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MECHANISM OF THE HYDROLYSIS OF CHLOROAZINES TO HYDRAZIDES AND CYCLIZATION TO OXADIAZOLES.[1]

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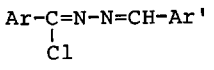
Both 1-chloro (and 1,4-dichloro)-1,4-diaryl-2,3-diaza-1,3-butadienes (1 and 2) have been used extensively as starting materials in heterocyclic synthesis.[2] The first step in these reactions generally involves displacement of one or both chlorine atoms. Despite the analogy with acyl chlorides,[3] nucleophilic substitution at the aza systems 1 and 2 has not been studied in detail.



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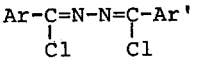

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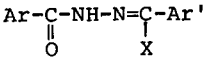

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The rates of hydrolysis of the unsubstituted monochloroazine[4] (1, Ar=Ar'=C $_6$H$_5$) were studied at 24.5° in 60% dioxan over the pH range 3.0-8.5. The pH was maintained constant using a Radiometer pH-stat assembly. The pH profile (Figure 1) shows regions in which the observed pseudo-first order rate constants are independent of pH (4-6) and, also where the hydrolysis is both acid (<pH 4) and base (>pH 7) catalysed. From pH 3-8 the product is in all cases the corresponding benzalbenzhydrazide (3, Ar = Ar' = C_6H_5, X = H). In more acidic or basic solution further hydrolysis of 3 (X = H) occurs with the formation of the corresponding benzoic acid. When the hydrolysis of 1 is run in the absence of buffers, the rate of hydrolysis increases markedly as the reaction proceeds, presumably due to acidic catalysis by the HCl generated.

Hydrolysis of 1, Ar = Ar' = C_6H_5, in the "plateau" (pH-independent) region was studied in more detail using a 0.1 M sodium acetate - 0.1 M acetic acid buffer at 50° in 60% dioxan (the apparent pH of this solution was 4.70). Under these conditions the rate of hydrolysis of 1 was (a)

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increased by the presence of an "inert" salt (such as $NaNO_3$), (b) decreased in the presence of a salt containing the common ion, Cl^- and (c) was very much dependent on the aqueous content of the solvent (Grunwald-Winstein m value[5] = 0.93 (r = 0.992) for solvents varying between 80% and 40% dioxan). The combined evidence suggest rate-determining azocarbonium ion formation (4) in this pH region, followed by rapid reaction with water (or other nucleophiles present in solution). Charge delocalization in the carbonium ion is available via the particularly favoured "octet-stabilized" structure 4b.

$$\underset{\text{4a}}{Ar\text{-}C^{+}=N\text{-}N=CH\text{-}Ar} \leftrightarrow \underset{\text{4b}}{Ar\text{-}C\equiv N^{+}\text{-}N=CHAr}$$

Variation of the aryl substituent Ar in 1 also supports this conclusion. Thus a plot of log k_{obsd} at pH 4.7 in 60% dioxan *vs.* the corresponding σ values[6] (for the series 1, Ar' = C_6H_5, Ar = XC_6H_5, where X = p-Me, H, p-Cl, m-NO_2 and p-NO_2) gave a ρ of -1.70 (r = 0.997). This is the expected value if something more than half the charge involved in carbonium ion formation were delocalised along the chain (as in 4b). It also falls within the gamut of values reported for the analagous hydrazidic halides.[7] In the same pH region the dichloroazines 2 are remarkably unreactive. Thus 2 (Ar = Ar' = C_6H_5) was recovered unchanged after 7 hr. reflux in 50% dioxan; under these conditions hydrolysis of 1 would be complete in less than 1 min.

In basic solution both 1 and 2 react relatively rapidly with HO^-. At $\{HO^-\}$ = 0.10 M, the hydrolysis of 1 at 50° showed a change-over in mechanism as Ar was varied (Figure 2). The chloroazines with strongly electron withdrawing substituents are correlated with a positive ρ value (*ca.* +0.67), consistent with bimolecular HO^- attack. However the Hammett plot (Figure 2) is clearly curved, the rate of hydrolysis also increasing with electron-donating substituents. This is similar to the behaviour noted for benzoyl chlorides[8] under certain conditions and the same explanation is offered in this case. Clearly there is a gradual change in mechanism from dissociative S_N1 to associative S_N2 as the substituent Ar becomes more electron withdrawing. Consistent with this view, the hydrolysis of 1 (Ar=p-MeC_6H_4, Ar' = C_6H_5) was zero order in hydroxide ion over the range 0.1 to 0.025 M $\{HO^-\}$.

The dichloroazines[9] 2 do hydrolyse in basic solution to form the oxadiazoles 5 quantitatively. At high $\{HO^-\}$ (= 0.2M) in 60% dioxan the substituent effect is formally the same as that observed for the monochloroazines with electron-withdrawing substituents. A ρ of +2.43 was calculated for 2 with Ar = Ar' = XC_6H_4; X = m-Cl, p-F, H and p-Me. Direct

Figure 1

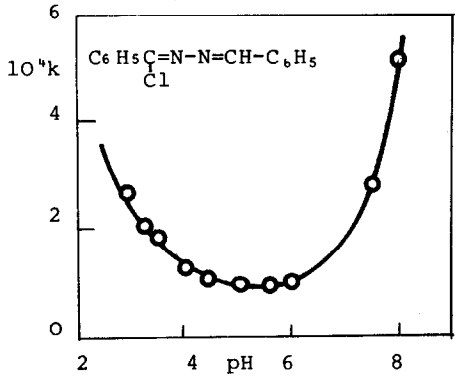


Figure 2

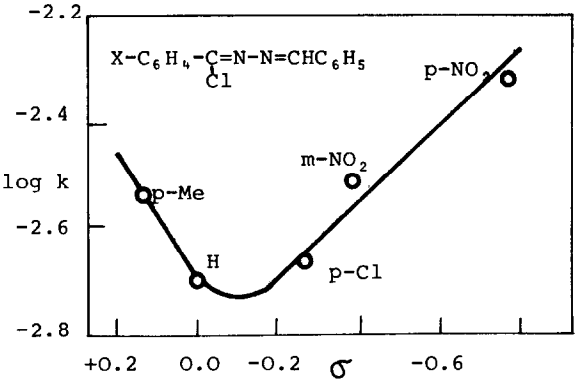
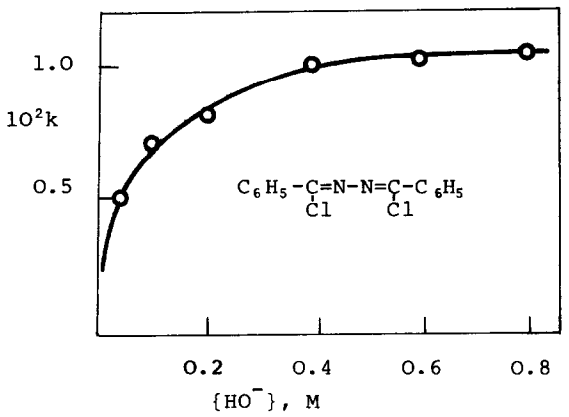


Fig. 1. Plot of observed rate constants (s^{-1}) for the hydrolysis of 1 (Ar=Ar'=C_6H_5) as a function of pH in 60% dioxan at 24.5°.

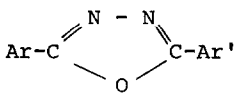
Fig. 2. Hammett plot for hydrolysis of monochloroazines in 60% dioxan containing 0.1 M NaOH at 50°.

Fig. 3. Plot of observed rate constants (s^{-1}) for oxadiazole formation from 2(Ar=Ar'=C_6H_5) as a function of $\{HO^-\}$ at 50° in 20% dioxan.

Figure 3



displacement of Cl^- by HO^- would give 3, X = Cl as an intermediate. This is a hydrazidic halide and under the strongly basic conditions used would rapidly dehydrohalogenate to give a 1,3-dipolar ion which is a resonance form of the 1,5-dipolar ion 6.[10] Cyclization of 6 yields the observed



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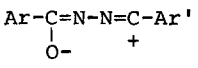

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product 5. Consistent with this is the isolation of 1,4-diethoxy-1,4-phenyl-2,3-diazabuta-1,3-diene (29%) in addition to 5 on refluxing 2 (Ar'=Ar'=C_6H_5)

in ethanolic NaOH. Presumably ethoxide ion acted initially as a nucleophile to displace Cl^-, followed by addition of ethanol to the rapidly formed 1,3-dipolar ion[11] (which, unlike 6 cannot readily cyclise).

However the detailed mechanism of HO^- attack is more complex since the observed rate does not show a simple dependence on $\{HO^-\}$. Although k_{obsd} is proportional to $\{HO^-\}$ at low $\{HO^-\}$, at higher $\{HO^-\}$, k_{obsd} changes from a first to zero order dependence on $\{HO^-\}$ (Figure 3). The expression $k_{obsd} = k_1k_2\{HO^-\}/(k_{-1} + k_1\{HO^-\})$ was used to correlate the kinetic data to better than $\pm 5^o$ with $k_1/k_{-1} = 21.6$ and $k_2 = 1.09 \times 10^{-2}\ S^{-1}$ for 2 (Ar = Ar' = C_6H_5) at 60^o in 20% dioxan (μ = 0.8) (See Fig. 3). The following scheme, involving tetrahedral intermediate ($T.OH^-$) formation gives a kinetic equation of the above format:

$$2 \underset{k_{-1}}{\overset{k_1\ (HO^-)}{\rightleftharpoons}} (T.OH^-) \xrightarrow[-Cl^-]{k_2} 5$$

It is difficult however to reconcile the observed substituent effects in Ar and Ar' with this scheme. Thus k_2 is increased (ρ = +2.4) and k_1/k_{-1} is decreased (ρ = -2.5) by the presence of electron withdrawing groups in Ar and Ar'. This is opposite to the expected effect on the basis of k_1 representing HO^- attack and k_2 the breakdown of the tetrahedral intermediate. In any event, the combined effect is such that at moderate $\{HO^-\}$ ($< 5 \times 10^{-2}$ M), the substituent effects on k_{obsd} (= $k_2.k_1/k_{-1}$ in this region) cancel one another so that the rate of oxadiazole formation is almost independent of chloroazine 2 structure.

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