

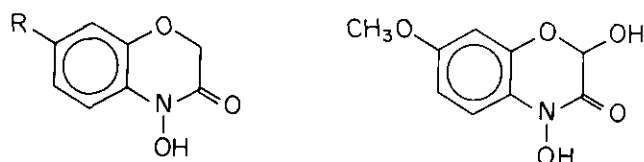
REACTION OF 7-SUBSTITUTED 4-HYDROXYL-1,4-BENZOXAZIN-3-ONES IN STRONGLY ACIDIC MEDIA

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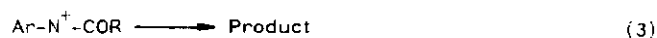
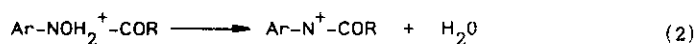
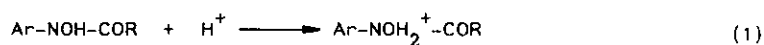
Abstract - Kinetic and product studies of the reaction of 7-substituted 4-hydroxyl-1,4-benzoxazin-3-ones in strongly acidic media produced biphasic Hammett plots which indicated the intermediacy of a highly electrophilic nitrogen compound with nitrenium ion character.

The *in vivo* mutagenicity of certain arylamines has been associated with their enzymatic oxidation to arylhydroxamic acids, further activation forming sulfate esters, and finally to formation of the ultimate carcinogen, a nitrenium ion.¹⁻³ The 1,4-benzoxazin-3-one derivatives (1a) and (2) are mutagenic.⁴ The *O*-acetylated derivative of 1a has been shown to react with nucleophiles,⁵ derivatives of nucleic acids among others,^{6,7} in reactions postulated to occur with the intermediacy of a nitrenium ion.⁸

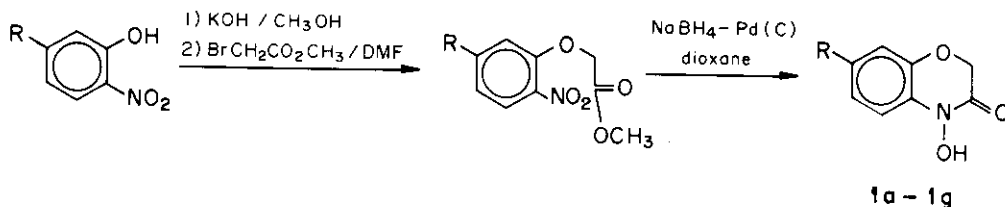


Compound	1a	1b	1c	1d	1e	1f	1g	2
R	CH ₃ O	CH ₃	H	F	Cl	CO ₂ CH ₃	CN	

The reaction of 1c in HCl to give 7-chloro-1,4-benzoxazin-3-one has been suggested to occur with formation of a nitrenium ion, in a sequence such as 1-3. We report herein kinetic studies on the decomposition of a series of 7-substituted 1,4-benzoxazin-3-ones (1a-1g) in HCl of different concentrations which support the scheme proposed.



The required hydroxamic acids (1a-g) were synthesized by reductive cyclization of the corresponding nitro esters, which were obtained by reaction of potassium *o*-nitrophenoxides with α -bromoacetate. All compounds gave spectral data consistent with the assigned structures.



The main products isolated from the reaction of 1c with concentrated HCl were 5-chloro- and 7-chloro-1,4-benzoxazin-3-ones, while for the analogous reaction of 1a the main product was 5-chloro-7-methoxy-1,4-benzoxazin-3-one.

The kinetics of the reactions was followed spectrophotometrically. At high HCl concentrations ($>1.7M$), the spectra of the reactants decreased continuously, while at low concentrations ($<1.7M$), an isosbestic point appeared. In all cases, however, the kinetics of the reactions were pseudo-first order with respect to reactants.

Figure 1 shows the rate constants as a function of H_0/pH for the unsubstituted compound (1c), and suggests independent decomposition of protonated and neutral forms of the compound, in equilibrium with each other as depicted in Scheme 1.

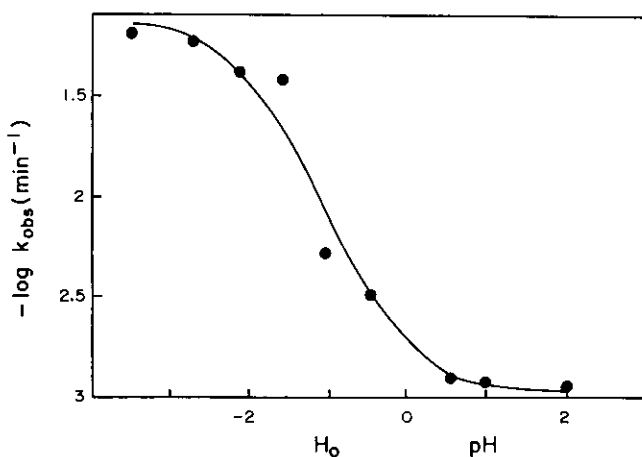
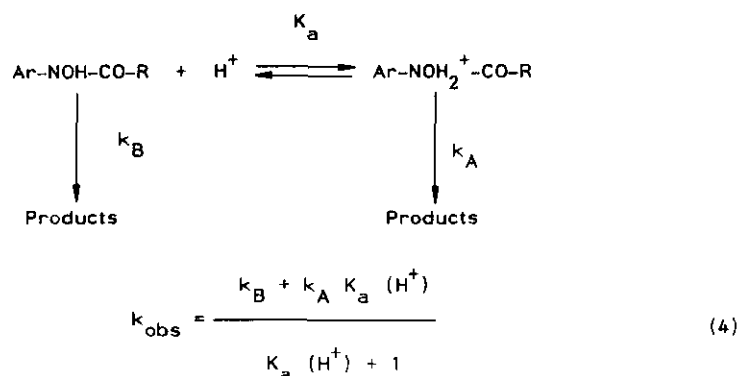


Figure 1. Decomposition of 1c in HCl of different concentrations at 31°C.

Scheme 1



Experimental points gave a strong fit to equation 4 describing the equilibrium in Scheme 1, and lead to values for k_B , k_A and K_a . $\text{p}K_a$ values obtained from similar studies conducted for other compounds of the series generated a linear Hammett plot with values of $\rho(\sigma^+) = 1.42$ and $r = 0.99$. Further evidence for the existence of a protonation equilibrium was obtained from the decomposition reaction of compound (2), a diprotic hydroxamic acid.⁹ Reactions followed pseudo-first order kinetics throughout the H_0/pH range studied. The rate constants determined gave rise to a plot against H_0/pH with 3 inflection points (Figure 2), corresponding to the dissociation processes involving protonated, neutral, monoanionic and dianionic species.

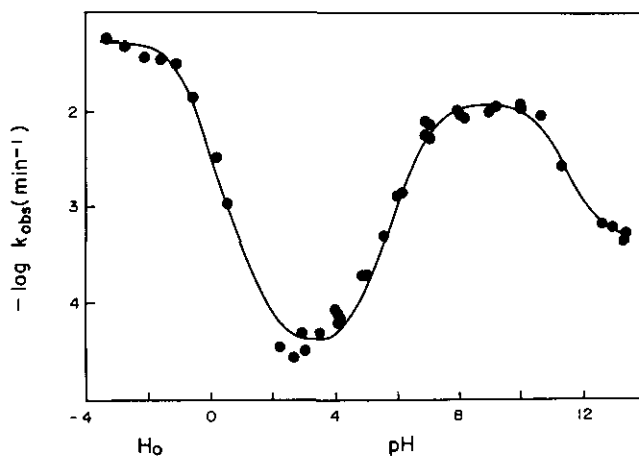


Figure 2. Decomposition of 2 in HCl of different concentrations (H_0 range) or different aqueous buffers (pH range) at 31°C . The line drawn corresponds to a least-squares fit of the experimental points to an extension of equation 4 which takes into account the four possible reactive species: protonated, neutral, monoanionic and dianionic.

The rates of decomposition of protonated (1a-g) (k_A values from equation 4) are plotted against Hammett parameters in Figure 3. The compounds fell into two distinct groups. Those with electron donating substituents were best correlated by Hammett parameters, the value of ρ being 0.71, and the correlation coefficient 0.99, as contrasted with 0.86 if σ^+ was used. Compounds with electron withdrawing substituents were best correlated by Hammett σ^+ parameters, the value of ρ being -4.08, and the correlation coefficient -0.96, as contrasted with -0.88 if σ was used.

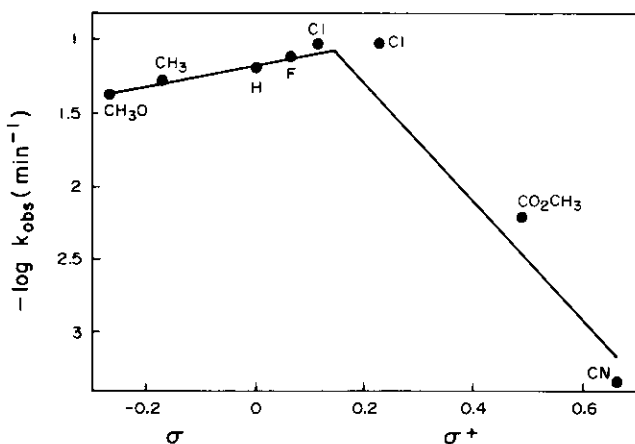


Figure 3. Hammett plot for the decomposition of protonated hydroxamic acids 1a to 1g, at 31°C.

It has been pointed out that Hammett plots with a concave downward break are indicative of a change in the rate determining step of an otherwise constant mechanism.¹⁰ This is consistent with equations 1-3, in which reaction 3 refers to the attack of chloride ion on the aromatic ring. Thus, in compounds with electron withdrawing substituents, the ionization step is rate determining; however, when the substituents stabilize the intermediate nitrenium ion sufficiently through electron release, nucleophilic addition by chloride ion becomes rate determining.

The signs and magnitudes of the ρ values and the nature of the parameters best describing the correlations are in agreement with this interpretation. When step 2 is rate determining, the transition state is electron deficient with respect to the ground state, and ρ is expected to be negative and best correlations are expected with σ^+ . The ρ value obtained might be compared with that for the decomposition of methanesulfonates of *N*-hydroxyacetanilides in chloroform ($\rho = -9.24$ with σ^+) which was shown to proceed

through a nitrenium ion.¹¹ The difference may be accounted for by a better leaving group and a less polar solvent in the case of sulfonate esters. When step 3 is rate determining, nucleophilic attack by chloride ion is facilitated by electron removal from the reaction center and a small positive ρ value is expected.

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