketene acetal was alcoholized with trichloroethanol using *p*-toluenesulfonic acid as the catalyst. After neutralization the product was purified by distillation. Symmetrical products were not formed.

Diethyl 2,2,2-trichloroethyl orthopropionate was prepared from ethyl orthopropionate (Fluka) and 2,2,2-trichloroethanol (Fluka). After transesterification the reaction mixture was neutralized with sodium ethoxide and fractionally distilled. B.p. 106–109°C/7 torr. NMR spectrum: 3H at δ 0.96 ppm (CH₃), 6H at δ 1.22 ppm (CH₃), 2H at δ 1.77 ppm (CH₂), 4H at δ 3.70 ppm (CH₂) and 2H at δ 4.16 ppm (CH₂). Other signals were not observed.

Diethyl 2,2,2-trichloroethyl orthoacetate was synthesized from triethyl orthoacetate and trichloroethanol. B.p. 107–108°C/10 torr. NMR spectrum: 6H at δ 1.20 ppm (CH₃), 3H at δ 1.45 ppm (CH₃), 4H at δ 3.65 ppm (CH₂) and 2H at δ 4.10 ppm (CH₂).

In the preparation of diethyl 2,2,2-trichloroethyl orthoformate, triethyl orthoformate (E. Merck) and trichloroethanol were used as the substrates. B.p. 92–96°C/6 torr. NMR spectrum: 6H at δ 1.25 ppm (CH₃), 4H at δ 3.74 ppm (CH₂), 2H at δ 4.20 ppm (CH₂) and 1H at δ 5.42 ppm (CH). Other signals were not observed.

Diethyl 2,2,2-trichloroethyl orthobenzoate was prepared by transesterification from triethyl orthobenzoate (Fluka) and trichloroethanol. B.p. 154–160°C/10 torr. NMR spectrum: 6H at δ 1.18 ppm (CH₃), 4H at δ 3.47 ppm (CH₂), 2H at δ 4.02 ppm (CH₂) and 5H at δ 7.53 ppm (aromatic).

1-Chloro-2,2-diethoxyethene was prepared by refluxing 1,1-dichloro-2,2-diethoxyethane (The British Drug Houses Ltd) with potassium *t*-butoxide in *t*-butanol.⁹ After the potassium chloride had been filtered off, the solvent and the ketene acetal were separated by distillation. The ketene acetal was alcoholized with 2,2,2-trichloroethanol and the product, diethyl 2,2,2-trichloroethyl monochloro-orthoacetate, was further purified. B.p. 113–114°C/5 torr. NMR spectrum: 6H at δ 1.26 ppm (CH₃), 6H at δ 3.49–3.98 ppm (CH₂) and 2H at δ 4.33 ppm (CH₂).

1,1,1-Trichloro-2,2-diethoxyethane was prepared from trichloroacetaldehyde and ethanol

using a large excess of concentrated sulfuric acid as the catalyst.⁹ B.p. 88–89°C/11 torr. The corresponding ketene acetal was prepared from this acetal by refluxing with potassium *t*-butoxide.⁹ The ketene acetal obtained was alcoholized with trichloroethanol to give diethyl 2,2,2-trichloroethyl dichloro-orthoacetate. B.p. 94°C/10 torr. NMR spectrum: 6 H at δ 1.24 ppm (CH₃), 4 H at δ 3.75 ppm (CH₂), 2 H at δ 4.28 ppm (CH₂) and 1 H at δ 5.63 ppm (CH). Other signals were not observed.

Kinetic measurements. Most of the kinetic measurements were made in 65/35 w/w dioxane-water mixtures. Dioxane (E. Merck AG) was purified by standard methods.¹⁰ The heavy water used was a product of Norsk Hydro-Elektrisk Kvaestofaktieselskap. The concentration of the catalyst, perchloric acid, varied between 10⁻⁴ and 10⁻² M. However, in the case of diethyl 2,2,2-trichloroethyl dichloro-orthoacetate higher acid concentrations (up to 0.2 M) were necessary owing to the slowness of the reaction. In these solutions the rate was not strictly proportional to the acid concentration, and so the results obtained at different concentrations were extrapolated to infinite dilution.

An equimolar solution of dichloroacetic acid and sodium dichloroacetate was used in the buffer experiments. A constant ionic strength was maintained with sodium chloride. In these experiments a mixture of dimethyl sulfoxide and water (2/1 v/v) was used as the solvent.

The hydrolysis of the ortho-esters was followed spectrophotometrically from the

Table 2. The hydrolysis of diethyl 2,2,2-trichloroethyl orthobenzoate in dichloroacetic acid-sodium dichloroacetate buffer (molar ratio 1/1) in 2/1 v/v dimethyl sulfoxide-water mixture at 25°C. The ionic strength was maintained at 0.1 M with sodium chloride.

[Cl ₂ CHCOOH] (M)	10 ³ <i>k</i> (s ⁻¹)	<i>k</i> _{HA} (M ⁻¹ s ⁻¹)
0.100	1.741	
0.0667	1.400	
0.0333	1.032	0.0106 ± 0.0020

appearance of the carboxylic acid ester at wavelengths between 230 and 240 nm. In the case of the benzoic acid derivative the wavelength was 270 nm. The initial concentration of the ortho-ester was usually 0.005 to 0.01 M. In the case of the benzoic acid derivative the concentration of the substrate was less, 0.001 M. Replicate determinations were made in each case.

The kinetic data collected in Tables 1 and 2 are consistent with the *A*-S_E2 mechanism. Firstly, the magnitudes of the solvent deuterium isotope effects, *k*_{D₂O}/*k*_{H₂O} = 0.98–1.83, are those observed previously for this mechanism in the hydrolysis of ortho-esters.³ In the hydrolysis of related compounds, acetals, *k*_{D₂O}/*k*_{H₂O} values lower than two have also been obtained for the rate-determining proton transfer mechanism.¹¹

Secondly, the general acid catalysis observed for the hydrolysis of the benzoic acid derivative (Table 2) shows directly that, at least in this case, the proton transfer is the rate-determining stage of the reaction. Unfortunately, only in the hydrolysis of this particular compound could the involvement of general acid catalysis be studied directly. The compounds were too sparingly soluble in water and thus necessitated the use of organic solvents. Dioxane-water mixtures could not, however, be used in the buffer experiments because of the specific salt effects, which are very significant in this solvent system.^{12,13} These difficulties are avoided in dimethyl sulfoxide-water mixtures.¹⁴ Unfortunately, this solvent system has an absorption maximum in the UV region and therefore only wavelengths higher than 250 nm can be used. Thus, the only hydrolysis which could be followed spectro-

Table 1. The hydronium ion-catalyzed hydrolysis of unsymmetrical ortho-esters RC(OEt)₂ (OCH₂CCl₃) in 65/35 w/w dioxane-water mixtures. Temperature 25°C.

R	L ₂ O	<i>k</i> (M ⁻¹ s ⁻¹)	<i>k</i> _{D₂O} / <i>k</i> _{H₂O}
CH ₂ CH ₂	H ₂ O	65.2	
	D ₂ O	75.5	1.16
CH ₃	H ₂ O	81.8	
	D ₂ O	103.1	1.26
H	H ₂ O	10.15	
	D ₂ O	9.92	0.98
Phenyl	H ₂ O	0.343	
	D ₂ O	0.425	1.24
ClCH ₂	H ₂ O	0.982	
	D ₂ O	1.058	1.08
Cl ₂ CH	H ₂ O	0.0026	
	D ₂ O	0.0047	1.83

photometrically was that of the benzoic acid derivative. A direct detection of general catalysis is, however, unnecessary for the hydrolysis of the remaining ortho-esters because of the structural effects. The site of protonation is the same for all the compounds studied, and thus the variation in the rates is due solely to differences in the dialkoxy-carbonium ion stabilities. Excepting the dichloroacetic acid derivative, the ortho-esters studied are more susceptible to acid-catalyzed hydrolysis than the benzoic acid derivative, and therefore the rate-determining proton transfer is even more favoured than in the hydrolysis of the orthobenzoate.

As discussed above, considerable structural variations in series of diethyl trichloroethyl ortho-esters do not effect a change in the mechanism. Direct information on the effect of the acid component

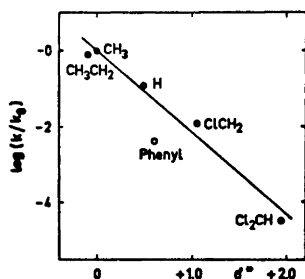


Fig. 1. Plot of $\log k$ against polar substituent constants for the hydrolysis of ortho-esters of the type $RC(OEt)_2(OCH_2CCl_2)$.

can thus be obtained. In Fig. 1 the logarithms of the rate coefficients are plotted against the polar substituent constants¹⁵ of the atoms or groups attached to the central carbon atom. Excepting the phenyl-substituted derivative, the correlation is seen to be fairly linear. The slope of this plot (δ^* -value) is -2.2 ± 0.2 . In addition to the inductive effects, the resonance effects cannot be wholly excluded. However, differences in the latter must be negligible for the substituents CH_3CH_2 , CH_3 , H, $ClCH_2$, and Cl_2CH . This being so, the structural effect in the hydrolysis of ortho-esters cannot be considered exceptional. The only difference from the hydrolysis of acetals is the diminished influence of structural effects. This is shown by the δ^* -value, -2.2 , which is markedly less than

the -3.8 observed for the hydrolysis of acetals.¹⁶

The rate coefficient for the hydrolysis of the benzoic acid derivative seems to be exceptionally low (Fig. 1). If only inductive polar effects were operating, a rate coefficient higher by a factor of ten would be expected. The actual rate is even more abnormal than can be seen from the plot of $\log k$ against σ^* since for this compound the resonance effects in the transition state should also be significant. Additional, more detailed information is needed before firm conclusions can be drawn.

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