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Halogenation of Acetone. A Method for Determining pK_as of Ketones in Aqueous Solution, with an Examination of the Thermodynamics and Kinetics of Alkaline Halogenation and a Discussion of the Best Value for the Rate Constant for a "Diffusion-Controlled Reaction". Energetic Requirements for a Diffusion-Controlled Reaction Involving Heavy-Atom Bond Formation

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Abstract: The pK_a of a simple ketone can be determined by analysis of the kinetics of halogenation in alkaline solution (*J. Am. Chem. Soc.* **1982**, *104*, 895). Details of the determination of the pK_a of acetone are reported. The stoichiometry of chlorination of acetone is 2.15 hypohalites per acetone; bromination consumes 2.83 hypobromites. The major product from chlorination is lactate and not acetate; lactate is a minor product from bromination of acetone. The kinetic significance of the possible side reactions is discussed. The determination of the pK_a requires knowledge of the rate constant for a diffusion-controlled reaction of nonspherically symmetrical molecules in water; the state of our knowledge of this rate constant is reviewed critically. It is shown that for reactions involving diffusion together of reactants which then undergo direct heavy-atom bond making it is very unusual for the diffusion limit to be reached, although the observed rate constant may become insensitive to the thermodynamic reactivity of the reactants.

Our interest in the aldol condensation[2-4] led us to look for a method for obtaining the pK_as of ketones in aqueous solution. Enolate formation is an essential step for a base-catalyzed aldol condensation, and the attack of the enolate upon a carbonyl group is frequently the rate-determining step. Ketones are much less acidic than water, so that direct determination of their pK_a values has not been possible. Indirect methods have been developed[5] and have led to results which are widely accepted[6] but are necessarily lacking in rigor. Bordwell et al.[7] have reported methods for determining pK_a values in dipolar aprotic solvents, but there is a large and unknown solvent shift in pK_a on going from dipolar aprotic solvents to water,[8] so that the problem remains unsolved for aqueous solutions. Wirz has reported[9] a flash spectroscopic method which gives enol pK_as and might give pK_as of ketones with a suitable chromophore; thus far it has only been applied to acetophenone.

In the course of a recent investigation concerning the equilibrium constants for enolization of simple carbonyl compounds,[10-12] we realized[11] that implicit in some pioneering work by Bartlett[13,14] was a potential method for determining the pK_a of simple ketones in water. Bartlett and Vincent[14] discovered that in alkaline solution there is a term in the rate law for chlorination of ketones which was first order in ketone, first order in hypochlorite, and zero order in hydroxide. Arguments favoring the interpretation that this term represents reaction of the enolates with HOCl and evidence that this reaction is diffusion controlled will be presented below. This interpretation means that the apparent rate constant for the term zero order in hydroxide is a function only of the rate constant for diffusion together of two species in water, the pK_a of the hypohalous acid, and the pK_a of the ketone. Since only the last value is unknown, it can at once be calculated.

Most studies of ketone halogenation have used bromine or iodine (or hypobromite or hypoiodite). For these reagents the total rates of the halogenation steps are faster because of the greater reactivity of the hypohalite ions, so that under the usual experimental conditions the overall rate-determining step is proton abstraction. For halogenation using bromine or iodine the stoichiometry has been reported[15,16] to be 3 mol of halogen per mol of methyl ketone, with the complicating feature that at high concentrations bromination of bromoform can occur at competitive rates leading to higher stoichiometric ratios. Deviations from this stoichiometry are common.[15] In the present work we discovered that for chlorination the stoichiometry, at least at low concentrations of reagents at room temperature, is approximately two chlorines per mole of ketone. The major product from the alkaline chlorination of acetone is lactic acid. For bromination and iodination the major product has been shown to be acetic acid, but lactic acid is present as a minor product. We will examine the question of the actual course of this reaction.

Two previous studies have shown that the course of butanone bromination can be diverted by hydrolysis.[17,18] The behavior of acetone is related but shows striking differences as a result of the difference of one carbon atom.

This method has been reported in a preliminary communication;[19] we now wish to present a detailed description of the method as it applies to acetone and the results of our studies of the halogenation of acetone. In an independent investigation Jencks and Tapuhi[16] studied the bromination and iodination of acetone, using high concentrations of buffers to make proton transfer faster than halogenation so that halogenation was rate limiting. Their

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results were consistent with ours and led to similar conclusions regarding the pK_a of acetone.

We will also present a discussion of the value to use for the rate constant for a "diffusion-controlled reaction"; the numerical value for this frequently used concept is in fact not well established for other than proton-transfer reactions.

Results

Kinetics: Derivation of Rate Equations. We will derive an equation relating the observed absorbance to the desired rate constant for halogenation; we assume that the first stage of halogenation is rate determining and is followed by further rapid halogenations with a total of *n* mol of halogen consumed per mole of ketone. In what follows, X = Cl or Br.

$$A_t = \epsilon_{OX}[OX^-]_t + \epsilon_K[\text{ketone}]_t$$

where A_t = absorbance at time t, ϵ_x = extinction coefficient of species x, $[x]_t$ = concentration of species x at time t, $dA/dt = \epsilon_{OX}d[OX^-]/dt + \epsilon_K d[\text{ketone}]dt = -(n\epsilon_{OX} + \epsilon_K)k_{app}[\text{ketone}][OX^-]$ since

$$d[OX^-]/dt = nd[\text{ketone}]/dt = nk_{app}[\text{ketone}][OX^-]$$

where n = stoichiometry ratio or the number of OX^- reacting per mole of ketone consumed. Then:

$$dA/dt = -(n\epsilon_{OX} + \epsilon_K)k_{app}([\text{ketone}]_0 - x)([OX^-]_0 - nx)$$

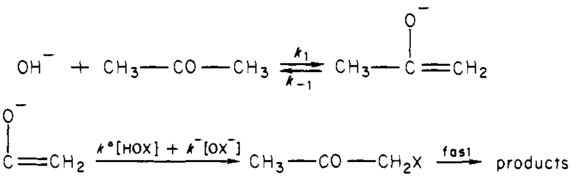
where x = amount of ketone converted = $(A_0 - A_t)/(n\epsilon_{OX} + \epsilon_K)$. It may readily be shown that if $[\text{ketone}]_0 >> [OX^-]_0$

$$\ln((A_t - A_\infty)/(A_0 - A_\infty)) = -nk_{app}[\text{ketone}]_0t \quad (1)$$

and that if $[OX^-]_0 >> [\text{ketone}]_0$

$$\ln((A_t - A_\infty)/(A_0 - A_\infty)) = -k_{app}[OX^-]_0t \quad (2)$$

The apparent rate constant for halogenation, with hypohalite excess, is interpreted in terms of the following model:



$$OH^- + CH_3{-}CO{-}CH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3{-}C(O^-){=}CH_2$$

$$CH_3{-}C(O^-){=}CH_2 \xrightarrow{k^\circ[HOX] + k^-[OX^-]} CH_3{-}CO{-}CH_2X \xrightarrow{fast} \text{products} \quad (3)$$

Making the steady-state assumption for the enolate we get:

$$-d[\text{ketone}]/dt = \{\{k^\circ[HOX] + k^-[OX^-]\}k_1[OH^-]\} \times [\text{ketone}]/\{k_{-1} + \{k^\circ[HOX] + k^-[OX^-]\}\}$$

$$[HOX] = K_w[OX^-]/K_a^{HOX}[OH^-]$$

$$-d[\text{ketone}]/dt = \{\{k^\circ K_w/K_a^{HOX}[OH^-] + k^-\}k_1[OH^-][OX^-]\} \times [\text{ketone}]/\{k_{-1} + \{k^\circ K_w/K_a^{HOX}[OH^-] + k^-\}[OX^-]\} \quad (4)$$

At high $[OX^-]$, i.e., $\{k^\circ K_w/K_a^{HOX}[OH^-] + k^-\}[OX^-] >> k_{-1}$

$$-d[\text{ketone}]/dt = k_1[OH^-][\text{ketone}] \quad (5)$$

and enolization is the rate-determining step. At low $[OX^-]$, i.e., $\{k^\circ K_w/K_a^{HOX}[OH^-] + k^-\}[OX^-] << k_{-1}$

$$-d[\text{ketone}]/dt = \{k_1k^\circ K_w/k_{-1}K_a^{HOX} + k^-K_a^{\text{ketone}}[OH^-]/K_w\}[OX^-][\text{ketone}] \quad (6)$$

We will be working in the low $[OX^-]$ region in the kinetics described in this paper.

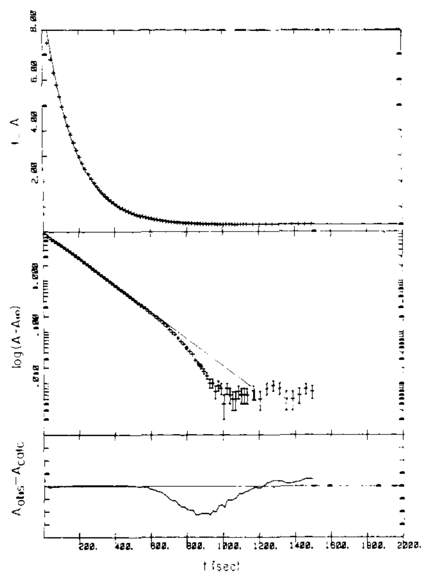


Figure 1. Typical reaction of hypobromite with acetone. $[\text{Acetone}]_0 = 9.21 \times 10^{-4}$ M, $[OBr^-] = 2.60 \times 10^{-4}$ M, [OH] = 0.00448 M. The three plots show absorbance as a function of time, ln $(A - A_\infty)$ as a function of time, and residuals $(A_{obsd} - A_{calcd})$ as a function of time. The deviations at long time are a reproducible characteristic of these kinetics.

Figure 1 shows the results of a typical kinetics experiment in which acetone is allowed to react with hypobromite. In order to have halogenation be rate determining, it was necessary to have very low hypobromite concentrations; accordingly these runs were carried out with ketone in excess. To confirm that the observed behavior was not due to trace impurities, repeated additions of small amounts of bromine to the same ketone solution were performed; the rate constants observed were similar provided that the hypobromite concentration was greater than 2×10^{-5} M. The kinetics followed first-order behavior for 3 or more half lives, but deviated from strict first-order behavior toward the end of the reaction. In the final calculations of rate constants for the initial, well-behaved, part of the reaction, points for $[OBr^-] < 2 \times 10^{-5}$ M were deleted. If the initial concentration of OBr^- is too high the kinetics will not be first order in OBr^- but rather will approach zero order. Using the results of the initial kinetic analysis we could calculate the rate constants for halogenation and reprotonation of the enolate and so determine the maximum concentration of OBr^- for first-order behavior; the value depends on $[OH^-]$, being 8×10^{-5} M at 0.0005 M OH^- and 1.4×10^{-4} M at 0.005 M OH^-. Data for excessively high initial $[OBr^-]$ were deleted where necessary. For those runs where the initial $[OBr^-]$ was greater than 2×10^{-5} M points at long times had to be deleted; these long time data were fitted separately to a first-order rate law and gave apparent rate constants in reasonable accord with those from runs where the initial $[OBr^-]$ was less than 2×10^{-5} M. It appears that there is a reproducible acceleration in the rate of disappearance of OBr^- when the concentration falls below 2×10^{-5} M. We do not have a good explanation for this behavior, although it looks very much as though there is a decomposition mode for hypobromite which is inhibited by hypobromite at concentrations greater than about 2×10^{-5} M. When we examined the behavior of the derivative of absorbance with respect to time as a function of hypobromite concentration, we found that the behavior at low hypobromite concentrations is not first order in hypobromite but rather is apparently two-thirds order in hypobromite. We have no satisfactory explanation for this behavior.

In order to test for the incursion of free radical pathways we tried flushing a solution with argon before adding bromine to initiate reaction and also interrupting a reaction to shine a bright light on the spectrophotometer cell. These experiments were done with $[OBr^-]_0 = 2.7 \times 10^{-4}$ M (argon and light) or 0.7×10^{-4} M (argon). In neither case was there any noticeable alteration in rate from the expected value. Accordingly we conclude that we are following the classical heterolytic pathway. The rate constants which we obtained are found in Table I of supplementary material. Figure 2 shows the dependence of the second-order rate constants upon the concentration of hydroxide.

Kinetics of chlorination were carried out both with ketone in excess and with halogen in excess. Figure 3 shows the results of a typical chlorination experiment with hypochlorite excess; good first-order kinetics were obtained for 3 or more half lives. The rate constants are found in Table I of supplementary material.

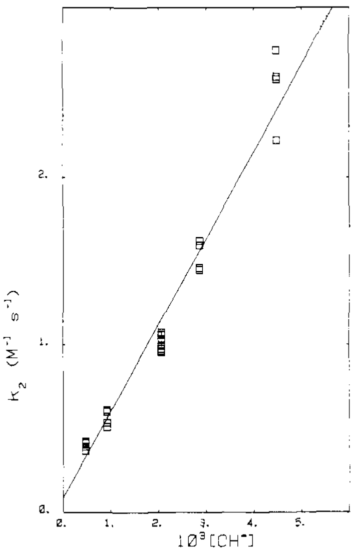


Figure 2. Second-order rate constants for the reaction of acetone with hypobromite as a function of hydroxide concentration. Reactions were carried out with $[\text{Acetone}]_0 \cong 10^{-3}$ M and $[\text{OBr}^-] \cong 10^{-4}$ M. The line was fitted by least-squares: $k_2 = 0.090 \pm 0.039 + (515 \pm 18)[\text{OH}^-]$.

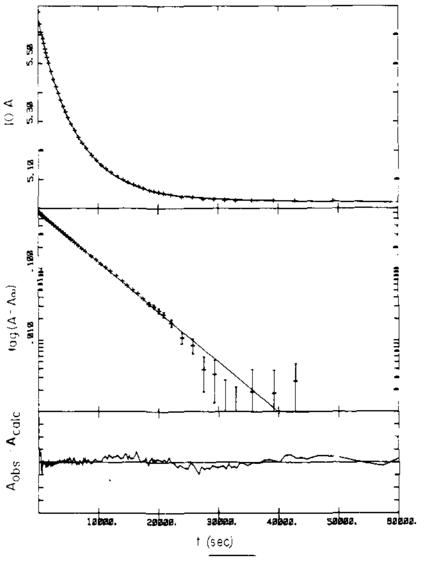


Figure 3. Typical reaction of hypochlorite with acetone. $[\text{Acetone}]_0 = 2.7 \times 10^{-4}$ M, $[\text{OCl}^-]_0 = 55 \times 10^{-4}$ M, $[\text{OH}^-] = 0.300$ M. The three plots are as for Figure 1.

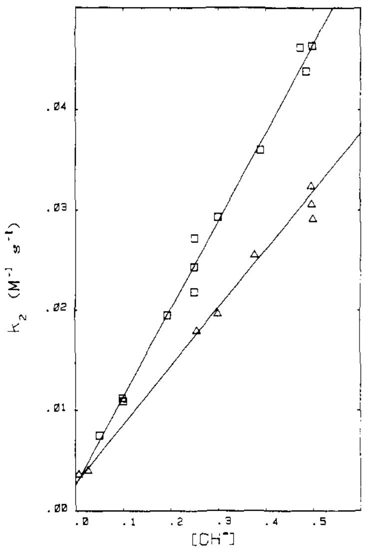


Figure 4. Second-order rate constants for the reaction of acetone with hypochlorite as a function of hydroxide concentration. (□) Reaction with hypochlorite excess; (△) reaction with ketone excess (calculated using stoichiometry = 3.0). The lines were fitted by least-squares. $k_2 = 0.0025 \pm 0.0009 + (0.0877 \pm 0.0029)[\text{OH}^-]$ for hypochlorite excess and $k_2 = 0.0027 \pm 0.0005 + (0.0583 \pm 0.0016)[\text{OH}^-]$ for ketone excess.

Table II. Product Studies for Halogenation of Ketones

	% lactate formed			
hypohalite	acetone NMR	acetone enzyme assay	hydroxy-acetone enzyme assay	methoxy-acetone enzyme assay
	$[\text{OH}^-] = 1.0$ M, Method 1			
OCl^-	84^a	85	80	87
OBr^-	21^a	17	41	59
OI^-	20^a	11	...	...
OCl^-		51		
OCl^-		92		
OBr^-		18		
	$[\text{OH}^-] = 0.1$ M, Method 2			
OCl^-	66^b	67	78^c	63^d 68
	Chloroacetone			
OCl^-	52^b	47		
	Dichloroacetone			
OCl^-	10^b	20 ± 7		

[a] 200 MHz. [b] 60 MHz. [c] 60 MHz NMR showed [lactate]/[acetate] = 11.5. [d] 60 MHz NMR showed ca. 10–20% methoxyacetate was present; integration for methoxyacetate was not possible.

Figure 4 shows the dependence of the second-order rate constants for chlorination of acetone upon the concentration of hydroxide by using second-order rate constants from experiments with ketone in excess, calculated from a stoichiometry number of 3.0, and second-order rate constants from experiments with hypohalite in excess. These two sets of data do not fit a single line. This requires that the stoichiometry be other than 3.

Product Studies. Experiments were carried out under conditions similar to those used in kinetics experiments, except that concentrations of ketone and hypohalite were about 100-fold higher, i.e., ca. 0.01 M and 0.08 M, respectively; the hydroxide concentration was 0.99 M. The product solution was treated first with a slight excess of NaHSO_3 in order to destroy the OX^- remaining in solution and then with enough KH_2PO_4 to give a 1:1 H_2PO_4^-:HPO_4^{2-} buffer with a pH of about 7. D_2O (10% v/v) was then added to provide a lock signal and the 200-MHz NMR was recorded. The solution from reaction of acetone with hypochlorite showed a weak signal at the position expected for acetate, but the major signal was a doublet at a position consistent with lactate. The identity of the species giving rise to the doublet was shown by control experiments, where authentic lithium lactate was added to a portion of the product solution, and confirmed by enzyme assay using lactate dehydrogenase (see Table II). Similar experiments with hypobromite showed that the major product was now acetate with minor amounts of lactate (see Table II). Experiments with hypoiodite gave similar results except that there was a yellow color to the enzyme assay solutions, which caused a large background correction, making the assay less reliable.

Analogous experiments with hydroxy- and methoxyacetone gave less than the expected amount of lactate, although this was the major product seen in the NMR spectrum. The products which might have been expected were acetate, from oxidation of the hydroxymethyl or alkoxymethyl group, and glycolate or methoxyacetate, from oxidation of the methyl. A signal attributed to the methyl group of acetate was sometimes detected, but was always small, being at most about 10% the intensity of the signal from lactate. Glycolate would be undetectable because the NMR signal from its hydroxymethyl group would fall too close to the solvent peak to be detected, but a peak attributed to the *O*-methyl of methoxyacetate was observed in the NMR spectrum of a product solution from methoxyacetone. Product studies on

Table III. Group Contributions for Halomethyl Groups Bonded to Carbonyl

group	value of contribution, kcal/mol		
	X = Cl	X = Br	X = I
[$XCH_2C(CO)$]	−10.1	−1.5	10.5
[$X_2CH(CO)$]	−12.6	(−1.5)[a]	(10.5)[a]
[$X_3C(CO)$]	−11.4	(−1.5)[a]	(10.5)[a]

[a] Assumed value; see text.

chlorination of monochloroacetone showed that it gives rise to 50% lactate, while dichloroacetone mainly gives acetate with only 10% lactate.

From the change in absorbance during a reaction of acetone with excess hypochlorite we can calculate the change in hypochlorite concentration. This allows calculation of the stoichiometry numbers in part a of Table I of supplementary material. The values show considerable scatter, but using all the points we get a stoichiometry of 2.45 ± 0.44; if the two points corresponding to a stoichiometry of greater than 3.0 are omitted, the average becomes 2.29 ± 0.26. In any case it is clear that the stoichiometry is less than 3 and closer to 2.

The product studies reveal that major amounts of lactate are formed during chlorination of acetone, although the exact amount depends upon the precise conditions. From kinetics currently in progress[20] on the chlorination of monochloroacetone we have a rate law for this reaction:

$$k_{obsd} = k_h[OH^-] + k_c[OCl^-]$$

where k_{obsd} is the pseudo-first-order rate constant for chloroacetone consumption, and the term zero order in hypochlorite represents hydrolysis of monochloroacetone to give hydroxyacetone, which undergoes slow further chlorination. For the chlorination reaction only the term zero order in hydroxide is defined by the data, although there is a hint of a term first order in hydroxide which might be significant at high hydroxide concentrations. Using the preliminary values of these rate constants (k_h = 1.50 ± 1.22, k_c = 10.3 ± 4.6) we calculated the stoichiometry numbers for the ketone excess kinetics shown in Table I of supplementary material and used these in turn to calculate second-order rate constants. Figure 5 shows that these rate constants are consistent with those measured under hypochlorite excess conditions, and thus that we can account for the data in terms of a simple picture. The stoichiometry will also be affected in a minor way by the partitioning of dichloroacetone, which gives mostly acetate. We have not been able to measure rates of halogenation of dichloroacetone under comparable conditions. Although we can rationalize the stoichiometry for chlorination kinetics with ketone in excess, we do not have precise values for all of the rate constants determining the stoichiometry nor accurately known rate laws. Thus it does not seem advisable to use the experiments with ketone in excess as part of the data set for determining the pK_a of acetone.

For kinetics with hypobromite we were forced to use ketone in excess; since the stoichiometry number indicated by the product studies is close to 3.00, any error produced by using a value which is not for the exact conditions of the experiments is likely to be small. However one must bear in mind that at low and falling [OBr^-] the stoichiometry may be less than 3.0. If this be the case, our calculated second-order rate constants will be too *small* by a factor of up to 3/2; in fact the rates of bromination appear to be *fast* when compared with the rates of chlorination. Clearly it would have been better to run the kinetics with hypobromite excess. This would however have entailed following a very small change in absorbance, with the total absorbance being small to start with; the absorbance change would have been only one tenth as large as those obtained with ketone in excess, because of the need for low [OBr^-] to have bromination be rate limiting.

Table IV. Thermodynamic Values for Compounds Discussed in This Paper[a]

compd	ΔH°_f(g)[b]	S°(g)[c]	ΔG°_f(g)[b]	ΔG_t[b,d]	ΔG°_f(aq)[b]
CH_3COCH_3	−51.8	70.45	−37.1	−2.1	−39.1
$ClCH_2COCH_3$	−51.7	80.81	−37.7	−2.6	−40.3
$Cl_2CHCOCH_3$	−54.2	87.61	−39.8	−3.2	−43.0
Cl_3CCOCH_3	−53.0	92.23	−37.6	−3.7	−41.3
$BrCH_2COCH_3$	−43.1	83.81	−26.1	−3.4	−29.5
$Br_2CHCOCH_3$	−43.1	93.61	−22.9	−4.7	−27.6
Br_3CCOCH_3	−43.1	101.23	−18.9	−6.1	−25.0
ICH_2COCH_3	−31.0	85.81	−17.2	−3.6	−20.8
$I_2CHCOCH_3$	−31.0	97.61	−17.0	−5.1	−22.2
I_3CCOCH_3	−31.0	107.23	−16.2	−6.7	−23.0

[a] At 25 °C; standard states are ideal gas at 1 atm and 1 M aqueous solution with an infinitely dilute reference state. [b] kcal mol^{-1}. [c] cal deg^{-1} mol^{-1}. [d] Free energy of transfer from gas to aqueous solution.

Table V. pK_a Values for Halogenated Acetones[a]

compd	pK_a value		
	X = Cl	X = Br	X = I
CH_3COCH_3	19.1[b]	19.1[b]	19.1[b]
XCH_2CCOCH_3	14.1[c]	14.3[c]	14.3[d]
$X_2CHCOCH_3$	11.7[c]	11.9[e]	11.9[d]

[a] In water at 25 °C. [b] This work. [c] Estimated from the rate constants for enolization catalyzed by $RCOO^-$ using a Marcus curve.[12] [d] Assumed to be the same as for the corresponding bromo compound. [e] Estimated assuming a constant ΔpK_a for each substitution of Br for Cl.

Thermodynamics. Approximate values for the group contributions needed to calculate equilibrium constants could be estimated from data in the literature. Heats of formation are available for $ClCH_2COOC_4H_9$, $Cl_2CHCOOC_4H_9$, $Cl_3CCOOC_4H_9$, $BrCH_2COOCH_3$, and ICH_2COOCH_3. These allowed estimation of the group equivalents in Table III. Since the three chlorinated methyl group contributions are essentially identical, we have assumed that the values for the three brominated methyl groups and the three iodinated methyl groups are likewise the same. This is equivalent to the assumption that there is a cancellation of effects from polar interactions with the carbonyl group just as with the chlorinated methyl groups. For chlorinated methyls on saturated carbon, increasing the number of chlorines leads to increasingly more negative contributions: −16.5, −18.9, −20.7;[21] for chlorinated methyls on carbonyl carbon, there is almost no change. This may mean that the more negative contribution to be expected with additional chlorines is cancelled by a positive contribution from polar interactions. This assumption cannot be tested at present, and we must bear in mind that it may not hold for bromine and iodine. Furthermore the values used for chloromethyl ketones are based on data for chloroacetate esters, and one must worry about whether there may be deviations from group additivity with such strongly electron-withdrawing groups. Consequently we consider it unwise to treat the enthalpy of formation estimates as better than ±5 kcal/mol. This is a large uncertainty, but as we will see it still permits useful estimates to be made. The other group contributions needed in order to calculate these new group contributions were taken from Benson.[21] With these values and values from Benson,[21] it was possible to estimate heats of formation. When bond contributions from Benson and Buss[22] were used, it was possible to estimate standard entropies, and so to calculate free energies of formation in the gas phase. Free energies of transfer were calculated using Hine's bond contributions.[23] Thus we were able to determine free energies of formation in aqueous solution for the haloacetones; these thermodynamic quantities are found in Table IV.

For the inorganic species, the free energies of formation in aqueous solution (conventional values, with $\Delta G_f[H^+]$ = 0.0) are: OCl^-, −8.8; OH^-, −37.60; OBr^-, −8.0; OI^-, −9.24.[24] It is now

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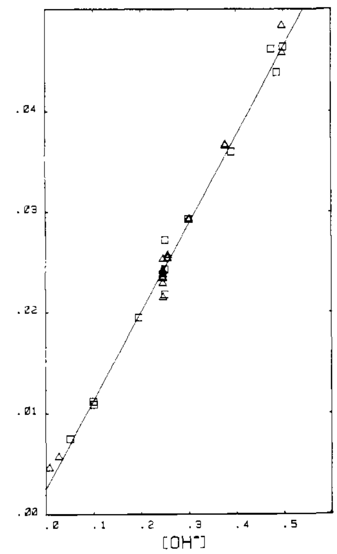

Figure 5. Second-order rate constants for the reaction of acetone with hypochlorite as a function of hydroxide concentration. (□) Reaction with hypochlorite excess; (△) reaction with ketone excess (calculated using initial stoichiometry ratios calculated as described in the text). The line was fitted by least-squares. $k_2 = 0.0016 \pm 0.0008 + (0.0879 \pm 0.0028)[\mathrm{OH^-}]$.

Table VI. Equilibrium Constants for Reactions of Ketone Enolates with HOX and OX^- [a]

	log K for HOX reaction			log K for OX^- reaction		
n	HOCl	HOBr	HOI	OCl^-	OBr^-	OI^-
0	33.6	26.2	19.3	12	5	−2
1	28.8	27.1	28.9	7	5	7
2	23.4	24.2	26.0	2	3	5

[a] In aqueous solution at 25 °C.

possible to calculate the equilibrium constants for each stage of the halogenation, for the neutral ketones as reactants. To calculate the equilibrium constants for the reactions of the enolates with hypohalous acid or hypohalite we need the pK_as of the ketones; the values which we will use are given in Table V. The pK_a for HOCl is 7.54,[25] for HOBr is 8.60,[26] and for HOI is 11.64.[27] The pK_a for HO^- is taken as 29 by using a value estimated by an electrostatic potential calculation by Schwarzenbach.[28]

Finally, the equilibrium constants for the reactions of acetone and halogenated acetones with hypohalous acids and hypohalites calculated by using these values are found in Table VI. These equilibrium constants and in particular the values for bromination and iodination must be subject to large uncertainties, because they are based on meager data. Nonetheless, it seems most unlikely that the errors are larger than 5 log units, and the values are often so large that even such very considerable uncertainties leave us able to make useful generalizations. The equilibrium constants for the reaction of enolates with hypohalous acid are all *large* and for the initial chlorination and bromination are enormous, being about log K = 30. The equilibrium constant for the initial stage of iodination is smaller although the equilibrium constants for all three halogens appear similar for the final stage. The equilibrium constants for the reactions of enolates with hypohalite ions are clearly smaller, as one would expect, and are subject to large errors because of the use of a very uncertain pK_a for OH^- ionizing to O^{2-}. The principal merit of these values is to demonstrate the rather surprising conclusion that O^{2-} as a leaving group cannot be ruled out a priori; the energetics are such that for a plausible value of the OH^- pK_a the direct reaction of an enolate with OX^- to expel O^{2-} is possible. The values for successive chlorinations should be reasonably good as relative values even though there is a large absolute uncertainty; they show the anticipated decline in equilibrium constant with progressive reaction. The irregular behavior for bromine or iodine is almost certainly not outside the uncertainty in the relative values. Although we feel that the direct reaction with expulsion of O^{2-} cannot be ruled out a priori, we doubt that this is in fact the mechanism. More elaborate mechanisms have been proposed[16] and look more plausible.

Discussion

Diffusion-Controlled Reaction Rates. In order to calculate the pK_a of acetone from the rate constant for reaction at zero hydroxide concentration, it is necessary to have a rate constant for a diffusion-controlled reaction. Although the concept of diffusion-controlled reactions is widely employed in organic chemistry, it is surprisingly difficult to settle upon the appropriate value to use in particular circumstances. There are two origins for this difficulty: the reaction distance, R_{ij}, and the solid angle α_R through which attack leads to reaction (eq 7[29,30] where N_L = Avogadro's

$$k_{\mathrm{diff}} = \alpha_R N_L R_{ij}(D_i + D_j)\phi_{ij}/(\exp(\phi_{ij}) - 1) \qquad (7)$$

number, R_{ij} = reaction distance, D_i, D_j = diffusion coefficients of the reactants, ϕ_{ij} = ratio of potential energy of the electrostatic interaction to the thermal energy). The reaction distance R_{ij} is generally taken as the sum of the van der Waals radii for the reacting atoms. There is room for some uncertainty since neither these radii nor the need to be in van der Waals contact is well established. For spherically symmetrical reactants, where the solid angle α_R is unquestionably 4π one can have fair confidence that the rate constant is correct within the uncertainty of ca. 2-fold resulting from imperfect knowledge of R_{ij}. It is unlikely that reaction can occur at distances much greater than van der Waals contact, and in fact R_{ij} is commonly taken to be the sum of the van der Waals radii; it is certain that R_{ij} cannot be less than the covalent bond distance, and it is almost certainly greater. Since the sum of the van der Waals radii is about twice the covalent bond length this gives an uncertainty of about 2-fold. For non-spherically symmetrical reagents such as those involved in the reaction under consideration, namely acetone enolate and hypochlorous acid, it is by no means certain that there will not be a significant steric effect, restricting reaction to a limited solid angle of attack. The problem can be restated in terms of the relative rates of diffusional separation of reactants after encounter and rotation relative to each other within a solvent cage (or what is equivalent, diffusion of one reactant within the surface layer of the solvent cage surrounding the other reactant). If during an encounter all parts of the surfaces of both reactants are likely to be presented to each other before diffusional separation, then the reactants are effectively spherical, and the traditional equation with $\alpha_R = 4\pi$ is appropriate. If diffusional separation is likely to occur before all possible rotational orientations have been sampled, then a value for α_R less than 4π should be used or a more elaborate model for diffusional encounter should be employed (vide infra).

Various experimental values for rate constants which are believed to be at or near the diffusion-controlled limit are presented in Table VII of supplementary material. The reaction of iodide ion with iodine molecule to give triiodide ion[31] is not a good model, because this is clearly a reaction with a very small steric factor involving spherical or nearly spherical species. There are also various rate constants for proton transfer[29] or ion recombination reactions,[32,33] but these rate constants are not suitable models

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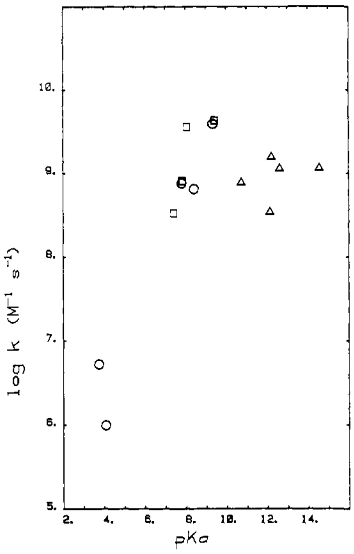

Figure 6. Rate constants for halogenation of organic anions as a function of the pK_a of the conjugate acid of the anion. (○) phenoxide ions;[36] (□) phenolate ions;[37] (△) disulfone anions.[38]

because of the special features (high proton mobility, electrostatic attraction) which should make them faster than the reactions we are concerned with. This leaves the rates of nitrosation of arylamines[34,35] and bromination of aryloxide[36,37] or disulfone anions.[38]

Williams et al.[34] have demonstrated that the rates of reaction of substituted anilines with NOCl and NOBr increase with pK_a for weakly basic anilines but level off for more basic anilines at ca. 3–4 × 10^9 M^{-1} s^{-1}. We feel that it is quite significant that the rates level off at a value distinctly less than the classical diffusion-controlled reaction rate of 7 × 10^9 M^{-1} s^{-1}; since this reaction is somewhat different from ours the exact amount by which the limiting rate is less than the classical value may differ.

Bromination reactions are clearly closely analogous to our hypohalous acid reactions, but there is no set of compounds showing an unambiguous leveling off with increasing nucleophilicity. Tee et al.[39] report values for the rate constant for the reactions of Br_2 with anions of uracil and related species. Their assumption that Br_3^- makes a negligible contribution to the observed rate has not been tested and could lead to spuriously high rate constants for Br_2. Bell and Rawlinson[36] found that the contribution of Br_3^- to the overall rate was larger for the more reactive phenoxides. All of the phenoxide rate data were corrected for the number of available sites for reaction, i.e., unsubstituted sites ortho or para to the aryl oxide. The data of Kulic and Vecera[37] required correction for the effect of ionic strength on the pK_a of the phenol since their kinetics were performed at ionic strength 0.8 ($NaClO_4$) and they used thermodynamic pK_a values for the phenols. This was done by following Bell and Rawlinson[36] and using an activity coefficient of 0.639 for 0.8 M $NaClO_4$ interpolated from the tables in Robinson and Stokes.[40] After this correction was made there is satisfactory agreement between the two sets of data. The Bell and Cox[38] data for bromination of disulfones cannot be directly compared to phenols but do seem to represent a series where the reactivity should vary and for which there is very little change in the observed rate constant. Although there is a serious danger of steric hindrance in these rather bulky anions, the charge is believed to be highly localized on carbon, with only electrostatic stabilization by the sulfones; this should make them more reactive than delocalized ions or enolates, where the charge is concentrated on oxygen, but reaction occurs on carbon. It is very suggestive that for these compounds the rate constant seems to be independent of the pK_a and is very similar to the value observed for the reactive phenoxides (the latter corrected for the number of accessible bromination sites). This behavior is illustrated in Figure 6. The value suggested by these data is in fact close to 10^9 M^{-1} s^{-1} and smaller than 5 × 10^9 M^{-1} s^{-1}.

Recently Kresge[41] has calculated the rate constant for the reaction of the enol of acetophenone and molecular bromine. The value so obtained is 2.5 × 10^9 M^{-1} s^{-1}, which is in good accord with our preferred value.[42]

In terms of the Marcus model (which need not be assumed to be rigorously valid, but simply provides a convenient framework for the following discussion) for a reaction with a sizeable intrinsic barrier[43] ($b > 10$) to be fully diffusion controlled means that $k_2 >> k_{-1}$ and this in turn requirs a very large thermodynamic driving force. In most cases where data are available, it has been found that b values are greater than 5 and often greater than 10.[44,45] In fact the driving force required to satisfy this constraint for $b > 15$ is so large that it is most improbable that it can be achieved without reagents which are so reactive that they attack the solvent too rapidly for experiments to be done. On the other hand it is quite possible to have enough thermodynamic driving force to approach this limit. Since the slope of a plot of log k vs. log K is small at large values of K, particularly for large values of b, the rate would be insensitive to changes in intrinsic reactivity and would seem the same for considerable variation of K leading to a spurious impression that the diffusion limit had been attained. This leads to the following conclusion: *in any process involving the reaction of closed-shell species with rate-determining breaking and/or making of covalent bonds to atoms other than hydrogen, transition to completely diffusion-controlled reactions will almost never be observed.* Halogenation is one of the few reactions where sufficient thermodynamic driving force is available, and even here it is not certain that the reaction of acetone enolate with hypohalous acids is entirely diffusion controlled for HOCl or HOBr, although it is certainly approaching this limit. For HOI it is clear that the reaction is not diffusion controlled. It is unlikely that many cases will be found where the thermodynamic driving force is greater, because already the background factor of reagent decomposition is a limiting factor in designing experiments.

It will immediately be objected that there are counter examples from the work of Williams on nitrosation of anilines[34] and of Ritchie on the recombination reactions of cations and anions.[32,33] Although the equilibrium constant for the diazotization of aniline by nitrosyl bromide is not really known it may be estimated by using the rate constant for nitrosation of aniline[34] and the rate constant for denitrosation of *N*-methyl-*N*-nitrosoaniline[46] as ca. 10^{13} M^{-1}. Although this is a large equilibrium constant it is small compared to the values which appear necessary to give diffusion-controlled reactions of hypohalous acids. This may be an illustration of the much greater reactivity of polarized unsaturated functional groups, relative to saturated analogues, so familiar from carbonyl chemistry. Alternatively it may mean that the rate-determining step is not actually bond forming but some complex-forming process, such as conversion of an encounter complex into a charge-transfer complex. This interpretation is supported by the observation that ammonia and glycine, which are more basic than aniline, react more slowly,[35] at rates well short of diffusion limited.

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Ritchie has argued that the rate-determining step in cation–anion recombination reactions is not covalent bond formation, but rather desolvation or solvent reorganization.[47] It is possible that several rapid processes, each having a small favorable equilibrium may lead to a reactive complex sufficiently much more stable than the initial diffusional encounter complex, that a covalent bond-making process with an appreciable kinetic barrier is still faster than separation of the original reactants without reaction, and so is not rate determining. In addition to enhanced ion pairing as a result of partial desolvation, there is the possibility of π-complex formation. The reaction of thiolates with aryl diazonium ions is highly likely to involve such a complexation step, because the reacting ions are large and polarizable and might easily undergo partial electron transfer. Furthermore, the atom with the highest concentration of positive charge, the N bonded to the aryl ring, is not the one to which the nucleophile becomes bonded. This means that the covalent bond-making step cannot be simple but must involve various atomic and electronic rearrangements; such a complex process is unlikely to be faster than diffusional separation without a very large driving force.

Ridd[35] gives values of the calculated diffusion-controlled rate constant for various solvents at various temperatures. Values for 25 °C (10^{-9} k) are MeOH 12.1, H_2O 7.4. Solc and Stockmayer[48] use a more elaborate model and allow for spherical molecules with only limited surface areas where reaction can occur. Although the mathematics get very complicated, they conclude that a quasi-chemical model reproduces the more rigorous results quite well. This allows discussion of the effective rate of encounter in terms of the rate constants for diffusional encounter, separation, reorientation within an encounter complex, and chemical reaction and the fractions of the surface of the reactants which allows reaction. The difficulty is to assign values to these a priori.

Substitution of numerical values into eq 1 of Solc and Stockmayer[48] shows that with plausible values for the fraction of surface which can react, e.g., 0.2 and 0.3 for acetone enolate and HOCl, respectively, and for the rate constants of diffusion within the cage, i.e., 10^{11} s^{-1}, the effective rate constant will be significantly less than the maximum value. Although there is no theoretically justifiable way to calculate the fraction of the surface area of a molecule which is able to react, the values which we used can be shown to be plausible as follows. For acetone enolate we used the "cavity surface area" defined by Hermann[49] and used his value for isobutane as an approximation to the surface area of acetone enolate. The area in which reaction could take place was estimated as twice the area in the cavity surface occupied by a water molecule, for each side of the enolate. This led to a fractional value of $4 \times 12.7/249.1 = 0.20$. For HOCl we used the fractional solid angle for a sphere the size of a chlorine atom able to react for encounter within 60° of the O–Cl axis from the side opposite the OH. The fraction so obtained is 0.25. Neither of these calculations gives more than a crude estimate; they simply show that our values are not ridiculous. The rate constant for diffusion within the cage is taken as the rate of solvent relaxation or diffusional separation, both of which were 10^{11} s^{-1}.[50] For encounter we use the theoretical value of 7×10^9 M^{-1} s^{-1}.[35] The values of $k_{\text{effective}}$ so obtained were 1.4×10^9 if reaction within the properly oriented encounter complex occurs with a rate constant of 10^{13} and 1.1×10^9 if this rate constant is 10^{12}. Solc and Stockmayer's model explicitly includes the phenomenon mentioned above, that completely diffusion-controlled reaction, even in the absence of any orientational restrictions, is only possible when the reaction within the complex is fast relative to diffusional separation.

Our conclusion is that at present the question of the best "average" value for the rate constant for diffusion-controlled reaction of unsymmetrical reagents has not been settled experimentally, and that this must be reflected in a wide uncertainty range. Our estimate, based on a simple-minded theoretical argument,[42] of $10^{9.23 \pm 0.5}$ M^{-1} s^{-1} includes the most reasonable experimental values and is consistent with the model of Solc and Stockmayer; it seems to us to remain the best value to use until the point is settled by definitive experiments. It should be noted that other views as to the best value to use are held at present.[16,51-53] The other values in common use are larger than that which we proposed; in view of the arguments presented above about the difficulty of ensuring that the thermodynamic driving force is large enough to give completely diffusion-limited reaction, it seems important to err on the side of a vaue for the diffusional rate constant which is too small rather than to err on the side of being too large.

It should be noted that even for simple proton transfer reactions between electronegative atoms in the thermodynamically favored direction, there is appreciable variation in what might be expected to be identical values. For oxy anions reacting with H_3O^+, k varies from 3.0×10^{10} to 4.1×10^{10} M^{-1} s^{-1};[22] for amines plus H_3O^+, k varies from 1.5×10^{10} to 4.3×10^{10} M^{-1} s^{-1}.[22] Since the problem is more severe for reactions at nitrogen (which is initially tricoordinate) than at oxygen (which is initially monocoordinate) we suspect that this reflects the orientational problem. (These values are all larger than 10^{10} M^{-1} s^{-1} because of the high mobility of H_3O^+.[22])

In view of the above argument one must ask if it is justifiable to use a value for a "rate constant for a diffusion-controlled reaction" in calculating pK_a values for acetone or other ketones. As a method for determining whether or not we are in fact at the diffusion-controlled limit, we take the rate constants for reaction of enolate with HOX, corrected for the pK_a of HOX, to give $k_{\text{rxn}}K_a^{\text{ketone}}$ and plot log $k_{\text{rxn}}K_a^{\text{ketone}}$ vs. log K (given in Table VI). Log $k_{\text{rxn}}K_a^{\text{ketone}}$ is available for HOCl (-10.14 ± 0.16), HOBr (-9.65 ± 0.19) (this work), and HOI (-10.48 ± 0.17).[16] The plot (not shown) reveals a small sensitivity of log $k_{\text{rxn}}K_a^{\text{ketone}}$ to log K and strongly suggests that we are at least close to if not at the diffusion limit for HOBr and HOCl, although HOI is almost certainly not at the diffusion limit. Thus we conclude that our procedure is justifiable, although it is necessary to admit that the data may still be slightly below the ultimate limiting value. Furthermore, although we have here a counter example to the generalization proposed above, our example shows how large the thermodynamic driving force must be for heavy atom bond-making reactions to become diffusion controlled.

pK_a Values for Acetone. Bartlett and Vincent[14] discovered that in alkaline solution the rate of chlorination of ketones was first order in ketone and first order in hypochlorite (in alkaline solution Cl_2 is essentially completely converted to Cl^- plus OCl^- [54]) and of mixed zero and first order in hydroxide. The term in the rate law first order in hydroxide is simply interpreted as the reaction of enolate ion with OCl^-. The term in the rate law zero order in hydroxide is kinetically ambiguous; it could represent either reaction of the enol with OCl^- or reaction of the enolate with HOCl. Since the slope and intercepts of plots of apparent second-order rate constants against hydroxide concentration are of comparable magnitude and the enol should be much less reactive than the enolate toward OCl^-, the first possibility appears very improbable.[55] Since it is known that enols react with halogens at diffusion-controlled rates[51] and that enolates are more reactive than enols and since it appears probable that HOCl will not be drastically less reactive than Cl_2,[56] it seemed plausible to propose that the reaction of enolate with HOCl will also be diffusion

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(55) If the intercept were due to reaction of enol with OCl^-, the microscopic rate constant would have to be comparable to or even larger than the microscopic rate constant for reaction of the enolate with OCl^-; this seems unlikely.

(56) Bell, R. P.; Yates, K. *J. Chem. Soc.* **1962**, 2285.

controlled.[57] If this be so, then the apparent rate constant for the term zero order in hydroxide is a function only of the rate constant for diffusion together of two species in water, the pK_a of HOCl, and the pK_a of the ketone. Since only the last value is unknown, it can at once be calculated.

We have reported that the results of Bartlett and Vincent[14] lead to reasonable pK_a values for acetone and acetophenone.[12] The speculation has been tested and appears to be correct.[19] Since by hypothesis the reaction of the enolate is diffusion controlled for HOCl, it should also be diffusion controlled for HOBr for which there is also a very large thermodynamic driving force. If then the kinetics of bromination lead to the same pK_a for a ketone as the kinetics of chlorination, the hypothesis is confirmed.

This test is not experimentally feasible for iodination under the sorts of conditions which we have employed. Under somewhat different conditions Jencks and Tapuhi[16] have determined a rate constant for the reaction of hypoiodous acid with the enolate of acetone, 2.5×10^8 M^{-1} s^{-1}, which is less than diffusion controlled. As we have shown above, this is consistent with the thermodynamics of these reactions, because the thermodynamic driving force for iodination, although still large, is much less than for chlorination or bromination. It does however mean that the logic of our test is less rigorous than we had hoped, because we have very few reagents which trap the enolate at diffusion-controlled rates. Our kinetic data are shown in Figures 2 and 5; in both cases the intercepts are undeniably different from zero. When the pK_a values for acetone are calculated, making due allowance for the difference in pK_a values of the two hypohalous acids, the results are 19.37 ± 0.51 (chlorination) and 18.96 ± 0.51 (bromination).[58,59] These values are identical within the precision with which the pK_a can be calculated and are close to the traditional value of 20 deduced by indirect arguments based on rate–equilibrium correlations by Bell.[5]

There is a dramatic increase in reactivity toward acetone enolate on going from OCl^- to OBr^-. The rate constants for reaction with the enolate of acetone are 2.0×10^4 M^{-1} s^{-1} for OCl^- and 2.8×10^7 M^{-1} s^{-1} for OBr^-. A similar effect has been observed for diisopropyl ketone.[60] The large value for the rate constant for the reaction of OBr^- was a source of experimental difficulties, since it was necessary to work at very low hypobromite concentrations in order to have halogenation the rate-limiting step and at very low hydroxide concentrations in order to make the term zero order in hydroxide a significant contributor to the rate law. It should be noted that this increase in reactivity is a purely kinetic phenomenon, because the thermodynamic driving force decreases in the series OCl^-, OBr^-, OI^-.

Interpretation. Mechanism for Lactate Formation. Formation of lactate as the major product from chlorination of acetone by hypochlorite was unexpected, because synthetically hypohalite oxidation is used to convert methyl ketones to acids with one less carbon. Lactate can arise by rearrangement of methyl glyoxal in alkaline solution. The facts require that most acetone which undergoes chlorination ends up as methyl glyoxal either by hydrolysis of dichloroacetate or by hydrolysis of monochloroacetone followed by halogenation of hydroxyacetone and hydrolysis of the 1-chloro-1-hydroxyacetone product (which should be *very* fast). We have demonstrated that acetol reacts more rapidly than acetone under comparable conditions (although enolization is largely rate limiting), so that the second route is viable. The first route requires the hydrolysis of an α,α-dihalo ketone. α,α-Dibromopropiophenone is known to hydrolyze readily in alkaline solution giving 1-phenylpropane-1,2-dione.[61] The methylglyoxal would be expected to undergo benzilic acid rearrangement to give lactate. This reaction is known to be rapid in alkaline solution.[62] The product studies (Table II) demonstrated that monochloroacetone gives rise to 50% lactate, while dichloroacetone gives rise to only 10% lactate. This suggests that the major diversion to lactate occurs at monochloroacetone. The product ratios do not quite match, but there is a real danger of imperfect mixing during the product studies with reactive halo ketones, since the reactions are rapid.[63] The usual synthetic conditions involve higher concentrations of hypochlorite and higher temperatures which lead to further reaction of lactate.[64]

Reaction of Hydroxyacetone. Hydroxyacetone (acetol) might react at either the methyl or at the methylene bearing the hydroxyl group. Studies of the rates of proton exchange in methoxyacetone[65] and dihydroxyacetone[66] showed that the methylenes exchange at rates similar to but somewhat slower than the methyl groups in acetone, and the methyl in methoxyacetone is somewhat slower than the methylene. In fact acetol reacts markedly *more* rapidly with hypochlorite than does acetone under comparable conditions (but with enolization and not halogenation as the rate-determining step), consuming 1 equiv of halogen at $[OH^-] = 0.5$ M. This suggests that reaction is primarily at the methylene carbon and leads to methylglyoxal which then rearranges. Methoxyacetone reacts at very similar rates. The major product is lactate, although there appear to be side reactions because the yield of lactate is low. This appears to be more pronounced in the case of hypobromite as halogenating agent. No other recognizable signals could be seen in the 200-MHz NMR of the product solutions from hydroxyacetone. Reaction at the methyl could lead to glycolate which would not be detectable. For the hypobromite reactions where enolization is expected to be rate determining at the high $[OBr^-]$ used for product studies, the amount of lactate formed from methoxyacetone matched the value predicted by using Hine's[67] rate constants for the two sites of enolization. From the rate constants for enolization we predict 57% lactate; hypobromite reaction gave 59% lactate. For hypochlorite the higher yield of lactate could be explained if halogenation is fully rate limiting for reaction at methyl leading to reaction at a rate slower than enolization, while enolization was largely rate limiting for reaction at the methylene. Aldolization is also a possible side reaction,[68] and the steady-state concentrations of methylglyoxal will be higher in these faster reactions, particularly in the product studies.

The stoichiometry of both of these reactions appears to be a function of $[OH^-]$; at 0.486 M $[OH^-]$ it is 1.25 (acetol) and 1.06 (methoxyacetone), while at 0.0129 M $[OH^-]$ it is 1.85 (acetol) and 1.88 (methoxyacetone). This suggests that there is a $[OH^-]$ dependent competition between rearrangement, which leads to a stoichiometry of 1 and further halogenation of methylglyoxal leading to a stoichiometry greater than 1. Since it is highly probable that rearrangement has an important term second order in hydroxide[69] such a hydroxide dependent shift in stoichiometry is quite possible. One must be cautious because the lower hydroxide concentrations lead to slower reactions which may also have more drift, giving spuriously high stoichiometries. Product studies showed that lactate was the major product, although under

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(57) The possibility that the term zero order in hydroxide represents reaction of enolate with Cl_2 can be dismissed by calculating the rate constant required for this rate law by using the known[74] equilibrium constant relating Cl_2 and ClO^- in alkaline solution. The rate constant required is much greater than the vibration limit.

(58) Uncertainties in pK_a are based on propagation of error calculations,[73] using the estimated standard deviation for the intercept from the least squares treatment, and an uncertainty of 0.5 in log ($k_{\text{diffusion}}$) which is taken as 9.23; see discussion of $k_{\text{diffusion}}$ in the text.

(59) We have used the thermodynamic pK_a values for HOCl and HOBr, and hence are calculating the thermodynamic pK_a value for acetone, even though the experiments are carried out at an ionic strength of 1 M. This implies an assumption that there are no large variations in activity coefficients for the different anions, which is unlikely to be a serious source of error given the other uncertainties in our results.

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(64) In experiments with mandelic acid, oxidation to benzoic acid on heating with hypohalite has been demonstrated.[20]

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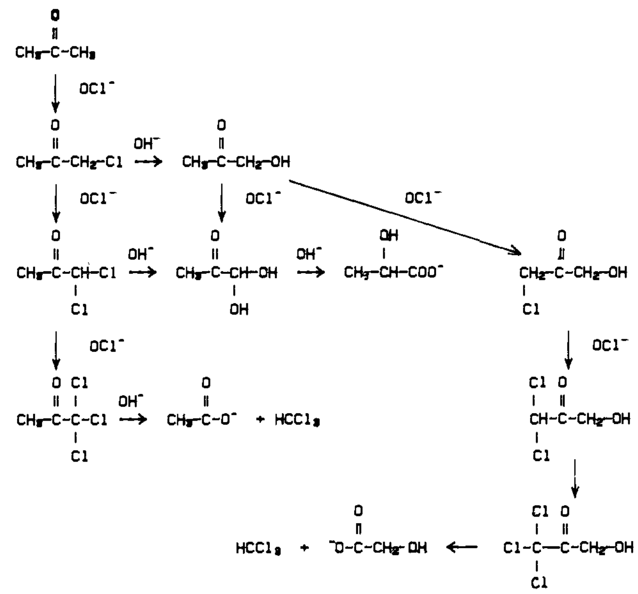
Scheme I



some conditions acetate (and methoxyacetate from methoxyacetone) could also be detected as a minor product.

Analysis of the kinetics of the reaction of hydroxyacetone with hypochlorite showed that the rate law was complex. The pseudofirst-order rate constants, k_{app}, could be fitted to eq 8 which is derived for a model analogous to that in eq 3. The parameters were evaluated by least squares.

$$k_{app} = (k_1a + k_1b[OH^-])/(1/[OCl^-] + a/[OH^-] + b) \qquad (8)$$

$$k_1a = k_1k^0K_w/k_{-1}K_a^{HOX} = 0.945 \pm 2.33$$

$$k_1b = k_1k^-/k_{-1} = 19.2 \pm 8.0$$

$$k_1 = 0.0397 \pm 0.020$$

k_1a corresponds to the intercept which we would use to evaluate the pK_a; in this case it is not defined by the data with useful precision. Unfortunately it appears unlikely that it will be possible to perform experiments at low enough hypohalite concentrations to determine it more accurately.

On the basis of results now in hand, the minimum reaction scheme for the halogenation of acetone is that shown in Scheme I. This allows for diversion at both the monohalo- and dihaloacetone stages and for incomplete conversion of hydroxyacetone to lactate. Further reactions can readily be imagined but we do not as yet have evidence requiring any additional paths.

Comparison with the Bromination of 2-Butanone. There have been two studies of the reaction pathway for the bromination of 2-butanone.[17,18] Although there are small quantitative differences in the results of these studies, which may well be a result of the slightly different conditions which were employed, there is good agreement that enolization is 60% at the methyl and 40% at the methylene and that 1-bromo-2-butanone is principally converted to propionate, while 3-bromo-2-butanone is principally converted to lactate by way of 3-hydroxy-2-butanone. These results clearly require that 3-hydroxy-2-butanone reacts preferentially at the methyl under at least some conditions, in sharp contrast to the behavior seen in the halogenation of acetone, where 1-hydroxy-2-propanone is halogenated at the hydroxymethyl group more rapidly than at the methyl group. This looks very much like a steric effect, but further speculation is unjustified until more rate data are available.

Limitations to Our Method for pK_a Determination. It is of interest to examine the range of pK_a values which are accessible to our kinetic approach. For ketones less acidic than acetone, we rapidly run into a limit set by the background reactions of hypochlorite solutions. Various control experiments show a consistent drift, which can be converted to an imprecise rate constant of about 3×10^{-7} s^{-1}. If the initial rate of halogen consumption by the reaction being studied is to be at least 10 times faster than this background reaction, the pK_a of the ketone cannot exceed 22. At the low pK_a end the reactions become fast and would require stopped-flow apparatus, but a more serious limitation is that our spectroscopic technique requires hypochlorite solutions with minor amounts of hypochlorous acid, i.e., with pH ≥ 9.5, and a minor amount of the enolate, i.e., a ketone p$K_a \geq 11.5$ for pH = 9.5. This does however mean that there should be no problem in covering the range of pK_a values from 22 down to values which can more conveniently be determined by titration, provided that one does not encounter other problems involving alternative reaction modes for more acidic compounds.

Conclusions

The method which we have described promises to provide a general solution to the problem of determining pK_a values for simple ketones. Chlorination is both the most experimentally convenient halogenation reaction and the one most likely to give useful results. It is important to work with hypochlorite in excess, and to prove that halogenation is cleanly rate limiting before attempting to calculate a pK_a.

Experimental Section

Materials. Approximately 1 M stock solutions of acetone in aqueous 1 M KCl were prepared by using Fisher "certified" A.C.S. spectrophotometric grade acetone which was used without further purification. The concentration of the solutions was checked by measuring the UV absorbance: λ_{max} 265 nm, ϵ_{max} 18.5.[70]

Baker "ANALAR 5% sodium hypochlorite" was used to prepare hypochlorite solutions of 0.0005–0.08 M by diluting with 1 M ionic strength NaOH–KCl of varying hydroxide concentrations. Sodium hydroxide was Fisher "Electrolytic A.C.S. 98.8%" grade NaOH. Potassium chloride was B.D.H. "ANALAR" grade. Potassium bromide was Fisher "Certified A.C.S." grade. Distilled water was twice further distilled, once from potassium permanganate solution in all-glass apparatus to remove organic impurities. Saturated aqueous bromine solutions (~0.2 M) were made from Fisher A.C.S. reagent grade bromine for the earlier kinetics runs and Merck "Ultra-pure 99.8%" bromine for later runs; no significant difference in values was observed for the two grades of bromine. The bromine solution, made from triple-distilled water, was kept in a glass-stoppered bottle.

Aldrich technical grade acetol, 1-hydroxy-2-propanone, was distilled at reduced pressure and the middle fraction boiling at 56 °C (25 mm) was used for kinetics. Only three proton signals could be found in the distillate (3 H at δ 2.1–2.2, 1 H at δ 3.6–3.8, and 2 H at δ 4.3). A 0.47 M stock solution in water was used for kinetics and product studies. Aldrich "99%" methoxyacetone was used without further purification. The purity was confirmed by NMR analysis: (3 H at δ 2.2, 2 H at δ 4.0, and 3 H at δ 3.4). The stock solution for kinetics was 0.214 M in water. Grade DL-X of DL-lactic acid lithium salt from Sigma was used to prepare a 0.110 M proton NMR comparison standard. Fisher "certified anhydrous" (<1% water) sodium acetate was used to prepare a 0.105 M standard for acetate. Eastman technical grade 3-hydroxy-2-butanone was distilled at 95 °C (105 mm); the proton NMR spectrum of the distillate indicated ca. 10 mole percent water but less than 2% of any other impurity.

Chloroacetone (Eastman) and dichloroacetone (Aldrich) were used without further purification.

Methods. All solutions used for kinetics were made 1 M in ionic strength by mixing appropriate amounts of sodium hydroxide and potassium halides (chloride for hypochlorite solutions, bromide for hypobromite solution).

Stock 0.1 N and 0.01 N thiosulfate solutions, preserved with carbonate and with benzoate, were standardized for iodine titrations with gravimetrically determined iodate solutions prepared from vacuum-dried reagent grade KIO_3 (99.8% minimum) supplied by Allied Chemical. Titrations involved volumetric pipetting of iodate solution into excess acetic acid–potassium iodide and determining the amount of thiosulfate solution required to consume the liberated iodine by means of a 2.0-mL Gilmont micrometer buret using soluble starch indicator; three titrations were averaged. The thiosulfate was kept in a glass-stoppered bottle in the dark and changed little over time.

Hypochlorite and hypobromite solutions were titrated in exactly the same manner as the iodate solution (excess acetic acid–potassium iodide,

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[70] Photoelectric Spectroscopy Group. "UV Atlas of Organic Compounds"; Butterworth: London, 1966; Vol. 1.

same buret, average of three titrations) as soon as possible before a kinetics run.

An absorbance measurement at 292 nm using a 10.0-cm cell filled with recently titrated 0.003 M OCl^-/0.01 M OH^- and the Cary 210 (base line 0.01 M OH^-) gave a value of 355 for the extinction coefficient of hypochlorite (lit.[25] 352 nm).

Aqueous HCl solutions were standardized volumetrically against weighed amounts of vacuum-dried TRIS base (Sigma reagent grade) using methyl red indicator. Hydroxide in the solutions used for kinetics was determined by titrating aliquots with standardized HCl solutions using phenolphthalein and methyl red indicators. The difference between the two end points was taken as a measure of carbonate concentration and applied as a carbonate correction to the phenolphthalein end point. In cases where sufficient hypohalite was present to destroy the indicator, hypohalite was first removed from an aliquot by adding an excess of acetone and waiting a few minutes before titrating. In order to find out whether this procedure introduced a large error, one sample kinetics solution (0.01 M OH^-/0.0003 M OCl^-) was also titrated by using a pH meter, taking the first end point at pH 7.5 and the second at pH 5.0 with the maximum dpH/dV in each case. The two methods gave values within 3% of each other.

Quartz UV cells (1-cm) were filled with 3.0 mL of the hypochlorite–hydroxide solutions that had been titrated no more than 3 h previously for hypochlorite. For the more dilute hypochlorite solutions, 10-cm UV cells filled with 25.0 mL were used. At least 15 min was allowed for the cell contents to come to a temperature of 25 °C. Reaction was initiated by injecting measured amounts of aqueous acetone solution into the cell with a Hamilton syringe; the absorbance at 292 nm was followed. Hypochlorite, hydroxide, and ketone initial concentrations were corrected for dilution.

Kinetics were carried out using either a Gilford Model 240 spectrophotometer equipped with a digitizer[71] or a Cary 210 spectrophotometer connected to a Dynabyte controller.[72] Either instrument could be fitted with thermostatted 1-cm or 10-cm cell holders. Neslab Exacal circulating baths were used to maintain the temperature at 25.0 ± 0.1 °C. Digital absorbance data were collected as previously described[71,72] and at the end of a run were transferred to a Xitan microcomputer for permanent storage and processing. Data were fitted to the appropriate equation by using weighted least-squares by means of programs essentially the same as those previously described.[2,73] For every run direct, semilog, and residual plots of the experimental data and the calculated line were drawn on an HP7225A plotter.

UV cells (10-cm) filled with 25.0 mL of hypobromite–hydroxide solutions titrated no more than 1 h previously for hypobromite were given 15 min to come to temperature. A series of four kinetic runs were carried out on the contents of each cell. The first run was initiated by injecting a 7- to 10-fold excess of acetone solution and following at 331 nm until all hypobromite was consumed. The second run was initiated by adding 0.01 mL of saturated aqueous bromine to the same cell. The third and fourth runs were initiated by adding 0.01 mL of 10-fold diluted bromine–water. A greater than 10-fold excess of acetone was still present during the second, third, and fourth runs. The third and fourth runs always gave faster reactions than were seen during most of the first and second runs, although the rate was the same as for the last portion of the first and second runs.

After the four kinetics runs on one cell, the cell contents were carefully emptied with three rinsings into an Erlenmeyer flask and titrated for hydroxide in order to gain a measure of how much the hydroxide changed during the kinetics procedure. The difference was significant (0.0001–0.0003 M) and the OH^- concentration for the run was taken to be the average of the initial and final values.

Product Studies. Method 1. Hypochlorite solution, 10 mL of 0.48 M solution (0.0048 mol), was added slowly and evenly to 40 mL of aqueous solution containing 0.05 mol of NaOH and 0.0005 mol of acetone over a period of 2 h. The hypochlorite concentration would have increased only very slowly at first, most of it being consumed in reaction with acetone (half-life approximately 5 min), and then risen steadily to reach a maximum concentration of between 0.07 and 0.08 M. After the reaction, 2$^1/_2$ h from initial hypochlorite addition, sodium bisulfite, 0.5 g, and KH_2PO_4, 13.6 g, were added. The measured pH was 6.4 with no detectable chlorine. This final solution, 1 mL, was mixed with D_2O, 0.1 mL, to give a sample for NMR analysis. The lactate enzyme assay was carried out on the buffered aqueous solution, without dilution, by using the procedure given in Sigma Technical Bulletin No. 726-UV/826-UV. The standard supplied by Sigma assayed at 99%. The error in the absorbance change was assumed to be the same at all lactate concentrations; the change was the difference between sample and blank readings, and at low lactate concentrations it was a small difference in large numbers. The error was taken as 0.01 absorbance.

Product studies with hypobromite were carried out in the same manner as with hypochlorite except that 25 mL of 0.2 M aqueous bromine (Merck ultrapure, 99.8%) was used instead of 10 mL of 0.5 M NaOCl. The initial volumes were adjusted accordingly so that the final volume was 50 mL. The lactate assay was carried out by using the same batch of reagents as the hypochlorite reaction mixture and gave a value of 17%.

Product studies with hypoiodite used the same procedure except that 25 mL of 0.2 M aqueous KI_3 was used and the addition–reaction time was only 1 h as opposed to 2 h for the other reactions. Iodoform was recovered in 60% yield. The enzyme assay on this product mixture was complicated by the fact that the product solution was colored. A separate blank was therefore run with product solution but without enzyme. After subtracting this absorbance (0.048) and the standard blank (0.189) from the sample with enzyme value (0.314), the lactate yield appeared to be 11%.

The same procedure was used for hydroxy- and methoxyacetone except that the addition and reaction period was 1 h rather than 2.

Method 2. To a solution which was 0.10 M in OH^- and 0.0057 M in OCl^-, 50.0 mL, was injected a concentrated solution containing 0.0001 mol of ketone. The final volumes of the solutions were 50.0–50.5 mL. After allowing the reaction to continue to completion, as evidenced by no further change in absorbance at 292 nm, hypochlorite was destroyed by adding a small excess of 2 M alcoholic SO_2. The product solution, 5.0 mL, was used for the lactate enzyme assay, carried out as before. The remaining 45.0 mL was concentrated to a volume of 0.5–1.0 mL by removing water on a rotary evaporator at 45 °C (30 mm). The resulting thick aqueous solutions containing the salts of the organic acid products at concentrations between 0.1 and 0.2 M were assayed for the proton ratio of lactate/acetate by NMR at 60 MHz.

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Registry No. Br_2, 7726-95-6; NaOCl, 7681-52-9; KI_3, 12298-68-9; OCl^-, 14380-61-1; OBr^-, 14380-62-2; OI^-, 15065-65-3; OH^-, 14280-30-9; $CH_3C(OH){=}CH_2$, 29456-04-0; HOCl, 7790-92-3; HOBr, 13517-11-8; HOI, 14332-21-9; CH_3COCH_3, 67-64-1; $ClCH_2COCH_3$, 78-95-5; $Cl_2CHCOCH_3$, 513-88-2; $BrCH_2COCH_3$, 598-31-2; $Br_2CHCOCH_3$, 867-54-9; ICH_2COCH_3, 3019-04-3; $I_2CHCOCH_3$, 88525-62-6; Cl_3CCOCH_3, 918-00-3; Br_3CCOCH_3, 3770-98-7; I_3CCOCH_3, 88525-63-7; $HCCl_3$, 67-66-3; $HOCH_2CO_2^-$, 666-14-8; $CH_3OCH_2CO_2^-$, 20758-58-1; $CH_3CH(OH)CO_2^-$, 113-21-3; CHI_3, 75-47-8.

Supplementary Material Available: Table I, kinetics results for halogenation of acetone and related compounds, in aqueous solution at 25 °C; Table VII, rate constants for diffusion-controlled (or nearly diffusion-controlled) reactions (9 pages). Ordering information is given on any current masthead page.

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