Reactions of carbonyl compounds in basic solutions. Part 33.[1] Effect of 2-trichloro- and tribromoacetyl substituents on the alkaline hydrolysis of methyl benzoate, as well as the hydrolysis of the corresponding benzoate anions and ionisation/ring–chain tautomerism of the corresponding acids

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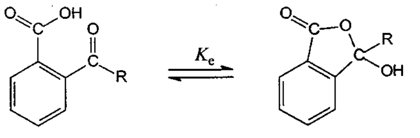
Received (in Cambridge) 23rd September 1998, Accepted 27th October 1998

Rate coefficients have been measured for the alkaline hydrolysis of methyl 2-trichloro- and tribromoacetylbenzoate, as well as the alkaline hydrolysis of the corresponding 2-trichloro- and tribromobenzoate anions, in 30% (v/v) dioxane–water at several temperatures. The relative rates of hydrolysis and activation parameters demonstrate relatively rapid hydrolysis *via* neighbouring group participation by the acyl-carbonyl group in the ester hydrolysis and slower hydrolysis *via* intramolecular fission of the adducts in the benzoate anion hydrolysis. The pK_a values of the corresponding benzoic acids have been measured in water and their ring–chain tautomeric equilibrium constants determined.

Reviews[2] of neighbouring group participation by proximate carbonyl groups in the alkaline hydrolysis of esters have been made recently. In these, criteria have been established for this type of intramolecular catalysis and further model systems have been studied.[3] Based on these investigations,[2,3] a series of studies of the synthesis and hydrolysis of reactive esters of aspirin and related anti-inflammatory drugs[4] and of metronidazole[5] as prodrugs have been made.

2-Trihaloacetylbenzoate esters can hydrolyse, in principle, in two ways. The first is by hydrolysis of the ester.[3] The second is by hydrolysis of the trihaloacetyl group itself. The latter can also occur for the product of ester hydrolysis, the 2-trihaloacetylbenzoic acid.[6]

Ring–chain tautomerism has been shown to occur in a number of 2-acetylbenzoic acids,[7,8] as shown in eqn. (1).



(1)

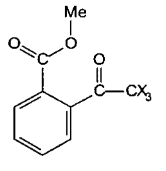
The equilibrium constant, K_e for the tautomeric equilibrium (1) is given by eqn. (2). A number of methods, *e.g.* IR, UV and ^{1}H NMR

$$K_e = a_{ring}/a_{chain} \qquad (2)$$

spectroscopy, can be used to make quantitative studies of these equilibria. However, if one of the tautomeric forms is predominant, it is difficult to use any of these methods. If the predominant form is relatively much less acidic than the other, it is possible to use measurement of pK_a values to estimate K_e. Thus, the true pK_a value, pK_a^T, is related to the observed value by the relation (3).[9] If the pK_a is known and a reliable estimate of the pK_a^T can be made, K_e can be calculated.

$$pK_a^T = pK_a - \log (K_e + 1) \qquad (3)$$

We describe here the preparation and alkaline hydrolysis of methyl 2-trichloro- and tribromoacetylbenzoates, **1a**,**b**, together with the alkaline hydrolysis of the corresponding benzoate anions and the ionisation of the corresponding benzoic acids. The latter measurements have been used to determine the equilibrium constants for the ring–chain tautomerism of the corresponding acids. The hydrolysis studies will serve as model systems for the hydrolysis of further reactive esters of metronidazole[10] as prodrugs.



1a X = Br
b X = Cl
c X = F

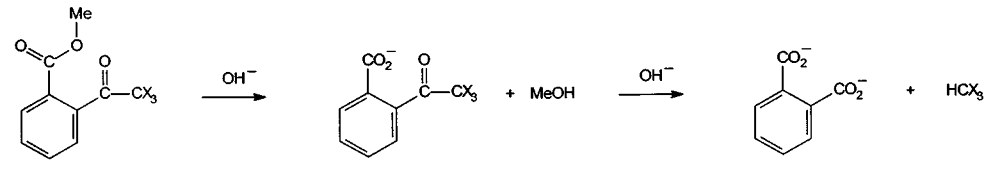
Results and discussion

Both the methyl esters **1a**,**b** suffer relatively rapid alkaline hydrolysis to the corresponding anions of the carboxylic acids. The latter react more slowly to the final products of hydrolysis. Thus, the hydrolysis of the 2-trihaloacetylbenzoate anions results in cleavage resulting in the formation of the trihaloform and the anion of phthalic acid.[11] This is shown in reaction (4) below.

The alkaline hydrolysis of the esters

The alkaline hydrolysis of the methyl esters is of first-order both in ester and hydroxide anion. Rate coefficients for the alkaline hydrolysis of the methyl 2-trihaloacetylbenzoates are shown in Table 1. The activation parameters are shown in Table 2.

The rates of hydrolysis of both esters are relatively rapid. The rate ratios of the esters to that of methyl benzoate (k_2 at 30 °C in 30% (v/v) dioxane–water equals 0.0328 dm^3 mol^{-1} s^{-1})[12] can be calculated to give the values shown in Table 3. The expected rate ratios for "normal" hydrolysis are also shown and are those estimated from the known polar and steric effects of



1a, b **2a, b** **3** (4)

Table 1 Rate coefficients (k_2) for the alkaline hydrolysis of methyl 2-trihaloacetylbenzoates and the corresponding benzoate anions in 30% (v/v) dioxane–water[a]

	k_2/dm^3 mol^{-1} s^{-1}				
2-Substituent	T/°C 30.0	40.0	50.0	60.0	λ/nm[b]
Methyl benzoate					
COCBr$_3$	13.4$_5$	22.5	33.6$_5$	54.4$_5$	280
COCCl$_3$	49.9	61.6	(37.3)[c]	(83.4)[d]	277
Benzoate anion					
COCBr$_3$	0.118	0.216	0.396	0.658	280
COCCl$_3$	0.468	0.866	1.39	2.37$_5$	277

[a] Rate coefficients were reproducible to ±3%. [b] Wavelength used to monitor alkaline hydrolysis. [c] At 25.0 °C. [d] At 45.0 °C.

Table 2 Activation parameters for the alkaline hydrolysis of methyl 2-trihaloacetylbenzoates and the corresponding benzoate anions in 30% (v/v) dioxane–water at 30 °C[a]

2-Substituent	$\Delta H^\ddagger$/kcal mol^{-1}[b]	$\Delta S^\ddagger$/cal mol^{-1} K^{-1}[b]
Methyl benzoate		
COCBr$_3$	8.6	−25
COCCl$_3$	6.3 (±1.0)	−30 (±3)
Benzoate anion		
COCBr$_3$	11.0	−27
COCCl$_3$	10.1	−27

[a] Values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are considered accurate to within ±300 cal mol^{-1} and ±1 cal mol^{-1} K^{-1}, respectively, except where shown in parentheses. [b] 1 cal = 4.184 J.

Table 3 Relative rate ratios of the alkaline hydrolysis of the methyl esters at 30 °C

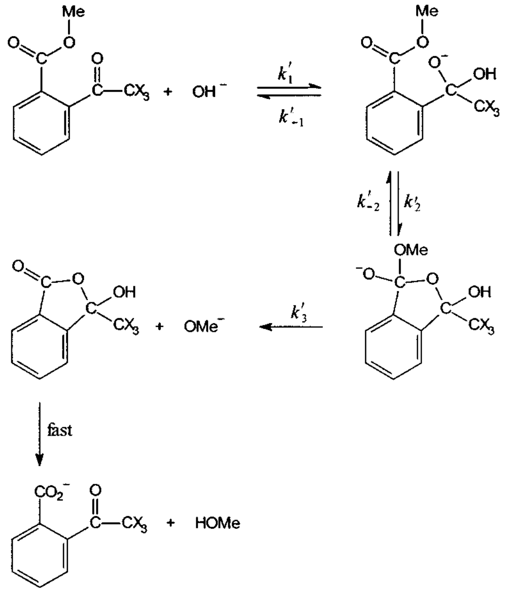
	k/k_o		
Ester	Observed	Expected for "normal" hydrolysis	Enhanced, r_e
1a	410	1.0	410
1b	1520	2.0	760
[**1c**	7270	5.0	1500][a]

[a] Lit.[3b] values in water.

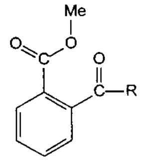
ortho-substituents on the alkaline hydrolysis of methyl and ethyl benzoates[13] together with the *para*-σ values of related acyl groups.[14] In both cases, rate enhancements, r_e, shown in Table 3, are *very* large, indicating the occurrence of intramolecular catalysis.[2] A mechanistic pathway for the alkaline hydrolysis of the methyl 2-acylbenzoates is shown in Scheme 1. The correlation of the rates of the alkaline hydrolysis of esters **4** in 70% (v/v) dioxane–water at 20 °C using σ^* and E_s for R[15] is shown in eqn. (5) below. The σ^* and E_s values for CBr$_3$ and CCl$_3$[14] are 2.43, −2.43 and 2.65, −2.06, respectively.

$$\log (k/k_o) = 1.30\,\sigma^* + 1.08\,E_s \qquad (5)$$

This predicts a faster rate for **1b** than **1a** by a factor of *ca.* five in 70% aqueous dioxane at 20 °C and compares well with the factor of *ca.* four observed in 30% aqueous dioxane at 30 °C. The faster rate of the trichloro substrate, compared to that of the tribromo substrate, arises mainly from the decreased steric bulk of the trichloromethyl group which favours formation of the adduct.



Scheme 1



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For the alkaline hydrolysis of the more reactive methyl esters employing neighbouring group participation by carbonyl groups, the enthalpies of activation are exceptionally small and are associated with rather large negative entropies of activation.[2a,3] As shown in Table 2, this is true for both the esters **1a**,**b** studied here.

The reaction pathway is shown in Scheme 1. The rate determining step for the esters **1a** and **1b** could be either the formation of the initial adduct, k'_1, or the intramolecular nucleophilic attack, k'_2. The former appears to be the case for very reactive systems such as the 2-formyl and acetylbenzoate systems,[2a,3] and for the two esters **1a** and **1b** studied here, based on the evidence from the entropy of activation.

The alkaline hydrolysis of the benzoate anions

The alkaline hydrolysis of the 2-trihaloacetylbenzoate anions is of first-order both in benzoate and hydroxide anions. Rate coefficients for the alkaline hydrolysis of the benzoate anions are shown in Table 1. The activation parameters are shown in Table 2.

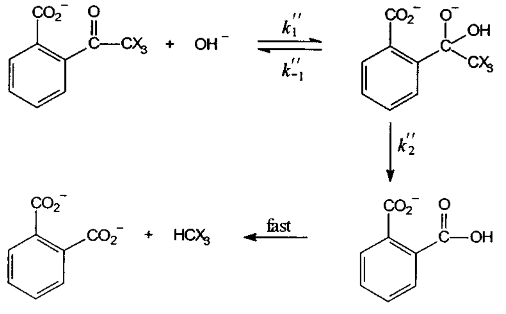
The rates of hydrolysis are considerably slower than those of the corresponding esters. Again the trichloro substrate reacts faster than the tribromo substrate. The activation parameters

Table 4 Ionisation of the 2-substituted benzoic acids in water at 25 °C[a]

2-Substituent	pK_a	Estimated pK^T_a	K_e
$COCBr_3$	5.10	3.1	100 (±25)
$COCCl_3$	4.99	3.1	78 (±20)

[a] The observed pK_a values were reproducible to ±0.02 unit and the estimated pK^T_a values are considered to be ±0.1 unit.

indicate a bimolecular pathway. The relative ease of formation of the adduct for the less bulky trichloro substrate decreases $\Delta H^\ddagger$ and increases the rate of reaction, *cf.* ref. 6(*b*). The reaction pathway is shown in Scheme 2, which is similar to that proposed for related substrates.[6] The rate determining step would appear to be the decomposition of the initial adduct, k''_2, to form the carbanion. The latter is relatively rapidly protonated to give the haloform.



Scheme 2

The ring–chain tautomerism of the acids

The IR spectra of the acids in tetrachloromethane or chloroform clearly indicate that the acids are predominantly cyclic, *i.e.* in tetrachloromethane the acids corresponding to **1a** and **1b** have lactone carbonyl stretching frequencies observed at 1818 and 1802 cm^{-1}, respectively, *alone*, *cf.* ref. 8,16. The ^1H and ^{13}C NMR spectra confirm the cyclic nature of the compounds, but do not allow quantitative measurements of the equilibrium to be made.

In Table 4 are shown the pK_a values of the acids, together with estimates of pK_a values of the chain tautomers. The latter are based on the pK_a value of 2-benzoylbenzoic acid in water (3.53_5),[17] together with the polar substituent effects of Ph, CBr_3 and CCl_3[14] and their transmission.[18] The K_e values for 2-tribromo- and trichloroacetylbenzoic acids in water are shown in Table 4 as 100 and 78, respectively. These are significantly greater than those for 2-acetyl- and benzoylbenzoic acids which are *ca.* 4 and 0.07, respectively.[8] The relatively large steric bulk and powerful electron-withdrawing effect of the CBr_3 and CCl_3 groups favour the formation of the ring tautomer.[7,8]

Experimental

Materials

The decomposition of tribromo- or trichloroacetic acid in dimethyl sulfoxide in the presence of phthalic anhydride gave 2-tribromo- or trichloroacetylbenzoic acid, respectively.[16] The methyl esters were prepared from the corresponding acid and diazomethane in diethyl ether.[19] The ^1H NMR spectra of the esters in $CDCl_3$ showed signals at 3.94 (3H, s, CH_3) and 7.59–7.69 (4H, m, arom *H*) ppm and the ^{13}C NMR spectra had 10 signals consistent with the structures. The purities of the acids and esters were monitored by ^1H and ^{13}C NMR and IR spectroscopy. The mp values of the acids, after repeated crystallization and drying under reduced pressure (P_2O_5), were in agreement with literature[16] values. The mp values of the previously unreported methyl esters are shown in Table 5, together with their appearance and elemental analysis.

Table 5 Physical properties of previously unreported methyl 2-trihaloacetylbenzoates

			Elemental analysis Found (%) (Required)		
Compound	Mp/°C	Appearance[a]	C	H	Other
1a ($C_{10}H_7Br_3O_3$)	113–115	Colourless	28.9	1.8	58.0 (Br)
		needles	(29.0)	(1.7)	(57.8) (Br)
1b ($C_{10}H_7Cl_3O_3$)	81–83	Colourless	42.6	2.6	37.5 (Cl)
		needles	(42.7)	(2.5)	(37.8) (Cl)

[a] Recrystallisation solvent benzene–hexane.

Measurements

Rate coefficients for the alkaline hydrolysis were determined spectrophotometrically by use of a Perkin-Elmer Lambda 16 UV–VIS spectrophotometer. The reactions were followed at the wavelengths shown in Table 1. The procedure was that described previously.[20] The substrate concentrations were *ca.* 1×10^{-4} mol dm^{-3} and the base concentrations were *ca.* 2×10^{-4} to 2×10^{-2} mol dm^{-3}. The primary products of the alkaline hydrolysis of the esters were found to be the anions of the corresponding acids in quantitative yield. The secondary products of the latter reaction and the alkaline hydrolysis of the corresponding benzoate anions were found to be the anions of phthalic acid and the trihaloform. The phthalic acid products were isolated in quantitative yield. The presence of the trihaloforms was confirmed by glc analysis. The kinetics of the latter reactions were found to be identical if studied using methyl ester or acid as substrate. Both reactions were found to be first-order in both base and substrate. For the ester hydrolysis, the second-order rate coefficients were checked by the method devised by Corbett,[21] which can be applied if the excess used is only two-fold. Good isosbestic points were observed for all substrates in both reactions by judicious variation in the base concentrations, *i.e.* the relative rate of ester to benzoate anion hydrolysis is >70. The products were both further confirmed spectrophotometrically by comparison of the spectrum of the acid in base with that of the reaction product.

The apparent pK_a values of the acids in water at 25 (±0.1) °C were measured as described previously.[19] The pK_a of benzoic acid in water was found to be 4.20 and the aqueous solution contained 2% dioxane to ensure solubility of the 2-substituted benzoic acids. Under the conditions of the measurements, the decomposition of the anion of the 2-trihaloacetylbenzoic acid was very slow and does not affect the determinations.

Acknowledgements

We thank Amy Bringes for carrying out some preliminary studies.

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Paper 8/07438K