Kinetic and Mechanistic Studies on the Acid-Catalyzed Debromination of α-Bromoacetophenones and α-Bromopropiophenones with Triphenylphosphine in Ethanol[1]

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Abstract: The debromination of phenyl-substituted α-bromopropiophenones or α-bromoacetophenones to give the corresponding ketone occurs with triphenylphosphine in ethanol (or with ethanol–nonpolar solvent mixtures) and is both acid and alcohol catalyzed. The reactions follow second-order overall rates and give "U" shaped ρ plots. These ρ plots can be separated into ethanol-catalyzed lines with positive slopes and curved acid-catalyzed plots with negative slopes. Data are presented which suggest that the acid catalysis is general. Solvent deuterium isotope effects (k_2^H/k_2^D) of 0.89–1.61 are found under various reaction conditions. The relative rates of debromination of α-bromoacetophenone:α-bromopropiophenone:α-bromoisobutyrophenone are 45:1.4:1.0. The accumulated data suggest mechanistic pathways involving attack of triphenylphosphine on bromine of acid or ethanol coordinated bromo ketones.

The reaction of α-bromo ketones with triphenylphosphine in aprotic media to give ketophosphonium bromides[3] has been shown to proceed *via* SN2-type displacement of bromide ion. The evidence for this conclusion has included kinetic studies of the reactions of α-bromoacetophenones (**1a–j**) or α-bromopropiophenones (**2a–f**) with triphenylphosphine (TPP, $\rho = +0.44, 0.67$)[4] and, more conclusively, studies on the reactions of several α-halo ketones and their corresponding α-mesyloxy ketones with optically active methylpropylphenylphosphine.[5]

Some years ago we found that a number of α-bromo ketones react with TPP in the presence of protic species (water, alcohols, acetic acid) to give debrominated ketone, triphenylphosphine oxide, and hydrogen bromide or an alkyl bromide, depending upon the protic species used.[6] We[3] and others[7,8] have since shown that the debromination reaction is a general one. The corresponding α-chloro ketones give ketophosphonium chlorides even in protic media.[3,9]

We now report kinetic studies on the debromination of phenyl-substituted α-bromoacetophenones, α-bromopropiophenones, and other bromo ketones with TPP in ethanol.

Results

Kinetics of the Debromination of α-Bromopropiophenones. The reaction of a series of phenyl-substituted α-bromopropiophenones with TPP was studied in absolute ethanol using a titrimetric method.[12] The reactions give triphenylphosphine oxide (TPPO) and debrominated ketone with little if any ketophosphonium bromide. The debromination of *p*-methoxy-α-bromopropiophenone (**2b**) with TPP proceeds slowly *via* second-order kinetics. Some upward curvature is found after *ca.* 75% of reaction. This is due to catalysis by acid (presumably HBr) which is slowly forming during the reaction.[13] Linear second-order k_2 values could be obtained in the initial presence of varying amounts of hydrochloric acid (Table I) to give

Table I. Acid Dependence of the TPP–**2b** Reaction in Ethanol[a]

[HCl]	k_2, M^{-1} min^{-1}
	0.0114
0.0257	0.125
0.0590	0.324
0.0853	0.468
0.112	0.632
0.138	0.800

[a] Reagents 0.03 *M* each; 0.22 *M* H_2O present, at 0.0°.

a plot which is linear for k_2 *vs.* [HCl] ($R = 0.9987$) and goes through the origin. A plot of k_2 *vs.* $[HCl]^{1/2}$ is

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(3) (a) I. J. Borowitz, K. Kirby, and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966); (b) I. J. Borowitz, K. Kirby, and P. E. Rusek, *ibid.*, **33**, 3686 (1968); (c) I. J. Borowitz, P. E. Rusek, and R. Virkhaus, *ibid.*, **34**, 1595 (1969).

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(5) I. J. Borowitz, K. Kirby, P. E. Rusek, and E. W. R. Casper, *J. Org. Chem.*, **36**, 88 (1971).

(6) I. J. Borowitz and L. I. Grossman, *Tetrahedron Lett.*, 471 (1962).

(7) (a) H. Hoffmann and H. J. Diehr, *Angew. Chem., Int. Ed. Engl.*, **3**, 737 (1964); (b) A. J. Speziale and R. C. Freeman, *J. Amer. Chem. Soc.*, **82**, 903 (1960); (c) A. J. Speziale and L. R. Smith, *ibid.*, **84**, 1868 (1962).

(8) (a) F. Hampson and S. Trippett, *J. Chem. Soc.*, 5129 (1965); (b) B. Miller, *Top. Phosphorus Chem.*, **2**, 133 (1965).

(9) Some α-halo ketones react with TPP or other tertiary phosphines to give enol phosphonium salts in aprotic media.[5,10,11] In such cases, when the reactions are run in protic solvents, dechlorination as well as debromination occurs. Whether dehalogenation occurs directly or *via* the solvolysis of enol phosphonium salts in these cases is not known.

(10) (a) A. J. Speziale and R. D. Partos, *J. Amer. Chem. Soc.*, **85**, 3312 (1963); (b) R. D. Partos and A. J. Speziale, *ibid.*, **87**, 5068 (1965).

(11) H. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **3**, 737 (1964).

(12) (a) D. B. Denney and M. J. Boskin, *J. Amer. Chem. Soc.*, **82**, 4736 (1960). (b) To minimize errors due to liberated HI, pyridine was added to the titration solution: P. D. Bartlett and G. Meguerian, *ibid.*, **78**, 3710 (1956). In our system, pyridine caused errors leading to deceptively slow reaction rates. Sodium acetate as an additive gave accurate results.

(13) This may be due to HBr produced by the solvolysis of the α-bromo ketone with ethanol, a very slow reaction (estimated k_2 at 0° for **1** = 1.4×10^{-7} M^{-1} min^{-1}): D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967).

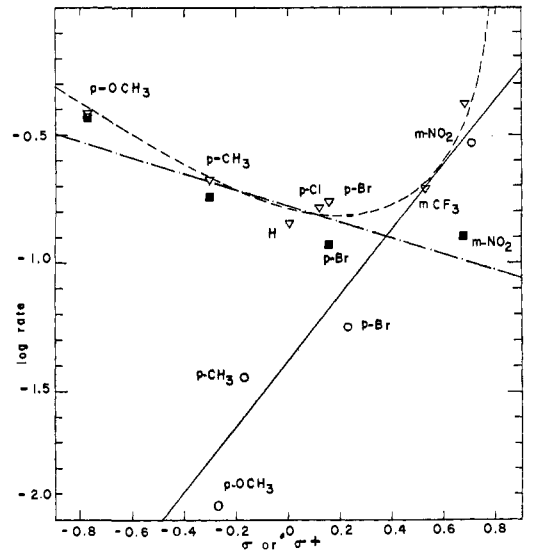


Figure 1. Debromination of α-bromopropiophenones with TPP: (▽) log total k_2 *vs.* σ^+; (○) log k_2^0 *vs.* σ; (■) log $(k_2 - k_2^0)$ *vs.* σ^+.

Table II. Acid Dependence of the TPP–**2f** Reaction in Ethanol[a]

[HCl]	k_2, M^{-1} min^{-1}
	0.287
0.0228	0.316
0.0590	0.410
0.0946	0.516
0.140	0.616
0.196	0.724
0.241	0.820

[a] Conditions as in Table I.

for k_2 *vs.* [HCl] (slope = 2.29, R = 0.997). The correlation for [HCl]$^{1/2}$ is poorer. In the absence of added acid, k_2 = 0.274 M^{-1} min^{-1}, in good agreement with the intercept k_i (Table II).

Reproducible overall second-order rate behavior is found for a series of α-bromopropiophenones in reaction with TPP in ethanol, 0.06 M HCl, and 0.22 M H_2O to at least 50% of reaction (Table III).[14]

$$\underset{\textbf{2a–f}}{XC_6H_4\overset{O}{\overset{\|}{C}}CH(CH_3)Br} + (C_6H_5)_3P \xrightarrow[HCl,\ H_2O]{C_2H_5OH} \underset{\textbf{3a–f}}{XC_6H_4\overset{O}{\overset{\|}{C}}CH_2CH_3} + (C_6H_5)_3PO \quad (1)$$

A Hammett ρ plot of these data *vs.* σ or σ^+ gives a "U" shaped curve (Figure 1). It is felt that the data might be best correlated by the use of σ^+ for the electron-donating groups (left side of curve) and σ or σ^+ for electron-withdrawing groups.[15] The data suggest that the observed rates are composed of solvent-catalyzed (k_2^0) and acid-catalyzed ($k_2 - k_2^0$) components.[17] An estimate of the k_2^0 values can be obtained by plotting the observed rate constants *vs.* [HCl] and extrapolating to the graph's origin, as already described for **2b** and **2f**. The resultant non-acid-catalyzed rates (k_2^0) for **2b**, **2c**, **2e**, and **2f** give a straight line when plotted *vs.* σ^+ with ρ = +0.92 (R = 0.982). A plot *vs.* σ gives ρ = + 1.26 but with R = 0.959 only (Figure 1). Subtraction of the k_2^0 values from the total k_2 values gives acid-catalyzed k_2 values which are plotted against σ^+ to give ρ = −0.32 (R = 0.878, Figure 1).

Table III. Debromination of α-Bromopropiophenones with TPP in Ethanol[a]

Bromo ketone	k_2, M^{-1} min^{-1}	Rel k_2	k_2^0	$k_2 - k_2^0$	% k_2^0/k_2
2a, X = H	0.143 ± 0.003	1.00			
2b, X = *p*-OCH_3	0.353 ± 0.001[b]	2.47	0.0114	0.34	3
2c, X = *p*-CH_3	0.212 ± 0.004	1.48	0.036	0.18	17
2d, X = *p*-Cl	0.158 ± 0.007	1.10			
2e, X = *p*-Br	0.172 ± 0.006	1.20	0.056	0.12	33
2g, X = *m*-CF_3	0.191 ± 0.001	1.34			
2f, X = *m*-NO_2	0.431 ± 0.020	3.01	0.287	0.14	67

[a] Reagents 0.03 M, [HCl] = 0.06 M, [H_2O] = 0.22 M, at 0.0 ± 0.01°. [b] Later, 0.378 ± 0.014 was used.

Table IV. Activation Parameters for the Debromination of α-Bromopropiophenones

Reaction system[a]	Temp, °C	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta H^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	$\frac{k_{H^+}\ \textbf{2b}}{k_{ROH}\ \textbf{2f}}$
2b, TPP, 0.06 M	0.0	12.7[b]	−23.9	12.2	18.7	
HCl, 0.22 M H_2O	29.1		−24.0	12.1	19.4	
	40.0		−24.2	12.1	19.7	
2f, TPP	0.0	10.6[c]	−32.3	10.0	18.9	1.29
	30.0		−32.5	10.0	19.8	1.90
	40.0		−32.6	10.0	20.2	2.11

[a] In C_2H_5OH, reagents 0.03 M. [b] For **2b**, k_2 = 3.85 ± 0.05 M^{-1} min^{-1} (29.1°), 7.35 ± 0.05 M^{-1} min^{-1} (40.0°). [c] For **2f**, k_2 = 2.03 ± 0.03 M^{-1} min^{-1} (30.0°), 3.50 ± 0.05 M^{-1} min^{-1} (40.0°).

curved (R = 0.9435); *i.e.*, it is a poorer fit. The slope is equivalent to k_3 ($k_3 = k_2/[HCl]$) = 5.75 M^{-2} min^{-1} which is in good agreement with k_3 = 5.70 M^{-2} min^{-1} derived from k_2^0 = 0.0114 and k_2 = 0.353 M^{-1} at 0.06 M HCl.

m-Nitro-α-bromopropiophenone (**2f**) reacts with TPP in ethanol to give second-order plots with no apparent autocatalytic behavior. A linear correlation is found

Since solvent catalysis contributes mainly to the rates of the bromo ketones with electron-withdrawing sub-

(14) Data at 0.60 M HCl were not reproducible.

(15) This is based on the known utility of σ^+ in acid-catalyzed reactions[16a] and on the better correlation coefficient obtained.

(16) (a) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, pp 203–211; (b) p 181.

(17) Acid and solvent catalysis was found for the debromination of 2,4,6-trimethyl-α-bromoacetophenone (6) with TPP in methanol.[6a]

Table V. Effect of Varying Acid Conditions on the Debromination of α-Bromopropiophenones with TPP–Ethanol

Bromopropiophenone	$[H_2O]$	[Acid], M	k_2[a]	k_2^0	$k_2 - k_2^0$	k_3[b]
2f (*m*-NO_2)	0.22			0.287		
				0.286		
		0.0218 HCl	0.372[c]	0.286	0.086	3.94
		0.0436 HCl	0.447[c]	0.286	0.161	3.69
	0.22	0.060 HCl	0.431	0.287	0.144	2.40
		0.060 HCl	0.508	0.286	0.222	3.70
2b (*p*-OCH_3)	0.22	0.060 HCl	0.353	0.0114	0.342	5.70
		0.060 HCl	1.30	0.0114	1.29	21.5
	0.22	0.0236 HBr[d]	0.127	0.0114	0.116	4.9
		0.0236 HBr	0.556	0.0114	0.545	23.1
	0.22	0.011 HBF_4	0.049	0.0114	0.038	3.46
	0.22	0.060 HOAc	0.0034[e]			
			0.009[f]			

[a] M^{-1} min^{-1}, at 0.0°. [b] $k_3 = k_2 - k_2^0/[acid]$. [c] Slope = 3.7, intercept = 0.287 ($\equiv k_3$). [d] In later runs, **2a** gave k_3 HCl/HBr = 1.24 at 0.06 M acid, 0.22 M H_2O, in good agreement with that above, 1.16. [e] Rate to *ca.* 15% of reaction. [f] Rate for 15–33% of reaction.

Table VI. Debromination of α-Bromoacetophenones with TPP in Ethanol[a]

Bromo ketone	k_2, M^{-1} min^{-1}	Rel k_2	k_2^0	$k_2 - k_2^0$	% k_2^0/k_2
1a, X = H	4.43 ± 0.14	1.00	0.163 ± 0.02[b]	4.27	4
1b, X = *p*-OCH_3	27.5 ± 0.3	6.21			
1c, X = *p*-CH_3	8.15 ± 0.05	1.84	0.097 ± 0.009	8.05	1
1h, X = *m*-OCH_3	4.25 ± 0.00	0.96			
1d, X = *p*-Cl	3.45 ± 0.08	0.78			
1e, X = *p*-Br	3.62 ± 0.03	0.82	0.433 ± 0.012[c]	3.19	12
1i, X = *m*-Br	3.15 ± 0.10	0.71			
1g, X = *m*-CF_3	3.07 ± 0.03	0.69			
1f, X = *m*-NO_2	4.35 ± 0.05	0.98	2.51 ± 0.11	1.84	58
1j, X = *p*-NO_2	4.66 ± 0.06	1.05			

[a] Reagents 0.03 M, 0.06 M HCl, 0.22 M H_2O, at 0.0°. [b] For 0–80 min. At 80–160 min, k_2 of nonacid reaction = 1.19 ± 0.12 M^{-1} min^{-1}. [c] After 80 min k_2 of nonacid reaction = 1.18 ± 0.04 M^{-1} min^{-1}.

stituents (the right-hand side of the total k_2 curve), this treatment reduces much of the curvature.

Activation parameters for the debromination of **2b** with TPP, ethanol, and acid, and **2f** with TPP in ethanol alone, are given in Table IV. The data are based on rates at 0° (Table III) and as indicated. The increase in k_2 **2b**/**2f** with higher temperature suggests that the curvature of the ρ plots in Figure 1 is at least somewhat temperature dependent.

While the rate of the solvent-catalyzed debromination of **2f** with TPP is relatively unaffected by the absence of water (Table V), the acid-catalyzed reaction is 1.5 times faster with anhydrous hydrogen chloride–ethanol than in the presence of 0.21 M water. A larger effect (3.8-fold rate increase) is noted for the acid-catalyzed debromination of **2b** with anhydrous hydrogen chloride. The substitution of hydrogen bromide for hydrogen chloride in the **2b**–TPP reaction gives a somewhat slower reaction rate in aqueous alcohol and a 4.7-fold increase in rate for anhydrous *vs.* aqueous alcohol.

Kinetics of the Debromination of α-Bromoacetophenones. Using the above-mentioned techniques, the debromination of a series of α-bromoacetophenones with TPP, ethanol, and hydrochloric acid to give the corresponding acetophenones is shown in Table VI.

$$\underset{\textbf{1a–j}}{XC_6H_4\overset{O}{\overset{\|}{C}}CH_2Br} + (C_6H_5)_3P \xrightarrow[HCl,\ H_2O]{C_2H_5OH} \underset{\textbf{4a–j}}{XC_6H_4\overset{O}{\overset{\|}{C}}CH_3} + (C_6H_5)_3PO \quad (2)$$

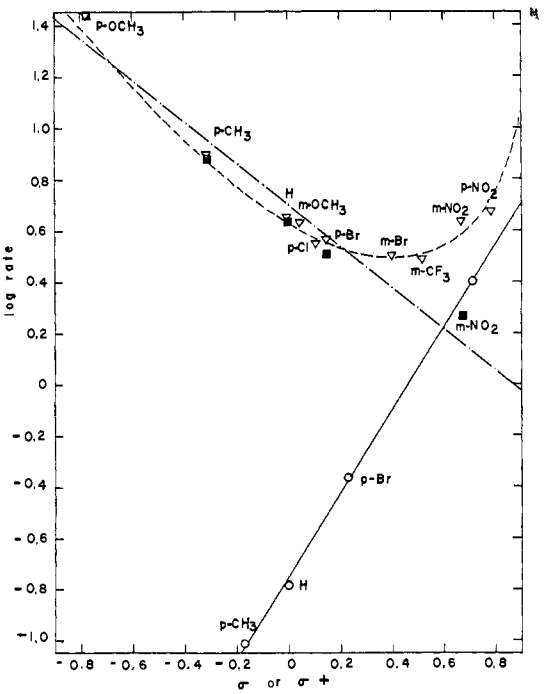


Figure 2. Debromination of α-bromoacetophenones with TPP: (▽) log total k_2 *vs.* σ^+; (○) log k_2^0 *vs.* σ; (■) log ($k_2 - k_2^0$) *vs.* σ^+.

The data correlate with σ or σ^+ values to give a curved ρ plot (Figure 2). For the reactions of **1a** and **1e** (*p*-Br) in ethanol without added acid, a rate increase of 2.7- and 7.4-fold after *ca.* 80 min is found. That this is probably due to catalysis by acid(s) formed

Table VII. Solvent Isotope Effects on the Debromination of α-Bromo Ketones with TPP at 0°

Bromo ketone	Solvent	[Acid], M	k_2, M^{-1} min^{-1}	k_3^D, M^{-2} min^{-1}	k_3^H, M^{-2} min^{-1}	k^H/k^D [a]
2b (*p*-OCH_3)	C_2H_5OD, D_2O [b]	0.0925 DCl	0.59	6.39	5.70 [c]	0.89
	C_2H_5OD	0.0925 DCl	1.41	15.1	21.5 [c]	1.42
2f (*m*-NO_2)	C_2H_5OD		0.244			1.18
		0.0157 DCl	0.333 [d]	2.12		1.61 [e]
		0.0523 DCl	0.595	11.4		
1c (*p*-CH_3)	C_2H_5OH, H_2O [b]	0.060 HCl	8.15 ± 0.05			1.19
	C_2H_5OD, D_2O [b]	0.060 DCl	6.87 ± 0.03			
1f (*m*-NO_2)	C_2H_5OH, H_2O [b]	0.060 HCl	2.51 ± 0.11			1.29
	C_2H_5OD, D_2O [b]	0.060 DCl	1.95 ± 0.13			

[a] Based on k_2^H/k_2^D for nonacid and k_3^H/k_3^D for acid-catalyzed reactions. [b] 0.22 M. [c] From Table V. [d] Slope = 2.3, intercept = k_2 = 0.236. For equivalent C_2H_5OH data, see Table V. [e] Based on slope = 3.7 (HCl), 2.3 (DCl).

during the reaction is suggested by the following observations.

In many of the acid-catalyzed bromoacetophenone and bromopropiophenone reactions, the acid concentration increases from the initial 0.06 M to *ca.* 0.08 M at the completion of the reaction. This increase does not affect the linearity of the points for *ca.* 75% of the reaction. Thereafter some upward curvature is noted.

Estimation of some of the k_2^0 values, as above, gives a linear Hammett plot, using σ values, with $\rho = +1.63$ ($R = 0.999$) for the solvent-catalyzed debrominations. The acid-catalyzed reactions ($k_2 - k_2^0$ values) give a slightly curved line with $\rho = -0.62$ ($R = 0.985$) using σ^+ values.[16a] Thus, in the bromoacetophenone series, there appears to be essentially complete separation of acid- and solvent-catalyzed debrominations, characterized by opposing signs of ρ values.

Deuterium Solvent Isotope Effects. The effect of deuterium isotopic substitution on the reaction rates of selected members of the **1** and **2** series was determined (Table VII). The second-order overall rates of debromination of several α-bromo ketones are given in Table VIII.

Table VIII. Rates of Debromination of α-Bromo Ketones with TPP, Ethanol, 0.22 M H_2O, and 0.060 M HCl at 0°

Bromo ketone	k_2, M^{-1} min^{-1}	Rel rate
$C_6H_5C(=O)CH_2Br$ (**1a**)	4.43	45
$C_6H_5C(=O)CH(CH_3)Br$ (**2a**)	0.143	1.4
$C_6H_5C(=O)C(CH_3)_2Br$ (**5**)	0.099	1.0
2,2,4-$(CH_3)_3$-$C_6H_2C(=O)CH_2Br$ (**6**)	1.32 ± 0.02	13.3
2-Bromocyclohexanone (**7**)	0.248 ± 0.012	2.51
$C_6H_5C(=O)CH(C_6H_5)Br$ (**8**)	18.8 ± 0.08 [a]	

[a] Reaction in absolute ethanol, no added acid. Acidity was *ca.* 0.0022 M at start, 0.017 M at end. The reaction in 0.060 M HCl was very fast with $k_2 = 80$ M^{-1} min^{-1}.

Discussion

The reaction of bromo ketones **1a–j** and **2a–f** with TPP–ethanol is both acid and solvent catalyzed. Those bromo ketones with electron-donating groups are primarily catalyzed by the various acidic species present in the reaction system (0.060 M HCl in 0.56% H_2O, 99.44% C_2H_5OH), *i.e.*, H_3O^+, $C_2H_5OH_2^+$, and appreciable amounts of "HCl."[18] This may be in the form of undissociated hydrogen chloride[18a,b] but is more likely associated H^+Cl^-.[18c] The overall pseudo-second-order rate constants contain terms for catalysis by at least these species. The data suggest that the reactions are general acid catalyzed. Thus the different rate constants for different acids which should be at about the same effective concentration (Table V), the generally positive albeit small solvent k^H/k^D values,[19] and the possible mechanistic analogy of these reactions to the acid-catalyzed enolization of acetophenones[20] are all compatible with general acid catalysis.[21] The apparent relative catalytic ability of HCl > HBr > HBF_4 suggests that undissociated or ion-paired HCl or HBr is more effective as acid catalysts than are $C_2H_5OH_2^+$ or H_3O^+ (the acids present in the HBF_4–H_2O–C_2H_5OH system). This conclusion may also explain the greater catalysis found for HCl or HBr in anhydrous ethanol (where "HX" and $C_2H_5OH_2^+$ are the principal acids) than in 0.22 M H_2O–ethanol (where the above acids and H_3O^+ are present). A greater catalytic effect of "HX" rather than H_3O^+ was noted in the acid-catalyzed decomposition of diphenyldiazomethane.[22]

The acid-catalyzed debrominations may proceed *via* path 1 (eq 3): a rapid protonation or association equilibrium of the bromo ketone carbonyl with one or more acids followed by a rate-determining attack on "soft" bromine by "soft" TPP.[23] This pathway is analogous to acid-catalyzed keto–enol tautomerism.[20] Electron-donating groups in **1** and **2** increase the rate of this reaction because they enhance the stability of the enol formed in the debromination step.

The solvent-catalyzed reactions may involve coordination of the bromo ketone carbonyl with ethanol followed by a rate-determining step with a transition state wherein removal of positive bromine occurs to a greater extent than does proton transfer to oxygen (path 2). Such a pathway gives a role to the protic species which is necessary to switch the reaction from ketophosphonium salt formation *via* an SN2 displacement of bromide ion to debromination. Electron-

(18) (a) I. I. Bezman and F. H. Verhoek, *J. Amer. Chem. Soc.*, 67, 1330 (1945); (b) R. A. Robinson and R. H. Stokes, "Electrolytic Solutions," 2nd ed, Butterworths, London, 1968; (c) H. O. Spivey and T. Shedlovsky, *J. Phys. Chem.*, 71, 2165 (1967); (d) H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, pp 452–484, 719, 727; (d) B. L. Murr and V. J. Shiner, *J. Amer. Chem. Soc.*, **84**, 4672 (1962).

(19) (a) C. G. Swain, R. F. W. Bader, and E. R. Thornton, *Tetrahedron*, 10, 182, 200 (1960); (b) K. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

(20) K. J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill New York, N. Y., 1965, p 472.

(21) Attempts to firmly establish the general nature of the acid catalysis involved by the use of buffer systems have thus far failed.

(22) J. D. Roberts and W. Watanabe, *J. Amer. Chem. Soc.*, 72, 4869 (1950).

(23) (a) R. G. Pearson and J. Songstad, *ibid.*, 89, 1827 (1967); (b) B. Saville, *Angew. Chem., Int. Ed. Engl.*, 6, 928 (1967).

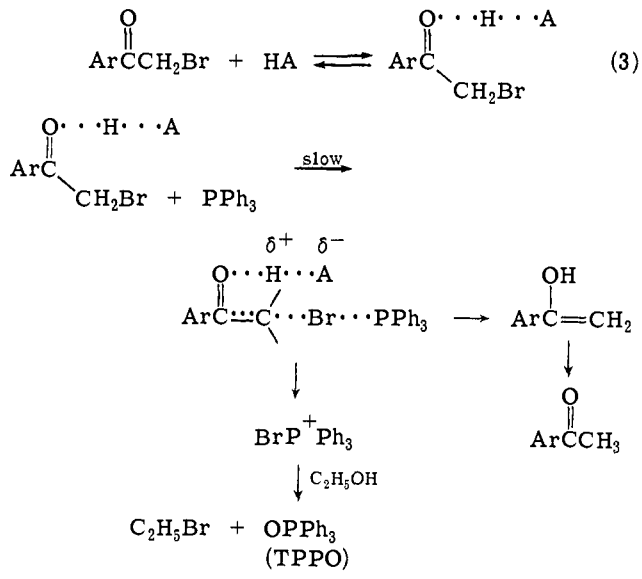
withdrawing substituents in **1** or **2** enhance this reaction since they stabilize incipient enolate formation. This pathway is supported by the small k^H/k^D values found since proton transfer in the transition state has occurred to only a small extent.[19,24,25] The large negative entropy of activation for the debromination of **2f** (Table IV) is indicative of the formation of much charge in the transition state.

The ρ values of +1.63, 0.92 for the solvent-catalyzed debromination of the bromoacetophenones and propiophenones, respectively, can be compared to +0.75 (at 30°) for the base-catalyzed bromination of acetophenones.[26a] The ρ values of −0.62, −0.32, for the acid-catalyzed debrominations can be compared to ρ = −1.24 (40°) for the perchloric acid–acetic acid catalyzed bromination of acetophenones,[26b] −0.46 (25°) for the HCl–acetic acid catalyzed bromination of acetophenones,[26c] and −0.34 to −0.64 for other acetophenone brominations.[16b]

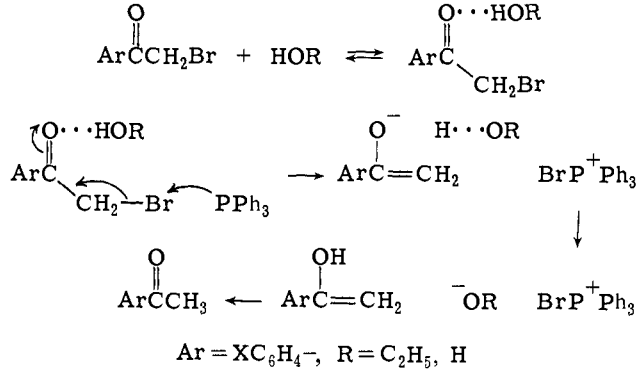
The postulate of attack on bromine is enforced by the relative lack of steric effects found with normally hindered bromo ketones (Table VIII). The relative rates for **1a**:**2a** of 31:1 are in contrast to the large SN2 relative rate ratio of 280:1 found for ketophosphonium bromide formation.[4b] Even more striking are the similar rates for **2a**, **5** (1.4:1) and **1a**, **6** (3.3:1). These similar reaction rates can be compared to the reported relative rates of 40:20:1 for the perchloric acid catalyzed enolization of acetophenone:propiophenone:isobutyrophenone (as measured by iodination).[27] The mesitoyl bromo ketone **6** reacts very slowly in SN2 reactions.[28] Debromination of **6**, as a consequence of steric hindrance to carbonyl addition or SN2 displacement, has been observed with Grignard reagents and other nucleophiles.[29] Displacement of TPP on bromine should not be so subject to steric factors since the "soft"–"soft" interaction can occur *via* longer bond formation in the transition state. The very rapid debromination of **8** confirms previous observations that α-halo ketones which are substituted by further electron-withdrawing groups react rapidly with TPP, *via* attack at bromine, to give enol phosphonium salts under anhydrous conditions.[5]

The finding that the debromination reactions are acid catalyzed and that acid and/or protic solvents can change the reaction course from ketophosphonium salt formation explains a number of observations on the reactions of α-bromo ketones with TPP. Thus we have found that the presence of 0.1 equiv of triethylamine prevents the alcohol-catalyzed debromination of **1a**, **2a**, or **5** but not of **1g** (*m*-CF_3) or **2f** (*m*-NO_2).

Path 1



Path 2



Ar = XC_6H_4−, R = C_2H_5, H

The presence of triethylamine slows down the acid-catalyzed debromination of **1a**, **2a**, or **5** enough so that ketophosphonium salt formation predominates. For **1g** or **2f**, solvent-catalyzed debromination is sufficiently important (Tables III, VI) so that the removal of acid by triethylamine still allows the debromination to occur. We believe that the action of triethylamine is simply that of removing free acid(s). The rate of formation of ketophosphonium bromide from TPP and **1a** in nitromethane (k_2 = 8.11 M^{-1} min^{-1} at 41.6°) is not affected by the presence of 0.1 equiv of triethylamine (k_2 = 8.08 M^{-1} min^{-1}). Our data explain the observations of Fukui who claimed that ketophosphonium bromide formation from **1a** (but not from α-chloroacetophenone) was catalyzed by bases including triethylamine.[30] What was actually observed was the inhibition of the acid-catalyzed debromination of **1a**. The debromination of α-bromo ketones with moisture and traces of acid either during a reaction period or upon work-up probably explains the "fast" reaction of **7** with TPP and some other TPP–bromo ketone reactions which failed to give either enol or ketophosphonium bromides.[6,11,31]

The correlation of attack by TPP on bromine of α-bromo ketones with HSAB theory[23] gains further

(24) (a) F. Westheimer, *Chem. Rev.*, 61, 265 (1961); (b) J. Bigeleisen, *Pure Appl. Chem.*, 8, 217 (1964).

(25) Similarly small solvent k^H/k^D values are found for (a) the enolization of acetone (as measured by bromination) [O. Reitz and J. Kopper, *Z. Phys. Chem., Abt. A*, 184, 429 (1939)] and for (b) olefin hydrations involving highly unsymmetrical transition states [V. Gold and M. A. Kessick, *J. Chem. Soc.*, 6718 (1965)].

(26) (a) D. N. Nanda, P. L. Nayak, and M. K. Rout, *Indian J. Chem.*, 7, 469 (1969); (b) M. K. Rout, P. L. Nayak, and L. N. Pattnaik, *J. Indian Chem. Soc.*, 10, 164 (1969); (c) H. H. Jaffé, *Chem. Rev.*, 53, 191 (1953).

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(29) R. C. Fuson, "Reactions of Organic Compounds," Wiley, New York, N. Y., 1962, p 450.

(30) K. Fukui, R. Sudo, M. Masaki, and M. Ohta, *J. Org. Chem.*, 33, 3504 (1968).

(31) (a) H. Hoffmann and H. J. Diehr, *Tetrahedron Lett.*, 583 (1962); (b) S. J. Trippett, *J. Chem. Soc.*, 2337 (1962); (c) P. A. Chopard and R. F. Hudson, *ibid.*, 1090 (1966).

credence by the failure of the "harder" α-chloro ketones to undergo such a reaction and the failure, usually, of the "harder" phosphites to cause debromination of α-bromo ketones in the presence of alcohols or acetic acid.[32]

Experimental Section[33]

The following compounds were obtained commercially and either recrystallized to a constant melting point and tlc purity or distilled: TPP, **1a**, **1d–f**, **1j**, **2a**, and the various substituted propiophenones other than *m*-CF_3. Resublimed iodine, anhydrous sodium thiosulfate, arsenic trioxide, and other inorganics were used as purchased. Other α-bromoacetophenones, **6**, and other bromo ketones have been previously described.[4,34] *m*-Methoxy-α-bromoacetophenone (**1h**),[35] *m*-bromoacetophenone (**1i**),[36] **2e**,[25,37] **2b**,[28] and **2d**[36] were prepared by bromination of the appropriate ketone.

***m*-Trifluoromethyl-α-bromoacetophenone (1g)**: 70–88% from *m*-trifluoromethylacetophenone; bp 71–72° (0.25 mm); nmr ($CDCl_3$) τ 2.10, −2.90 (m, 4, aryl), 5.52 (s, 2, CH_2).

Anal. Calcd for $C_9H_6OBrF_3$: C, 40.48; H, 2.26. Found: C, 40.26; H, 2.26.

***p*-Methyl-α-bromoacetophenone (1c)**: 66% from the reaction of bromoacetyl bromide and toluene; mp 51–52° [after four recrystallizations from 30–60° petroleum ether (lit.[37] mp 48°)]; nmr ($CDCl_3$) τ 2.50 (m, 4, aryl), 5.77 (s, 2, CH_2), 7.60 (s, 3, CH_3).

Anal. Calcd for C_9H_9OBr: C, 50.73; H, 4.26; Br, 37.50. Found: C, 51.03; H, 4.29; Br, 37.87.

***p*-Methyl-α-bromopropiophenone (2c)**: 65% by procedure as for **1c**; mp 79–80° (lit.[37] mp 76–77°), nmr ($CDCl_3$) τ 2.4 (m, 4, aryl), 7.75 (q, 1, methine H), 7.60 (s, 3, CH_3Ar), 8.15 (d, 3, $CHBrCH_3$).

***m*-Trifluoromethylpropiophenone.** *m*-Bromobenzotrifluoride (4.5 g, 0.02 mol) in diethyl ether (10 ml) was added slowly to magnesium (0.5 g, 0.02 g-atom) in ether (20 ml). After addition of several drops of reactant, ethylene dibromide (1 drop) was added to initiate reaction and then the rest of the reactant was added at a rate sufficient to keep the reaction at reflux. The reaction mixture was then heated at reflux for 1 hr and cooled to 0°, and propionitrile (0.9 g, 0.02 mol) was added slowly with rapid stirring. The mixture was stirred for 1 hr, hydrolyzed with iced 1 *N* H_2SO_4 (*ca.* 100 ml), and extracted with ether to give *m*-trifluoromethylpropiophenone (2.4 g, 0.012 mol, 60%): bp 83–86° (0.3 mm) [lit.[39] bp 123–125° (5 mm)]; nmr (CCl_4) τ 1.85–2.55 (m, 4, aryl), 7.03 (q, 2, CH_2), 8.82 (t, 3, CH_3).

***m*-Trifluoromethyl-α-bromopropiophenone (1g).** A. Bromination of the above ketone gave the bromo ketone: 68%; bp 66–67° (0.2 mm); nmr (CCl_4) τ 1.8–2.55 (m, 4, aryl), 4.8 (q, 1, CHBr), 8.1 (d, 3, CH_3).

B. Reaction of diethylcadmium[40] with *m*-trifluoromethylbenzoyl chloride gave crude *m*-trifluoromethylmethylpropiophenone which was brominated in CCl_4 to give the bromo ketone in overall 10% yield.

Anal. Calcd for $C_{10}H_8OBrF_3$: C, 42.73; H, 2.85; Br, 28.50. Found: C, 42.53; H, 2.81; Br, 28.74.

***m*-Nitro-α-bromopropiophenone (2f)**: 75%; mp 64–64.5°; nmr ($CDCl_3$) τ 1.80 (m, 4, aryl), 4.63 (q, 1, CH), 8.03 (d, 3, CH_3).

Anal. Calcd for $C_9H_8NO_3Br$: C, 41.89; H, 3.12; Br, 30.96. Found: C, 41.65; H, 3.15; Br, 31.21.

Debromination Reactions. The general procedure for the debromination reactions has been described.[3,6] After separation of ketophosphonium bromides as benzene-insoluble precipitates and TPPO as heptane- or hexane-insoluble material, debrominated ketone was isolated by distillation *in vacuo*. Identification of the ketones was made by nmr and tlc, of TPPO by ir and tlc, and of the ketophosphonium salts by melting point and ir. No unreacted bromo ketones were found under the conditions used.

Debromination Kinetics. All measurements were done under prepurified nitrogen. Most liquids used were freshly dried and distilled through spinning-band, silver-jacketed Vigreux or glass bead-packed columns. Standard iodine–potassium iodide, sodium thiosulfate, HCl, NaOH, and other solutions were prepared by the usual techniques.[41]

The following procedure for the debromination of *p*-bromo-α-bromoacetophenone (**1e**) is typical of the kinetic method used. To a long-necked glass-stoppered flask fitted with a stopcock containing a side arm, immersed in an ice–water bath, was added a solution (20–25 ml) of TPP (0.0380 *M*) in ethanol containing 0.1206 *N* HCl, 0.42 *M* H_2O. The solution was equilibrated for at least 30 min. The TPP was prepared by weighing and checked by titration with iodine.[12] Then an equal volume of an ice-cold solution of **1e** (0.0380 *M*) in ethanol was added by calibrated pipet. Zero reaction time was counted when one-half of the bromo ketone solution was added. After addition of **1e**, the resultant solution was shaken (in the ice–water bath) for 30 sec. Aliquots (*ca.* 3 ml) were removed at appropriate time intervals by a gas-tight syringe and added to a quenching solution containing acetonitrile (5 ml), 0.0512 *N* iodine–KI (4.70 ml), and saturated potassium acetate (5 drops).[12] Excess iodine was back-titrated with sodium thiosulfate solution (0.0498 *N*) to a visual end point. With this procedure, fadeback of iodine coloration was slow. It was much faster without the sodium acetate. The TPP solution, rather than the bromo ketone solution, must contain the HCl for best results. By this method, [TPP] was determined from [I_2] remaining in the quenching solution. Reactions were carried out to 1–2 half-lives for **3a–f** (with 0.03 *M* reagents) and 2–3 half-lives for **1a–j** (with 0.02 *M* reagents).

Plots of **1**/[TPP] *vs.* time gave straight lines whose slopes were k_2. Acid-free reactions were similarly done in absolute ethanol. The reaction mixtures remaining at the end (for the acid-catalyzed runs) were examined by tlc. Only debrominated ketone and TPPO were present. Some of the bromo ketones were also debrominated with TPP and with ethanol in larger scale reactions.

In the alcohol-catalyzed reactions, small yields (1–3%) of ketophosphonium bromides were found in the reactions of **1b** or **2f** with TPP but not in similar reactions of **1f** or **2c**. Since a full study was not done, no corrections in the k_2^0 values due to phosphonium salt formation were attempted. ρ values and correlation coefficients were calculated by known formulas.[26c]

Acknowledgment. We are indebted to Professors Arno Liberles and Chris Vogel for stimulating discussions.

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