Large Stereoelectronic Effect in 1,3-Dehydrohalogenation to form a 1,3-Dipole

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The E-hydroximidoyl chloride (5), prepared on photoisomerisation of (1) to (2) and by subsequent hydrolysis, is shown to lose HCl to give benzonitrile oxide 6×10^7 fold slower than the Z-isomer (3).

1,3-Elimination from reactive halides in the presence of a base is a widely used method for the preparation of 1,3-dipoles, which are used as substrates in cycloadditions in one of the most versatile heterocyclic syntheses.[1] We have now for the first time prepared isomeric hydroximidoyl chlorides and shown that their reactivity is critically dependent on the substrate structure.

Direct chlorination of either E- or Z-oximes (9) in CHCl₃ or in aqueous HCl leads to the Z-chloride (3), whose structure has been determined by X-ray crystallography.[2] α-Chloro nitrosoalkanes (6) are intermediates, isolable when tautomerisation to (3) is blocked [e.g when the hydrogen in (6) is replaced by an alkyl group]. Although simple oxime isomers differing in configuration about the C=N bond are known, all attempts to isomerise (3) to (5) photochemically or by using acid or heat failed.

Acylation of (3) leads to the esters (1) (R = Me or ClCH₂) which were successfully photoisomerised (in pentane–benzene using u.v. irradiation) to a 60:40 mixture of (1) and (2). These esters were separated using preparative t.l.c. [silica gel with pentane–diethyl ether (75:25) as eluent] and characterised.†

Deacylation of the two esters (1) and (2) (R = ClCH₂) is pH-independent (water catalysed) at low pH and catalysed by hydroxide ion at pH > 7 (see Figure 1); the less hindered Z-ester (1) reacts about twice as rapidly as (2). Following ester hydrolysis (2) gives the E-hydroximidoyl chloride (5) which then undergoes dehydrohalogenation at a measurable rate at high pH (see Figure 1).‡ The rate of dehydrohalogenation increases with [HO⁻] at low pH but then becomes pH independent at high pH giving an apparent pK_a of 9.8. This is consistent with a mechanism involving rapid reversible proton
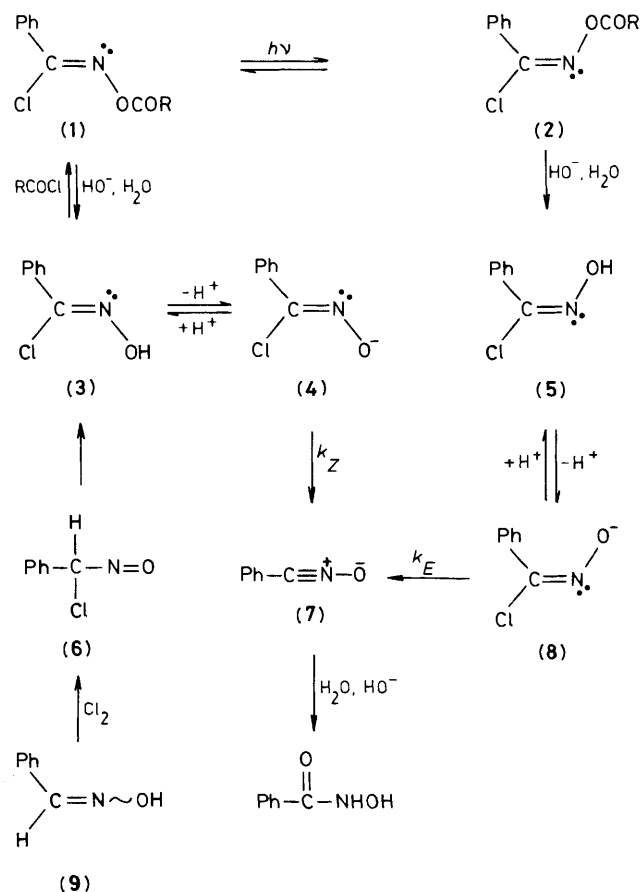
loss to give the reactive anion (8) which then loses Cl⁻ in the slow step to give benzonitrile oxide (7). Benzonitrile oxide (7) was shown to be the initial product of reaction of (5) by the identity of the u.v. spectrum obtained with that of an authentic sample of (7), by the characteristic subsequent reaction of (7) with HO⁻ and H₂O to form benzohydroxamic acid (see Figure 1) and by trapping with acrylonitrile. At some pHs the three
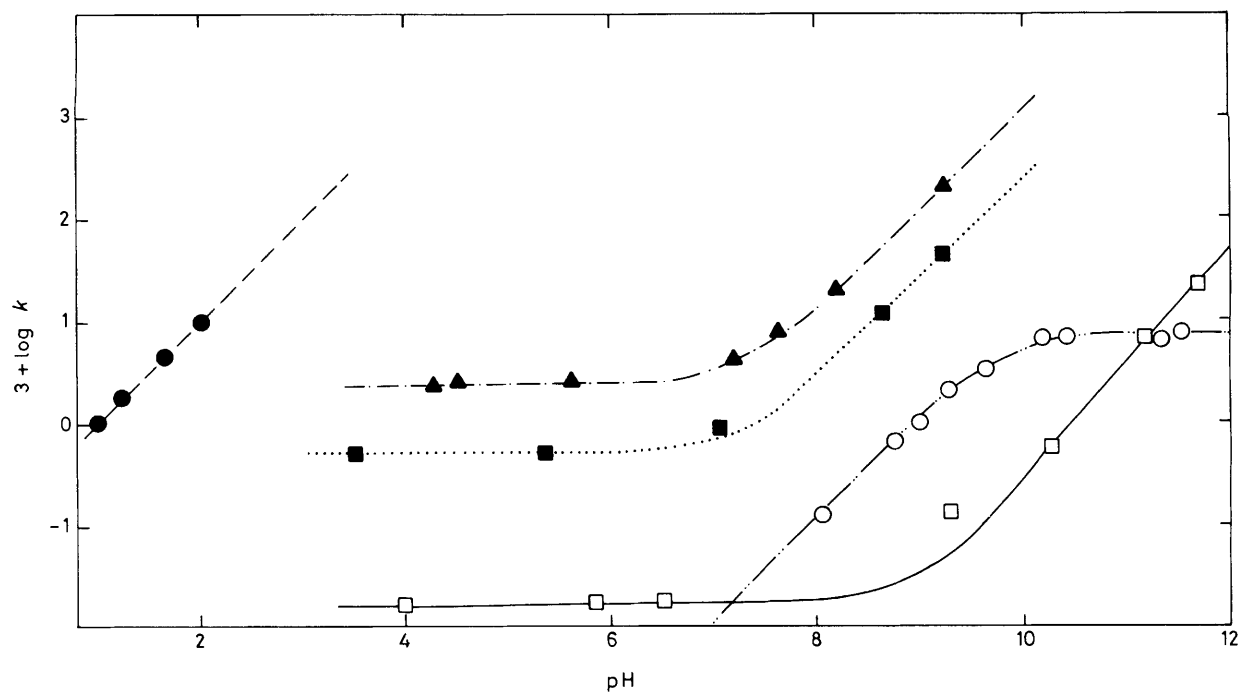
Figure 1. Plots of the log of the observed rate constant (k in s^{-1}, 25 °C, H_2O) for the reaction of (1; R = $ClCH_2$), ▲; (2; R = $ClCH_2$), ■; (3), ●; (5), ○; (7), □, as a function of pH.

reactions [deacylation of (2), HCl loss from (5), and subsequent reaction of (7) with solvent species] are competitive. This is particularly critical when R = Me for which (2) undergoes slower deacylation, but could conveniently be overcome by the addition of 1—5% morpholine. The morpholine accelerates the formation of (5) from (2) and traps (7) rapidly (to form an amidoxime) but leaves the rate of dehydrohalogenation of (5) to (7) (k = 7.5 × $10^{-3} s^{-1}$) unchanged.

The corresponding Z-isomer (3) is far more reactive and its rate of dehydrohalogenation could only be followed at low pH (Figure 1). The rate of reaction is proportional to [HO^-], consistent with the counter ion (4) being the reactive species. Assuming the same pK_a as determined for the E-isomer (5),[3] k_Z can be estimated as 4.5 × $10^5 s^{-1}$. Thus the Z-isomer (3) undergoes 1,3-elimination to the nitrile oxide (7) ca. 6 × 10^7 fold more rapidly than the E-isomer (5).[4]

Such a large configuration dependence in these 1,3-eliminations is consistent with the stereospecificity of the reverse reaction of nucleophiles with nitrilium ions[5] and with the related benzenediazonium ions.[6] There have been reports[7] of difficulties in the formation of 1,3-dipoles under some conditions which can now be clearly attributed to the slow rate of 1,3-dipole formation from the E-isomer, while a

claim[8] that the configurations about the C=N bond is unimportant in determining reactivity is clearly incorrect.

References

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4 Although (5) and (3) did not equilibrate under our reaction conditions, the Z-isomer of O-methyl benzohydroximidoyl chloride has been shown to be more stable than the E-isomer in the presence of strong acid (J. E. Johnson, N. M. Silk, E. A. Nalley, and M. Arfan, *J. Org. Chem.*, 1981, **46**, 546).

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