Steric Effects in the Nucleophilic *versus* General Base-catalysed Intramolecular Carboxy-group-assisted Solvolysis of Esters

By H. D. BURROWS and R. M. TOPPING*

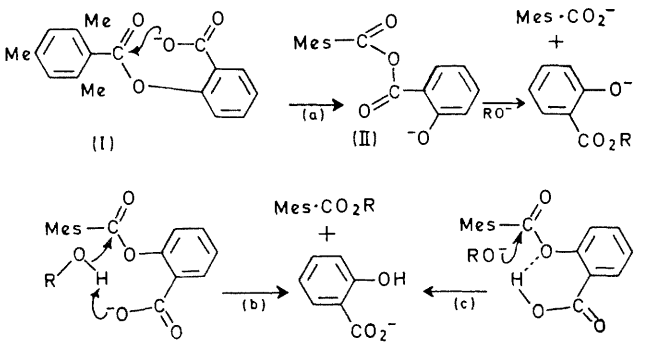
(*School of Molecular Sciences, University of Sussex, Brighton* BN1 9QJ)

Summary Intramolecular participation by carboxylate anion in the solvolysis of the hindered ester 2-carboxyphenyl mesitoate in anhydrous methanol, occurs entirely by a nucleophilic mechanism in contrast to aspirin which previously has been shown to involve the kinetically equivalent general base mechanism.

MUCH of the evidence[1-3] in support of a mechanism for the hydrolysis of esters such as aspirin monoanion, involving a rate-determining intramolecular nucleophilic attack by the carboxylate anion upon the ester carbonyl group to give the mixed anhydride of acetic and salicylic acids (which is hydrolysed in turn in a subsequent fast step) recently has been either refuted or re-interpreted.[4-7] The kinetically equivalent process involving participation of carboxylate as a general base is now preferred on the basis of lack of ^{18}O incorporation[5] into salicylate during aspirin hydrolysis in $H_2{}^{18}O$, solvent effects,[4] solvent deuterium isotope effects [$k(H_2O)/k(D_2O)$],[7] structure–reactivity correlations,[5] entropy considerations,[5] inability to trap an anhydride intermediate,[6] and the reactions of certain aspirin analogues.[6,8,9] A critical factor in determining which of the kinetically inseparable general base or nucleophilic mechanisms actually operates was shown to depend upon the relative basicities of attacking group and leaving group[6,7] although the *nature* of the attacking base also appears to affect its catalytic performance;[9] we have now shown that steric effects can be a deciding factor.

The products expected from the reaction of the hindered aspirin analogue, 2-carboxyphenyl mesitoate (I) in dry methanol are (i) mesitoic acid and methyl salicylate only when the carboxy-group acts as an *intra*molecular nucleophile and solvolysis proceeds *via* an anhydride intermediate [route (a) in Scheme]; (ii) methyl mesitoate and salicylic acid only when the carboxy-group acts either as an *intra*molecular general base [route (b)] or general acid [route (c)] or as a result of *inter*molecular attack by methoxide ion upon the hindered ester carbonyl group of (I). The products realised by heating under reflux a solution of ester (I) (10^{-4}M) and tris(hydroxymethyl)aminomethane

(10^{-3}M) in anhydrous methanol for five days were mesitoic acid and methyl salicylate in 100% yield (superimposition of u.v. spectra). No other products could be detected (v.p.c.; t.l.c.). The apparently unambiguous conclusion to be drawn is that the ester (I) has reacted entirely *via intra*molecular nucleophilic attack of carboxylate anion to give the anhydride (II) which is selectively cleaved by methoxide ion at the 'unhindered' salicylyl carbonyl group [route (a)]. This result is in contrast to that observed with aspirin itself[5,6] although differences in pK_a between attacking—and leaving—groups should be similar for the two analogous esters. Two points of interest emerge. Firstly, participation of carboxylate as a general base which occurs exclusively in the solvolysis of aspirin in water or methanol is entirely suppressed in favour of participation of carboxylate as a nucleophile when steric accessibility of the ester carbonyl is reduced as in ester (I), demonstrating the (perhaps not unexpected) greater steric requirements of the general base mechanism, a result which may prove to have general applicability. Secondly, the catalytic role of carboxylate in model systems or in enzymic processes will clearly be determined by a combination of *both* electronic and steric factors.



SCHEME. Mes=2,4,6-trimethylphenyl

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