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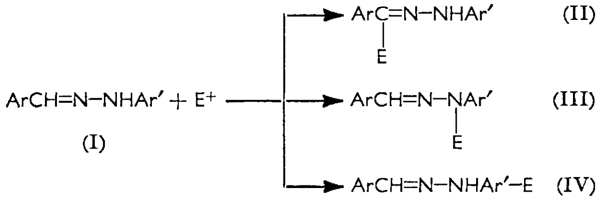
Isotopic, Steric, and Reagent Variation Effects in the Bromination of Hydrazones

By A. F. Hegarty and F. L. Scott

The bromination of benzylidene-*p*-nitrophenylhydrazine in 70% acetic acid at 20° has been measured by an electrometric method. Kinetic measurements at various bromide ion concentrations have shown that molecular bromine is the only brominating species of importance, and also that the rate-determining step in the brominations studied involved bromine attack followed by rapid deprotonation. The rate of bromination of [α-^{2}H]benzylidene-*p*-nitrophenylhydrazine afforded a k_H/k_D of 0·97, indicating no methine C–H stretching in the transition state. The kinetics of bromination of a variety of 2- and 2,6-substituted benzylidene-*p*-nitrophenylhydrazines have shown that the bromination process was insensitive to steric factors.

THE arylidene arylhydrazine system (I) may be formally regarded as a triply ambident nucleophile. Thus, electrophilic substitutions such as nitration,[1] bromination,[2] nitrosation,[3] and attack by reagents such as diazonium ion,[4] tetracyanoethylene,[5] and diethyl azodicarboxylate,[6] may occur at methine carbon as in (II), amino nitrogen as in (III), or at the *para*- and *ortho*-positions in the phenylhydrazine ring as in (IV). Bromination, for example, of an aldehyde hydrazone in acetic acid gives the hydrazidic bromide (II; E = Br), together with ring-substitution products if the hydrazine ring has not been deactivated. These reactions have many common features, such as the failure to yield methine-attack products when the amino hydrogen is replaced by a methyl group,[7] and all may have a common pathway in prior attack at the most basic centre, the amino nitrogen, followed by rearrangement to the other positions. Alternatively, the reactions at all three positions might be competitive and independent processes. We have reported the effect of substituents in Ar and Ar′ on the bromination reaction,[2] and we now extend this to study the brominating species involved, and the effect of isotopic substitution and steric effects at the reaction site.



EXPERIMENTAL

Materials.—Bromine, potassium bromide, and potassium nitrate were of AnalaR grade. The reaction solutions were prepared from water which had been triply distilled from alkaline potassium permanganate and acetic acid which had been distilled from chromium trioxide (b. p. 117—118°). The 70% acetic acid used as solvent was prepared by mixing 70 volumes of acetic acid and 30 volumes of water.

Substrates.—The hydrazones were prepared by refluxing *p*-nitrophenylhydrazine (10^{-2} mole) and the appropriate aldehyde (10^{-2} mole) in acetic acid (50 ml.) for 15 min. The *ortho*-substituted benzylidene-*p*-nitrophenylhydrazines were recrystallised to constant m. p. from aqueous ethanol (m. p.s in parentheses are from ref. 8 unless stated otherwise): 2-nitro, m. p. 261—262° (263°); 2,6-*dichloro*, 226—227° (Found: C, 50·5; H, 3·0; Cl, 22·6; N, 13·8. $C_{13}H_9Cl_2N_3O_2$ requires C, 50·35; H, 3·0; Cl, 22·9; N, 13·55%); 2-chloro, 249° (249°); 2-bromo, 251—252° (lit.,[9] 241—242°); 2-fluoro, 208—209° (lit.,[10] 205°); unsubst. 194° (192°); 2,4,6-*trimethyl*, 246—247° (Found: C, 68·0; H, 6·0; N, 14·85. $C_{16}H_{17}N_3O_2$ requires C, 67·9; H, 6·05; N, 14·85%). [α-^{2}H]Benzaldehyde was prepared by decarboxylation of deuterobenzoylformic acid.[11] Benzoylformic acid (6 g.) was dissolved in deuterium oxide (20 ml.), and exchange was completed by removal of the solvent by azeotropic distillation with benzene. Benzoic anhydride (19 g.), pyridine (33 ml.), and benzene (100 ml.) were added, and the solution was refluxed for 12 hr. The solution was then washed with 10% hydrochloric acid (5 × 20 ml.), 10% sodium hydrogen carbonate (5 × 20 ml.), and water (20 ml.). The organic layer was reduced to 40 ml. by distillation, and [α-^{2}H]benzaldehyde (2·9 g., 69%) was obtained by distillation *in vacuo* (b. p. 55—56°/6 mm.). The aldehyde (1 g.) was added to *p*-nitrophenylhydrazine (1·44 g.) in absolute ethanol (15 ml.) without acid catalyst, and [α-^{2}H]benzylidene-*p*-nitrophenylhydrazine was precipitated in nearly quantitative yield by the addition of water. Mass spectrum and n.m.r. analysis (the absorption at τ 2·18 in deuterochloroform with tetramethylsilane as reference was assigned to the methine proton) showed that 65% of the isotope was present and that it was not labile under the conditions used to study the kinetics. This last result is surprising since enamines, which are structurally similar to hydrazones, readily undergo exchange with deuterium oxide at the methine position.[12]

Kinetic Method.—The kinetics were followed by an electrometric method [2] in which low bromine concentrations

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were measured by recording the diffusion current of bromine at a rotating platinum electrode. The electrode was polarised by 0·2 v (with respect to a silver–silver chloride reference electrode) which was supplied by a Metrohm Polarecord, which, as a sensitive galvanometer, also recorded the diffusion current as a function of time. All kinetic experiments were at 20°. In the solvent used, 70% acetic acid containing an excess of bromide ion, bromine is largely converted into tribromide ion but the recorded diffusion current was independent of their relative amounts present, *i.e.*, the diffusion current is a measure of ($Br_2 + Br_3^-$). To simplify the kinetics the reactions were studied under pseudo-first-order conditions with the hydrazone initially in at least a twenty-fold excess. Since the hydrazones were not sufficiently soluble in 70% acetic acid to be added in concentrated form, they were made up, usually in 10^{-2}M-solution in glacial acetic acid. The bromine solutions were similarly prepared in glacial acetic acid. Then 1·0 ml. of each of these solutions was used in a kinetic experiment and added in the reaction cell to 20 ml. of solvent which contained sufficient water, potassium bromide, and potassium nitrate so that the final composition of the total of 22 ml. reaction solvent used was 70% v/v acetic acid–water with ionic strength 0·2M. In a typical kinetic experiment nitrogen was passed through the 20 ml. of solvent for 10 min. to minimise the possible aerobic oxidation of the hydrazones. The bromine solution was then added by means of a syringe through a self-sealing cap. The galvanometer recorded a diffusion current proportional to the amount of bromine added (but, as experienced by other workers,[13] with a clean platinum electrode the current does not reach a steady value rapidly; this was readily overcome by storing the electrode in a dilute bromine–potassium bromide solution when not in use). The hydrazone solution was then rapidly added by means of a syringe to start the reaction, and the recorder plotted a concentration (in arbitrary units) against time curve. The actual initial concentration of the hydrazone used varied with its reactivity, but was usually in the range 5×10^{-4} to 5×10^{-5}M, the lower concentrations being used with the more reactive hydrazones. Since the compounds were coloured, the time to achieve a homogeneous solution was readily estimated as 1—2 sec., and thus a complete rate determination could be carried out in 30 sec. The curves were then analysed to give the observed rate constants (k_{obs}); as the reaction is pseudo-first-order, even the arbitrary concentration units need not be changed. Since the reaction times were so short, the reaction of bromine with the solvent was not significant with initial concentrations greater than 10^{-6}M, and no correction had to be made.

Product Analysis.—The monobromination of benzylidene-*p*-nitrophenylhydrazine to give *N*-(*p*-nitrophenyl)-benzhydrazidic bromide, m. p. 190°, has been reported.[14] *N*-(*p*-Nitrophenyl) *ortho*-substituted benzhydrazidic bromides were prepared in the following manner. The hydrazone (10^{-2} mole) was suspended in acetic acid (40 ml.) and stirred while bromine (0·6 ml.) was added during 3 hr. More bromine (0·8 ml.), and a longer stirring time (6 hr.), was required for the *o*-nitro-hydrazone, while with mesitaldehyde *p*-nitrophenylhydrazone only 0·5 ml. of bromine was used, since larger amounts gave ring bromination. The hydrazidic bromides were precipitated by the addition of water, and washed thoroughly with water and ether. They were then recrystallised several times to constant m. p. from glacial acetic acid (Table 1).

Table 1

The hydrazidic bromides ArCBr=N·NH·C_6H_4·NO_2

Ar	M. p.	Found (%)				Formula	Reqd. (%)			
		C	H	Br	N		C	H	Br	N
2-Cl·C_6H_4	170—171°	44·2	2·4	23·0	11·9	$C_{13}H_9BrClN_3O_2$	44·0	2·6	22·5	11·85
2-Br·C_6H_4	179	38·9	2·3	40·5	9·5	$C_{13}H_9Br_2N_3O_2$	39·1	2·3	40·1	10·5
2-NO_2·C_6H_4	145	42·8	2·4	21·9	15·3	$C_{13}H_9BrN_4O_4$	42·8	2·5	21·9	15·3
2-F·C_6H_4	181—183	46·6	2·6	23·2	12·5	$C_{13}H_9BrFN_3O_2$	46·1	2·7	23·6	12·4
(2,6-Cl_2)C_6H_3	165	39·4	2·0	20·7	10·2	$C_{13}H_8BrCl_2N_3O_2$	40·1	2·1	20·5	10·8
(2,4,6-Me_3)C_6H_2	224	53·4	4·5	21·8	11·6	$C_{16}H_{16}BrN_3O_2$	53·0	4·5	22·1	11·6

RESULTS AND DISCUSSION

The standard substrates used to study the bromination reaction were arylidene-*p*-nitrophenylhydrazines. Under the conditions used, the *p*-nitro group so effectively deactivated the hydrazine ring to which it was attached that only methine bromination (with the formation of hydrazidic bromides) occurred. The reaction was studied in 70% acetic acid containing an excess of bromide ion, under which conditions the active brominating species may be either (or both) molecular bromine and tribromide ion.[15] By measuring the response of the bromination reaction to various concentrations of bromide ion, the rate-controlling step of the reaction may be determined, and the relative effectiveness of molecular bromine and tribromide ion as electrophiles towards the substrate can also be estimated.

In general terms the bromination of a hydrazone (ArH) may take place in two steps, the first involving the formation of an intermediate, and the second the loss of a proton: [16]

$$\mathrm{ArH} + \mathrm{Br_2} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (\mathrm{ArHBr})^+ + \mathrm{Br}^-$$

$$\mathrm{ArH} + \mathrm{Br_3}^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (\mathrm{ArHBr})^+ + 2\mathrm{Br}^-$$

$$(\mathrm{ArHBr})^+ \xrightarrow{k_3} \mathrm{ArBr} + \mathrm{H}^+$$

Using a steady-state approximation for the concentration

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of the intermediate $(ArHBr)^+$, the following equation is obtained:

$$k_{obs}(1 + K[Br^-]) = \frac{k_1 + k_2K[Br^-]}{1 + k_{-1}/k_3[Br^-] + k_{-2}/k_3[Br^-]^2}$$

where k_{obs} is the observed overall rate constant for the reaction, and K is the equilibrium constant for the reaction $Br_2 + Br^- \rightleftharpoons Br_3^-$. This assumes that the intermediates formed from attack by both electrophilic species are the same. This appears reasonable from Dubois and Aaron's[17] data for the bromination of anisoles, where the ρ values for the bromination by both species are similar; however, Atkinson and Bell,[18] while studying the bromination of olefins, assumed that different intermediates were formed since to do otherwise would imply that tribromide ion is a stronger electrophile than molecular bromine in some reactions, and this is difficult to accept. If the first step determines the overall rate of reaction, then $k_{-1} + k_{-2} \ll k_3$ (or $k_3[B]$ if a base is involved in the removal of a proton), and the expression then reduces to:

$$k_{obs}(1 + K[Br^-]) = k_1 + k_2K[Br^-], \text{ or } = k_1,$$

if tribromide ion is not an electrophile, while, if loss of a proton is rate-controlling, then $k_{-1} + k_{-2} \gg k_3$ and

$$k_{obs}(1 + K[Br^-]) = \frac{k_1 + k_2K[Br^-]}{k_{-1}/k_3[Br^-] + k_{-2}/k_3[Br^-]^2},$$

$$\text{or} = \frac{k_1k_3}{k_{-1}[Br^-]}$$

if tribromide ion is not an electrophile. Thus, depending upon which set of conditions exist, there is a unique relationship between $k_{obs}(1 + K[Br^-])$ and $[Br^-]$.

We have measured the rate of bromination of benzylidene-*p*-nitrophenylhydrazine at several concentrations of bromide ion, maintaining the ionic strength constant at 0·2M by the addition of potassium nitrate. Figure 1 shows a plot of $k_{obs}(1 + K[Br^-])$ against $[Br^-]$ with[19] $K = 84$. The precise value of K is not accurately known and it may vary with the salt used to maintain constant ionic strength, but the results are not appreciably affected by any small variation of the constant. Even though k_{obs} varies considerably over the range 0·2—0·02M $[Br^-]$, the function $k_{obs}(1 + [KBr^-])$ is relatively independent of $[Br^-]$. As noted above, this result has a dual implication. Not only is tribromide ion ineffective as a brominating species in this reaction, but also proton loss is a fast reaction, the observed rate constant being determined by the electrophilic first step.

It has previously been supposed that tribromide ion will always be a less electrophilic agent than molecular bromine, although there may be little difference between them with substrates of high reactivity, on the principle that selectivity will generally decrease with increasing reactivity. Our results are in accord with this, since the reaction with hydrazones is relatively slower than those reactions in which the tribromide ion term becomes important, but the principle must be viewed with some doubt since k_2/k_1 is not always proportional to reactivity.[18] Some caution must also be exercised in interpreting such results, since, even though the ionic strength was maintained constant, specific salt effects might mask a small tribromide ion reactivity, and indeed plots of $k_{obs}(1 + K[Br^-])$ against $[Br^-]$ have given different slopes if various inert salts are used.[20]

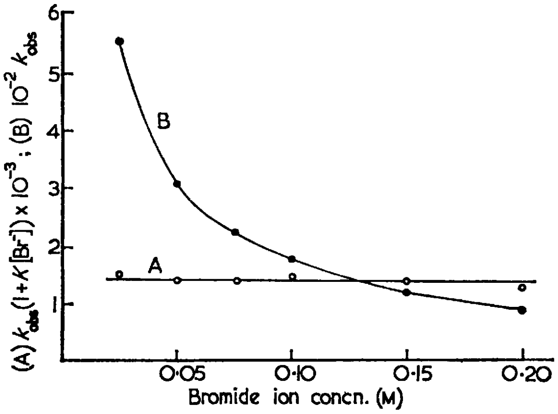

FIGURE 1 Bromination of benzylidene-*p*-nitrophenylhydrazine; relationship between bromide ion concentration and (A) $k_{obs}(1 + K[Br^-])$, and (B) k_{obs}, with $I = 0·2$M

To confirm that proton loss is a relatively fast reaction and that the C–H bond is not appreciably stretched in the transition state, the effect of the replacement of hydrogen by deuterium on the methine carbon was studied. The rate of bromination of [α-^{2}H]-benzylidene-*p*-nitrophenylhydrazine ($k_{obs} = 164$ l. mole^{-1} sec.$^{-1}$ in 70% acetic acid containing 0·1M-potassium bromide) was approximately the same as the rate for the bromination of the protium compound ($k_{obs} = 159$ l. mole^{-1} sec.$^{-1}$ under the same conditions), indicating the absence of a primary kinetic isotope effect. In fact, the deutero-compound reacted more rapidly ($k_H/k_D = 0·97$; data from six experiments), probably owing to a small secondary α-isotope effect,[21] but this deviation from unity is too close to the experimental error to allow a more definite conclusion.

Zollinger[22] identified steric hindrance in the intermediate as an important factor in determining the magnitude of k_{-1}, which might thus lead to an isotope effect. We have examined the rates of bromination of a series of *ortho*-substituted benzylidene-*p*-nitrophenylhydrazines in 70% acetic acid containing 0·1M-potassium bromide. The results are given in Table 2; the rate constants are expressed in l. mole^{-1} sec.$^{-1}$, and most of the values represent the mean of 3—6 experiments. An attempt was made to correlate these data by means

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TABLE 2

Bromination of *ortho*-substituted benzylidene-*p*-nitrophenylhydrazines ($ArCH{=}N{\cdot}NH{\cdot}C_6H_4{\cdot}NO_2$)

Ar	k_{obs}
2,4,6-Trimethylphenyl	230
Phenyl	159
2-Chlorophenyl	96
2-Bromophenyl	90
2-Fluorophenyl	102
2,6-Dichlorophenyl	66
2-Nitrophenyl	48

of the Taft equation using E_s and σ^* values for the *ortho*-substituted benzoates.[23] However, only a very small steric correction was required, the data fitting the reduced equation $\log k/k_0 = \rho^*\sigma^*$. This is seen clearly in Figure 2, where log *k* values are plotted against σ^*. The broken line is drawn from data[2] for substituents in the 3- and 4-positions in the benzylidene ring ($\rho = -0{\cdot}62$), and even the most highly substituted compounds do not deviate from this by more than 10%. Thus *ortho*-substituents provide little steric hindrance to the approach of bromine to the methine position.

We previously described[2] the bromination reaction in terms of the formation of an azabromonium ion intermediate, basing this picture on the response of the reaction to substituent effects. Substituents in the hydrazine ring have a larger effect ($\rho = -2{\cdot}2$) than those in the aldehyde ring ($\rho = -0{\cdot}62$), indicating a charge distribution that has considerable immonium ion character. Such conclusions would be limited, however, if different electrophiles, each with its own steric and substrate nucleophilicity requirements, were involved in the reaction to different extents. Our present results from the variation of bromide ion concentration show that molecular bromine is the only brominating species of importance. These data also suggest that the transition state for bromination may be pictured as involving a nucleophilic displacement (probably by the π-electrons of the azomethine bond, $>C{=}N-$) on the bromine molecule. The absence of a primary kinetic isotope effect in the methine function supports this idea also. Moreover, the reaction shows little steric sensitivity to the entry of the reagent, so that bromine which has the least steric requirement of the possible brominating species (*e.g.*, bromine, tribromide ion, protonated *N*-bromo-compound) most readily fits this condition.

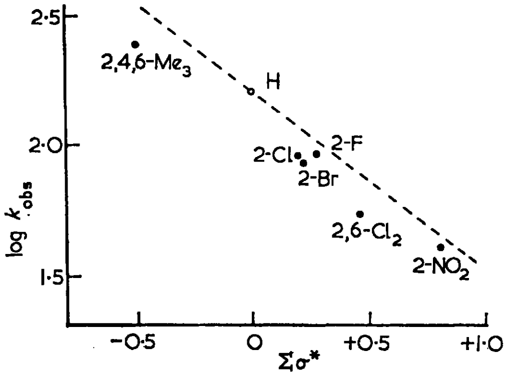

FIGURE 2 Bromination of *ortho*-substituted benzylidene-*p*-nitrophenylhydrazines, $ArCH{=}N{\cdot}NH{\cdot}C_6H_4{\cdot}NO_2$; the open circle represents the unsubstituted compound ($Ar = C_6H_5$)

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