Competition between Neighbouring-group Participation by Carbonyl Groups and Carbon Acids in Ester Hydrolyses

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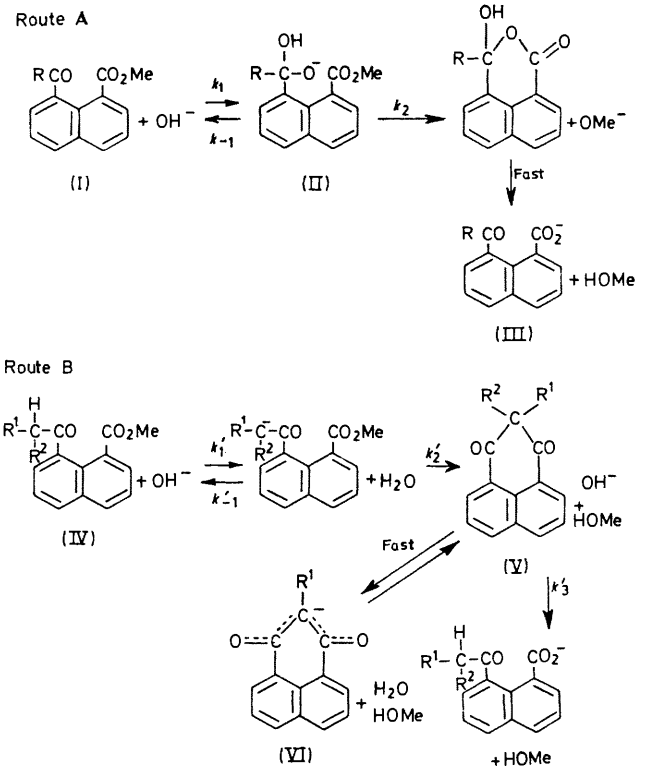
Summary The alkaline hydrolyses of methyl 8-acyl- and 8-aroyl-1-naphthoates have been examined: intramolecular catalysis by the neighbouring carbonyl group occurs for the 8-formyl and 8-(3′- and 4′-substituted benzoyl) esters; whereas, the 8-acetyl, 8-propionyl, and 8-isobutyryl esters display catalysis by the neighbouring carbon acid.

INTRAMOLECULAR catalysis of ester hydrolysis by carbonyl groups has been clearly established in several cases.[1,2] A study of the alkaline hydrolysis of methyl 8-acyl- and 8-aroyl-1-naphthoates has been made. The hydrolysis of methyl 8-formyl-1-naphthoate (Ia; R = H) clearly involves neighbouring-group participation by the 8-formyl group (route A).† The rate ratio for the hydrolysis of this ester, compared to that for methyl 1-naphthoate at 30° in 70% (v/v) dioxan–water, is $8{\cdot}3 \times 10^3$; whereas, for *direct* hydrolysis, a rate ratio of about 2×10^{-2} would be expected. The 8-acetyl, 8-propionyl, and 8-isobutyryl esters (IVa; $R^1 = R^2 = H$, IVb; $R^1 = Me$, $R^2 = H$, IVc; $R^1 = R^2 = Me$) react very rapidly in aqueous dioxan containing an excess of base. However, the immediate products of these reactions are the phenalene-1,3-diones (V). These intermediates have been isolated and/or identified. The two diones (Va; $R^1 = R^2 = H$, Vb; $R^1 = Me$, $R^2 = H$), which can ionise in base, are relatively stable in this anionic form (VI), which is predominant in the alkaline solution. These hydrolyse very slowly to the final product of overall hydrolysis, (III). However, the dione (Vc; $R^1 = R^2 = Me$), which cannot ionise in base to (VI), hydrolyses relatively rapidly. The ratio of the rate of cyclisation to that of ring fission is about 25 at 40° in 70% (v/v) dioxan–water. The cyclisation reaction of methyl [2′,2′,2′-$^2H_3$]-8-acetylnaphthoate was about 6 times slower than the 8-acetyl ester itself at 30°. This clearly identifies the ionization step, k_1', as the rate-determining step. Further, the effect of α-methyl substitution is to retard the rate in the expected order for such a step, *i.e.* the rate ratios are appoximately 1(IVa): 0·19 (IVb): 0·035 (IVc) at 30°. It is possible to detect a contribution to the hydrolysis of the trideuterioester which does not proceed by Route B. This is found by observing the disappearance of the ester at the same time as the formation of the cyclised product. The rate of hydrolysis of this ester, *not* proceeding by cyclisation to (V), is still very enhanced, compared with that expected from a direct hydrolytic mechanism. This clearly operates by Route A.

A study of the alkaline hydrolysis of a series of methyl 8-(3′- or 4′-substituted benzoyl)-1-naphthoates in 70% (v/v) dioxan–water at 60° gives a reaction constant, ρ, of 1·73.



This compares closely with reaction constants for the alkaline hydrolysis of methyl 3- and 4-substituted benzoates, methyl 2-(3′- and 4′-substituted benzoyl)benzoates and methyl *cis*-3-(3′- and 4′-substituted benzoyl)acrylates under comparable conditions.[2] The last two systems hydrolyse with intramolecular catalysis from the neighbouring carbonyl groups. Moreover, the hydrolysis of the 8-benzoyl

† This route could involve a concerted step, rather than through the intermediate (II) as shown.[2]

ester (Ib; R = Ph) has a rate ratio of $1{\cdot}9 \times 10^{-1}$ at 30°, compared with that for methyl 1-naphthoate, whereas, a rate ratio of only about 5×10^{-3} would be expected for a direct hydrolytic path. This evidence clearly indicates hydrolysis by Route A. However, the 8-pivaloyl ester (Ic; R = CMe_3) hydrolyses rather slowly with a similar rate ratio of only about 9×10^{-3} at 60°. Study of the solvent effects, kinetic solvent isotope effects, model substrates, and activation parameters confirms these conclusions.

It is apparent that steric control of mechanism operates in these systems. The 'bulk' steric effect of the 8-substituent strongly inhibits the normal, direct hydrolytic mechanism. The proximity and favourable geometry of the carbonyl group at the 8-position facilitates intramolecular catalysis from this group (Route A). However, the latter pathway has certain spatial requirements itself on formation of the tetrahedral intermediate at the 8-carbonyl carbon. When the 8-keto-group has a very weakly acidic carbon acid, with a pK_a equal to about 19,[3] ionisation produces a very strongly nucleophilic carbon acid anion. Rapid intramolecular attack is driven by the release of steric 'crowding' on cyclisation (Route B) and helped by the very favourable geometry of attack and proximity. When intramolecular catalysis by Route B is structurally impossible and by Route A is inhibited by resonance or steric 'bulk' effects, a very highly favourable hydrolytic mechanism pathway, employing neighbouring group participation, will not exist.

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