Elimination–Addition Mechanisms of Acyl-group Transfer Reactions: A Novel *E1cB* Mechanism in the Hydrolysis of 2,4-Dinitrophenyl 4-Hydroxybenzoate

Sergio Thea,[a] Giuseppe Guanti,[a] Giovanni Petrillo,[a] Andrew Hopkins,[b] and Andrew Williams[b]

[a] *Istituto di Chimica Organica dell'Universita, C.N.R., Centro di Studio sui Diariloidi e loro Applicazioni, Corso Europa, 16132 Genova, Italia*

[b] *University Chemical Laboratory, Canterbury, Kent CT2 7NH, U.K.*

Evidence is offered for the intermediacy of an unprecedented *para*-oxoketen intermediate in a dissociative mechanism for the hydrolysis of the title ester.

We are interested in the structural, electronic, and stereochemical factors favouring dissociative mechanisms of acyl-group transfer. Provision of suitable electron-releasing systems such as a charged atom α to the acyl function will tend to stabilise an incipient acylium ion and promote the dissociative process. It is possible to envisage stabilisation by a remote anion by mesomeric transfer of electrons through an aromatic nucleus; we therefore investigated the hydrolysis of 2,4-dinitrophenyl 4-hydroxybenzoate (**1**).†

The dinitrophenyl ester (**1**) decomposes in aqueous buffers at 25 °C with quantitative liberation of 2,4-dinitrophenol (as assessed by u.v.–visible spectrometry) according to equation (1). Buffer-independent rate constants (k_o), obtained by

$$k_{obs} = k_o + k_{buffer}\,[Buffer] \quad (1)$$

extrapolating k_{obs} to zero buffer concentration or by mechanically buffering the reaction by means of a modified pH-stat apparatus[1] (the two methods gave consistent results) obey equation (2); k_a and k_b are defined as in Scheme 1 and are respectively 6.0×10^{-4} s^{-1} and 6.65×10^{-2} dm^3 mol^{-1} s^{-1}. The ionisation constant measured spectrophotometrically for the phenolic group of (**1**) has a value of 2.1×10^{-8} mol dm^{-3} compared with the kinetically determined one of 1.8×10^{-8} mol dm^{-3} for the same conditions.

$$k_o = (k_a + k_b\,[OH])/(1 + a_H/K_a) \quad (2)$$

An associative hydrolytic mechanism might account for the pH dependence having a plateau (see Figure 1) which could originate from nucleophilic attack of hydroxide ion on neutral substrate ($k_{OH} = k_a K_a/K_w$) as in path A of Scheme 1. The 4-methoxy-analogue (Figure 1) is some 250-fold less reactive to hydroxide ion attack than compound (**1**); the 4-methoxy-derivative should be 1.6-fold *more* reactive on the basis of the sensitivity of the bimolecular reaction to substituents in the acid moiety (ρ *ca.* 2.0).[2]

We propose that the hydrolysis of (**1**) in the plateau region follows a dissociative path as depicted in Scheme 1 (path B) where ionisation of the substrate is followed by rate-determining decomposition of the conjugate base (**2**) to give 2,4-dinitrophenoxide ion and the *para*-oxo-keten (**3**).‡

The possibility that the enhanced rate constant refers to nucleophilic attack by hydroxide ion on the 2,4-dinitrophenyl moiety in an S_NAr process was ruled out by labelling studies which indicated exclusive CO–O fission. The 2,4-dinitrophenol from the reaction using ^{18}O-enriched water (6.20% enriched) has an $M + 2$ mass spectral peak with 1.24% intensity (natural isotopic composition 1.224%) and O–Ar cleavage should give 7.42% enrichment.

Trapping studies with aniline support the involvement of an intermediate; the rate constant at pH 10.05 in 0.01 M-carbonate buffer at ionic strength 0.1 M increases in the presence of aniline by 8.7 and 20.6%, respectively, for concentrations of

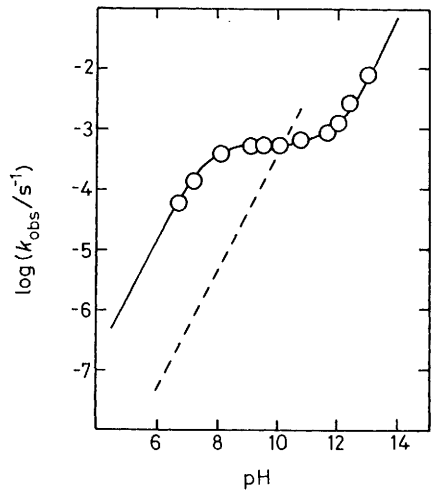
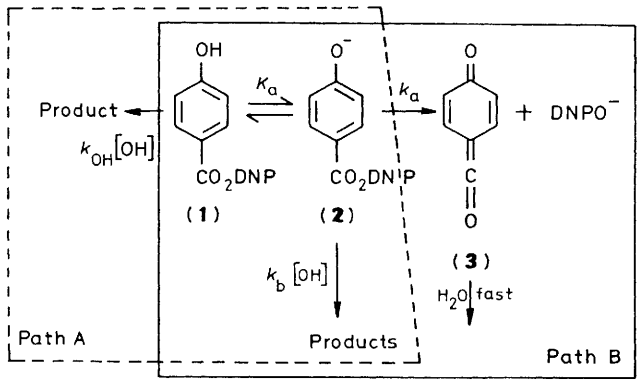


Figure 1. Dependence on pH of the hydrolysis of 2,4-dinitrophenyl 4-hydroxybenzoate (**1**) at 25 °C and zero buffer concentration; the ionic strength was maintained at 0.1 M with KCl. The full line is that calculated from equation (2) and parameters from the text; the dashed line is the dependence on pH of the hydrolysis of the 4-methoxy-analogue.



Scheme 1. DNP = 2,4-dinitrophenyl.

† This compound was synthesised from 4-hydroxybenzoic acid and 2,4-dinitrophenol using dicyclohexylcarbodi-imide; it gave satisfactory elemental and spectroscopic analyses.

‡ The pH-independent rate constant k_2 might relate to nucleophilic attack of water on (**2**) but arguments based on reactivity similar to those used by us for carbamate and phosphoramidate esters (A. Williams, *J. Chem. Soc., Perkin Trans.* 2, 1972, 808; A. Williams and K. T. Douglas, *ibid.*, 1972, 1454; 1973, 318) can be used to reject this possibility.

aniline of 0.102 and 0.219 M. Product analysis shows yields of 17.9 and 31.4%, respectively, of the 4-hydroxybenzanilide which are some two-fold larger than the amount expected from the kinetics. These results are consistent with a mechanism involving an intermediate which is trapped by aniline *after* the rate-determining step. The acceleration of the rate indicates the concurrent operation of an associative mechanism for the aniline reaction.

Alternative explanations are that the keten formation may not be completely rate-limiting or that a solvent effect due to increasing organic content (aniline) is operating. These interesting possibilities do not invalidate the results of the trapping experiments and will be discussed in the full paper.

The Arrhenius parameters for k_a are $\Delta S^{\ddagger} = +40$ kJ mol^{-1} K^{-1} and $\Delta H^{\ddagger} = 103$ kJ mol^{-1} at 25 °C. A positive entropy of activation is usually considered diagnostic for unimolecular reactions,[3] consistent with our proposed mechanism.

The term k_b can only refer to the bimolecular reaction of hydroxide ion with the ionised 4-hydroxy ester (Scheme 1). The rate constant for this reaction is some 27-fold smaller than that calculated from the Hammett equation (7 points, log $k_{OH} = 1.25 + 1.93\,\sigma$, $r = 0.997$) determined by us for the hydrolysis of 2,4-dinitrophenyl benzoates at 25 °C, 0.1 M-ionic strength. This low value is probably due to the neglect of the electrostatic effect.

The presence of labile hydrogen atoms on an atom adjacent to the carbonyl group has been considered a prerequisite for the occurrence of *E1cB* mechanisms.[4] To our knowledge this paper reports the first example of a dissociative mechanism in a carboxylic acid ester devoid of α-protons. Previous workers have reported *ortho*-analogues of the proposed *para*-oxoketen intermediate on the basis of gas-phase fragmentation reactions.[5] The factors responsible for reactions taking this novel mechanism as opposed to the path normally traversed will be discussed in the full paper.

We are grateful to NATO for partial financial support of this research.

Received, 15th February 1982; Com. 158

References

1 S. Thea and A. Williams, *J. Chem. Soc., Perkin Trans.* 2, 1981, 72.
2 J. F. Kirsch, W. Clewell, and A. Simon, *J. Org. Chem.*, 1968, **33**, 127; M. Caplow and W. P. Jencks, *Biochemistry*, 1962, **1**, 883, and also the present work.
3 W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969; K. T. Douglas, *Progr. Bioorg. Chem.*, 1976, **4**, 194.
4 A. Williams and K. T. Douglas, *Chem. Rev.*, 1975, **75**, 628.
5 V. Dvorak, J. Kolc, and J. Michl, *Tetrahedron Lett.*, 1972, 3443; O. L. Chapman, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.*, 1973, **95**, 4061; W. M. Horspool and G. D. Kandelwal, *Chem. Commun.*, 1970, 257; N. Dennis, A. R. Katritzky, and S. K. Parton, *J. Chem. Soc., Perkin Trans.* 1, 1974, 750; A. Williams and G. Salvadori, *J. Chem. Soc. B*, 1971, 1105.