Studies on the Mechanism of Acid-Catalyzed Bromination of a Hindered Alkyl Aryl Ketone: 2,4,6-Trimethylacetophenone.[1] Rate Dependence on Bromine Concentration

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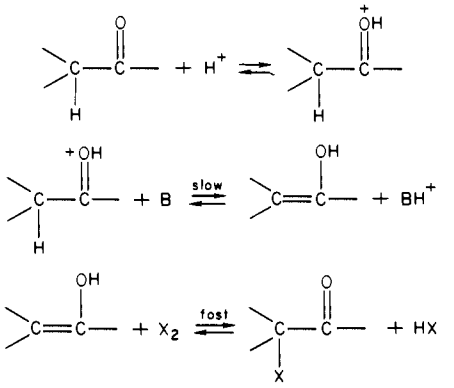
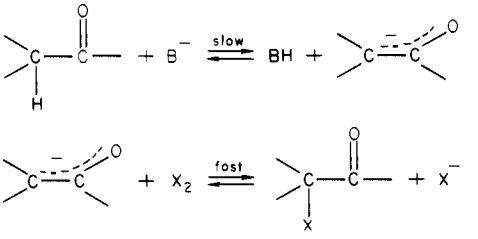
Abstract: According to the generally accepted Lapworth mechanism for halogenation of ketones, where the rate of reaction is independent of halogen concentration, the slow, rate-determining step is the formation of enol or enolate. The rate of reaction of bromine with 2,4,6-trimethylacetophenone (**1**) was found to depend on bromine concentration at moderately high concentrations. In the proposed mechanism, reaction of bromine with enol is rate determining—the enolization step being faster. A carbocation (**4**) instead of a bromonium ion is proposed as the intermediate from reaction of enol with bromine. Rates were determined by following the decrease in bromine concentration at 449 nm under these conditions: 50% acetic acid (v/v), HBr catalysis, and ionic strength adjusted with sodium perchlorate at 25 °C. With excess ketone, the average pseudo-first-order rate constant was 1.82×10^{-3} s^{-1}. At a fixed bromine concentration and at varying equal concentrations of both ketone and bromine, k_2 values were 4.34×10^{-2} and 4.39×10^{-2} L mol^{-1} s^{-1}, respectively. In studies on the effect of bromide ion on the rate, molecular bromine was found to be the active brominating agent with Br_3^- contributing to only 0.6% of the rate constant. Added chloride ion increased the rate; this was explained by Br_2/Cl^- interchange to form Br–Cl, a more effective brominating agent. Only bromo ketone was isolated in a preparative-scale reaction containing chloride ions. Added acetate ions decreased the rate as a result of a decrease in proton concentration by formation of acetic acid. Perchloric acid increased the rate. From variable-temperature studies, E_a = 61.5 kJ mol^{-1} and $\Delta H^{\ddagger}$ = 59.0 kJ mol^{-1}. The rate of reaction of bromine with hindered ketone, **1**, was nearly 900 times as fast as that with the unhindered analogue, acetophenone, under comparable conditions.

During previous studies,[2] hindered ketones were reacted with bromine on a number of occasions. Unexpectedly rapid reactions with bromine in carbon tetrachloride were qualitatively noted. Although rates of reactions of bromine with alkyl ketones and some alkyl aryl ketones have been widely investigated, no studies with hindered alkyl aryl ketones have been reported. According to the generally accepted Lapworth mechanism[3] acid- or base-catalyzed halogenation of ketones is dependent on the concentration of ketone and acid or base but independent of halogen concentration and nature of halogen except predictably at very low halogen concentrations[4-6] (10^{-8}–10^{-5} M). The rate-determining step is conversion of ketone to enol or enolate followed by a rapid reaction with halogen (Schemes I and II). A readily available representative hindered ketone, 2,4,6-trimethylacetophenone, was selected as the standard substrate for the present kinetic study. In addition, an unhindered analogue, acetophenone, was selected for comparative studies under the same conditions.

Scheme I. General Mechanism for Acid-Catalyzed Halogenation



Scheme II. General Mechanism for Base-Catalyzed Halogenation



Experimental Section

Preliminary Studies. A Beckman DB spectrophotometer was used to monitor bromine reacting with the ketone in carbon tetrachloride with time at 417 nm. The following observations were made in these preliminary investigations: (1) The reaction showed a long induction period. (2) Subsequent to the induction period, the reaction conformed to a first-order pattern. (3) A slight deviation from a first-order pattern was noted for the final 10–15% of the reaction. It was concluded that the induction period was due to the lack of acid catalysis at the beginning of the reaction which was autocatalytic due to the formation of hydrogen bromide.

The following results were observed with acetic acid solvent: (1) The reaction showed similar trends in 100% acetic acid and 50% H_2O/50% AcOH. (2) The induction period was considerably reduced in the presence of sulfuric acid and to a lesser extent with hydrochloric acid. (3) Addition of sodium bromide markedly reduced the rate of the reaction. (4) No induction period was evident in the presence of hydrobromic acid.

The following experimental conditions were optimum; (1) solvent, 50% aqueous acetic acid; (2) HBr, 0.500 M; (3) Br_2, 0.00100–0.00500 M; (4) 2,4,6-trimethylacetophenone, ca. 0.0500 M; (5) λ 439 nm (ϵ 129), the isosbestic point for the Br_2–Br_3^- system. The bromine solution in 50% aqueous acetic acid obeyed Beer's law in the entire range of concentra-

(1) Previous paper: Pinkus, A. G.; Gopalan, R. *J. Chem. Soc., Chem. Commun.* **1981**, 1016–1017. We call attention to a typographical error in this paper: aqueous $MeCO_2H$ was one of the solvent systems in place of the $MeCO_3H$ printed on p 1017.

(2) Pinkus, A. G.; Servoss, W. C. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1600–1603 and references therein. Pinkus, A. G.; Riggs, J. I., Jr.; Broughton, S. M. *J. Am. Chem. Soc.* **1968**, *90*, 5043–5044.

(3) Lapworth, A. *J. Chem. Soc.* **1904**, 30–42. Watson, H. B. *Chem. Rev.* **1930**, *7*, 173–201. Bell, R. P. "Acid–Base Catalysis"; Clarendon: Oxford, 1941; p 135 ff. Anantakrishnan, S. V.; Venkataraman, R. *Chem. Rev.* **1943**, *33*, 27–55.

(4) Bell, R. P. "The Proton in Chemistry"; Cornell University Press: Ithaca, NY, 1959; p 179 and references therein.

(5) Yates, K.; Wright, W. V. *Can. J. Chem.* **1963**, *41*, 2882–2888.

(6) Dubois, J.-E.; El-Alaoui, M.; Toullec, J. *J. Am. Chem. Soc.* **1981**, *103*, 5393–5401.

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Table I. Effect of Bromine Concentration on the Rate of Reaction of 2,4,6-Trimethylacetophenone with Bromine (Ionic Strength Not Maintained)[a]

$10^3[Br_2]$, M	$10^4 k_{obsd}$, s^{-1}	$10^3[Br_2]$, M	$10^4 k_{obsd}$, s^{-1}
1.9	10.7	4.6	7.18
2.5	9.1	5.1	6.72
2.9	8.13	6.9	5.89
3.9	7.3	9.1	5.61

[a] $[MesCOCH_3] = 0.0500$ M; [HBr] = 0.500 M; solvent = 50% AcOH (v/v); temperature = 25.0 ± 0.1 °C; λ 439 nm. $MesCOCH_3$ is the abbreviation for 2,4,6-trimethylacetophenone used in all tables.

Table II. Effect of Bromine Concentration on the Rate of Reaction of 2,4,6-Trimethylacetophenone with Bromine at Constant Ionic Strength[a]

$10^3[Br_2]$, M	$10^3 k_{obsd}$, s^{-1}	$10^3[Br_2]$, M	$10^3 k_{obsd}$, s^{-1}
1.17	1.78	4.30	1.71
1.80	1.96	5.83	1.70
2.06	1.78	8.10	1.83
3.40	1.91	10.0	1.86

$10^3 k_{obsd}$ (av) = 1.82 s^{-1}

[a] $[MesCOCH_3] = 0.0500$ M; [HBr] = 0.100 M; $[NaClO_4] = 0.400$ M; solvent = 50% AcOH (v/v); temperature = 25.0 °C.

tions used for kinetic studies. The presence of 2,4,6-trimethylacetophenone did not alter the absorbance of bromine solutions. Table I shows a decrease in pseudo-first-order rate constants with increase in bromine concentration. Satisfactory first-order rate constants were obtained (Table II) with sodium perchlorate used to maintain constant ionic strength. The isosbestic point under the latter condition shifted to 449 nm.

Reagents. 2,4,6-Trimethylacetophenone (bp 100 °C (4 mmHg)) was prepared by the Friedel–Crafts reaction between mesitylene and acetyl chloride. Its purity was checked by its ^1H NMR spectrum. Fisher analytical reagent grade bromine was used without further treatment. Acetic acid was a Mallinckrodt sample of 99.7% assay. Hydrobromic acid solutions were freshly prepared before the beginning of each reaction by diluting bromine-free Mallinckrodt analytical reagent acid. Diluted solutions were standardized by titration against standard sodium carbonate (Mallinckrodt analytical reagent) solution to a methyl orange end point. These solutions did not liberate bromine during the course of several hours.

Analytical grade sodium perchlorate ($NaClO_4 \cdot H_2O$) was dehydrated by heating the solution for 48 h at 120 °C in an oven. Solutions of 2,4,6-trimethylacetophenone were prepared in acetic acid. Other solutions were prepared in water. No noticeable volume change was observed when equal volumes of water and acetic acid were mixed.

Rate Measurements. The reaction was followed by measuring the decrease in bromine concentration from reaction solutions by observing the changes in absorbance with a Beckman DB spectrophotometer with use of stoppered 10-cm cells. As a check, the visible spectrum of the bromine–bromide solutions (λ 449 nm, ε 111.4) was recorded with a Cary spectrophotometer to obtain the same isosbestic point as with the Beckman DB spectrophotometer. Wavelength calibrations of the two spectrophotometers were also checked with alkaline potassium chromate solutions.

Since bromine concentrations used were low, the reaction was fast and the cells were stoppered; loss of bromine due to evaporation was insignificant. This was confirmed by constancy of absorbance of a solution of bromine during the course of an hour.

Suitable volumes of bromine, hydrobromic acid, and sodium perchlorate were pipetted into a dry 1-cm cuvette placed in the cell holder maintained at 25.00 ± 0.03 °C. The reaction mixture was stirred thoroughly as soon as the ketone solution at 25 °C was added, and the cell was tightly stoppered. A timer was switched on when half of the ketone solution was delivered into the cell. Absorbances were recorded at various time intervals. The rate constants, k_{obsd}, were evaluated by least-squares analysis of ln A vs. time plots with a UNIVAC-FORTRAN computer. The reactions were followed up to 80% of the reaction with linear plots; the rate constants were reproducible to better than ±3%. Least-squares analysis of the data gave satisfactory ln (absorbance) vs. time plots with correlation coefficient in the range 0.95–0.99. Whenever this coefficient was less than 0.95, the data were rejected.

Table III. Effect of 2,4,6-Trimethylacetophenone Concentration on the Rate of Reaction with Bromine[a]

$10^3[MesCOCH_3]$, M	$10^3 k_{obsd}$, s^{-1}	$k_2 = \frac{10^2 k_{obsd}}{[MesCOCH_3]}$, L mol^{-1} s^{-1}
26.7	1.21	4.53
33.3	1.44	4.32
38.0	1.61	4.24
43.3	1.89	4.36
46.0	1.95	4.23
48.0	2.05	4.27
54.0	2.49	4.61
88.1	3.70	4.20
101.7	4.41	4.34
		(av 4.34)

[a] $[Br_2] = 0.00200$ M; [HBr] = 0.100 M; $[NaClO_4] = 0.400$ M; solvent = 50% AcOH (v/v); temperature = 25.0 °C.

No photocatalytic bromination of 2,4,6-trimethylacetophenone occurred. The rate constants were the same whether the reaction solution was exposed to the light beam during the entire period of the kinetic run or only during the brief periods of recording the absorbances.

Product Identification. From a larger scale run, the product, 2,4,6-trimethylbromoacetophenone, was isolated and identified by means of its melting point and expected IR and ^1H NMR spectra. Spectra of the crude product showed no significant amounts of extraneous bands as compared with a purified sample, indicating that no significant amounts of other products were formed under the conditions of the study. The α-monobromo ketone, mp 55–66 °C, was previously prepared[7] by reaction of the ketone with bromine in acetic acid. A confirmatory synthesis of the compound was carried out[8] with a Friedel–Crafts reaction of bromoacetyl chloride with 1,3,5-trimethylbenzene.

Bromination of 2,4,6-Trimethylacetophenone in the Presence of Chloride Ion (Product Isolation). The ketone (1.62 g, 0.20 M) and 0.60 g (0.20 fw) of sodium chloride were dissolved in 50 mL of 50% aqueous acetic acid containing 0.01 M of HCl. To this solution, cooled in ice, was added gradually with stirring 1.6 g (0.20 M) of bromine during a 30-min period. The reaction mixture was stirred for 30 min more and then poured into 50 mL of cold water. The organic product was extracted with two 50-mL portions of *n*-hexane. The hexane layers were combined and washed with aqueous sodium bicarbonate and water and then dried over anhydrous sodium sulfate. The solvent was removed with a flash evaporator, and the ^1H NMR spectrum of the residue was recorded. The spectrum was found to be identical with that obtained with the α-bromo ketone, prepared in the absence of chloride ion. In both spectra, the resonance signal due to $-CH_2-Br$ was observed to be the same, occurring at δ 4.07; no absorption appeared at the position expected for the chloro ketone. This shows that no chloro ketone is formed when bromination is done in the presence of Cl^- ions.

Results

Effect of Bromine and 2,4,6-Trimethylacetophenone Concentrations. Generally reactions were carried out with a large excess concentration of 2,4,6-trimethylacetophenone to that of bromine so that pseudo-first-order kinetics were followed. In addition, an excess amount of ketone precluded dibromination and consequent kinetic complications. Each reaction was conducted in the presence of hydrobromic acid, whose concentration far exceeded that of bromine. Hydrobromic acid had a dual function in the bromination, first as a proton source to catalyze the reaction and eliminate the induction period and second to supply bromide ion which reacts with bromine to form tribromide (Br_3^-) making the reaction conform to excellent pseudo-first-order kinetics. The initial addition of excess bromide ensured that the small amount of bromide produced had no complicating influence on the reaction.

The reaction was followed at different initial concentrations of bromine, keeping all other parameters constant. The rate constants thus obtained are reported in Table II. The k_{obsd} values

(7) Guss, C. O. *J. Am. Chem. Soc.* **1953**, *75*, 3177–3179. Dauben, W. G.; Rogan, J. B. *Ibid.* **1959**, *78*, 4135–4139.

(8) Jacobs, W. A.; Heidelberger, M. *J. Biol. Chem.* **1915**, *21*, 455. Kao, T.-Y.; Miao, C.-S. *J. Chin. Chem. Soc. (Peking)* **1945**, *12*, 71–74. Kao et al. used bromoacetyl bromide in a Friedel–Crafts acylation; their product had mp 54 °C.

Table IV. Rates of Reaction of 2,4,6-Trimethylacetophenone and Bromine at Equal Concentrations[a]

$10^4[MesCOCH_3]$, M	$10^4[Br_2]$, M	10^2k_2, L mol^{-1} s^{-1}
18	18	4.47
20	20	4.32
27	27	4.66
38	38	4.20
50	50	4.31
		(av 4.39)

[a] [HBr] = 0.100 M; [$NaClO_4$] = 0.400 M; solvent = 50% AcOH (v/v); temperature = 25.0 °C.

Table V. Effect of Bromide Ion as Hydrobromic Acid on the Rate of Reaction of 2,4,6-Trimethylacetophenone and Bromine[a]

$10^2[HBr]$, M	10^4k_{obsd}, s^{-1}	10^2k_2, L mol^{-1} s^{-1}	$K/(K + [Br^-])$
0.500	85.2	17.0	0.7664
1.00	76.5	15.3	0.6212
2.50	51.8	10.4	0.3961
5.00	30.6	6.12	0.2470
10.0	20.1	4.20	0.1409
15.0	14.5	2.90	0.09856
20.0	11.8	2.36	0.07579
30.0	10.4	2.08	0.05183
35.0	9.30	1.86	0.04476
45.0	8.34	1.67	0.03516
50.0	8.16	1.63	0.03176

[a] [$MesCOCH_3$] = 0.0500 M; [Br_2] = 0.0027 M; [HBr] + [$NaClO_4$] = 0.500 M; solvent = 50% AcOH (v/v); temperature = 25.0 °C.

are constant within experimental error limits, indicating that the reaction is first order in bromine. The order of the reaction with respect to 2,4,6-trimethylacetophenone was determined by the isolation method. The rate constants, k_{obsd}, obtained at a fixed concentration of bromine and different concentrations of the ketone are presented in Table III. The values of k_{obsd}, when divided by respective 2,4,6-trimethylacetophenone concentrations, afford fairly constant k_2 values. This implies that the reaction is first order in ketone also, the overall order being 2. Hence, the reaction may be represented by the rate expression

$$\text{rate} = k_2[Br_2][MesCOCH_3]$$

As further proof for second-order behavior, bromination was carried out at equal initial concentrations of ketone and bromine. Plots of the reciprocal of bromine concentrations vs. time were linear, the slopes of which gave the second-order rate constant, k_2 (Table IV). These k_2 values are reasonably close to each other and also agree with values in the third column of Table III, thereby validating the overall second-order behavior of the reaction.

Effect of Bromide Ion Concentration. (1) Added as Hydrogen Bromide. It has been well established[9] that bromide ion influences the rates of bromination of various organic compounds. This is basically due to formation of tribromide ion by reaction between Br_2 and Br^-. When there is no prior addition of Br^- to the reaction medium, Br^- formed during substitution complicates the reaction path, necessitating the use of complex rate expressions. The problem is eliminated by prior introduction of an excess of bromide ion into the reaction medium. Under this condition, small amounts of bromide formed during reaction do not affect the reaction and simple rate laws describe the kinetics. These principles apply to the present reaction. The reaction was very fast, and the data did not satisfactorily fit a first-order rate law when no bromide was added initially. In addition, the reaction was retarded with time, presumably due to formation of bromide ion with time. The effect of the concentration of bromide ion on reaction rate was investigated. The rate constants obtained with different excess amounts of bromide ion in the reaction medium are in Table V. At any instant of the reaction the measured absorbance corresponds to total bromine, $[Br_2]_t$ (Br_2 and Br_3^-), in the system. Hence the rate expression may be written as

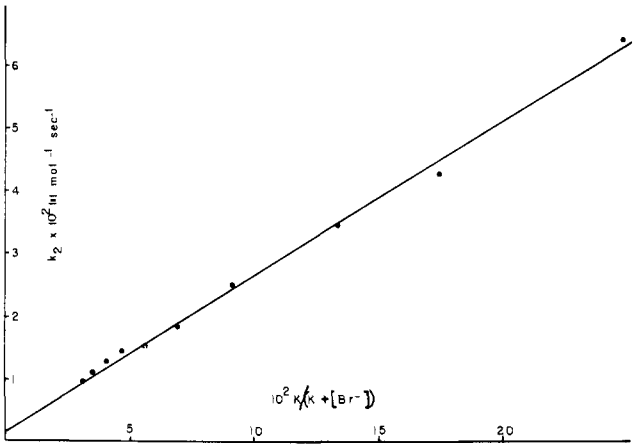

Figure 1. Effect of sodium bromide on bromination of acetomesitylene.

$$-dx/dt = k_2[MesCOCH_3][Br_2]_t \quad (1a)$$

$$Br_3^- \rightleftarrows Br_2 + Br^- \quad (1b)$$

$$[Br_2]_t = [Br_2]_f + [Br_3^-] \quad (2)$$

where $[Br_2]_f$ refers to free molecular bromine. Combining (1) and (2) and rearranging,

$$[Br_2]_f = \frac{K}{K + [Br^-]}[Br_2]_t \quad (3)$$

The initial concentration of Br^- is large compared to that formed in the reaction and hence Br^- can be deemed a constant. Consequently, $K/(K + [Br^-])$ is also a constant for a particular initial bromide concentration.

Assuming that free molecular bromine is the active substituting species, the rate expression becomes

$$-dx/dt = k[MesCOCH_3][Br_2]_f \quad (1a')$$

Substituting for $[Br_2]_f$ from eq 3,

$$\frac{-dx}{dt} = k[MesCOCH_3]\frac{K}{K + [Br^-]}[Br_2]_t \quad (4)$$

Comparing (1a) and (4),

$$k_2 = \frac{kK}{K + [Br^-]} \quad (5)$$

The term k denotes the specific rate constant for substitution by molecular free bromine. If molecular bromine were the brominating species, as per eq 5, a plot of k_2 vs. $K/(K + [Br^-])$ should be linear, the slope of which is k. The k_2 values when plotted against $K/(K + [Br^-])$ gave an excellent straight line with a correlation coefficient of 0.995. This unequivocally shows that molecular bromine is the predominant brominating species. However, if it were the sole brominating agent, the intercept of this plot should be zero. Actually the line does not pass through the origin and has a small intercept value (0.009203). This may be explained by assuming that $[Br_3^-]$ is also active in the bro-

(9) (a) Bartlett, P. D.; Tarbell, D. S. *J. Am. Chem. Soc.* **1936**, *58*, 466–474. de la Mare, P. B. D. *Q. Rev. Chem. Soc.* **1949**, *3*, 126–145. Atkinson, J. R.; Bell, R. P. *J. Chem. Soc.* **1963**, 3260–3269. Bell, R. P.; Pring, M. *J. Chem. Soc. B* **1966**, 1119–1126. Rolston, J. H.; Yates, K. *J. Am. Chem. Soc.* **1969**, *91*, 1583–1491. (b) K as defined in this paper is the dissociation constant of Br_3^-: $K = ([Br_2][Br^-])/[Br_3^-]$. Since in most of the recent literature values K is defined as an association constant, the reciprocal of our K_{diss} is given as 60.9 L mol^{-1} (av) for comparison with literature values. The conditions used in the present paper are 50% aqueous acid (v/v), 25.0 °C, [HBr] = 0.50–50.0 × 10^{-2} M, [HBr] + [$NaClO_4$] = 0.50 M, and λ 449 nm. This value can be compared with recent spectrally determined literature values ranging from 53 to 136. K values vary with concentration, temperature, ionic strength, counterion, and wavelength of light used for those determined by spectral means. (Values from references in ref 9a by de la Mare and Rolston and Yates and citations therein.)

Table VI. Effect of Chloride Ion on the Rate of Reaction of 2,4,6-Trimethylacetophenone and Bromine[a]

$[Cl^-]$, M	k_2, L mol^{-1} s^{-1}	$[Cl^-]$, M	k_2, L mol^{-1} s^{-1}
0.00500	0.397	0.253	3.94
0.0670	1.75	0.376	4.48
0.129	3.52	0.438	5.13
		0.500	5.26

[a] $[MesCOCH_3] = 0.00300$ M; $[Br_2] = 0.0028$ M; [HCl] = 0.00500 M; $[NaCl + NaClO_4] = 0.495$ M; temperature = 25.0 °C; solvent = 50% AcOH (v/v).

Table VII. Effect of Bromide Ion on the Rate of Reaction of 2,4,6-Trimethylacetophenone and Bromine[a]

$[Br^-]$, M	10^2k_2, L mol^{-1} s^{-1}	$[Br^-]$, M	10^2k_2, L mol^{-1} s^{-1}
0.00500	22.7	0.253	2.25
0.0670	6.56	0.376	1.39
0.129	3.73	0.438	1.06
		0.500	1.04

[a] $[MesCOCH_3] = 0.00300$ M; $[Br_2] = 0.0028$ M; [HBr] = 0.00500 M; $[NaBr + NaClO_4] = 0.495$ M; temperature = 25.0 °C.

mination of 2,4,6-trimethylacetophenone. However, the small value of the intercept is indicative of the much smaller role of Br_3^- compared to that of Br_2.

(2) Added as Sodium Bromide. In order to study the effect of bromide ion on the reaction, varying amounts of hydrobromic acid were used (Table V). Since protons catalyze the reaction, it was desirable to ascertain the effect of bromide ion independent of the effect of acid concentration. Hence the reaction was carried out with different concentrations of sodium bromide keeping the acid concentration constant. When the rate constants, k_2, were plotted against $K/(K + [Br^-])$, a linear plot (Figure 1) was obtained with slope = 0.2478 and intercept = 0.001596. This confirms that molecular bromine is the brominating agent. The value of the intercept, which corresponds to the rate constant for the reaction by Br_3^-, is only 0.6% of the specific rate constant. Hence it is obvious that Br_3^- is not an effective brominating agent in this reaction.

Effect of Chloride Ion. The effect of chloride ions on reaction rate was studied for comparison with the effect of bromide. Reactions were conducted at different initial concentrations of chloride ion, keeping the other experimental parameters constant. The second-order rate constants obtained in this manner are reported in Table VI. These reactions were followed by measuring the decrease in absorbance at λ 429 nm (ϵ 131), which was found to be the isosbestic point for the system. The following UV spectral parameters for the system were used: solvent = 50% AcOH (v/v); $\mu = 0.500$ ($NaClO_4$). The effect of Cl^- on the rate is the reverse of that by Br^- (Table VII). These runs were made at the same halide concentrations as the bromide ones in order to make a better comparison. At the halide concentration of 0.00500 M, the k_2 value for Cl^- is nearly twice that for Br^-. This ratio increases at high $[X^-]$ and is 500 times that for Br^- at $[X^-] = 0.500$ M.

These results can be rationalized by assuming that chloride ion interacts with Br_2 to form Br_2Cl^-: $Br_2 + Cl^- \rightleftarrows Br_2Cl^-$. The Br_2Cl^- species can undergo dissociation to form Br–Cl and Br^-. Hence in the presence of chloride ion, there are likely to be two molecular halogen species, Br–Br and Br–Cl. Of these two, the Br–Cl may be expected to be a more active halogenating species because the Br–Cl bond is more polar than the Br–Br bond thus increasing the positive charge on bromine since chlorine is more electronegative. Bromination being electrophilic, the reaction is faster with $Br^{\delta+}$–$Cl^{\delta-}$ compared to Br–Br. This order was previously reported[10] in additions to alkenes of Br_2 and BrCl. Catalysis by chloride was also reported[11] in bromine addition to alkenes.

(10) White, E. P.; Robertson, P. W. *J. Chem. Soc.* **1939**, 1509–1515.
(11) Nozaki, K.; Ogg, R. A. *J. Am. Chem. Soc.* **1942**, *64*, 697–716. Swedlund, B. E.; Robertson, P. W. *J Chem. Soc.* **1945**, 131–133. Swedlund, B. E.; Robertson, P. W. *Ibid.* **1947**, 630–634.

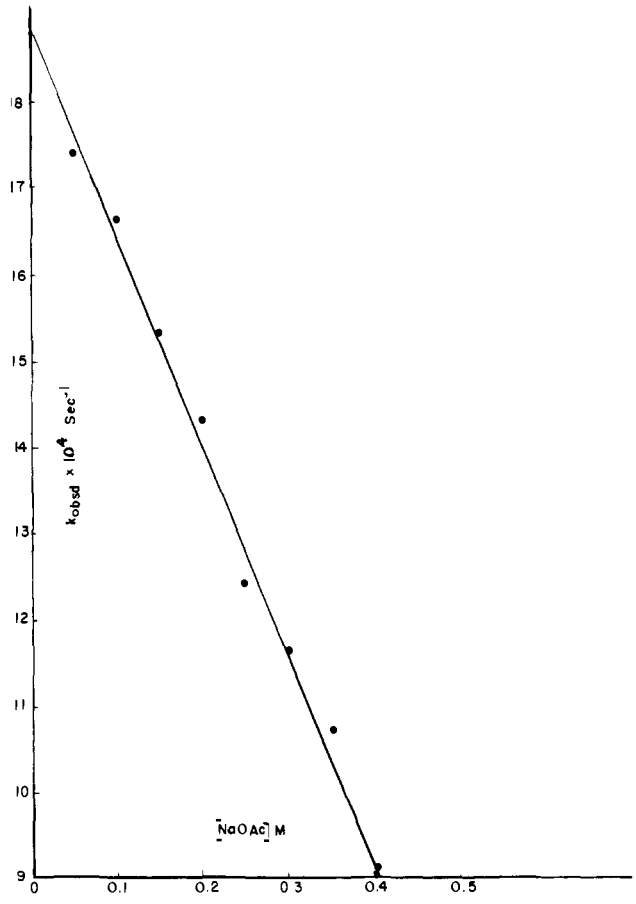

Figure 2. Effect of sodium acetate on bromination of acetomesitylene.

The influence of chloride ion also confirms that halogenation (bromination) and not enolization is the rate-limiting step with 2,4,6-trimethylacetophenone. No change in k_2 values would be expected on the addition of Cl^- if enolization were slower than bromination as reported with unhindered ketones.

Effect of Acetate Concentration. Since the reaction was carried out in aqueous acetic acid medium, it was of interest to determine the effect of acetate ion on the reaction. The reaction was carried out in the presence of various concentrations of sodium acetate. The reaction is inhibited by an increasing amount of sodium acetate. The catalytic influence of a salt on a reaction can be represented by the general equation

$$k_{cat} = k_0 + b[\text{salt}]$$

where k_0 is the rate constant of the uncatalyzed reaction and b is the catalytic constant. A plot of [NaOAc] vs. k_{obsd} values gives a straight line (Figure 2) with a *negative* slope. Hence the effect of NaOAc on the reaction can be represented by the equation

$$k_{obsd} = 0.001885 - 0.002405[\text{NaOAc}]$$

Effect of Perchloric Acid. In order to determine the effect of a strong acid other than hydrobromic acid on the rate of the reaction, perchloric acid was selected. It was found that perchloric acid has a positive catalytic effect on the reaction: increasing $[HClO_4]$ increases the rate constant. A plot of k_{obsd} vs. $[HClO_4]$ is linear (Figure 3) with slope = 0.00225 and intercept = 0.00169. The intercept represents the rate constant when $[HClO_4] = 0$. Thus the catalysis by perchloric acid can be represented by the equation

$$k_{cat.} = k_0 + a[HClO_4]$$

$k_{cat.}$ is k_{obsd} in the presence of $HClO_4$; k_0 represents the rate constant for the uncatalyzed reaction ($[HClO_4] = 0$); and a is the catalytic constant.

Effect of Temperature. In order to determine thermodynamic activation parameters, the effect of temperature on the rate was

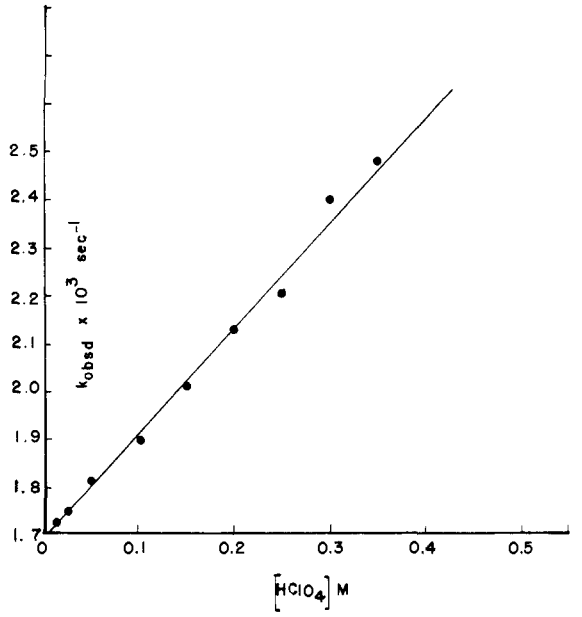

Figure 3. Effect of perchloric acid on bromination of acetomesitylene.

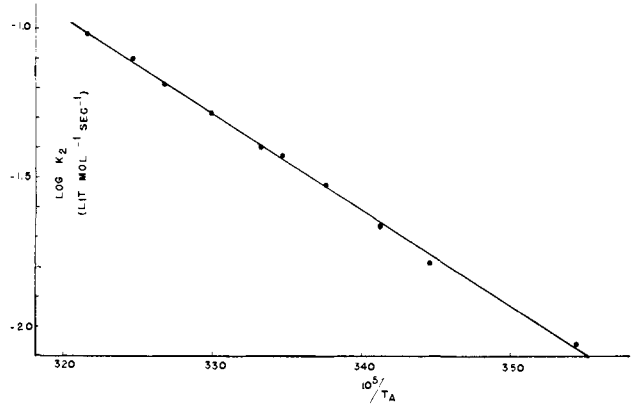

Figure 4. Arrhenius plot for bromination of acetomesitylene.

studied under the conditions listed. The reaction was followed at 10 temperatures, in the range 9.0–37.8 °C. A satisfactory linear correlation was obtained by plotting log k_2 values against $1/T$ (Figure 4). Activation parameters evaluated by a least-squares analysis of this plot are E_a = 61.5 ± 3 kJ mol^{-1} (14.7 ± 0.2 kcal mol^{-1}) and activation enthalpy $\Delta H^{\ddagger}$ = 59.0 ± 3 kJ mol^{-1} (14.1 ± 0.2 kcal mol^{-1}).

Bromination of Acetophenone. In order to make a comparison of the rate of bromination of an analogous unhindered ketone, acetophenone was studied under the same conditions. Although the bromination of acetophenone has been reported by several authors,[12] none of the studies was under the experimental conditions used for 2,4,6-trimethylacetophenone in the present investigation. In order to make a better comparison between the two compounds, the bromination of acetophenone, under the conditions chosen for 2,4,6-trimethylacetophenone, was carried out. The reaction followed a zero order as reported for bromination of all unhindered ketones but unlike that with 2,4,6-trimethylacetophenone. The k_0 values are given in Table VIII.

Discussion

Mechanism. The main pertinent observations that must be accommodated in the mechanism are as follows: the first-order dependence on bromine and 2,4,6-trimethylacetophenone concentration (second order overall) and molecular bromine as the active brominating species. Since there is an induction period which is eliminated by strong acids, the conversion of the keto form into a reactive substrate, the enol form, is indicated in the first enolization steps (eq i, Scheme III). In the enolization steps, the protonation step k_a is fast as compared with the loss of a proton from carbon, k_b. In unhindered ketones the subsequent steps, reaction of bromine with enol, are fast, the formation of enol (k_b) being the rate-determining step. In the present case it is postulated that the bromination step (eq ii) becomes rate determining because reaction of the bromine molecule with the carbon-to-carbon double bond is hindered by the *o*-methyl groups which would be partially blocking the perpendicular approach of bromine to the π cloud of the planar C=C system. Another possibility is that the enolization step for the hindered ketone is rapid (as compared with the usual relatively slow rate for unhindered ketones). In either case the slow rate-determining step is reaction of the enol form with halogen.

Since with unhindered ketones subsequent steps to the rate-determining enolization steps are fast, information on details of the mechanism of addition of bromine to the enol has generally been unavailable. Newman[13] proposed a cyclic mechanism for the reduction of α-bromo ketones with hydrogen bromide to form bromine and ketone. Since this is the reverse of the bromination reaction of ketones, the reverse reaction (eq iv) can be considered as a possibility for the enol bromination mechanism. The rate of halogenation of ketones is predictably[4] dependent on halogen concentration at *very low* halogen concentrations[6] as demonstrated for chlorine[14] and bromine[5] (in the range 10^{-5}–10^{-8} M for the latter). Although reactions of some ketones with halogens are dependent on halogen concentration at moderately high halogen concentrations, at high pH ranges,[15,16] the reactive form of the halogen here is hypohalite ion. Mechanisms have been proposed by Yates and Wright[5] for the reaction of bromine with enols involving bromonium[17] and carbonium intermediates with the latter being preferred.

The addition of bromine to alkenes has been thoroughly studied; the results can be used as a basis for possible mechanisms on the reaction with the enol form. In the addition of bromine to alkenes, it is well established[18,19] that the first step is formation of a bromonium ion and bromide and the second step involves attack of bromide or tribromide on the bromonium ion to form a *trans*-1,2-dibromide. This is shown in step ii, the formation of the bromonium ion, **1**. Step iii, the reaction of the bromonium ion, **1**, with Br^- or Br_3^-, is postulated to be fast. If this mechanism is applied to the present case, one would expect an intermediate of type **3** to be formed from nucleophilic attack of Br^- or Br_3^- on the carbon attached to OH, which would subsequently decompose into the final product, **2**. In the present investigation since an excess of bromide ion was used, it is more likely that this is the major nucleophile in this final step. However, a nucleophilic attack of bromide or tribromide ion at the more hindered carbon containing the OH group would not appear to be reasonable as compared with attack at the other less hindered carbon of the

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Table VIII. Rate of Bromination of Acetophenone[a]

$10^3[Br_2]$, M	10^7k_0, mol L^{-1} s^{-1}	$10^3[Br_2]$, M	10^7k_0, mol L^{-1} s^{-1}
1.49	1.22	2.64	1.24
2.02	1.29	3.21	1.16
2.60	1.21	3.80	1.23

10^7k_0 (av) = 1.23 mol L^{-1} s^{-1}

[a] $[PhCOCH_3]$ = 0.0500 M; [HBr] = 0.100 M; $[NaClO_4]$ = 0.400 M; temperature = 25.0 °C; solvent = 50% AcOH (v/v).

three-membered bromonium ring to give the same intermediate (**3**). Another possibility suggested here is removal of the OH proton by bromide or tribromide to form HBr + Br_2 and breaking of the C–Br bond to open up the three-membered ring (eq v). A molecular model of the bromonium ion in the present case, in fact, indicated nonbonded interactions which would tend to increase the energy of the transition state to its formation. Models of the alternative carbocation intermediate **4** on the other hand show that it can adopt a relatively low-energy conformation. This would be in accord with the intermediate preferred by Yates and Wright.[5] A recent study by Bienvenue-Goetz and Dubois,[20] on effects of substituents on rates of bromination of alkenes, showed that when the substituent was a conjugatively electron-donating group, the results were consistent with a carbocation-like transition state whereas for nonconjugated substituents, the transition state was bromonium type. An additional experiment was carried out in the present investigation which eliminates some of these possibilities. The reaction of 2,4,6-trimethylacetophenone with bromine in the presence of chloride ion was carried out on a preparative scale. If the reaction took place via a bromonium ion, then in addition to attack by bromide ion at either carbon which would produce the observed 2,4,6-trimethylbromoacetophenone (eq iii) competing attack by chloride ion is possible. Attack by path a (Scheme III) at the more hindered OH carbon would form intermediate **4**, which would produce the bromo ketone **2**, the only observed product. Attack by path b would lead to the chloro ketone **5**, which was not formed. If the intermediate is the carbocation **6**, then attack by chloride (or bromide) would only produce 2,4,6-trimethylbromoacetophenone. On the basis of steric considerations, however, the carbocation intermediate **6** (which would also yield the observed bromo ketone) is favored.

One additional point may be made regarding the relative rate of the bromination of 2,4,6-trimethylacetophenone as compared with that of an unhindered analogue, acetophenone. Qualitatively, it is evident that reaction of bromine with the former is much faster. However, it is difficult to compare the two on a quantitative basis. One possible approach to this is via the expression for the first-order constant (R_1) derived by Bell and Page[21] for the bromination of acetophenone

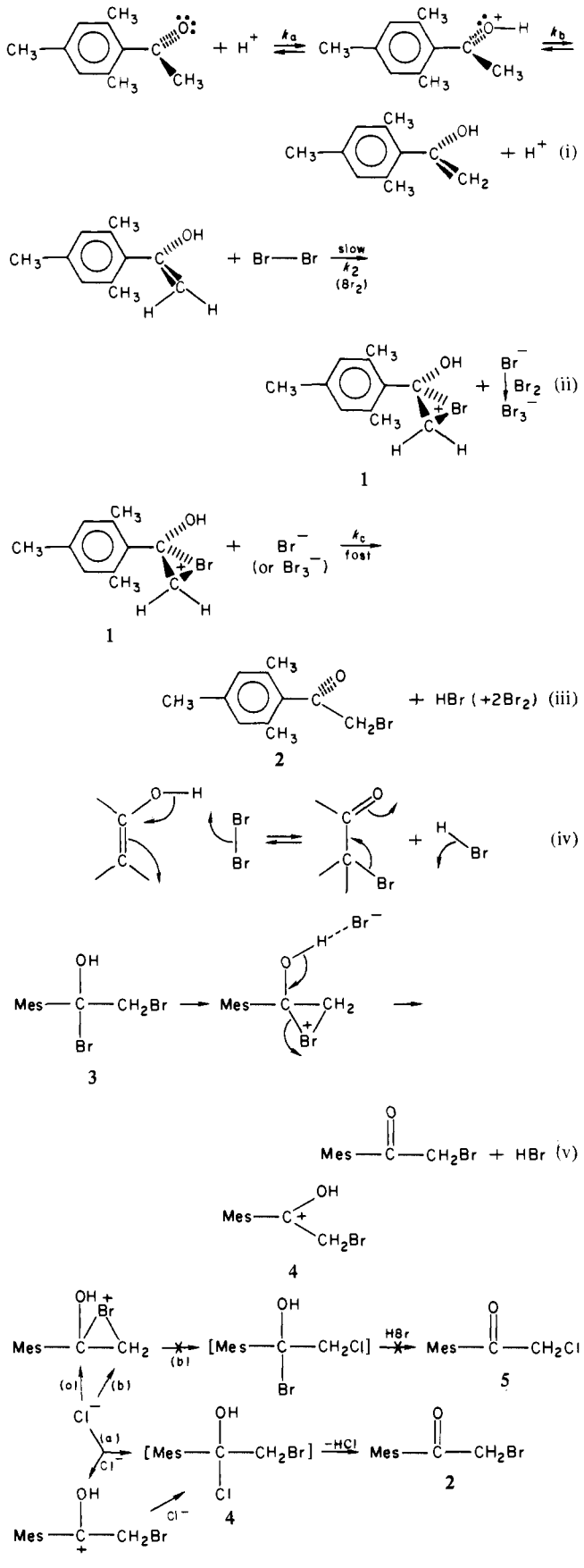
$$k_1 = \frac{-K + [Br^-]}{\epsilon[Br^-][\text{ketone}]} \frac{dA}{dt}$$

where K is the equilibrium constant for $Br_3^- \rightleftarrows Br_2 + Br^-$, ϵ is the extinction coefficient, and dA/dt represents the slope of absorbance vs. time plot. Thus

$$k_1 = \frac{-0.0164 + 0.1}{(111.4)(0.1)(0.05)}(1.37 \times 10^{-5}) = 2.06 \times 10^{-6}\ s^{-1}$$

On this basis, the corresponding first-order rate constant for the bromination of 2,4,6-trimethylacetophenone is 1.80×10^{-3} s^{-1}. Thus, the relative rate,[22] k_1(2,4,6-trimethylacetophenone)/k_1-

Scheme III. Mechanisms for Bromination of 3,4,6-Trimethylacetophenone



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(22) One of the referees stated that the concentration of ketone for the second-order reactions must be specified for the rate ratio to be meaningful. The measurements were at the same concentrations.

(acetophenone), is 873.

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Supplementary Material Available: Tables of the effect of sodium bromide, sodium acetate, perchloric acid, and temperature on the rate of reaction of 2,4,6-trimethylacetophenone and bromine (4 pages). Ordering information is given on any current masthead page.

Surfactant–Polymer Interactions and Their Effects on the Micellar Inhibition of the Neutral Hydrolysis of 1-Benzoyl-1,2,4-triazole

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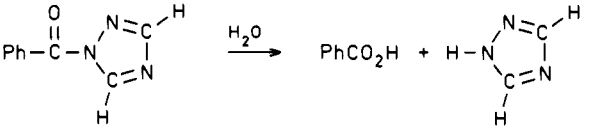
Abstract: Binding of sodium dodecyl sulfate (SDS) to atactic poly(*N*-vinylpyrrolidone) (PVP) has been studied by conductivity measurements. It is proposed that in addition to normal micelles of SDS an additional pseudophase of mixed micelles of PVP and SDS is present in solution. The effect of polymer–surfactant binding on the catalytic/inhibitive activity of SDS micelles has been investigated by studying the rates of the pH-independent hydrolysis of 1-benzoyl-1,2,4-triazole (**1**). Though the polymer itself has no effect on the hydrolysis reaction in water, addition of PVP to SDS solutions decreases the micellar inhibition, and pseudo-first-order rate constants (k_{obsd}) are higher than those in the absence of PVP. Ultrafiltration experiments using a model substrate indicate increased solubility of the substrate in the micellar pseudophase upon addition of PVP. On the basis of the enzyme model of micellar catalysis, a kinetic scheme is presented to explain the observed rate effects. It is argued that the microenvironment at the binding sites of the mixed micelles of SDS and PVP is more polar than that at the binding sites of unperturbed micelles. Comparative studies with *N*-isopropylpyrrolidone (*N*-iPP) reveal the basic differences in the interaction of micelles with a macromolecule and with a polar additive of low molecular weight.

The formation of complexes between surfactants and nonionic, water-soluble polymers has already been recognized more than two decades ago.[1] These mixed systems find application in tertiary oil recovery[2] and also serve as model systems to understand the interactions between a biomacromolecule (such as protein) and a biological membrane. Measurements of a physical property such as conductivity[3a-d] or surface tension[3a,c,e] of the surfactant–polymer mixture in solution indicate that the surfactant binds to the polymer forming a polymer–surfactant complex. This binding is cooperative. It increases with increasing hydrophobicity of the polymer[4a] and the surfactant molecule.[3c,4b] However, the charge on the head group[4b] and the nature of the counterion of the surfactant molecule[4c,d] also affect the binding process significantly. Viscosity measurements[3a,b] suggest that these complexes behave as polyelectrolytes in aqueous medium. Attempts have been made to study the molecular structure of these complexes by NMR[5a,b] and ultrasonic relaxation spectroscopy,[6] light scattering,[7] and pressure-jump relaxation kinetics.[8] These studies have led to the idea that the complexes are formed by incorporation of micelles along the polymer chain, and they have been described as micellar clusters or mixed micelles. The thermodynamics of these mixed micelles have been discussed by Nagarajan[9a] and by Gilanyi and Wolfram.[9b] In spite of all these efforts, a well-defined picture of the structure of the polymer–surfactant complexes and the nature of the interactions involved in complex formation is yet to emerge. Also, no studies have been reported on the effect of the polymer on the catalytic/inhibitive activity of the micelles. This is surprising in view of the worldwide interest in micellar effects on chemical reactions. Herein we report a first example of the effect of a water-soluble polymer (atactic poly(*N*-vinylpyrrolidone), PVP) on the inhibition of a reaction by micelles of sodium dodecyl sulfate (SDS).

The reaction chosen is the neutral hydrolysis of 1-benzoyl-1,2,4-triazole (**1**) in water. The reaction is pH independent in the range pH ~3–5 and involves water-catalyzed nucleophilic attack of water at the amide carbonyl.[10]



This reaction is sensitive to the polarity of the reaction medium and hence is useful to probe the local microenvironment at the binding sites of the micelles[11] and of the surfactant–polymer complexes.

Before presenting the kinetic results, we will demonstrate the presence of SDS/PVP complexes in aqueous solution as revealed by conductivity measurements.[12]

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