Reactions of Carbonyl Compounds in Basic Solutions. Part VII.[1] The Mechanism of the Alkaline Hydrolysis of Methyl Pseudo-8-acyl-1-naphthoates and Pseudo-5-formylphenanthrene-4-carboxylate

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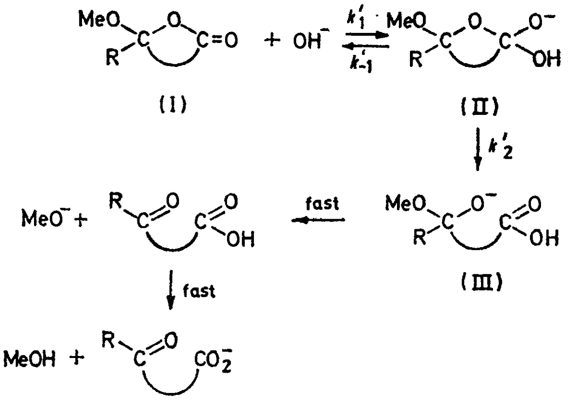
Rate coefficients have been measured for the alkaline hydrolysis of a series of methyl pseudo-8-acyl-1-naphthoates and methyl pseudo-5-formylphenanthene-4-carboxylates in 70% (v/v) dioxan–water at several temperatures. The entropies and enthalpies of activation have been evaluated. The results are related to the effects of the substituents and ring size for the pseudo-esters. Solvent isotope effects have been studied for selected pseudo-ester hydrolyses. All the evidence indicates a hydrolysis mechanism with a rate-determining addition of hydroxide anion to the pseudo-ester carbonyl group, followed by rapid collapse of the tetrahedral intermediate to form the carboxylate anion of the corresponding acid as product.

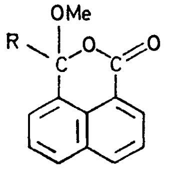
THE mechanism of the alkaline hydrolysis of alkyl pseudo-esters has received remarkably little attention. The rate coefficients for the alkaline hydrolysis of some substituted methyl pseudo-2-benzoylbenzoates have been measured[2] and the alkaline hydrolysis of methyl pseudo-2-formylbenzoate has been investigated.[3] A recent preliminary report[4] describes the effect of several leaving groups, *e.g.* OMe, OPh, N_3, Cl, on the rates of the alkaline hydrolysis of pseudo-2-benzoylbenzoates. These studies suggest a mechanism involving addition of the hydroxide anion to the carbonyl group and a possible mechanistic scheme is shown below for a methyl pseudo-ester (I). The formation of the tetrahedral intermediate is favoured over that of a concerted displacement because of the evidence for such intermediates in closely related reactions.[5] While k_2' is, in principle, reversible, the final formation of the carboxylate anion does not allow this step to be reversed, as in normal ester hydrolysis.



The present study reports an investigation of the mechanism of the alkaline hydrolysis of a series of methyl pseudo-8-acyl-1-naphthoates and methyl pseudo-5-formylphenanthrene-4-carboxylate, using a series of mechanistic probes. These include kinetic studies, employing activation parameters and solvent isotope and substituent effects.

RESULTS AND DISCUSSION

The alkaline hydrolysis of all the methyl pseudo-esters studied is of first order both in pseudo-ester and hydroxide anion. The product of the hydrolysis is the corresponding carboxylate anion, *unlike* that for certain of the corresponding normal esters.[1] Rate coefficients for the methyl pseudo-esters in 70% (v/v) dioxan–water at several temperatures are shown in Table 1. The activation parameters for these reactions are shown in Table 2.



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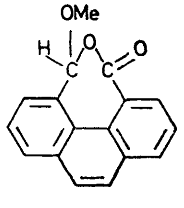

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TABLE 1

Rate coefficients for the alkaline hydrolysis of methyl pseudo-esters in 70% (v/v) dioxan–water *

	Substnt. [R in (IV)]	10^2k_2/l mol^{-1} s^{-1}				
		20·0 °C	30·0 °C	40·0 °C	50·0 °C	60·0 °C
1	H	114	213	484	838	1380
2	Me	4·58	10·7	18·3	37·6	67·0
3	CH_2Me	1·05	2·18	4·51	10·2 †	18·1
4	$CHMe_2$	0·151	0·304	0·734	1·80 †	3·35
5	Ph	2·03	4·64	8·98	17·5	34·0
6	Compd. (V)	6·06	11·4	21·1	45·6	71·9

* Rate coefficients were reproducible to within ±3%.
† At 50·5 °C.

TABLE 2

Activation parameters for the alkaline hydrolysis of methyl pseudo-esters at 30·0 °C *

	Substnt. [R in (IV)]	$\Delta H^‡$/cal mol^{-1}	$\Delta S^‡$/ cal mol^{-1} K^{-1}
1	H	11,800	−18
2	Me	12,300	−23
3	CH_2Me	13,400	−22
4	$CHMe_2$	14,800	−21
5	Ph	12,900	−22
6	Compd. (V)	11,700	−24

* Values of $\Delta H^‡$ are accurate to within ±500 cal mol^{-1} and $\Delta S^‡$ to within ±2 cal mol^{-1} K^{-1}.

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[1] Part VI, K. Bowden and A. M. Last, preceding paper.

[2] M. S. Newman and S. Hishida, *J. Amer. Chem. Soc.*, 1962, **84**, 3582.

[3] M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Amer. Chem. Soc.*, 1965, **87**, 4545.

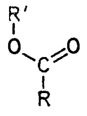
[4] M. V. Bhatt, G. Venkoba Rao, and K. Sunder Raja Rao, *Chem. Comm.*, 1971, 822.

[5] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.

The mechanism shown previously is closely analogous to the normal mechanism for the alkaline hydrolysis of esters and lactones, *i.e.* $B_{AC}2$ according to the Ingold notation.[6] A much less likely possibility would appear to be direct nucleophilic displacement by attack at the 8-substituent carbon, *i.e.* $B_{AL}2$ according to the same notation.[6]

Substituent Effects.—The order of reactivity of the pseudonaphthoates shown in Table 1, *i.e.* H > Me > Ph > CH_2Me > $CHMe_2$, clearly indicates that a combination of steric and polar factors are involved, *cf.* ref. 7. A suitable correlation and separation of substituent effects is not possible because of the comparatively small range of rates observed and unsuitability of the substituent parameters available, *e.g.* E_s for R in (IV). These results, together with those of Bhatt *et al.*,[4] show that both the $B_{AL}2$ and $B_{AC}2$, with k'_2 as the rate-determining step, paths are very unlikely. Both possibilities would require very much more distinct dependance on the steric and/or polar effects of the substituent or leaving group, *cf.* refs. 6—8.

The alkaline hydrolysis of the pseudo-esters may be compared with that of lactones. Lactones, which are cyclic esters, undergo alkaline hydrolysis much more readily than comparable normal esters.[9,10] The normal esters have the preferred conformation which is '*trans*', (VI); whereas, simple lactones, up to 7-membered, exist in a '*cis*' conformation (VII) caused by the constraints of ring formation. The latter state inhibits resonance interactions and increases the initial state energy of lactones compared to esters.[9,10] Consequently, the lactones are more readily hydrolysed. The pseudo-esters studied here must exist in a '*cis*' conformation. If the pseudo-esters hydrolyse by the same mechanistic path as the lactones, *i.e.* $B_{AC}2$,[10] this should result in two consequences. First, the pseudo-esters should react more readily than the corresponding normal esters. A direct comparison cannot be made as the latter esters do not hydrolyse by the direct ester mechanism.[1,11] However, a comparison is shown in Table 3 of the actual rates of alkaline hydrolysis of the pseudo-esters and chain esters, together with the 'estimated' rate of hydrolysis of the normal ester by a direct hydrolysis mechanism.[1,11] The latter estimates have been made by comparison with suitable model compounds.[1,11] All the pseudo-esters hydrolyse much faster than the 'estimated' values for the direct hydrolysis of the normal esters as expected. However, the observed rates of hydrolysis for the two normal formyl esters are much greater than those for the corresponding pseudo-esters. This confirms the operation of a very favourable path for the hydrolysis of the former esters, which employs neighbouring-group participation by the formyl group.[10] Second, the ring size of the pseudo-ester should determine the relative rates in a comparable series of these substrates. In Table 4 is shown the relative hydrolytic lability of the five-, six-, and seven-membered lactones. While the pseudo-esters do not either have the greater flexibility of the lactones or exactly comparable structures to each other, it is clear that both series follow the same general pattern of reactivity.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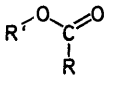
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Table 3

Rate coefficients of alkaline hydrolysis of certain esters in 70% (v/v) dioxan–water

Ester	10^3k_2/l mol^{-1} s^{-1} Pseudo-ester	 Normal ester [1,11]	 'Estimated' for normal ester by direct hydrolysis mechanism [1,11]
Methyl 8-formyl-1-naphthoate at 60·0 °C	13,800	191,000 *	1·0
Methyl 8-benzoyl-1-naphthoate at 60·0 °C	340	16·6	<0·5
Methyl 5-formyl-phenanthrene-4-carboxylate at 40·0 °C	211	19,500	<0·001

* Extrapolated value from data in ref. 11.

Table 4

Ring size and alkaline hydrolysis rate effects

Ring size	Relative rates Lactones in 60% (v/v) dioxan–water at 0 °C [10]	 Pseudo-esters in 70% (v/v) dioxan–water at 20 °C
5	0·027	0·4 *
6	1·0	1·0
7	0·046	0·053

* Alkaline hydrolysis of 3-methoxyphthalide (methyl pseudo-2-formylbenzoate) in 70% (v/v) aqueous dioxan at 20 °C has a rate coefficient, k_2, of 0·5 l mol^{-1} s^{-1}.[12]

The enthalpies of activation for the methyl pseudo-8-acyl-1-naphthoates appear to increase mainly with the steric 'bulk' of the acyl substituent (Table 2). The entropies of activation are invariant within the experimental error, except for that for the formyl ester. The less negative value of $\Delta S^{\ddagger}$ for the latter ester appears to be derived from steric 'bulk' factors again. While the enthalpy of activation for hydrolysis of the methyl pseudo-5-formylphenanthrene-4-carboxylate is the same as the corresponding naphthoate, the entropy of activation of the former ester is considerably less than that of the latter, *i.e.* $\Delta\Delta S^{\ddagger}$ *ca.* −6 e.u. (Table 2). This probably arises from the more flexible seven-membered ring

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[6] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Bell and Sons Ltd., London, 1953, ch. 14.

[7] R. W. Taft, jun., in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, ch. 13.

[8] C. D. Gutsche, 'The Chemistry of Carbonyl Compounds,' Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1967, ch. 2.

[9] T. C. Bruice and S. J. Benkovic, 'Bio-organic Mechanisms,' vol. 1, W. A. Benjamin, Inc., New York, 1966, pp. 21—22, 244 and references therein.

[10] R. Huisgen and H. Ott, *Tetrahedron*, 1959, **6**, 253.

[11] K. Bowden and A. M. Last, *J.C.S. Perkin II*, 1973, 345.

[12] K. Bowden and G. R. Taylor, unpublished studies.

losing more ' freedom of motions ' in going from the initial to the transition state.

TABLE 5

^{18}O-Enriched water hydrolyses at 50·0 °C

Methyl ester or control acid	Enrichment/atom % * $M + 2/M$	 $(M\text{-CO}_2) + 2/(M\text{-CO}_2)$	 $(M\text{-PhCO}) + 2/h(M\text{-PhCO})$
8-Benzoyl-1-naphthoic acid	1·8(±0·1)	1·5(±0·2$_5$)	None
Methyl pseudo-8-benzoyl-1-naphthoate	2·7(±0·3)	1·7$_5$(±0·5)	1·5(±0·5)

* Solvent enrichment 1·5$_9$ atoms %.

Oxygen-18 *Exchange*.—The results of the ^{18}O-enriched water hydrolysis of the 8-benzoyl-1-naphthoate are shown in Table 5. The mass spectral analysis of the product showed that an overall enrichment of 2 atoms per molecule had taken place. The mass spectral breakdown of the enriched product indicated that one enrichment occurred at the keto-carbonyl and one at the carboxyl group. The evidence clearly excludes the possibility of a $B_{AL}2$ path, as it has been shown that the carboxy-group of the 8-benzoyl-1-naphthoic acid anion does not undergo exchange once formed (see Table 5 and Experimental section). If a $B_{AL}2$ path operated, single enrichment at the keto-carbonyl would occur. This assumes that significant rapid exchange does not occur at the lactone-carbonyl group *before* hydrolysis. This appears to be *very* unlikely.[13] The mechanism shown previously would have a double enrichment arising from (i) attack at the ester-carbonyl group by hydroxide anion and (ii) base-catalysed exchange between the 8-benzoyl-1-naphthoate anion product and the enriched water. The latter process has been shown to occur under the reaction conditions (see Table 5 and Experimental section).

Kinetic Solvent Isotope Effects.—The kinetic deuterium solvent isotope effects were examined for the alkaline hydrolysis of methyl pseudo-8-formyl- and pseudo-8-benzoyl-1-naphthoate in 70% aqueous dioxan as shown in Table 6. In both cases, rate enhancements in the deuterium oxide solvent were observed and are similar to those found for related hydrolyses occurring by attack of hydroxide anion at a carbonyl group.[14]

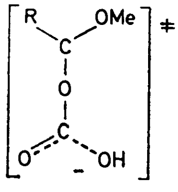
TABLE 6

Solvent isotope effects on the alkaline hydrolysis of methyl pseudo-esters *

Substnt. [R in (IV)]	10^2k_2/l mol^{-1} s^{-1} In 70% (v/v) dioxan–water	 In 70% (v/v) dioxan–deuterium oxide	k_{H_2O}/k_{D_2O}
H (30·0 °C)	213	250	0·85
Ph (60·0 °C)	34·0	42·5	0·80

* See Table 1.

Proposed Mechanism.—All the evidence discussed is in favour of the reaction scheme shown previously. This is very similar to those established previously for related esters and lactones.[5,10] The rate-determining step would appear to be the attack of hydroxide anion on the pseudo-ester carbonyl group, k_1'. The internal ' alkoxide ' will be a better leaving group than hydroxide anion, because of its decreased basicity and the release of ring strain resulting from this fission, k_2'. The transition state can be drawn as two geometric isomers, (VIII) and (IX), as viewed parallel to the plane of the aromatic system. Steric ' bulk ' effects will arise by the increased spatial requirements of the reaction site interacting with the ' bulk ' of R in (VIII) or (IX). The polar effect of R will be small because of the distance of the substituent from the reaction site.



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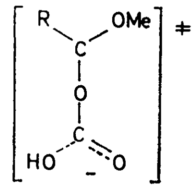

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EXPERIMENTAL

The methyl pseudo-8-acyl-1-naphthoates, excepting the 8-benzoyl compound, and methyl pseudo-5-formylphenanthrene-4-carboxylate were prepared by the esterification of the corresponding acid using methanol and concentrated sulphuric acid.[15] Methyl pseudo-8-benzoyl-1-naphthoate was prepared by Weeks and Zuorick's method[16] by the reaction of the acid chloride[17] with anhydrous methanol containing urea. After repeated recrystallisation to constant m.p. and drying in a vacuum desiccator (P_2O_5), the esters had either m.p.s in good agreement with literature values[15,16,18,19] or, if previously unreported, satisfactory elemental analyses. The ^{1}H n.m.r. and i.r. spectra of all the esters confirmed the structures of these pseudo-esters[20] and indicated them to be pure. The physical constants of the pseudo-esters are given in Table 7, together with their appearance, recrystallisation solvent, and the elemental analyses of the previously unreported esters. The λ-values quoted in Table 7 are those used in the kinetic measurements (and not the $\lambda_{max.}$ values for the esters). Solvents were purified as previously described.[21]

Kinetic Procedure.—The kinetic procedure was as previously described.[11] The wavelengths used for the spectrophotometric monitoring of the hydrolyses are shown in Table 7. The substrate and hydroxide anion concentrations were between 5×10^{-5} to 1×10^{-4} and 1×10^{-3} to 2×10^{-2}M, respectively. The reactions between the substrate and hydroxide anions were first-order in both species

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[13] M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *J. Amer. Chem. Soc.*, 1961, **83**, 4193.

[14] K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 149.

[15] P. T. Lansbury and J. F. Bieron, *J. Org. Chem.*, 1963, **28**, 3564.

[16] D. P. Weeks and G. W. Zuorick, *J. Amer. Chem. Soc.*, 1969, **91**, 477.

[17] F. A. Mason, *J. Chem. Soc.*, 1924, 2116.

[18] J. Zink, *Monatsh.*, 1901, **22**, 986.

[19] G. M. Badger, J. E. Campbell, J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, 1950, 2326.

[20] K. Bowden and A. M. Last, *J.C.S. Perkin II*, in the press.

[21] K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 145.

and were carried out with an excess of base. This ensured first-order behaviour and no deviations were noted over three ' half-lives ' of the reaction. The products of the alkaline hydrolysis were found to be the anion of the corresponding carboxylic acids in quantitative yield in all cases, and further were confirmed spectrophotometrically by comparison of the spectrum of the acid in base with that of the reaction product.

TABLE 7

Physical constants of methyl pseudo-esters

Substnt. [R in (IV)]	M.p. (t/°C)	Lit. m.p. (t/°C)	Ref.	λ/nm
H	104	105	18 [a]	309
Me	103	102·5—103	15 [b]	324
CH_2Me	73·5—74	*c*	*a*	325
$CHMe_2$	112—113	*d*	*a*	325
Ph	130	132—133	16 [a]	324
Compd. (V)	174—175	176—177	19 [e]	324

[a] Colourless prisms from methanol or aqueous methanol. [b] Pale yellow needles from aqueous methanol. [c] Found: C, 74·3; H, 5·8; O, 20·0. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8; O, 19·8%. [d] Found: C, 74·8; H, 6·45; O, 18·9. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3; O, 18·7%. [e] Colourless needles from methanol.

Oxygen-18 *Exchange Studies*.—The alkaline hydrolyses were studied by use of ^{18}O-enriched water (1·5 g atoms %, Yeda R and D Co.). Hydrolyses were conducted under normal conditions for approximately 10 ' half-lives ' of the ester. After neutralisation and removal of the solvent, the acid was isolated and purified. The mass spectrum of each sample and controls (using *both* ester with ordinary water and acid with enriched water) was recorded on an A.E.I. MS9 spectrometer. Repeated scans of the spectra were made.

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