Reactions of carbonyl compounds in basic solutions. Part 21.[1] The mechanisms of the alkaline hydrolysis of substituted methyl 2-(2-oxopropyl)- and 2-(2-oxo-2-phenylethyl)-benzoates and 2-(2-acetylphenyl)- and 2-(2-benzoylphenyl)-acetates

Keith Bowden * and Jane M. Byrne

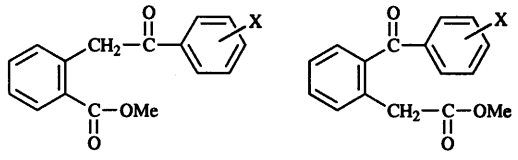
Department of Biological and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, Essex, UK CO4 3SQ

Rate coefficients have been measured for the alkaline hydrolysis of methyl 2-[2-oxo-2-(3- or 4-substituted phenyl)ethyl]benzoates, 2-[2-(3- or 4-substituted benzoyl)phenyl]acetates, 2-(2-oxopropyl) and 2-(1,1-dimethyl-2-oxopropyl)benzoates, 2-(2-acetylphenyl)acetate and 2-(2-acetylphenyl)-2,2-dimethylacetates in 70% (v/v) dioxane–water at 30.0 °C. Those for the six parent esters were also measured at 45.0 and 60.0 °C and the enthalpies and entropies of activation have been evaluated. The relative rates of hydrolysis, activation parameters and substituent effects have been used to demonstrate neighbouring participation by the keto-carbonyl groups in the alkaline hydrolysis of the esters under study. For comparable systems, participation by six-membered ring intermediates appears somewhat less advantageous than five-membered.

Introduction

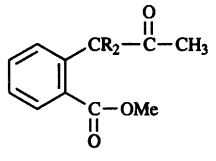
Neighbouring group participation by suitably situated carbonyl groups in the alkaline hydrolysis of esters has been recently reviewed.[2] An important factor has been shown to be the size of the ring formed in such participation. Thus four-, five-, six- or seven-membered rings appear to be employed in the intramolecular catalysis by carbonyl groups. However, it has been shown that, for the hydrolysis of the flexible methyl propionates, butyrates and valerates, having an ω-benzoyl group, the order of ease of ring formation is $5 \gg 6 > 7$.[3] For the hydrolysis of methyl benzil-2-carboxylates, the evidence favours a five-membered ring structure, rather than the alternative six-membered ring available.[4] Furthermore, the influence of *gem*-dialkyl effects[5] on such intramolecular catalysis by carbonyl groups has not been established. The criteria employed to detect and delineate neighbouring group participation includes rate enhancements,[6,7] distinctive activation parameters[7,8] and Hammett reaction constants.[4,7–9]

We describe here the alkaline hydrolysis in aqueous dioxane of a series of methyl 2-(2-oxo-2-phenylethyl)benzoates, **1**, and 2-(2-benzoylphenyl)acetates, **2**, with varied *m*/*p*-substitution in both the benzoyl groups, as well as methyl 2-(2-oxopropyl)benzoate and 2-(2-acetylphenyl)acetate, **3a** and **4a**, together with *gem*-dimethyl substitution at both the methylene links, **3b** and **4b**. The relative rates, activation parameters and the effects of substitution are discussed in terms of detailed mechanisms.

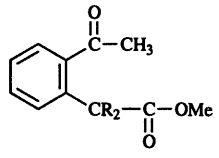


1

2



3a R = H
3b R = CH_3



4a R = H
4b R = CH_3

Table 1 Rate coefficients (k_2) for the alkaline hydrolysis of methyl 2-[2-(substituted phenyl)-2-oxoethyl]benzoates and 2-[2-(substituted benzoyl)phenyl]acetates in 70% (v/v) dioxane–water at 30.0 °C[a]

	k_2/dm^3 mol^{-1} s^{-1} (λ/nm)[b]	
Substituent	2-(2-Oxo-2-phenylethyl)-benzoates	2-(2-Benzoylphenyl)-acetates
H	0.319 (297)	0.0908 (248)
4-CH_3	0.249 (300)	0.0803 (256)
4-OCH_3	0.230 (304)	0.0663 (264)
4-Cl	0.567 (300)	0.148 (259)
3-CF_3	0.725 (298)	0.270 (236)

[a] Rate coefficients were reproducible to within ±3%. [b] Wavelength used to monitor alkaline hydrolysis.

Results

The alkaline hydrolysis of the methyl esters is of first-order in both ester and hydroxide anion. Rate coefficients for the alkaline hydrolysis of methyl 2-[2-oxo-2-(3- or 4-substituted phenyl)ethyl]benzoates and 2-[2-(3- or 4-substituted benzoyl)-phenyl]acetates at 30.0 °C in 70% (v/v) dioxane–water are shown in Table 1 and, for the parent esters, at 30.0, 45.0 and 60.0 °C in Table 2. The latter Table also contains the rate coefficients for the alkaline hydrolysis in the same medium of methyl 2-(2-oxopropyl)- and 2-(1,1-dimethyl-2-oxopropyl)-benzoates, and methyl 2-(2-acetylphenyl)acetate and 2-(2-acetyl phenyl)-2,2-dimethylacetate at the same temperatures. The activation parameters for the esters, included in Table 2, are shown in Table 3.

Discussion

Three criteria have been used in the investigation of the

Table 2 Rate coefficients (k_2) for the alkaline hydrolysis of methyl substituted benzoates and phenylacetates in 70% (v/v) dioxane–water[a]

	k_2/dm^3 mol^{-1} s^{-1}			
	at 30.0 °C	at 45.0 °C	at 60.0 °C	λ/nm[b]
Benzoates: substituent				
2-CH_2COPh	0.319	0.834	1.98	297
2-CH_2COCH_3	0.181	0.618	1.63	232
2-$C(CH_3)_2COCH_3$	0.0250	0.0707	0.182	325
Phenylacetates: substituent				
2-COPh	0.0908	0.202	0.414	248
2-$COCH_3$	0.593	1.13	2.24_5	242
2-$COCH_3$-α,α-$(CH_3)_2$	0.572	1.41_5	3.44	324

[a,b] See Table 1.

Table 3 Activation parameters for the alkaline hydrolysis of methyl substituted benzoates and phenylacetates in 70% (v/v) dioxane–water at 20.0 °C[a]

	$\Delta H^{\ddagger}$/kcal mol^{-1} [b]	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} [b]
Benzoates: substituent		
2-CH_2COPh	11.6 (±0.1)	−22 (±1)
2-CH_2COCH_3	14.1 (±0.6)	−15 (±2)
2-$C(CH_3)_2COCH_3$	12.7 (±0.1)	−24 (±1)
Phenylacetates: substituent		
2-COPh	9.6 (±0.1)	−32 (±1)
2-$COCH_3$	8.3 (±0.4)	−32 (±1)
2-$COCH_3$-α,α-$(CH_3)_2$	11.4 (±0.3)	−22 (±1)

[a] Uncertainties shown in parentheses. [b] 1 cal = 4.184 J.

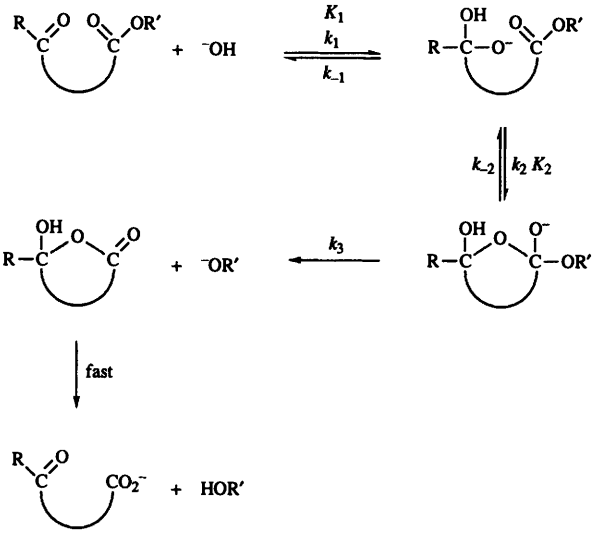
Table 4 Relative rate ratios for the alkaline hydrolysis of the methyl esters in 70% (v/v) dioxane–water at 30 °C

	Observed	Expected for 'normal' hydrolysis	Enhanced, r_e
Benzoates: substituent			
2-CH_2COPh	10.5	0.3	35
2-CH_2COCH_3	18	0.3	60
2-$C(CH_3)_2COCH_3$	1.4_5	0.05	29
Phenylacetates: substituent			
2-COPh	1.0	0.5	2
2-$COCH_3$	6.5	0.5	13
2-$COCH_3$-α,α-$(CH_3)_2$	6.0	0.003	2000

occurrence of this type of neighbouring group participation in the present study, *i.e.* relative rates, activation parameters and reaction constants.

Relative rates

The rates of the alkaline hydrolysis of various parent esters in 70% aqueous dioxane at 30.0 °C are shown in Table 2. The rate ratios for the hydrolysis of the esters to that of either methyl benzoate (k_2 at 30.0 °C equal to 0.0174 dm^3 mol^{-1} s^{-1})[7] or phenylacetate(k_2 at 30.0 °C equal to 0.0898 dm^3 mol^{-1} s^{-1})[10] can be calculated to give the values shown in Table 4. Estimates of the rate ratios for unassisted hydrolysis using the known steric and polar effects of 2-substituents on the alkaline hydrolysis of methyl benzoates and phenylacetates,[11,12] as well as the Taft–Ingold equation,[13] also shown in the latter Table.[8] In all cases, except that of methyl 2-(2-benzoylphenyl)acetate, **2** (X = H), the rate enhancements, r_e, are significant, *i.e.* ≥10, and clearly indicate that hydrolysis is very likely to be occurring with intramolecular catalysis. Furthermore, the actual rate of alkaline hydrolysis of methyl 2-(2-acetylphenyl)-2,2-dimethylacetate, **4b**, is very similar to that of methyl 2-(2-acetylphenyl)acetate, **4a** (see Table 2). If hydrolysis had been occurring by the 'normal' unassisted pathway for these esters, a very great difference in rates would be expected, arising from the steric 'bulk' of the *gem*-dimethyl group. Thus, it would appear very likely that both these esters are hydrolysing with intramolecular catalysis and the rate-determining step is the formation of the adduct, *i.e.* k_1 in Scheme 1, which will be almost unaffected by the steric 'bulk' factor.



Scheme 1

Activation parameters

For the alkaline hydrolysis of the more reactive esters employing neighbouring group participation by proximate formyl or keto groups, the enthalpies of activation are exceptionally small.[2] These are associated with rather large negative entropies of activation. The exact mechanistic significance of these results can only be tentatively suggested. For methyl 2-(2-benzoyl and 2-acetylphenyl)acetate, **2** (X = H) and **4a**, the enthalpies of activation are much smaller and the entropies of activation are much more negative, as has been observed for the alkaline hydrolysis of several methyl 2-acylbenzoates and related esters.[2] This strongly indicates a facile hydrolysis pathway for these esters employing intramolecular catalysis, with the addition of hydroxide anion as the rate-determining step (k_1 in Scheme 1) being very probable. This particular criterion does not allow any decision to be reached for the remaining esters shown in Table 3.

Reaction constants

Substituent effects have been a very useful probe of mechanism in these types of systems,[2] not only in indicating the mechanistic path but in suggesting the detailed kinetic pathway. The effect of substitution in the phenyl ring for the benzoyl esters, **1** and **2**, was assessed using the Hammett eqn. (1).

$$\log (k/k_0) = \rho\sigma \qquad (1)$$

The expected reaction constant ratio ρ/ρ_0 for 'normal' disassociated alkaline hydrolysis can be estimated to be 0.13 from the apparent transmission factors[14] for *both* systems. The reference reaction constant, ρ_0, for the alkaline hydrolysis of methyl benzoates under identical conditions is 2.20.[15] The

Table 5 Hammett reaction constants (ρ) for the alkaline hydrolysis of the methyl esters in 70% (v/v) dioxane–water at 30.0 °C[a]

System	ρ	$\log k_o$	r	s	n
2-[2-Oxo-2-(3- or 4-substituted phenyl)ethyl]benzoates	0.747	−0.454	0.987	0.070	5
2-[2-(3- or 4-substituted benzoyl)phenyl]acetates	0.838	−0.980	0.980	0.099	5

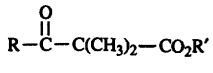
[a] r is the correlation coefficient, s the standard deviation and n the number of substituents used.

observed values of ρ/ρ_0, for methyl 2-(2-oxo-2-phenylethyl)benzoates, **1**, and methyl 2-(2-benzoylphenyl)acetates, **2**, are 0.34 and 0.38, respectively. These values are considerably greater than that estimated for 'normal' hydrolysis above and indicate hydrolysis occurring by intramolecular catalysis. The ρ values observed here are not as high as those obtained for methyl 2-benzoylbenzoates, 8-benzoyl-1-naphthoates and *cis*-3-benzoylacrylates in the same medium, which were 2.07 (30 °C), 1.73 (60 °C) and 2.56 (1 °C), respectively. The latter esters are all considered to hydrolyse employing intramolecular catalysis.[8,15] These systems involve five-, six- and five-membered ring intermediates, respectively. However, ρ values of *ca.* 0.88, 0.23 and 0.0 (30 °C) are observed for the same reaction of methyl 3-benzoylpropionates, 4-benzoylbutyrates and 5-benzoylvalerates, respectively, which involve five-, six- and seven-membered ring intermediates.[3] Only the hydrolysis of the 3-benzoylpropionates is considered to involve intramolecular catalysis. Thus, the present results indicate that intramolecular catalysis is occurring for *both* systems in the present study.

Mechanistic pathway

The reaction pathway is shown in Scheme 1. All the esters under study would involve six-membered ring intermediates. However, the rings are not simple and include part of an aromatic ring and a methylene group. The ease of formation of these six-membered rings, as shown by the rate enhancements for comparable keto groups, is somewhat less than that for five-membered rings, *cf.* ref. 2(*a*). The evidence of the reaction constants for the hydrolysis of the benzoyl esters in this study would indicate that negative charge is commencing transfer to the ester carbonyl oxygen as the intramolecular attack proceeds, as previously observed in the hydrolysis of substituted phenyl 2-benzoylbenzoates.[16]

A previous study has been made by Washburn and Cook[17] of the hydrolysis of aryl 4-substituted 3-oxo-2,2-dimethylbutyrates, **5**, for which a *gem*-dimethyl effect might be expected.



5

Unfortunately, the reason for the study of these *gem*-dimethyl esters was that they were non-enolizable and the corresponding unsubstituted system, which can ionize in base, cannot be used as a reference system. For the phenylacetate esters studied here, **4**, the similar rates of alkaline hydrolysis for **4a** and **4b** can be considered diagnostic for the rate-determining steps involving attack of hydroxide anion at the keto-carbonyl group. Likewise, the reduction in rate by a factor of about 0.12 for the benzoate ester **3b**, compared to the ester **3a**, is almost exactly that expected from the combined steric and polar factors of two α-methyl groups inhibiting the formation of a tetrahedral intermediate.[18] Thus, any effects from the *gem*-dimethyl cannot be detected in this system as it would occur in the intramolecular step, *i.e.* k_2 in Scheme 1.

Table 6 Physical constants of previously unreported methyl esters

Formula	Mp/°C[a]	Elemental analysis Found (%) (Required) C	H	Other
Methyl ester, **1** X				
4-CH_3	66	75.7	5.9	
($C_{17}H_{16}O_3$)		(76.1	6.0)	
4-OCH_3	75	71.9	5.6	
($C_{17}H_{16}O_4$)		(71.8	5.6)	
4-Cl	62	66.2	4.5	12.2$_5$ (Cl)
($C_{16}H_{13}ClO$)		(66.6	4.5	12.3)
3-CF_3	60	63.3	4.0	17.6 (F)
($C_{17}H_{13}F_3O_3$)		(63.4	4.0$_5$	17.7)
Methyl ester, **2** X				
3-CF_3	85	63.3	4.0	17.5 (F)
($C_{17}H_{13}F_3O_3$)		(63.4	4.0$_5$	17.7)
Methyl ester, **3b**	oil (bp 96–98 °C/0.2 mmHg)	7.09 (70.9	7.3 7.3)	
Methyl ester, **4b**	oil (bp 108–110 °C/0.2 mmHg)	70.8 (70.9	7.2 7.3)	

[a] Recrystallised from methanol.

Experimental

Materials

The methyl esters were prepared from the corresponding carboxylic acids[19,20] by the reaction of the appropriate carboxylic acid with diazomethane in ether. The purity of the potentially tautomeric methyl esters was monitored by ^1H and ^{13}C NMR spectroscopy. The chemical shifts of the methoxy methyl group of the esters were observed in $CDCl_3$ at 3.74–3.76 ppm for **1**, 3.54–3.56 ppm for **2**, 3.81–3.84 ppm for **3**, and 3.65–3.70 ppm for **4**. The mps of the esters, after repeated recrystallization and drying under reduced pressure (P_2O_5), or bps of the esters were in agreement with lit. values[20,21] or are shown in Table 6, together with the elemental analysis.

The solvents were purified as described previously.[15]

Measurements

Rate coefficients for the alkaline hydrolysis of the esters were determined spectrophotometrically by use of a Perkin-Elmer Lambda 5 UV–VIS spectrometer. The reactions were followed at the wavelengths shown in Tables 1 and 2. The procedure used was that described previously.[9] The products of the reactions were found to be the anions of the corresponding acids in quantitive yield in all cases and were further confirmed spectrophotometrically by comparison of the spectrum of the acid in base with that of the reaction product.

Acknowledgements

We thank the SERC and Rhône-Poulenc for the award of a CASE studentship (to J. M. B.) and Dr M. Caton for his advice and interest.

References

1 Part 20. K. Bowden and K. D. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1994, 77.
2 (*a*) K. Bowden, *Adv. Phys. Org. Chem.*, 1993, **28**, 171; (*b*) K. Bowden, *Chem. Soc. Rev.*, 1995, **25**, 431.
3 M. V. Bhatt, M. Ravindranathan, V. Somayaji and G. V. Rao, *J. Org. Chem.* 1984, **49**, 3170.
4 K. Bowden and F. P. Malik, *J. Chem. Soc., Perkin Trans.* 2, 1992, 5; 1993, 7.
5 A. L. Parrill and D. P. Dolata, *Tetrahedron Lett.*, 1994, 7319.

6 M. L. Bender, J. A. Reinstein, M. S. Silver and R. Mikulak, *J. Am. Chem. Soc.*, 1965, **87**, 4545.
7 K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 149.
8 K. Bowden and M. P. Henry, *J. Chem. Soc.* (*B*), 1971, 156.
9 K. Bowden and A. M. Last, *J. Chem. Soc., Perkin Trans. 2*, 1973, 345.
10 K. Bowden and J. M. Byrne, unpublished studies.
11 N. B. Chapman, J. Shorter and J. H. P. Utley, *J. Chem. Soc.*, 1963, 1921; Y. Iskander, R. Tewfik and S. Wasif, *J. Chem. Soc.* (*B*), 1966, 424.
12 J. G. Watkinson, W. Watson and B. L Yates, *J. Chem. Soc.*, 1963, 437.
13 R. W. Taft, *J. Am. Chem. Soc.*, 1952, **74**, 2729.
14 K. Bowden, *Can. J. Chem.*, 1963, **41**, 2781.
15 K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 145.
16 F. Anvia and K. Bowden, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1805.
17 W. N. Washburn and E. R. Cook, *J. Am. Chem. Soc.*, 1986, **108**, 5962.
18 R. W. Taft, in *Steric Effects in Organic Chemistry*, ed. M. S. Newman, Wiley, New York, 1956, ch. 13.
19 K. Bowden and J. M. Byrne, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1921.
20 L. Legrand and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1964, 1787; H. Cousse, G. Mouzin, J. Rieu, H. Lauressergues, J. Tarayre and A. Stener, *Eur J. Med. Chem-Chim. Ther.*, 1974, **9**, 397, M. Renson and L. Christiaens, *Bull. Soc. Chim. Belg.*, 1962, **71**, 394; M. Flammang and C. Wermuth, *Eur. J. Med. Chem.-Chim. Ther.*, 1976, **11**, 83; R. B. Tirodkar and R. N. Usgaonkar, *J. Ind. Chem. Soc.*, 1969, **46**, 935; W. E. Parnham, H. E. Reiff and P. J. Swartzentruber, *J. Am. Chem. Soc.*, 1956, **78**, 1437; D. Price, D. Davidson and M. T. Bogert, *J. Org. Chem.*, 1938, **2**, 540.
21 H. E. Zimmerman and M. D. Taylor, *J. Am. Chem. Soc.*, 1957, **79**, 1920; R. G. R. Bacon and J. C. F. Murray, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1267; D. A. Evans, G. F. Smith and M. A. Wahid, *J. Chem. Soc.* (*B*), 1957, 590.

Paper 6/01524G
Received 4*th March* 1996
Accepted 29*th May* 1996