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

Anthony F. Hegarty* and Maria Mullane

Chemistry Department, University College, Belfield, Dublin 4, Ireland

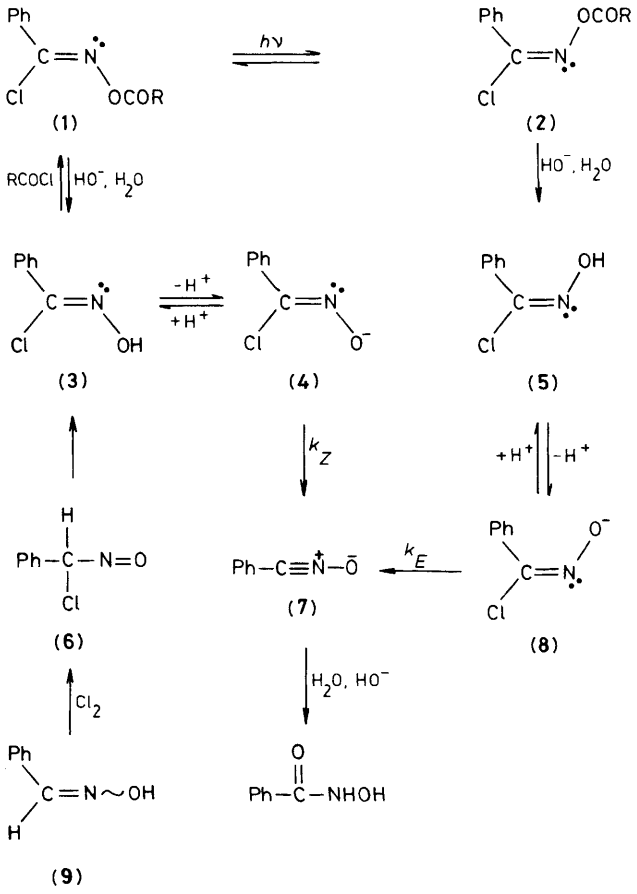
The *E*-hydroximidoyl chloride (**5**), prepared on photoisomerisation of (**1**) to (**2**) and by subsequent hydrolysis, is shown to lose HCl to give benzonitrile oxide 6×10^7 fold slower than the *Z*-isomer (**3**).

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 $CHCl_3$ 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 $ClCH_2$) 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 = $ClCH_2$) 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 H_2O to form benzohydroxamic acid (see Figure 1) and by trapping with acrylonitrile. At some pHs the three



† All new materials gave C, H, N, Cl analyses within acceptable limits; (**1**; R = Me), m.p. 43—44 °C (*ex* hexane); ^{1}H n.m.r. δ 2.3 (s, 3H); (**2**; R = Me), 59—60 °C; δ 2.12 (s, 3H); (**1**; R = $ClCH_2$), 57—58 °C; δ 4.32 (s, 2H); (**2**; R = $ClCH_2$), δ 4.18 (s, 2H).

‡ Reaction rates were measured in water (μ = 1.0, $NaClO_4$) at 25 °C by following changes in the u.v. spectra using a Cary 210 spectrophotometer.

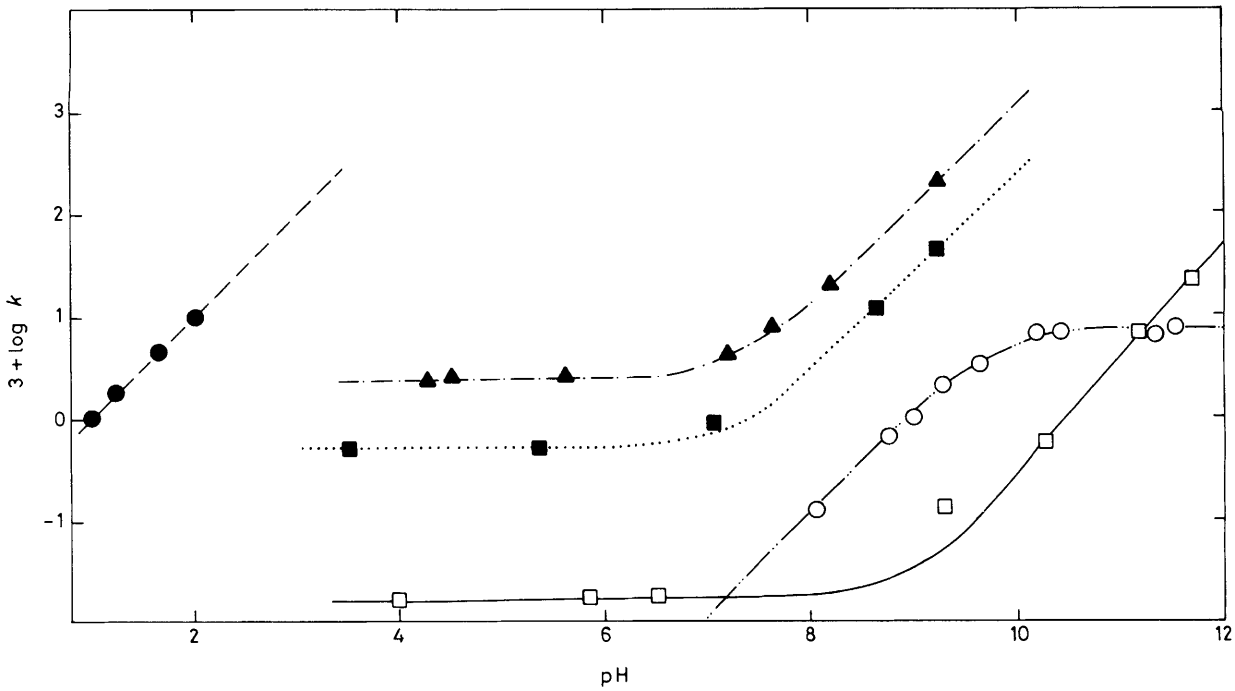


Figure 1. Plots of the log of the observed rate constant (k in s^{-1}, 25 °C, H_2O) for the reaction of (**1**; R = $ClCH_2$), ▲; (**2**; R = $ClCH_2$), ■; (**3**), ●; (**5**), ○; (**7**), □, as a function of pH.

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.

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