Intramolecular Nucleophilic Keto-group Participation in Ester Solvolysis

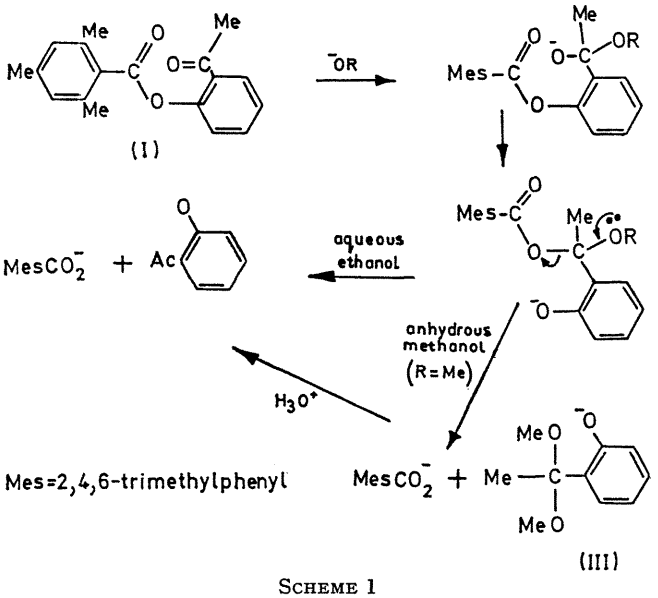
By H. D. BURROWS and R. M. TOPPING*
(*The Chemical Laboratory, University of Sussex, Brighton* BN1 9QJ)

Summary A rate-determining intramolecular nucleophilic attack by the conjugate base of the solvated keto-carbonyl group upon the ester carbonyl group of 2-acetylphenyl mesitoate greatly facilitates solvolysis and, in anhydrous methanol, results in acetal formation under basic conditions.

THE ability of suitably positioned aldehyde- and keto-carbonyl groups to facilitate ester hydrolysis has long been recognised[1,2] and the results of kinetic analysis have indicated the labilisation of the ester to arise in part through direct intramolecular participation involving some form of the hydrated carbonyl group.[3-6] Such facilitation has been suggested to have possible implications in enzymic processes of carboxylate[6] and phosphate[7] esters. Although the first suggestion of the possibility of intramolecular carbonyl-group participation was made with reference to keto-carbonyl,[3] the most convincing evidence in terms of rate enhancement was gained from analogous systems involving aldehyde-carbonyl,[5] and the degree to which keto-carbonyl is capable of such participation is still uncertain.[4,8] We now describe a system in which (*a*) the detection of intramolecular keto-group participation in the solvolysis of an ester is facilitated by steric suppression of the competitive intermolecular process and (*b*) the elucidation of the mechanism of such participation is indicated by the nature of products formed.

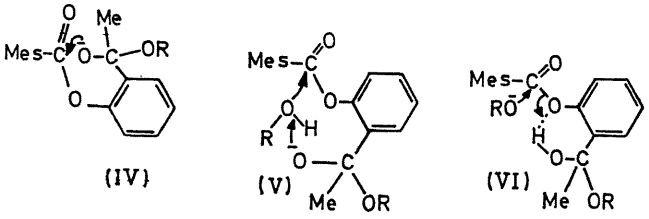
For both isomeric esters 2-acetylphenyl mesitoate (I) and 4-acetylphenyl mesitoate (II), a study of the influence of variation in pH upon the rate of scission of the ester bond reveals a first-order dependence with respect to both hydroxide ion and ester concentrations. However, under comparable conditions (pH 11·28, $\mu = 1{\cdot}0$M, $T = 30°$, solvent 9·5% ethanol–water) the 2-isomer (I) is hydrolysed 130 times more readily than the 4-isomer (II). Such a factor constitutes clear evidence for some form of participation of the keto-carbonyl group [*e.g.* as in (IV), (V) or (VI), Scheme 2] in the hydrolysis of the ester (I). The *nature* of the products (mesitoic acid and 2- or 4-hydroxyacetophenone from esters (I) and (II), respectively), however, unlike the analogous system involving amide group participation,[9]

provides no clue as to the mechanism of the participation. Such information was obtained from the nature of the products when the solvolysis of the ester (I) was examined in anhydrous methanol–methoxide solutions. Under such conditions a *concerted* disappearance of both the ester- and keto-carbonyl groups of the ester (I) was observed (Raman spectra) at a rate identical to that of a corresponding change in the u.v. spectrum which had indicated the formation of



SCHEME 1

a product ($pK'_a = 16{\cdot}2$) which lacked the 365 nm. absorption band characteristic of 2-hydroxyacetophenone anion. All evidence indicated that the products in anhydrous methanol–methoxide solutions were mesitoic acid and the dimethyl acetal (III) of 2-hydroxyacetophenone with all other intermediates at low steady state concentrations (Scheme 1). This result is notable for two reasons. Firstly, the formation of the acetal (III) would appear to be compatible only with a nucleophilic mechanism as in (IV). In anhydrous methanol, the operation of a mechanism involving general base catalysis [as in (V)] or general acid catalysis [as in (VI)] might be expected to result, in either case, in the formation of methyl mesitoate and 2-hydroxyacetophenone. These products [also to be expected from intermolecular attack by methoxide ion upon the ester carbonyl



SCHEME 2

group of (I)] were realised in less than 4% yield. Secondly, the hitherto unknown acetal (III) is highly unstable in aqueous solution (especially in neutral or acidic media) and attempts to prepare it using traditional methods failed. Its formation under *alkaline* conditions as a natural consequence of the sequence of reactions outlined in Scheme 1 provides strong support for such a scheme. Extrapolation of this reasoning to aqueous systems, though not without risk, provides a ready explanation for the difference in hydrolytic rates of the esters (I) and (II) and is fully in accord with previous suggestions.[3–6]

Solvolysis of the unhindered ester, 2-acetylphenyl benzoate, was shown also to involve participation of the keto-group and to be 355 times faster than solvolysis of hindered ester (I), indicating the importance of the intramolecular cyclisation step in the determination of the overall rate.

We thank the S.R.C. for a research studentship (to H.D.B.).

(*Received, June 11th,* 1969; *Com.* 836.)

[1] G. Vavon and J. Scandel, *Compt. rend.*, 1946, **223**, 1144.
[2] L. Holleck, G. A. Melkonian, and S. B. Rao, *Naturwiss.*, 1958, **45**, 438.
[3] M. S. Newman and S. Hishida, *J. Amer. Chem. Soc.*, 1962, **84**, 3582.
[4] M. S. Newman and A. L. Leegwater, *J. Amer. Chem. Soc.*, 1968, **90**, 4410.
[5] M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, 1962, **84**, 4589.
[6] M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *J. Amer. Chem. Soc.*, 1965, **87**, 4545.
[7] F. Ramirez, B. Hansen, and N. B. Desai, *J. Amer. Chem. Soc.*, 1962, **84**, 4588.
[8] K. Bowden and G. R. Taylor, *Chem. Comm.*, 1967, 1112.
[9] R. M. Topping and D. E. Tutt, *J. Chem. Soc.* (*B*), 1967, 1346; 1969, 104.