THE MECHANISM OF

ACETATE-CATALYZED ENOLIZATION

FACTORS AFFECTING THE TRANSITION STATE IN ACETATE-CATALYZED ENOLIZATION. THE INFLUENCE OF METHYL AND BROMINE SUBSTITUENTS ON THE RATE OF BROMINATION OF ACETONE

by

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TITLE: Factors Affecting the Transition State in Acetate-Catalyzed Enolization. The Influence of Methyl and Bromine Substituents on the Rate of Bromination of Acetone

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SCOPE AND CONTENTS:

The acetate-catalyzed bromination of acetone is shown to occur by an enolization mechanism, although the reactions involved in this process are more complex than has been supposed.

A study of the activation parameters for the enolization of some bromoacetones, and an observed linear free energy relationship between enolization rate constants, and acid ionization constants, shows that the transition state for this process resembles enolate and not enol.

Bromine substitution in ketones accelerates enolization rates on both sides of the carbonyl group.

The acetate-catalyzed enolization of 2-butanone favours the methylene group by a factor of nearly two. This fact is interpreted in terms of methyl groups being inductively electron-withdrawing in their effect in forming an enolate transition state.

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GENERAL INTRODUCTION

Ketone enolate anions are widely used synthetic intermediates. They are used, in reactions such as alkylations and condensations[1], to synthesize more complex molecules which can be of biochemical, medical or theoretical importance. The reactions which produce these anions, as well as the reactions they undergo, have always been of fundamental theoretical interest, and these reactions have been widely studied since the beginning of the century.

Enolate anions, as generally used, are formed from ketones by using strongly basic catalysts in non-aqueous media[1]. A related species, the enol, can be formed in acidic media, or by acid catalysis in aqueous media. The area between these extremes, the use of weakly basic catalysts in aqueous media for ketone enolization, is less well defined, and evidence indicative of the formation of either enol or enolate anion under these circumstances can be cited. This report is concerned with work recently carried out in this area.

Recent work on the rates and products of enolization of simple unsymmetrical ketones, using nmr spectroscopy and other methods, is of great interest concerning the question of enol vs. enolate as the transition state for enolization. This work is reviewed in the historical

introduction. Some of the work reported here, on the acetate-catalyzed deuterium exchange into 2-butanone, shows that the protons at CH_2 can be up to twice as reactive as the protons at CH_3 in this enolization process.

Some recent work has been taken to indicate that some reactions of ketones previously thought to be due to enolization, in fact go via the unenolized ketone[2,3]. Such processes would necessarily have to be first-order in the reagent which attacks the ketone, and it should be possible to infer their occurrence from the kinetics. With this in mind, an examination was undertaken of the reactions involved when a simple ketone, acetone, is brominated under conditions of acetate catalysis. It is shown here that ketone bromination is somewhat more complex than has previously been assumed; it is found that reactions not previously considered important in the bromination process, such as the nucleophilic displacement of bromine from monobromoketones, and the competitive bromination and hydrolysis of tribromoketones, have to be included in the kinetic scheme. However, the results obtained can all be explained in terms of enolization and reaction with the enol, without the need to invoke reaction with unenolized ketones.

The activation parameters for the acetate-catalyzed enolization of acetone, bromoacetone and 1,1-dibromoacetone were obtained; the rate differences between these

compounds are shown to be largely due to differences in their activation entropies, which are rationalized in terms of solvation differences at the transition state.

Bromine-substituted ketones have been shown, here and elsewhere[4], to have enhanced base-catalyzed enolization rates at the substituted α-position. It is demonstrated in this thesis that the enolization rate at the unsubstituted α' site, on the other side of the carbonyl group from the bromine substituent, is also enhanced, and that this enhancement increases as the number of bromine substituents increases. It is found possible to compare the ability of a carbonyl group to transmit inductive effects with that of a methylene group, and the latter is found to be roughly half as effective. A linear free energy relationship between the enolization rates of some bromine-substituted ketones, and the ionization constants of bromine-substituted acids, was found; this is taken as evidence for the transition state resembling enolate, rather than that resembling enol, in base-catalyzed enolization in water.

All the results, together with those of previous workers, are assessed in terms of factors affecting the transition state for enolization; the role of alkyl groups is expressed in terms of a change of sign in their inductive effect towards sp^2- and sp^3-hybridized carbon.

HISTORICAL INTRODUCTION

The ketone enolization reaction is generally considered in terms of (a) acid catalysis and (b) base catalysis. As will be seen, it is perforce studied by observing the reactions which the enol or enolate product undergoes; generally by reaction with halogens, with solvent (racemization), or by exchange with deuterium-substituted solvents. This reaction has recently (since 1965) received much attention, since modern methods of instrumental analysis, particularly nmr and mass spectroscopy, and glpc analysis, have enabled the reaction of individual sites within an unsymmetrical ketone to be studied more easily than was previously possible. This modern work will be emphasized here; the older work in this area has recently been reviewed[5].

(a) Acid Catalysis

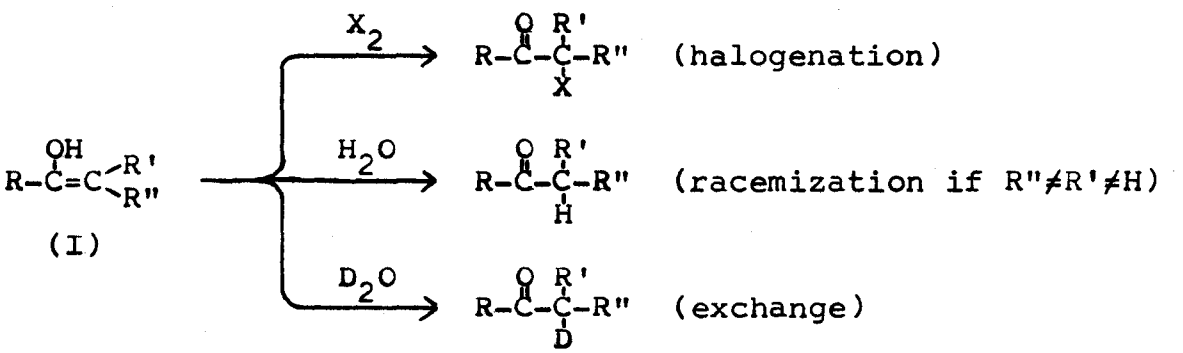
Simple Ketones

Lapworth[6] found that the rate of the reaction between bromine and acetone in aqueous acid is dependent on the concentrations of acid and acetone, but independent

of the bromine concentration. Dawson and Leslie[7] found the iodination of acetone to be similar, and Rice and Fryling[8] found the reaction rate to be the same for each of the three halogens chlorine, bromine and iodine. This is consistent with Lapworth's proposed enolization mechanism[6]:

$$CH_3COCH_3 \xrightarrow[\text{slow}]{H^{\oplus}} CH_3\text{-}\overset{OH}{\overset{|}{C}}{=}CH_2 \xrightarrow[\text{fast}]{X_2} CH_3COCH_2X$$

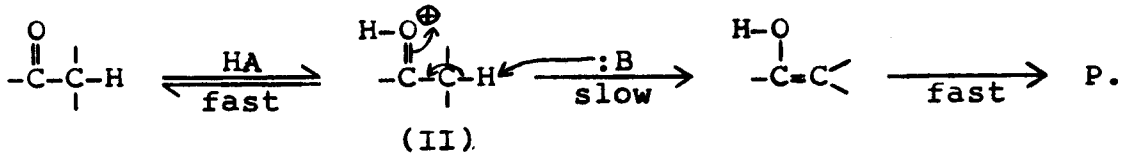
The rate of halogenation of a ketone with an asymmetric α-carbon was found to be the same as its rate of racemization[9,10], and the rates of acid-catalyzed bromination and deuteration are the same in D_2O[11]. These reactions must therefore all proceed <u>via</u> a common intermediate, formed in a common rate-determining step:



Enols, such as I, can be studied by observing the products formed from them, as shown; the rates of enolization can be studied by observing the rates of consumption of reagents by reaction with the enol as long as this reaction is substantially faster than enolization.

The enolization reaction is subject to general

acid-base catalysis - for reviews see refs 19 and 20. The function of the acid catalyst is to protonate the carbonyl oxygen in a fast pre-equilibrium step, the actual rate-determining step being an attack of base on the ketone conjugate acid. Thus Lapworth's mechanism[6] can be modified as shown:



(II)

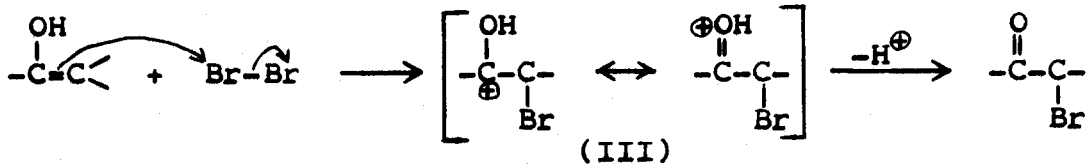
There is much evidence in support of this pre-equilibrium protonation, for instance, the isotope effect studies of Swain et al.[21], the comparison between cyclohexanone enol ketonization and 1-methoxycyclohexene hydrolysis by Lienhard and Wang[22], the nuclear-substituted acetophenone iodination studies of Rout et al.[23], and the similarity of the solvent isotope effect on the ketonization of acetone enol and the hydrolysis of ethyl isopropenyl ether noted by Dubois and Toullec[24].

The kinetic expression concerning enolization in carboxylate buffers[19] contains terms such as $k[\text{ketone}][H_3O^{\oplus}]$ and $k[\text{ketone}][HA]$ (general acid catalysis). These, however, are kinetically indistinguishable from $k[\text{ketone}.H^{\oplus}][H_2O]$ and $k[\text{ketone}.H^{\oplus}][A^{\ominus}]$, writing ketone.$H^{\oplus}$ for the ketone conjugate acid, II, above. Bender and Williams[25] note that the relative rates of enolization of acetone and protonated acetone are 1 to 10^{11}, so water is an effective base

under these conditions. Thus the general-acid-catalyzed part of the ketone enolization reaction in carboxylate buffers represents the attack of conjugate bases on the ketone conjugate acid; the general-base-catalyzed part represents the attack of bases on the ketone itself. The interesting occurrence of a termolecular term in the enolization of acetone, k[ketone][acid][base], has received extensive discussion (see ref 19, p 148, and references contained therein). It has not been observed in other similar reactions where it should have been important (ref 19, p 151). In terms of the argument used here, if the termolecular term exists, it may imply that the proton on the positive oxygen in II remains attached to the acid anion from which it came by a tight hydrogen bond.

It was mentioned above (p 5) that rates of enolization can be studied by following halogenations only if the enol reacts much faster than it is formed. The reaction between bromine and enols has been studied by Yates and Wright[26], and in a series of papers by Dubois et al.[27,28], among others. Dubois and Toullec[27] found that the enol reacts with bromine some 10^5 times faster than it is formed, for the HBr-catalyzed enolization of various alkyl ^{t}butyl ketones. Yates and Wright[26] found that bromine concentrations of 10^{-6} M or lower were required to study the bromination of enols, so in most cases cited in the literature enolization is rate-determining.

Yates and Wright[26] consider the intermediate in enol brominations to be the bromo-carbonium ion III rather than the bromonium ion IV:



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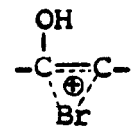
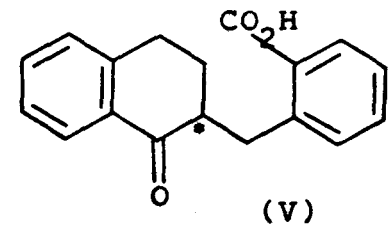


(IV)

Sytilin[2] has studied the HBr-catalyzed bromination of acetone, using a "Redoxistat", an apparatus for determining the integral consumption of bromine with time (also see ref 31). This gave a trace on a recorder drum, which was graphically differentiated to give values of the slope at zero time, from which initial rate constants were calculated. He found that graphs of rate vs. HBr concentration did not quite go through the origin - there was a small non-catalytic reaction. He measured the rate at various bromine concentrations between 10^{-2} and 10^{-3} M, and found that graphs of rate vs. bromine concentration were not parallel to the bromine concentration axis, indicating that a reaction that was first order in bromine was competing with the normal zero-order one. He found this "non-catalytic" reaction to have a lower activation energy than the normal acid-catalyzed enolization, although the rate constants indicate this reaction to be slower

than the normal one. The author does not discuss a mechanism, but the inferred large negative entropy of activation could indicate some sort of cyclic mechanism.

Before passing to the consideration of substituted and unsymmetrical ketones, it is worth noting that Marquet et al.[30] observed some retention of optical activity in the chlorination of o-2-carboxybenzyl-1-tetralone, V, a result which would not be anticipated from a consideration of the normal enolization mechanism, which would predict complete racemization.



(V)

Haloketones and Unsymmetrical Ketones

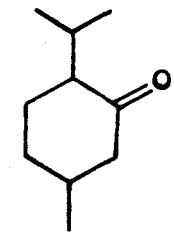
Unsymmetrical ketones can enolize in two ways:

$$R\text{-}CH{=}C(OH)\text{-}CH_3 \longleftarrow R\text{-}CH_2\text{-}C(=O)\text{-}CH_3 \longrightarrow R\text{-}CH_2\text{-}C(OH){=}CH_2$$

The product formed by reaction with these two enols should indicate which one is preferred, which in turn should throw some light on the effects of substituent R groups on the enolization process.

It was found quite early on that the bromoketone products from the acid-catalyzed bromination of unsymmetrical alkyl ketones indicated preferential enolization towards the substituted site; for instance, $CH_3COCH(CH_3)_2$

gives almost exclusively $CH_3COCBr(CH_3)_2$ under conditions of acid catalysis[12,13]. This preferential enolization is supported by the results of Bartlett and Vincent[14], who studied the acid-catalyzed iodination and racemization of l-menthone, VI, and found a rate ratio of 3.7:1 in favour of the more substituted site.



(VI)

The rates of iodination of methyl alkyl ketones in acid were found to increase with the size of the alkyl group[15], but the rates of bromination of α-alkyl acetophenones were found to decrease as the size of the alkyl group was increased[16]. These conflicting results probably indicate the interplay of the inductive and steric effects of alkyl groups in this reaction; a phenomenon which may also be inferred from the figures of Bartlett and Stauffer[9], who compared the total rates of acid-catalyzed enolization of some optically active sec-butyl ketones with their rates of racemization.

Inductively electron-withdrawing α-substituents were found to reduce acid-catalyzed enolization rates. Hughes, Watson and Yates[17] found halogen-substituted acetones to react with bromine more slowly than acetone itself; Watson et al.[18], and Rout et al.[23,32], found the bromination rates of acetophenones to be accelerated by electron-donating nuclear substituents, and retarded by electron-withdrawing ones.

The acid-catalyzed chlorination of various chloroacetones, and bromoacetone, has been studied by Bańkowska[33]. He found that the chlorination of $CH_3COCHCl_2$ in the presence of various acid catalysts gave both $ClCH_2COCHCl_2$ and CH_3COCCl_3, with the former predominant. Chlorination of CH_3COCH_2Cl, however, gave more $CH_3COCHCl_2$ than $ClCH_2COCH_2Cl$, with CH_3COCH_2Br exhibiting similar behaviour. Bańkowska also found that reaction with potassium iodide caused the removal of halogens from haloketones[33c], and that this reaction became easier when more than one halogen was present.

The polybromination of ketones, catalyzed by HBr, generally gives products with the bromines symmetrically situated[13]; see the experimental bromoketone preparations in this thesis, p 117, e.g.:

$$CH_3COCH_3 + 2Br_2 \xrightarrow[\text{autocatalyzed}]{\text{neat, HBr}} BrCH_2COCH_2Br + BrCH_2COCHBr_2$$

However, bromoketones are known to rearrange under these conditions - Rappe has discussed this phenomenon[34], and this author has also experienced bromoketone rearrangements (p 109). This ability to rearrange, as well as the possible reversibility noted by Bańkowska[33], should be borne in mind when bromoketone and polybromoketone products are used as evidence of preferential ketone enolization.

Shah and Pishawikar[35] exhaustively brominated various ketones using HBr catalysis, and they found it impossible to prepare perbromoketones in this way - they give a formula for the structure of the highest bromoketone which could be prepared: "The number of bromines incorporated equals the number of enolizable α-hydrogens minus the number of carbonyl groups".

The orientation of enolization of a number of ketones was studied by Cardwell and Kilner[36]. In an investigation considered to be a classic study of hyperconjugation as well as of enolization[5], they found that the orientation of enolization was controlled by the ability of alkyl groups to be hyperconjugated with the developing enol double bond in the transition state. They compared acid-catalyzed enolization with elimination, according to the hypothesis of Hughes[37], and found the Saytzeff rule to be obeyed in both cases. Thus 2-butanone, for instance, will be preferentially brominated in the CH_2 group. However, the bromination method of Catch et al.[12,39] was used to obtain the bromoketones, and they were separated by distillation, the amounts of each of the possible monobromoketones being determined to give numbers for the enol preference. It is difficult to estimate the accuracy of these analyses[36], and rearrangement of the first-formed bromoketones is possible[38].

Gaudry and Marquet[40] have studied the deuterium

exchange and bromination of cyclohexyl methyl ketone, cyclopentyl methyl ketone and benzyl methyl ketone, catalyzed by HBr, in ether, carbon tetrachloride and methanol. Benzyl methyl ketone reacts at the benzyl position preferentially in all cases; the other ketones exchange and brominate at CH in methanol, but brominate at CH_3 in ether and carbon tetrachloride. The authors consider the latter case to be an example of predominant steric control.

Rappe has studied the acid-catalyzed deuterium exchange and halogenation of simple dialkyl ketones[38,41,42,45], and some diones[43], by nmr (also see Bothner-By and Sun[44]). He finds 2-butanone to exchange and brominate preferentially at CH_2[45], in agreement with previous authors, and that solvent changes do not cause drastic changes in the relative rates at the two sites[42]. His study of the deuterium exchange of various dialkyl ketones[38] is inconclusive; no predominant effect can be seen to be operating[38], but the consideration of steric and inductive effects, as well as hyperconjugation, appears to be necessary. Also, this study was performed by integrating weak, partially deuterium-exchanged and (for some ketones) highly split nmr peaks, in dioxane/water, DCl catalyst. A correction of some integrals for the interfering C_{13} satellite peaks of dioxane should be required[46] but is not mentioned[38].

Rappe's study of the bromination of 2-butanone in D_2O, DCl catalyst[41], indicates exchange and bromination to

be competitive reactions, i.e. the unbrominated 2-butanone showed partial D-exchange. He interprets this by assuming that enolization is not the rate-determining step. In view of the previously mentioned results of Dubois and Toullec[27] and Yates and Wright[26] this result is very surprising; the enols formed should be captured by bromine some 10^5 times faster than by D_2O[27].

Dubois and Toullec[27] have correlated the HBr-catalyzed enolization rates of a series of ketones of formula $^tBuCOCH_2R$, with R = CH_3, CH_3CH_2, $CH(CH_3)_2$ and $C(CH_3)_3$, with Taft's E_s values for these groups[48]. The good linear relationship obtained is characteristic of the operation of a predominantly steric effect; this is probably the best instance of the separation of steric effects from electronic ones in this reaction.

Very recently Jullien et al.[47] have studied the deuterium exchange of some substituted ketones, using mass spectroscopy to determine the rate and position of deuterium incorporation. Their results are reproduced in Table I, p 15; they appear to confirm much of the earlier work with regard to rates and positions of enolization. This author regards these results as probably the most useful of those so far discussed. The authors[47] contend that the direction of enolization is controlled by polarizability effects ($Cl > CH_3 > H > F$) and not by the operation of the inductive effect ($CH_3 < H < Cl < F$).

TABLE I

Acid-Catalyzed Enolization Rates of some Unsymmetrical Ketones[a]

$10^6 k_{\alpha}$[c] ±10%	ketone[b] α	α'	$10^6 k_{\alpha'}$[c] ±10%	$10^6 k_{H^{\oplus}}$ $sec.^{-1}$	$k_{\alpha}/k_{\alpha'}$
51.2	$H-CH_2-CO-CH_3$		51.2	307	-
0.28	$F-CH_2-CO-CH_3$		2.97	9.47	0.09
15.0	$Cl-CH_2-CO-CH_3$		2.56	35.7	5.9
136.3	$CH_3-CH_2-CO-CH_3$		42.9	386	3.2
60.0	$CH_3-CH_2-CO-CH_2-CH_3$		60.0	240	-

[a] M. Chevallier, J. Jullien and T-L. Nguyen, Bull. Soc. Chim. Fr., 3332 (1969).

[b] The medium was D_2O; DCl, 0.05 - 0.3 M; ionic strength 0.3; ketone concentration, about 2 gram atoms of α-H per litre; temperature 41.8 - 41.9°; exchange monitored by mass spectroscopy.

[c] Statistically corrected rate constants.

Mechanistic Implications

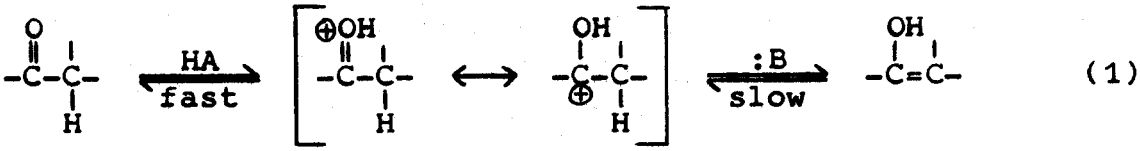
The mechanism of acid-catalyzed enolization, as inferred from the preceding evidence, will be considered here briefly for the sake of completeness; see Chart 1, p 17, which is a condensation from the evidence on pps 4-9.

Halogen α-substitution lowers the overall enolization rate (see Table I, and p 10). This is undoubtedly due to the reduction in ketone basicity resulting from halogen substitution, which causes a reduced equilibrium concentration of the ketone conjugate acid, the intermediate necessary for the mechanism under consideration to apply, as suggested by Gould (ref 20, p 384). Haloketone basicity has recently been investigated by Levy[49]; the H_0 values necessary to half-protonate some haloketones are shown in Table II, p 18. Here the reduction in basicity caused by halogen substitution can be clearly seen; the numbers show an additivity characteristic of inductive effects.

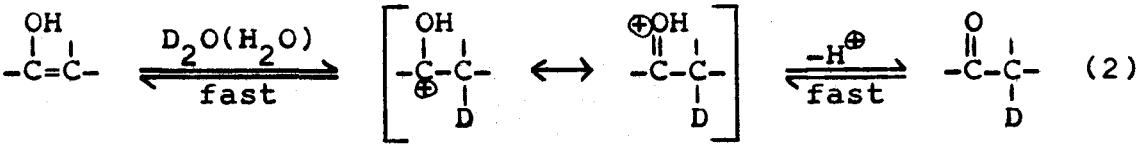
It is fairly clear that monohaloketones (with the interesting exception of fluoroacetone, which will be considered in the discussion) direct the second halogen to the halogen-bearing carbon (e.g. Table I, p 15, and Bańkowska[33]), when secondary rearrangement is suppressed. This is probably due to the increase in the relative acidity of the adjoining α-proton caused by the induct-

CHART 1

The Mechanism of Acid-Catalyzed Enolization



(1)



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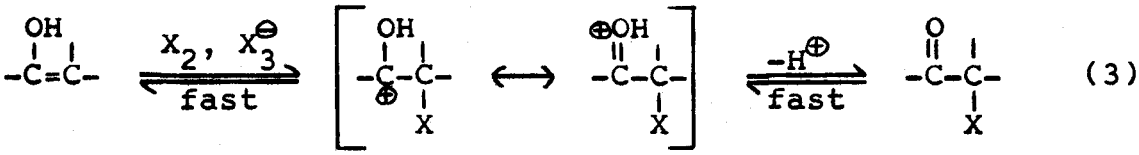


(3)

Notes: (i) The terms "fast" and "slow" refer to the forward reaction (left to right).

(ii) HA is any acid in the system; :B any base, solvent, acid anion, etc.

(iii) A number of solvent molecules will be hydrogen-bonded around the carbonyl oxygen; these are not shown.

(iv) X_2, $X_3^{\ominus}$ refers to any halogenating species present.

(v) Reaction 3 is considered to be 10^5 times faster than reaction 2, which is itself essentially the reverse of reaction 1.

TABLE II

The Basicities of some α-Halogeno-Ketones[a]

Ketone	$-H_0$[b]
CH_3COCH_3	7.5
CH_3COCH_2F	10.7
CH_3COCH_2Cl	10.6
CH_3COCH_2Br	10.6
FCH_2COCH_2F	12.7
CH_3COCF_3	14.7
CH_3COCCl_3	14.6
$F_2CHCOCHF_2$	~17

[a] G. C. Levy, Chem. Commun., 1257 (1969).

[b] $-H_0$ value of the acid required to half-protonate the ketone; more basic ketones require stronger acids to protonate them.

---

ively electron-withdrawing halogen (e.g. the nmr signal from the CH_2Br group of bromoacetone is nearly two ppm downfield from the acetone signal - see p 112). 1,1-Dihaloketones are apparently halogenated mainly at the unsubstituted α-position (Bańkowska[33]). This may not be a primary effect but a result of rearrangement, or it

could be a steric effect taking over from the inductive effect; there is insufficient evidence to decide. Polyhaloketones may have their basicities reduced sufficiently to prevent an acid-catalyzed reaction from occurring at all in the media generally used; thus the halogenation of 1,1,3-tribromoacetone in 2N hydrochloric acid is reported to be a base-catalyzed reaction[17b]. Also, it is possible to prepare hexabromoacetone by a base-catalyzed reaction (p 115), but not, apparently, by an acid-catalyzed one[35].

Alkyl ketones generally enolize in the direction resulting in the more substituted enol[36]. Since the enolization transition state presumably resembles the enol product, the factors which cause substituted alkenes to be more thermodynamically stable than terminal ones should also cause the more substituted enol to be favoured. This is generally attributed to hyperconjugation[36], or polarizability[47], and not to inductive effects. The inductive effect, however, may increase the ground-state basicity, and hence the equilibrium concentration of the ketone conjugate acid, and the overall rate, a little. Thus, if we examine Table I, p 15, we see that 2-butanone enolizes to the methylene side more than three times as often as to the methyl side, and that the methylene rate is nearly three times faster than the acetone rate. However, this is not the whole story; this trend does not continue even to diethyl ketone, where the accelerating effect

Simple Ketones

The base-catalyzed reaction between ketones and halogens was early shown to be more complex than the acid-catalyzed one, the reaction being the well-known haloform reaction:

$$RCOCH_3 + 3I_2 + 4OH^{\ominus} \longrightarrow RCO_2^{\ominus} + CHI_3 + 3H_2O + 3I^{\ominus} .$$

This reaction has been used as a preparative method for converting methyl ketones to carboxylic acids since the early days of organic chemistry (e.g. ref 51).

The rate-determining step of this reaction was suggested to be enolization by Lapworth[52]. Bartlett[53], and Bell and Longuet-Higgins[54], showed the reaction rate to be dependent on the ketone and base concentrations, but independent of the halogen concentration, and that the rate laws for the chlorination, bromination and iodination of acetone in the presence of hydroxide were similar. Thus the initial step of the haloform reaction was shown to be similar to acid-catalyzed enolization, and the following mechanism was proposed[20]:

$$CH_3COCH_3 \xrightarrow[\text{slow}]{OH^{\ominus}} \left[{}^{\ominus}CH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 \longleftrightarrow CH_2\text{=}\overset{\overset{O^{\ominus}}{|}}{C}\text{-}CH_3 \right] \xrightarrow[\text{fast}]{X_2}$$

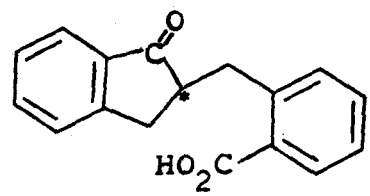
(VII)

$$XCH_2COCH_3 \xrightarrow[\text{fast}]{} P.$$

This differs from the acid-catalyzed mechanism in

that here a proton is removed from the ketone itself rather than its conjugate acid, forming an enolate anion, VII, rather than an enol.

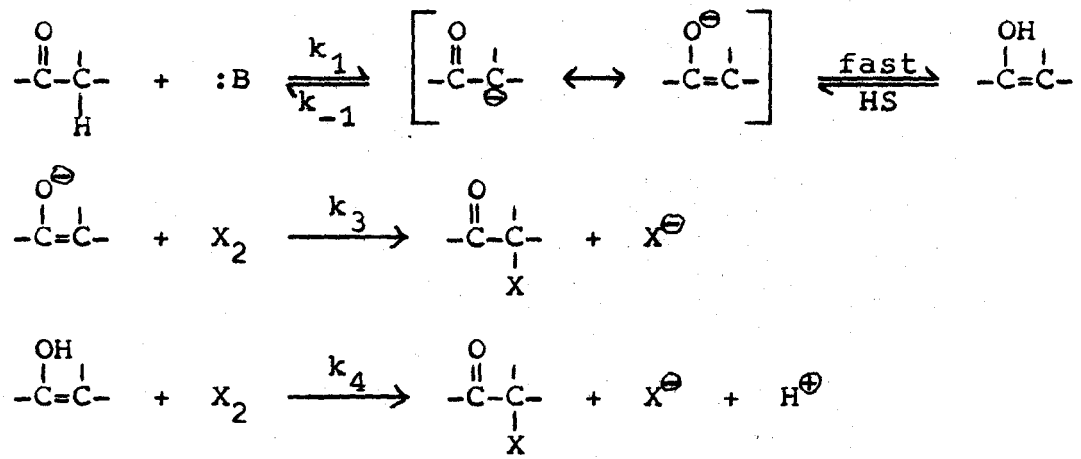
The same considerations apply to the enolate anion VII as applied to the enol I (p 5); racemization, deuterium exchange and halogenation should all occur at the same rate. Hsü and Wilson[55] have shown that the rates of bromination and racemization of d-2-o-carboxybenzyl-indan-1-one (VIII) are the same in aqueous acetic acid containing acetate and, with Ingold[56], that the rates of deuteration and racemization of phenyl sec-butyl ketone are the same in D_2O/dioxane mixtures containing NaOD. However, it should be noted that Rappe and Bergander[150] found the racemization of VIII to be intramolecularly catalyzed, and they feel that this invalidates the results of Hsü and Wilson[55].



(VIII)

Ketone enolization exhibits general-acid, general-base catalysis, as already mentioned (p 5), and this area of the problem has been extensively studied by Bell[19], as part of his continuing study of proton-transfer reactions. Bell considers the mechanism outlined above, enolate ion formation, to apply to base-catalyzed enolizations[19]: "Observed rates of base-catalyzed racemization, isotope exchange, or halogenation are therefore rates of ionization

rather than rates of enolization", and he quotes Hammett[57]: "There is no reason to suppose that the formation of an electrically neutral enol form represents anything more than an unimportant bypath into which a portion of the reacting substance may transiently stray." However, the enolate ion will be in rapid equilibrium with the enol, both of which can react with halogen:



Approximate values for k_3 and k_4 were obtained for the bromination of ethyl malonate by Bell and Spiro[58], and a consideration of the rate constants, and the relative concentrations of enol and enolate, led them to conclude that the anion was brominated above pH 3 and the enol brominated below pH 3. This was also shown to apply to the iodination of ethyl malonate[59], and for the iodination of 2-ethoxycarbonylcyclohexanone[60] reaction occurred to an equal extent <u>via</u> enol and enolate anion at about pH 5. Bell concludes[19] that "both routes can contribute significantly under different conditions, though the rate-

determining step in base catalysis is always the formation of the anion".

Another possible base-catalyzed mechanism, the ternary, synchronous, "push-pull" or concerted mechanism, results in direct enol formation without any anionic intermediate through the simultaneous action of acid and base:

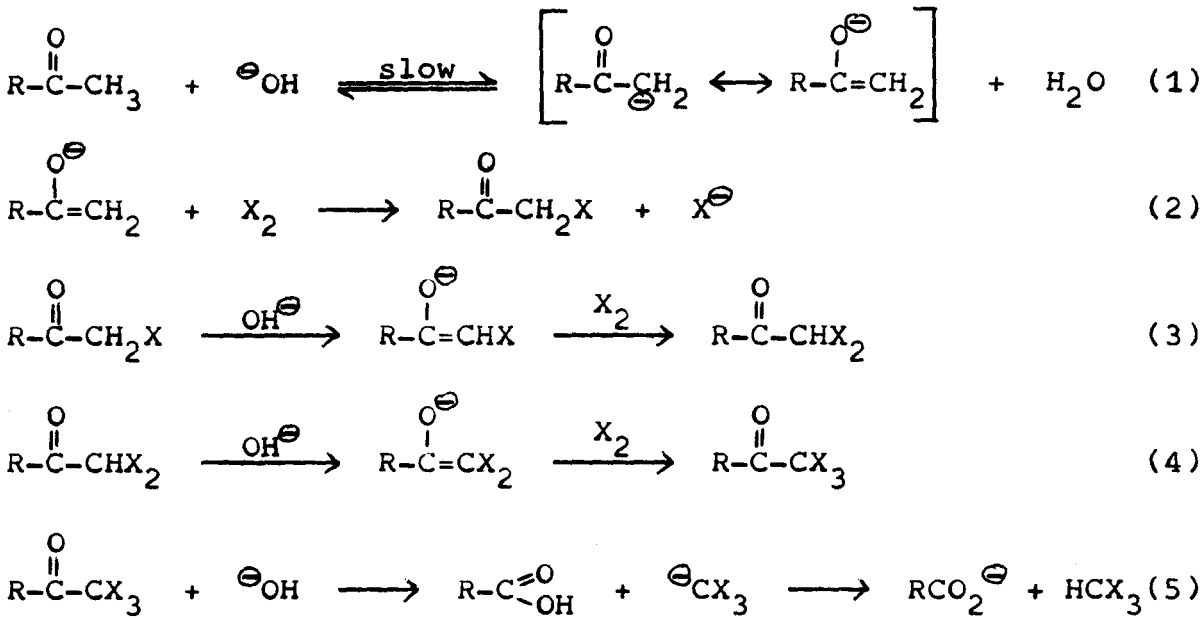
This mechanism was advocated, mainly by Swain[61], to explain the termolecular term k[ketone][HOAc][$OAc^{\ominus}$] observed by Dawson and Spivey[62], and Bell and Jones[63], in the full kinetic expression for the iodination of acetone in acetate buffers (see above, p 6). This mechanism has received much discussion in the literature[19,20], but is now generally thought not to apply[19,63], although the termolecular term in acetone enolization experiments is still not satisfactorally explained (but see above, p 7).

The Haloform Reaction

As mentioned above, the actual product isolated when a ketone is halogenated under basic conditions in water is a haloform. The haloform reaction has been studied by Bartlett[53], and by Cullis et al.[64,65], and the mechanism shown in Chart 2, p 25, is proposed[66], with all

CHART 2

The Haloform Reaction



Notes: (i) All other reactions are assumed to be much faster than 1.

(ii) The enolate anions depicted may be protonated to enols before reacting, depending on the pH of the medium (see p 23).

(iii) The catalyzing base depicted is hydroxide; the reactions (especially 5) may vary with other bases, see p 28.

(iv) X_2 represents any halogenating species, $X_3^{\ominus}$, $OX^{\ominus}$, etc.

reactions being faster than the first enolization.

Several assumptions are implicit in this scheme. Firstly, halogen substituted ketones must enolize faster than the ketone itself under base-catalyzed conditions. This has been shown to be the case by several workers, for instance by Bell and Lidwell[4], who found the rates of halogenation of acetone, monochloroacetone and 1,1-dichloroacetone to be in the ratio 1:400:3000, and, more recently, by Lewis, Allen and Wallick[67], who found the acetate-catalyzed bromination rates of $PhCOCH_3$, $PhCOCH_2Br$ and $PhCOCHBr_2$ to be in the ratio 1:53:104 (statistically corrected). This assumption is not unreasonable, therefore, and may be rationalized by saying that the inductively electron-withdrawing halogen removes electron density from the molecule, increasing the acidity of the remaining protons and facilitating their removal by base[66]. Presumably this effect is felt more strongly by the protons on the same carbon as the substituent, which means that the second halogen should be introduced at the same site as the first, rather than at the other side of the carbonyl group, if this position is available[66]; this is the second assumption implicit in the scheme in Chart 2. Thirdly, reaction 5 in Chart 2, the hydrolysis of the trihaloketone, is assumed to be faster than its further halogenation. Little is known about this reaction other than that it is accelerated by bases[68]; this reaction will be

considered in more detail below and in the discussion.

The best conditions for the haloform reaction are given by Morgan, Bardwell and Cullis[64]; among other things they found that the iodine present in an iodination reaction may undergo other reactions, as well as reacting with the enolate, for instance:

$$I_2 + 2OH^{\ominus} \longrightarrow I^{\ominus} + IO^{\ominus} + H_2O$$

$$3IO^{\ominus} \longrightarrow 2I^{\ominus} + IO_3^{\ominus}$$

For iodine these reactions may be very fast[69], and $IO_3^{\ominus}$ will not halogenate ketones[64]. If iodine is not added last (as $I_3^{\ominus}$, dropwise to the ketone in solution in strong hydroxide[70]) these side reactions may cause the yield of iodoform to be considerably reduced[64,70].

The products of the haloform reaction have been carefully investigated by Cullis and Hashmi[65]. They found that acetone and n-alkyl methyl ketones used more than three iodine molecules per ketone molecule, and found α-iodo-carboxylic acids as well as carboxylic acids and iodoform in the products, but no di-iodo acids. Methyl iso-propyl ketone and methyl tert-butyl ketone used less than three iodine molecules, and gave iodoacetic acid as well as the products noted above. Pinacolone also gave tert-butyl iodide.

These results suggest: (i) that enolization may occur away from the methyl group in methyl ketones as

well as towards it; (ii) that the hydrolysis of tri-iodo ketones may not always be faster than further iodination; (iii) hydrolyses other than those producing haloforms may be possible; (iv) in the case of crowded ketones it may be difficult to form tri-iodo derivatives.

More recently it has been found by Rappe[71] that mono- and di-bromopropionic acids could be isolated from the reaction mixture during the acetate-catalyzed bromination of 2-butanone. He also found that 1,1,1,3-tetrabromo- and 1,1,1,3,3-pentabromo-2-butanone could be cleaved by acetate, but that 1,1,1-tribromo-2-butanone could not. Some evidence for the alkaline hydrolysis of 3,3-dibromo-2-butanone was also found[71].

The above observations indicate that the generally accepted scheme of the haloform reaction, Chart 2, may require modification and elaboration, especially if bases other than hydroxide are used.

Kinetics of Ketone Iodinations

It was mentioned above that halogenating agents are not involved in the rate-determining step of base-catalyzed enolization. If the ketone is in a large excess, this means that ketone halogenations are zero-order in halogen, and a graph of halogen concentration *vs.* time will be linear[72]. This has been very often observed, and the

usual method for obtaining enolization rates is from the slopes of these graphs. Iodine is generally used; its concentration at various times can be determined by iodimetric titration (with sodium thiosulfate) or spectrophotometrically by the changing absorbance of the ion $I_3^{\ominus}$ [25,62,73-77].

The actual halogenating agent involved in reaction with the enolate has been discussed by several workers - e.g. refs 3, 19, 20, 65, 78 and 79. Depending on conditions it may be X_2 [19,20], $X_3^{\ominus}$ [77], HOX [65], $OX^{\ominus}$ [78,79] or possibly other species[3]; this is not important insofar as the enolization process is concerned as these species all react with the enolate in a subsequent fast step (and are all oxidizing agents with a high redox potential[69], see below).

The shortcomings of the iodination method have been discussed in many papers[25,73,79-81]. Iodine (and bromine) can react with carboxylate buffers and amines; it is a strong oxidizing agent and can react quickly with impurities[4,25]; it can react with strong bases to give inert $IO_3^{\ominus}$ species (see p 27); it can remove halogens from haloketones[33c,81] and thus cause the iodination reaction to be to some extent reversible.

As a typical example of the approach to ketone enolization studies used by many authors we may consider the work of Feather and Gold[74] in more detail. These authors studied the enolization of various alkyl ketones

catalyzed by pyridines. The reaction rates were determined from the zero-order rate of iodine consumption, the ketone concentration being greater than the iodine concentration in the approximate ratio 1:3000[74]. Some initial acceleration in the rate of iodine consumption was noted, as in many other cases (see below), and was attributed to impurities[74]. The reaction products, and the number of iodine atoms introduced, were not determined, and statistical corrections, for the differing numbers of enolizable protons in the ketone being iodinated, are not mentioned[74]. Quoting a brief passage: "For all ketones it is considered that substitution occurs to a significant extent only in one of the CH_3, CH_2 or CH groups adjacent to the carbonyl group. This is plausible in view of the disparity of concentrations of ketone and iodine and the expectation that the activation of C-H bonds by an iodine substituent would only be weakly transmitted across the carbonyl group." For isopropyl methyl ketone: "it is likely that the reaction occurs preferentially in the methyl group...."[74]. This type of reasoning is quite common in ketone iodination studies; in particular the products of weak-base-catalyzed halogenation have not been determined at all until quite recently (see below). Rappe[81] feels that all studies carried out using iodimetic titration "are of limited importance"; the present author would not go this far (in some cases it is difficult to

decide whether or not the products are important to the conclusions reached in individual papers) but he feels that possible experimental ambiguities should always be borne in mind when enolization rate data are used in support of theoretical conclusions, such as "proton tunnelling"[79] and the geometry of the enolization transition state[74].

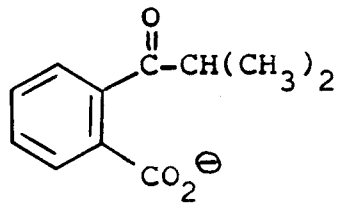
Kinetic ambiguities have been noticed by many authors. In particular a sigmoid rate acceleration at the beginning of iodine concentration vs. time graphs is common[25,79,80]; this is generally attributed to impurities, for instance Bender and Williams[25] attribute it to impurities oxidizing $I_3^{\ominus}$. This anomaly can be reduced, but not eliminated, by ketone purification[76]. Bell and Lidwell[4] noticed a similar phenomenon in their bromination study of several haloketones; they had trouble purifying some of their compounds and impurities may account for some of it. However, Bell and Yates[50] found that the inclusion of the rates of chlorination of chloroacetone and dichloroacetone in the total rate expression for the rate of chlorination of acetone gave a sigmoid concentration/time graph similar to that observed experimentally.

The Uses of Enolization Rate Measurements

Enolization rate measurements have provided data

for many of the basic concepts of organic chemistry. Space limitations permit only a very brief examination of these, which will be given in this paragraph; the considerations of the preceding paragraph should always be borne in mind.

Base-catalyzed enolization studies have provided much evidence for the theoretical interpretation of the Brönsted correlation between catalysis constants and the pK_a of the catalyst, for general-base-catalyzed reactions. For a review see ref 19, chapter X. The enolization rates of many ketones, catalyzed by various bases, obey the Brönsted relationship[4], but hydroxide ion often does not fall on a line with the other buffer bases used[4]. Harper and Bender[80] found intramolecular catalysis to apply to the ketone IX. Dicarboxylate catalysis was studied by Lienhard and Anderson[88]; they found that two catalyzing groups in the same molecule were not more effective than one.

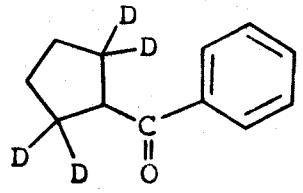


(IX)

The amine-catalyzed enolization of ketones has been studied by several groups. Bender and Williams[25] found evidence to suggest that in some cases the reaction goes <u>via</u> the formation of a protonated ketimine (Schiff base) which then undergoes proton abstraction to give an enamine; this mechanism is similar to that proposed by Shilov, Yasnikov and co-workers[75]. Tagaki and Westheimer[89] proposed the operation of a similar mechanism in the

enzyme-catalyzed deuterium exchange of acetone. Coward and Bruice[73] found no evidence to suggest concerted intramolecular general-base, general-acid catalysis in ketones containing one or more tertiary amino groups. Feather and Gold[74] studied catalysis by various pyridines in the enolization of various alkyl ketones, and found that "steric crowding reduces the rate for crowded compounds despite the increase in acidity".

Isotope effects in enolization processes have been the subject of much study[21,67,76,77,79,82-86] and review[5,87]. Generally speaking they are in agreement with, or not inconsistent with, the enolate mechanism already discussed; the large primary effect usually observed indicates a transition state resembling enol(ate) rather than ketone, with C-H bond breaking more developed as the base strength decreases, as would be expected on the basis of Hammond's postulate[90]. Emmons and Hawthorne[77] observed a secondary isotope effect of some 20% in the acid- and base-catalyzed enolization of the ketone X, which is taken to indicate the action of hyperconjugation in base-catalyzed as well as in acid-catalyzed enolization. Gould[20] had not found the argument conclusive, but Tee[5] regards this as more consistent with the concerted enol mechanism rather than the enolate mechanism. Bell[87] feels this could be due to



(X)

the operation of either a hyperconjugative or an inductive effect.

Studies of the steric requirements of the direction of enolization of steroidal ketones[91,151] indicate that the proton is abstracted in a direction perpendicular to the plane of the carbonyl group[74,82] in order to permit continuous overlap of the developing p orbital (from the C-H bond) with the π system of the carbonyl group at the transition state[91]. This result has been supported recently by the application of the principle of least motion to the enolization process by Tee[92].

Linear Free Energy Relationships

Apart from the already-mentioned Brönsted correlation, several other linear free energy relationships have been found to apply to base-catalyzed ketone enolizations. Most of these throw light on the extent of negative charge development at the enolization transition state.

Evans and Gordon[93] found that increasing α-substitution in α-substituted acetophenones decreased their base-catalyzed enolization rate. The conclusion was drawn that inductive electron release by the alkyl substituents destabilizes the transition state for enolate anion formation[37,94]. Later Taft[95] found that the results of Evans and Gordon[93] fitted his $\sigma^*\rho^*$ correlation quite

well, with a ρ^* of +1.59. This figure implies the development of considerable negative charge in the transition state[95]; ρ^* for the ionization of carboxylic acids in water at the same temperature is +1.72[95].

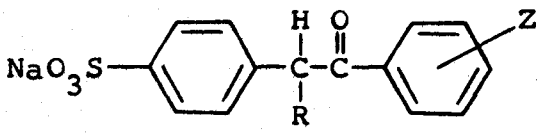
Conant and Carlson studied the rate of racemization of several ketones catalyzed by alkoxide in alcohol[96]; analysis of their numbers again indicates considerable development of negative charge, and of the enol double bond, at the transition state[5].

Nuclear-substituted acetophenones have been studied by several groups[18,23,32,97,98,100]; electron-withdrawing substituents cause rate enhancement[97]. Fischer, Packer and Vaughan[99] studied the acetate-catalyzed bromination of substituted benzyl phenyl ketones in aqueous acetic acid. They found a correlation of rates with Hammett's σ constants, with a ρ of +1.73. Comparing this with the similar correlation these workers observed for the acid-catalyzed enolization of these ketones, with a ρ of +0.39[29], again implies negative charge development for the base-catalyzed reaction, although it is difficult to say how much.

Kursanov et al.[100] studied the D-exchange of nuclear-substituted acetophenones in the $EtO^{\ominus}$/EtOD system. They found electron-withdrawing groups (p-NO_2, p-Br) increased the rate of D-exchange, whereas electron-donating ones (p-OMe, p-NMe_2) reduced it. The ρ value from

the good Hammett $\rho^{\wedge}$ plot obtained was +1.43. This value, obtained in ethanol, can be used to estimate the value in water by considering the ionization constants of benzoic acids in both systems[101]; the resulting value is +0.73, which could imply that less than a full negative charge should be present at the transition state in water.

Recently Grunwell[102] studied the acetate-catalyzed iodination rates of the ketones XI in water, and also found their pK_a's. The Hammett plots resulted in a ρ_{kin} of +1.113 ± 0.066 for the enolization rates, and a ρ_{thermo} of +1.751 ± 0.053 for the pK_a's. Subtraction of these two numbers gives 0.64, which indicates that about 64% of a negative charge is present at the transition state for acetate-catalyzed enolization[102].



(XI)

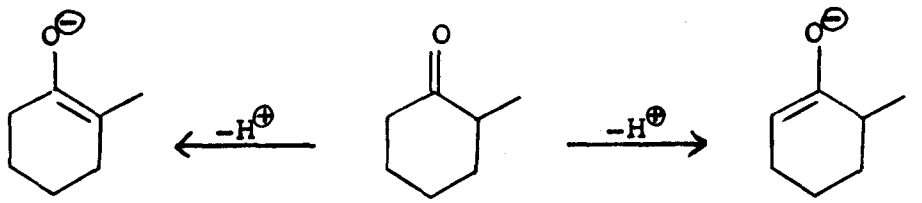
Enolate Anions

We may begin the discussion of the direction of enolization of unsymmetrical ketones, and the factors which affect it, with a brief consideration of enolate anions. These are widely used synthetic intermediates[1], generally prepared using strong bases in non-aqueous solvents. Sufficiently strong bases may even produce homoenolate anions from suitable ketones[103]. However, the relative

stabilities of the differing enolates which can be prepared from unsymmetrical ketones should provide information concerning the effects of alkyl groups in these systems, and these effects may also apply to enolizations in water.

The enolates of unsymmetrical ketones can be trapped and isolated as their acetates by reacting them with acetic anhydride[104,105], as lithium or potassium salts[106], or as trialkyl silyl enol ethers[107]. The product distribution can then be studied; that first observed results from kinetic control. The initial mixture can then be equilibrated, and the resulting product distribution compared with the initial one. The results of these studies[104-7], using ketones such as α-methyl cyclohexanone, α-methyl cyclopentanone and some acyclic dialkyl ketones, indicate in general that the kinetically controlled product tends to be that from preferential enolization towards the less substituted site, whereas the equilibrium product tends to be that from preferential enolization towards the more substituted site. In other words the more substituted enolate is more stable but may not be formed first.

Rate/equilibrium disparities of this type have been discussed by Hine in terms of the principle of least motion[108]. Since this principle has not yet received widespread recognition, a detailed discussion will not



(XIII) (XII) (XIV)

be given here; however, qualitatively it can be seen that motion of the methyl group in reaction XII → XIV above, caused by the shortening of a single bond to a double bond, will be less than in reaction XII → XIII. Hence the activation energy for XII → XIV will be slightly smaller (since moving part of a molecule requires energy to overcome inertia).

(XV) (XVI)

Returning to perhaps more familiar ground, House[109] feels that resonance structure XV is destabilized by α-alkyl substituents for electrostatic reasons, and structure XVI stabilized by hyperconjugation. If we assume that XV is closer to the transition state for proton removal than XVI, inductive destabilization may be the reason why less substituted enolates are formed first. However, XVI certainly more nearly approximates the situation when the proton is fully removed and equilibration is allowed to occur, and hyperconjugation may be the reason for the greater stability of the more substituted enolate. However, this

reasoning could be considered to be equivalent to regarding resonance structures as separate species, if the transition state is, in fact, already a resonance hybrid.

The pK_a's of various ketones, determined thermodynamically, have recently been given by Zook, Kelly and Posey[110]. They find that increasing alkyl substitution in dialkyl ketones increases their pK_a. The increments due to adding alkyl groups are small and irregular, not as well defined as the change due to halogen substitution discussed by Levy[49], but the trend is definite. In other words this study indicates that more substituted enolates are less stable thermodynamically than less substituted ones. The authors only studied one ketone that was capable of forming more than one enolate, methyl neopentyl ketone; their results suggest that enolization occurs towards the methyl group in this ketone[110]. No obvious connection between these thermodynamic acidities, and kinetic acidities derived from proton exchange rates (e.g. Pearson and Dillon[111]) is apparent[110].

Rappe has studied the relative stabilities of the enols and enolates of 2-butanone by using the extended Hückel method to calculate their energies[45,112]. He finds the 1-enolate to be energetically favoured over the 3-enolate (but only by 0.2 Kcal/mole), but that the 3-enol is favoured over the 1-enol by 1.4 Kcal/mole. This author does not find these numbers particularly compelling, but

they support House's contention[109] that inductive and hyperconjugative effects almost cancel one another in enolate anions, causing factors usually considered of minor importance (nature of cation, solvent) to influence the equilibria of structurally isomeric enolates.

Unsymmetric and Substituted Ketones

Early studies of unsymmetric dialkyl ketones led to the view that base-catalyzed enolization in water occurred at the least substituted α-position[20,94]. Hughes suggested an analogy between base-catalyzed enolization and Hofmann orientated elimination[37]. This viewpoint was discussed by Cardwell[94], who pointed out that "alkyl groups inductively hinder the loss of a proton to a base, but that once this has occurred they stabilize the resulting ion in a resonant or hyperconjugative manner".

The evidence for enolization towards the least substituted site comes mainly from the haloform reaction (see p 24). Here it may be noted that Suknevich and Chilingaryan[113] obtained acetic acid as well as propionic acid from the haloform reaction of calcium hypochlorite on 2-butanone; taking this into consideration, along with the evidence in the section on the haloform reaction above, leads to the conclusion that enolization at the more substituted site may be competitive with enolization

at the less substituted site of dialkyl ketones.

It was pointed out above (p 26) that haloketones enolize faster than unsubstituted ketones. The effects of substitution by halogen, and $SO_3^{\ominus}$, can be seen in the work of Bell et al.[4,54,114,115] given in Table III, p 42. Also, it is fairly apparent from this table that alkyl substitution reduces base-catalyzed enolization rates. This may be due to the already-mentioned inductive effect, or it may be for steric reasons.

Apart from nmr studies, to be considered in the next section, several recent studies of the direction of base-catalyzed enolization exist. In particular the results of Jullien and Nguyen[116], given in Table IV, p 43, are most instructive. Protons of cyclohexanone are removed <u>faster</u> than protons of acetone (the only two alkyl ketones in the table). Fluorine substitution causes a rate acceleration, but at the <u>other side</u> of the carbonyl group. Chlorine causes a substantial rate acceleration on <u>both sides</u>. Benzyl ketones have enhanced rates at the benzyl position, but the effect of phenyl groups at the other side of the carbonyl group is very small. Obviously more than one effect is at work here.

A study of 3-fluoro-2-pentanone by Cantacuzène et al.[117] shows that this ketone brominates at the methyl group ($Br_2/CCl_4/CaCO_3$) in agreement with the above, and also that the 3-bromo derivative can be obtained with NBS

TABLE III

Catalytic Constants from some Ketone Brominations at 25° [a,b]

Ketone	k_0 $sec.^{-1}$ [c]	$k_{H^{\oplus}}$ $M^{-1}sec.^{-1}$	$k_{OH^{\ominus}}$ $M^{-1}sec.^{-1}$	$k_{OAc^{\ominus}}$ $M^{-1}sec.^{-1}$
CH_3COCH_3	4.7×10^{-10}	2.7×10^{-6}	2.5×10^{-1}	2.4×10^{-7}
$CH_3CH_2COCH_2CH_3$	-	2.7×10^{-6}	3.8×10^{-2}	-
$(CH_3)_2CHCOCH(CH_3)_2$	-	1.8×10^{-6}	2.1×10^{-3}	-
CH_3COCH_2Br	2.9×10^{-7}	8.6×10^{-6}	-	1.8×10^{-5}
$CH_3CH_2COCHBrCH_3$	5.5×10^{-8}	1.9×10^{-7}	-	2.2×10^{-6}
CH_3COCH_2Cl	5.3×10^{-8}	6.3×10^{-5}	-	1.1×10^{-5}
$CH_3CH_2COCHClCH_3$	5.2×10^{-8}	8.8×10^{-7}	-	1.2×10^{-6}
$SO_3^{\ominus}CH_2COCH_3$	1.9×10^{-6}	4.0×10^{-5}	80	5.2×10^{-4}
$SO_3^{\ominus}CH_2COCH_2SO_3^{\ominus}$	2.4×10^{-5}	-	-	1.6×10^{-3}
$ClCH_2COCH_2Cl$	3.4×10^{-6}	-	-	2.1×10^{-3}

[a] R. P. Bell, G. R. Hillier, J. W. Mansfield and D. G. Street, J. Chem. Soc., B, 827 (1967).

[b] The rate constants quoted are overall values and are not statistically corrected.

[c] Catalysis by water molecules.

TABLE IV

Base-Catalyzed Enolization Rates of some Unsymmetrical Ketones [a]

$10^6 k_\alpha$ [c] ± 10%	Ketone [b] α	α'	$10^6 k_{\alpha'}$ [c] ± 10%	$10^6 k_B$ $sec.^{-1}$	$k_\alpha/k_{\alpha'}$
~1.1	$CH_3-CO-CH_3$		~1.1	~6.6	-
1.3	$FCH_2-CO-CH_3$		6.8	23.1	0.19
5.8	$FCH_2-CO-CH_2F$		5.8	23.2	-
109.7	$ClCH_2-CO-CH_3$		21.0	282.3	5.2
2.9	$CH_2-CO-CH_2$ / $CH_2-CH_2-CH_2$		2.9	11.7	-
~0	$FCH-CO-CH_2$ / $CH_2-CH_2-CH_2$		~2.5	~4.9	small
30.3	$ClCH-CO-CH_2$ / $CH_2-CH_2-CH_2$		14.8	60.0	2.05
~13.8	$PhCH_2-CO-CH_3$		~1.0	~30.5	~14
1.4	$PhCHF-CO-CH_3$		6.7	21.5	0.21
53.0	$PhCHCl-CO-CH_3$		4.4	66.3	12.0
-	$Ph-CO-CH_2CH_3$		0.6	1.2	-
-	$Ph-CO-CHFCH_3$		<0.1	<0.1	-
-	$Ph-CO-CHClCH_3$		1.2	1.2	-

[a] J. Jullien and T-L. Nguyen, Bull. Soc. Chim. Fr., 4669 (1968).

[b] Conditions: $AcOD/D_2O$ (75-25%); AcONa, 1.57 M; temperature 35.4 - 35.5°; ketone concentration, about 2 gram-atoms of α-H per litre; exchange monitored by mass spectroscopy.

[c] Statistically corrected rate constants.

in CCl_4. Diazoacetone gives CH_3COCDN_2 with D_2O in the presence of sodium azide[118]. Chloroacetone was found to give acetol very quickly on reaction with NaOH[119], but deuterium exchange was even faster in $NaOD/D_2O$. Interestingly, the product isolated was $CH_3COCHDCl$, not CH_3COCD_2Cl[119].

Fischer, Packer and Vaughan found that α-bromobenzyl phenyl ketones brominated more slowly than the unbrominated ketones; this was attributed to a steric effect[99]. Hulett found $(CH_3)_2CBrCOCH(CH_3)_2$ to be less reactive than $(CH_3)_2CHCOCH(CH_3)_2$, but he attributes this to the formation of the inert species $(CH_3)_2CBr.C(OH)_2.CH(CH_3)_2$[79]. Alcais[120] studied the successive bromination of ethyl acetoacetate and ethyl benzoylacetate, and he discusses the rate differences he observed in terms of a "variable contribution of conjugation energy in the transition complex". Thus it is apparent that in these systems also, factors other than inductive and hyperconjugative effects may be important.

Schellenberger and Huebner[121] studied the acid- and base-catalyzed iodination of 2-butanone. They allowed the ketone to react with radioactive iodine, carried out an iodoform reaction on the product, and counted the resulting iodopropionic acid and iodoform. Acid-catalyzed enolization gave most activity in the iodopropionic acid, and acetate-catalyzed enolization gave most activity in the

iodoform, indicating preferential enolization towards the methylene group and the methyl group, respectively[121]. However, in view of the possibility of radio-iodine removal by the iodine added later (a lot of activity was apparently lost), these results should be regarded as indicative rather than conclusive.

NMR Studies

Nmr spectroscopy has been applied to the study of ketone enolization in three main ways: direct observation of enols, identification and analysis of the products of ketone halogenation, and observation of the reduction in peak areas caused by the substitution of α-D for α-H in ketones.

Direct observation of enols has been mainly confined to studies of β-diketones, which have a high enol content[122,123]. Simple ketones have much lower enol contents[124]; the enols of 2-butanone could not be conclusively identified in the pure ketone even with the aid of an HA-100 nmr spectrometer and a C-1024 time-averaging computer[125].

Bromoketones have easily identifiable nmr spectra[13], and the products of the bromination of 2-butanone have been studied in this way by Rappe[3,71,81,126,127]. (The only previous study of the products of base-catalyzed halogen-

ation is that of Cullis et al.[64,65].) Rappe's results lead him to propose <u>five</u> ketone halogenation mechanisms[3], two acid-catalyzed (see p 20), one free radical (see p 100) and two base-catalyzed, of which neither is the same as the base-catalyzed deuterium exchange mechanism[81].

In an early study[71] Rappe used the bases sodium acetate and sodium bicarbonate, in two-phase systems with water and ketone, and sodium acetate was also used in one-phase systems of acetic acid/water (1:1) and pure acetic acid. The 2-butanone was brominated in these systems with (usually) less than one equivalent of bromine in order to avoid polyhalogenation. Chlorine was also used. The bromoketone or chloroketone products were extracted into carbon tetrachloride and identified by nmr, the amounts of the various products present being determined by integration. The two-phase systems gave mostly monobromoketones, with 3-bromo-2-butanone forming at least half of the total mixture in most cases. The same trend was apparent in the one-phase systems, but more extensive polybromination occurred, either because the bromoketones were soluble in the medium in this case, and available for further reaction, or because of a change in mechanism[71]. Bromoform was not a major product in most cases.

Rappe[71] defines the ratio K_{Br} as being the percentage of the products formed from a primary 3-halogenation divided by the percentage from a primary 1-halogen-

ation. He found K_{Br} to be 1.5-2 for the one-phase systems, and 5-7 for the two-phase system[71]. He interprets this by assuming the reaction in the one-phase system to be acid-catalyzed (by the acetic acid present), and the reaction in the two-phase system to be base-catalyzed and to be mechanistically different from the haloform reaction observed when this ketone is treated with strong bases and halogens in water (which is halogenation in the methyl group, with $K_{Br} \approx 0$).

This "two base-catalyzed mechanisms" concept is further explored in succeeding papers[81,127]. The mechanism of the reaction operating in the pH region between 5.5 and 7 Rappe designates "Hal B I"; this reaction is catalyzed by weak bases such as acetate and bicarbonate and gives mainly 3-halogenated products. At pH's above 12 another mechanism, "Hal B II", takes over; here the reaction is catalyzed by hydroxide and gives exclusively 1-halogenation and a haloform reaction. As the pH increases from 5 to 12, the acidic component (from the haloform reaction) also changes, from α-bromopropionic acid to propionic acid[127].

In both reactions, Hal B I and Hal B II, Rappe finds the iodination rate to be slower than the bromination rate, using a somewhat cursory analytic procedure[81,126]. In the same papers he discusses brominations in D_2O, and finds bromination and deuteration to proceed independently of one another in both reactions. This evidence leads him

to the supposition that, if deuteration goes by enolization, both types of halogenation are reactions with the unenolized ketone[81,126].

In what is probably his most comprehensive paper on this work[3], Rappe discusses the halogenating agent in the various reactions. A study of the reaction between hypobromous acid and 2-butanone leads him to the supposition that the reaction Hal B I, found at pH 5.5-7, is the result of the action, on unenolized 2-butanone, of a halogenating agent formed in a reaction between hypohalous acids and halides:

$$X_2 + H_2O + B^{\ominus} \rightleftharpoons HXO + HB + X^{\ominus}$$

$$HXO + X^{\ominus} \longrightarrow \text{halogenating agent}$$

$$\text{unenolized ketone} + \text{halogenating agent} \rightarrow \text{haloketone}^3.$$

The reaction Hal B II, pH > 12, is assumed by Rappe to be an attack of hypohalite ion on unenolized 2-butanone[3].

It seems almost superfluous to remark that almost all of the above-reported work of Rappe is at variance with both of the possible mechanisms for ketone halogenation so far discussed, which lead to the zero-order reaction of the halogenating agent with the enol(ate) derived from the ketone.

Recent work by Thorpe[128] indicates that the product ratio for the acetate-catalyzed bromination of 2-butanone,

determined by glpc analysis, is in fact almost the same as that from the acetate-catalyzed deuterium exchange under identical conditions (k_{CH_2}/k_{CH_3} = 1.83 ± 0.11 for bromination, = 1.70 for deuterium exchange)[128]. It is thought that bromoketone rearrangement could possibly explain some of Rappe's data - recently Grisbaum and Brueggemann[129] found the major product from the carbonate-catalyzed bromination of 2-butanone to be 1,3-dibromo-2-butanone and not the expected 1,1- or 3,3-isomers, although this may be a result of rearrangement on the glpc column they used for the separation (SE-30) rather than in the reaction mixture.

Deuterium Exchange

The deuterium exchange of ketones can be studied by nmr spectroscopy. Exchange at individual sites of unsymmetrical ketones can be followed by monitoring the decreasing integral areas of the peaks corresponding to the protons on either side of the carbonyl group. The first reported application of this method is that of Warkentin and Lam[130] in 1964, concerning the exchange of the vinylic and allylic hydrogens of 6,6-dimethylcyclohex-2-en-1-one. Since that time much work has been done concerning the relative rates of exchange under conditions of base catalysis at two sites in 2-butanone[5,44,45,131-133],

methoxyacetone[44,134], dialkyl ketones[46,135] and cycloalkyl ketones[136-9]. Acid-catalyzed exchange has also been studied (see above, p 13), and the method has been extended to other exchange reactions, such as those occurring in sulfinyl compounds[140] and sulfones[141].

Warkentin and Tee have studied the hydroxide-, acetate-, and p-nitrophenoxide-catalyzed D-exchange into 2-butanone[5,132,133]. They found that a methylene proton is just as reactive as a methyl proton in hydroxide-catalyzed exchange in water, contrary to what might have been expected from the results of the haloform reaction on this ketone. For the weaker catalysts the methylene protons are more reactive than the methyl protons, by as much as a factor of two for acetate. The relative rates were not significantly affected by changes in temperature or ionic strength, although the results were not compelling[133], but the relative methyl reactivity was found to increase with increasing organic solvent concentration in the reaction medium. Their results led Warkentin and Tee to postulate a transition state for base-catalyzed enolization resembling enol and not enolate, in effect reviving the concerted mechanism of Swain[61] (see above, p 24)[5,133].

The D-exchange into 2-butanone has also been studied by Rappe[45,131] and by Bothner-By and Sun[44]. These results in general agree with those already discussed, but Rappe finds the relative rates at the two sites to be

approximately equal for all bases[45], in contrast to Warkentin and Tee's results[133]. He suggests that the extrapolation method used to derive catalytic constants by Warkentin and Tee[5,133] is wrong[131]. Rappe also finds that the relative rates are different from those derived from halogenation reactions (see above, p 47), which leads him to propose different mechanisms for exchange and halogenation[3]. Further publications in this area[142,143] concern some of the work in this thesis, and will be considered in the discussion.

Methoxyacetone has been studied by Hine et al.[134] and by Bothner-By and Sun[44]. Hine et al.[134] find different bases to give different relative rates; in particular they found that all the catalysts studied gave faster exchange at the methyl group, except for hydroxide, which gave faster exchange at the methylene position. This result would not be predicted on the basis of the inductive effect of the methoxyl group[134].

Warkentin and Barnett[46], and Rappe and Sachs[135], have studied the D-exchange of dialkyl ketones in dioxane/D_2O, catalyzed by $OD^{\ominus}$. The results obtained by Warkentin and Barnett are given in Table V, p 52. The results and in particular the general conclusions of the two studies are here in agreement despite some experimental anomalies in the work of Rappe and Sachs[135], discussed by Warkentin and Barnett[46]. Steric effects appear to predominate in

TABLE V

Base-Catalyzed Deuterium Exchange of some Dialkyl Ketones [a]

ketone [b] α α'	k_α [c]	$k_{\alpha'}$ [c]
CH_3COCH_3	25.4	25.4
$CH_3COCH_2CH_3$	12.8	11.0
$CH_3COCH(CH_3)_2$ [d]	8.61	0.673
$CH_3COC(CH_3)_3$	4.17	-
$CH_3COCH_2CH_3$	12.8	11.0
$CH_3COCH_2CH_2CH_3$	8.84	5.00
$CH_3COCH_2CH(CH_3)_2$	6.90	2.90
$CH_3COCH_2C(CH_3)_3$	5.33	0.277

[a] J. Warkentin and C. Barnett, J. Amer. Chem. Soc., 90, 4629 (1968).

[b] Conditions: dioxane/D_2O (2:1); NaOD, 0.01-0.05 M; temperature 32°; ketone concentration 5-10% v/v; exchange monitored by nmr spectroscopy.

[c] Per hydrogen rate constants, x 10^2 $M^{-1}sec^{-1}$; ± <5%.

[d] The ketone $CH_3COCH(CD_3)_2$ was also used; the numbers listed are for this ketone as they are considered more accurate.

these exchange processes, reducing all the rates in comparison with that for acetone, for all the ketones studied except 2-butanone, where it is possible to infer the existence of an accelerating polar effect caused by the β-methyl group[46]. In most cases reaction at the methyl group predominates (see also House and Kramar[104]), this is probably due to steric hindrance to the approach of the attacking reagent at the more hindered position.

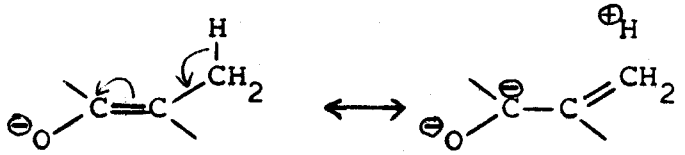
Here it may be mentioned that a recent study of the condensation of chloral with various ketones in acetic anhydride, catalyzed by sodium acetate, by Kiehlmann and Loo[144], showed similar product distributions to those which would be predicted from the work of Warkentin and Barnett[46]. For 2-butanone Kiehlmann and Loo also found enhanced methylene reactivity, but they found rather more selectivity for the methyl group in more highly alkylated ketones than did Warkentin and Barnett, a result which is not too surprising considering the quite different reagents and conditions used in the two studies.

Cycloalkyl ketones have been studied by several workers[136-9]. Cyclopropyl methyl ketone is found to enolize slowly, compared to isopropyl methyl ketone, and away from the ring, for acid- and base-catalyzed reactions. This is in line with the poor ability of the strained cyclopropyl ring to form part of the double bond in an enol or enolate[139]. The same tendency is evident in other cycloalkyl ketones[139].

Summary

Probably the prevailing impression given by the preceding evidence is one of confusion. Even the very phrase "base-catalyzed enolization" can no longer be used to describe ketone halogenations, if Rappe is to be believed. Apart from Rappe's ideas, we have two possible enolization mechanisms, the generally adopted enolate mechanism advocated mainly by Bell[19], and the concerted enol mechanism of Swain[61], recently revived by Warkentin and Tee[133]. Probably the bulk of the preceding evidence, particularly the linear free-energy relationships, favours the enolate mechanism, but if this is the true mechanism a lot of anomalies remain.

It appears that the direction of enolization of unsymmetrical and substituted ketones can be influenced by the inductive, steric, mesomeric and hyperconjugative effects of the substitutents. Inductive effects are generally assigned the more important role in the base-catalyzed reaction, but their action alone cannot explain the action of fluorine and methoxyl substituents. Alkyl substituents can act inductively, sterically or hyperconjugatively. With regard to hyperconjugation, generally written:



(XVII)

the present author fails to see how structures such as XVII, with its adjacent negative charges, can contribute to the stability of an enolate, or, for that matter, an enol. However, if hyperconjugation is to be discarded, some other stabilizing factor must be found. This might mean that the sign of the inductive effect of alkyl groups in these systems needs re-evaluation. The inductive effect of a methyl group, as generally accepted, is the main reason for the revival of the concerted enol mechanism by Warkentin and Tee[133]; however, Rappe[131] disagrees with their results.

The work in this thesis was undertaken with four main objectives in mind: (i) to resolve the controversy between Warkentin and Tee, and Rappe, regarding the effects of different bases on the enolization of 2-butanone; (ii) to determine whether or not ketone halogenation in fact goes by enolization in the weak-base-catalyzed reaction designated "Hal B I" by Rappe; (iii) to try to isolate and investigate the inductive effect of a substituent (bromine) and to see how it affects the enolization rates on both sides of the carbonyl group; (iv) to try and determine whether or not the enolization transition state contains negative charge in the weak-base-catalyzed process, and hence to differentiate between the enol-like and enolate-like transition states for this reaction.

RESULTS AND DISCUSSION

The work to be discussed falls fairly naturally into three parts: (i) the acetate-catalyzed deuterium exchange studies on 2-butanone; (ii) the investigation of the reactions involved in the acetate-catalyzed bromination of acetone; and (iii) the rate constants and activation data derived from the bromination of various ketones and bromoketones. Each topic is discussed separately, "in context", and this section is concluded with a discussion of these results, together with those of other workers, in terms of a preferred mechanism for base-catalyzed enolization.

The Acetate-Catalyzed Deuterium Exchange of 2-Butanone

Warkentin and Tee[5,133] found that the rate ratios for the base-catalyzed D-exchange of 2-butanone were:

$$R = k_{CH_2}/k_{CH_3} \simeq 1.0 \text{ for } OD^{\ominus} \quad (\sim 35^{\circ})$$
$$\simeq 1.5 \text{ for } p\text{-}NO_2C_6H_4O^{\ominus} \quad (59.2^{\circ})$$
$$\simeq 2.1 \text{ for } OAc^{\ominus} \quad (59.2^{\circ})$$

The latter two figures were derived, from the overall rate data obtained, by taking the intercept of a plot of k^{obsd}/C

vs. $C^{-\frac{1}{2}}$, where C is the base concentration[5,133]. Rappe[45,131], however, found that R ≃ 1.0 for catalysis by hydroxide, acetate, carbonate and bicarbonate. He discusses the results[131] and suggests that the discrepancy is "due to the extrapolation technique used by Warkentin and Tee and the incorrect omission of a term arising from solvent catalysis"[135]. In view of this, it was felt necessary to study the uncatalyzed (solvent catalysis) reaction, and the acetate-catalyzed reaction, by a different method, in order to clarify this point. The method chosen was the buffer method developed by Bell and Jones[63].

The observed rate constant for enolization in acetate buffers can be represented as a sum of terms[63]:

$$k^{obsd} = k_0 + k_{D_3O^{\oplus}}[D_3O^{\oplus}] + k_{OD^{\ominus}}[OD^{\ominus}] + k_A[DOAc] + k_B[OAc^{\ominus}] + k_p[DOAc][OAc^{\ominus}] \quad (1)$$

In a buffer solution the pD and hence $[D_3O^{\oplus}]$ and $[OD^{\ominus}]$ remain constant upon dilution. Consequently, as $[DOAc]$ and $[OAc^{\ominus}]$ are varied at constant buffer ratio, the first three terms in eq 1 remain constant. Writing r = buffer ratio = $[DOAc]/[OAc^{\ominus}]$, and assuming k_p to be negligibly small in comparison to k_A and k_B, eq 1 reduces to eq 2:

$$k^{obsd} = k' + (k_A r + k_B)[OAc^{\ominus}] \quad (2)$$

If k_p is indeed negligibly small, a plot of k^{obsd} *vs.* $[OAc^{\ominus}]$ will be linear, with slope $(k_A r + k_B)$ and inter-

cept k'. Here the acetic acid concentration was kept low to emphasize the base-catalyzed reaction and, because k_A should be smaller than k_B[134], the important contributor to the slope was expected to be k_B. However, both k_A and k_B can be obtained in principle by varying the buffer ratio r, and this was done. If k_p is not negligible relative to the other terms, the plots should be curved.

The experimental techniques for using nmr spectroscopy to determine the rate constants for deuterium exchange at the two sites of 2-butanone have been previously described[5,133], and those used here are given in the experimental section. Briefly, 10% solutions of 2-butanone were made up in buffers of acetic acid/sodium acetate in D_2O, using constant buffer ratios of 1:10 and 1:20. Various acetate concentrations between 1 and 0.1 M were used, and the ionic strength was kept constant using sodium chloride. The samples were sealed into nmr tubes and were maintained at 54.8°, along with a tube containing 2-butanone in D_2O without catalyzing species. The samples were integrated every day over the peaks corresponding to the CH_2, CH_3 and β-CH_3 groups. Rate constants for the two positions were derived from graphs of the logarithm of the number of protons remaining at each position, against time - a typical rate plot is given in the experimental section (p 123), along with the pseudo-first-order D-exchange rates observed (p 124). A plot of these rate constants

FIGURE 1

Plot of observed pseudo-first-order rate constants against acetate concentration for H-D exchange of 2-butanone; buffer ratio 0.0936.

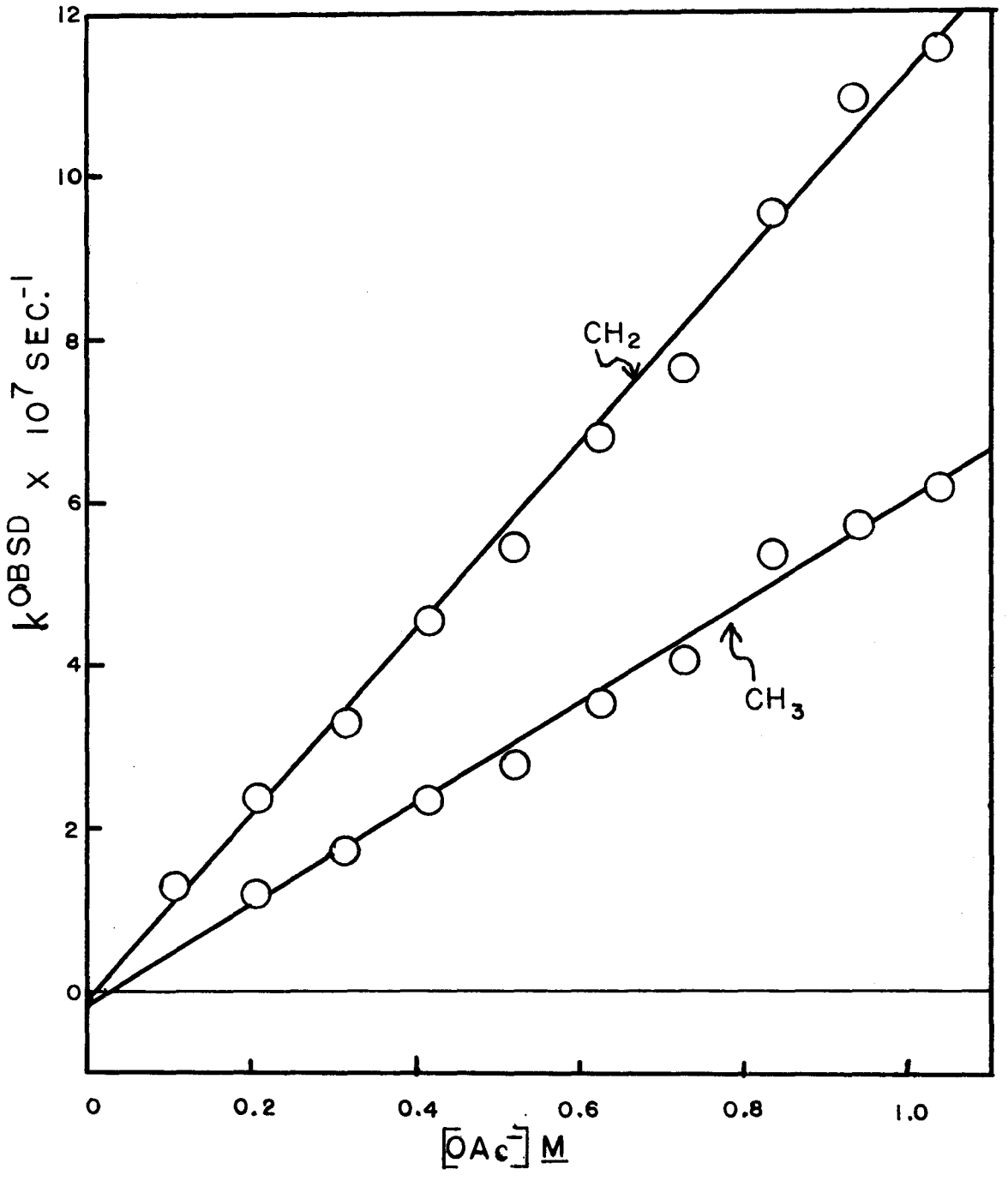


TABLE VI

Acetate Catalysis Constants, k_B, at 54.8°, for the H-D Exchange of 2-Butanone

	$k_B \times 10^7$ l.M^{-1}sec.$^{-1}$		Ratio
	CH_2[a]	CH_3[a]	k_{CH_2}/k_{CH_3}[a]
Buffer Ratio 0.0936	11.40 ± 0.31	6.19 ± 0.22	1.84 ± 0.12
Buffer Ratio 0.0469	11.54 ± 0.88	5.88 ± 0.23	1.96 ± 0.23
Average	11.47 ± 0.59	6.03 ± 0.22	1.90 ± 0.17
Previous Results[b]	11.8 ± 0.5	5.47 ± 0.70	2.16 ± 0.36

[a] Reactivity is defined on the per hydrogen basis; i.e. these rate constants are statistically corrected.

[b] At 59.2°; see ref 133.

against acetate concentration is given in figure 1, p 59, (see also figure 10, p 125) and the acetate catalysis constants derived from the slopes of these graphs (see eq 2) are given in Table VI, p 60.

The errors involved in kinetic measurements by nmr are not low; however, most of the rate constants quoted here are accurate to better than 5%, according to the standard deviations given with each rate constant, and it is felt that a high degree of confidence can be placed in the results.

The only important reaction under these conditions is acetate-catalyzed enolization. The termolecular term is shown to be of small importance, since the plots are straight lines, and k' must be very close to zero since the plots go through the origin. Catalysis by DOAc must also be small, since the results for the two buffer ratios are, within experimental error, the same, and the slopes of the graphs are taken to represent acetate catalysis alone.

The rate ratio for acetate-catalyzed exchange (k_{CH_2}/k_{CH_3} = 1.9 at 54.8°) is in qualitative agreement with that reported by Warkentin and Tee (2.1 at 59.2°)[133].

For comparison purposes, the ratio k_{CH_2}/k_{CH_3} for catalysis by $OD^{\ominus}$ was also measured at 54.8°; two measurements gave 0.88 ± 0.05 and 0.84 ± 0.08. These values are very different from the rate ratio for acetate catalysis

(1.9) measured at the same temperature.

In order to try to obtain values for the rate constants of the uncatalyzed reaction a sample of 2-butanone in D_2O without catalyzing species was also studied at 54.8°. After two months at this temperature no sign of exchange could be observed - the nmr peaks were still sharp and unsplit[132] and the integrals unchanged from their original values. Thus rate constants for the uncatalyzed reaction could not be determined. This contrasts with Rappe's findings[45,131], which were that he could observe sufficient exchange to calculate rate constants after "several months" at 30°. Along these lines it is worth noting that a 10% sample of 2-butanone in D_2O which has been maintained at room temperature (22-23°) still shows no sign of exchange after 2½ years.

This result is in accord with the previous estimate of Warkentin and Tee[133] that the uncatalyzed reaction would contribute 1% or less to the total reaction at 60°, with acetate concentrations in D_2O of 0.1 M or more. In support also is Hine's estimate[134] that the uncatalyzed deuteration of methoxyacetone would contribute a maximum value of 0.2% of the total to base-catalyzed reaction rates, under a wide variety of conditions. It is probable that a high rate of "uncatalyzed exchange", where observed, is really the result of catalysis by impurities. Specifically, it is thought that procedures such as washing nmr tubes

with soap, cleaning with chromic acid and rinsing with bicarbonate, or even using new, unused nmr tubes as supplied, would result in a sufficient base concentration on the walls of the nmr tube to give very slow exchange such as that observed by Rappe. Throughout this work all nmr tubes were cleaned with chromic acid and rinsed several times with distilled water, which ensures that the difficulties outlined above are avoided.

The conclusion is drawn that the uncatalyzed reaction is too slow to be studied in this way - it is worth noting that the values for the uncatalyzed reaction quoted by Rappe[45] ($k_{CH_2}^{obsd}$ = 2.1 x 10^{-8} $sec.^{-1}$, $k_{CH_3}^{obsd}$ = 8.9 x 10^{-9} $sec.^{-1}$, at 30°) are much higher than that reported by Bell and Lidwell[4] for acetone (7.8 x 10^{-11} $sec.^{-1}$, at 25°, statistically corrected).

Returning to the acetate-catalyzed reaction, this work firmly establishes that the relative catalytic constants (k_{CH_2}/k_{CH_3}) for D-exchange into 2-butanone depend on the nature of the catalyzing base. This dependence is to be expected from the analogy between enolization and bimolecular elimination[37]. In the latter reaction, product ratios depend on the base employed[146], although it is not certain whether this effect is caused by the strength of the base or its steric requirements[146]. Also, it is simply not reasonable to expect that different bases would give the same rate ratio for 2-butanone and different

rate ratios for methoxyacetone[134].

The factors affecting the direction of enolization would be expected to differ for different bases, since, according to Hammond's postulate[90], for the weaker base acetate, the transition state will be further along the reaction coordinate than it will be for the stronger base hydroxide. Hence whatever factors affect the direction of enolization should affect the two transition states to different extents due to the different stages of development of the enol double bond. It should be noted that nowhere in Rappe's publications does he give any reason why different bases should give the same rate ratio.

A paper based on the above work was published in 1968[142]. Recently Rappe has published a paper[143] which is basically in reply to this work; this will be considered here. In this paper he again finds the rate ratio for acetate catalysis to be lower than that given here, i.e. 1.2 at 54.8°.

Rappe has taken the results of Warkentin and Tee[133], and divided their observed rate constants in sodium acetate solutions into contributions from catalysis by $OAc^{\ominus}$ and $OD^{\ominus}$, at 59.2°. These data are shown in Table VII, p 65, with the addition of an extra column in which the rate ratios for $OD^{\ominus}$ catalysis, which can be derived from these numbers, are given. The average rate ratio for $OD^{\ominus}$ catalysis, from these numbers, is 0.84 ± 0.10 (leaving out the number

TABLE VII

Rate Data for the Acetate-Catalyzed D-Exchange of 2-Butanone at 59.2° [a]

$[OAc^{\ominus}]$ M (1)	$k^{obsd} \times 10^7$ sec.$^{-1}$ CH_2 (2)	CH_3 (3)	$k^{OAc^{\ominus}} \times 10^7$ sec.$^{-1}$ CH_2 (4)	CH_3 (5)	$k^{OD^{\ominus}} \times 10^7$ sec.$^{-1}$ CH_2 (6)	CH_3 (7)	$\frac{k^{OD^{\ominus}}_{CH_2}}{k^{OD^{\ominus}}_{CH_3}}$ (8)
0.104	3.60	3.19	1.23	0.57	2.37	2.62	0.905
0.136	4.34	3.88	1.60	0.74	2.74	3.14	0.873
0.260	6.56	5.75	3.07	1.42	3.49	4.33	0.806
0.468	10.8	8.68	5.5	2.56	5.3	6.12	0.866
0.490	11.0	5.94(!)	5.8	2.68	5.2	3.26(!)	(1.595)
0.630	14.6	12.0	7.4	3.4	7.2	8.6	0.837
0.930	19.1	13.4	11.0	5.1	8.1	8.3	0.976
0.946	19.7	13.9	11.2	5.2	8.5	8.7	0.977
1.310	21.3	14.3	15.5	7.2	5.8	7.1	0.817
1.310	20.6	14.8	15.5	7.2	5.1	7.6	0.671
1.500	26.7	21.5	17.7	8.2	9.0	13.3	0.677

[a] The numbers in columns 1, 2 and 3 are from J. Warkentin and O. S. Tee, J. Amer. Chem. Soc., 88, 5540 (1966). Columns 4, 5, 6 and 7 are from C. Rappe, Acta Chem. Scand., 23, 2305 (1969), who also provided the exclamation marks; calculated using the values extrapolated by Warkentin and Tee, $k^{OAc^{\ominus}}_{CH_2} = 11.8 \times 10^{-7}$ M^{-1}sec.$^{-1}$; $k^{OAc^{\ominus}}_{CH_3} = 5.47 \times 10^{-7}$ M^{-1}sec.$^{-1}$.

in brackets in column 8 of Table VII). Rappe feels that because this number is smaller than the 1.0 reported for catalysis by $OD^{\ominus}$ in the same paper of Warkentin and Tee, "it is apparent that the treatment of the experimental data according to Warkentin and Tee is not correct"[143]. However, the proper numbers with which to compare this value of 0.84 ± 0.10 are not the Warkentin and Tee figures, which were obtained at 0° and ~35°, and with varying ketone concentrations, or the results of Warkentin and Barnett[46] obtained in aqueous dioxane solutions, but the value of 0.84-0.88 obtained by this author at 54.8° (see above)[142]. In fact, that the agreement should be so good, considering the errors accumulated in the 0.84 ± 0.10 number, is quite surprising.

It is true that there is a 4.4° temperature difference between this study and that of Warkentin and Tee. This author recently tried to obtain activation parameters for the deuteroxide-catalyzed exchange at the two sites of 2-butanone. This work was discontinued as the errors involved were too high to give meaningful activation parameters, but a steady decrease in the rate ratio, as the temperature was raised, was noticed. Thus (for constant ketone concentrations) the ratio is about 1.2 at 0°, about 1.0 at 35°, about 0.85 at 60° and so on, indicating that the activation energy for exchange at the methyl group exceeds that for exchange at the methylene group. This

study indicated that the difference in the rate ratio caused by a 4.4° temperature difference was insignificant (i.e. less than the probable error), so it is quite reasonable to compare rate ratios at 59.2° with those at 54.8°. The fact that actual rate constants were the same (see Table VI) could probably be attributed to the approximation involved in using the extrapolation method, as well as the difference between individual operators (a factor of only 1.6 is involved, as determined from the activation data for acetone, to be discussed below).

Rappe's use of fully deuterated acetic acid and acetate ion[143] is quite unnecessary; this author observed no interference between the α-CH_3 peak of 2-butanone and the acetate CH_3 peak in performing these measurements, and the agreement between Rappe's number[143] and that quoted here for the rate of CH_3-exchange is proof that there is none. The disagreement between the rate ratio given here (1.9) and Rappe's (1.2)[143], in fact comes from a difference in the observed rate constants for CH_2-exchange. The source of this disagreement is unknown. In these laboratories it was recently found by Thorpe[128] that the rate ratio for the exchange of 2-butanone in a 1:1 acetic acid/sodium acetate buffer (at a different ketone concentration from that used here) was 1.7. The same number was obtained in the duplicate determination using a different nmr spectrometer (Varian T-60 vs. Varian A-60), which tends to

indicate that there are no artifacts due to instrumentation on our part.

The Reactions Involved in the Bromination of Acetone

It was mentioned in the historical introduction that there are several modern studies of ketone bromination[2,3] which indicate that some[2] or all[3] of the reaction may go by non-enolic mechanisms. The major evidence for an enolic mechanism is the fact that halogen is not involved in the rate-determining step in ketone halogenations. If ketone is present in a large excess, this means that halogen will be consumed in a zero-order fashion. It was decided to study the kinetics of ketone bromination, using the 1:10 acetic acid/sodium acetate buffer described above, which gives catalysis by acetate ion only. The reaction in this buffer should be that designated "Hal B I" by Rappe, since the buffer is in the pH region where this is supposed to apply (pH 5-7)[3]. It was thought that demonstration of zero-order bromination kinetics for this reaction should provide strong evidence against Rappe's non-enolic mechanism[3], since it is very difficult to conceive of a method whereby a brominating agent can be consumed zero-order by reaction with an unenolized ketone. The method chosen for following the kinetics was to

monitor the changing redox potential of the system at a platinum electrode, a method developed mainly by Bell and Robinson[147].

The brominating system was made up by dissolving bromine in potassium bromide solution, adding it to the buffer and allowing it to equilibrate until a steady potential was recorded, thus allowing any possible halogenating agents such as Rappe postulates[3] (see p 48) to be formed. A consideration of the equilibria involved[69] indicated that the bromine should be present in this system mainly as Br_2 or $Br_3^{\ominus}$, but all the possible brominating agents considered, if formed, (see p 29) will be in equilibrium with these (as will Rappe's "halogenating agent", p 48), and thus ketone brominations can be followed by the changing redox potential regardless of the nature of the brominating species. Thus, in the reaction schemes to be considered below, "Br_2" refers to any brominating species.

If we consider the usual haloform reaction mechanism (see p 25), it is possible to derive an equation connecting bromine concentration and time, as shown below:

$$\underset{\text{A}}{CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3} + OAc^{\ominus} \xrightarrow{k_1} CH_3\text{-}\overset{\overset{O(H)}{|}}{C}{=}CH_2 \xrightarrow[3Br_2]{\text{all fast}} CH_3CO_2^{\ominus} + CHBr_3$$

$$-\frac{d[Br_2]}{dt} = 3k_1[A] \qquad (t = \text{time})$$

$$\therefore \quad -\int_{[Br_2]_0}^{[Br_2]_t} d[Br_2] = 3k_1\int_0^t [A]\,dt$$

If we keep [A] constant, in a large excess relative to bromine, we can obtain a zero-order expression:

$$[Br_2]_0 - [Br_2]_t = 3k_1[A]t$$

$$\text{or} \qquad [Br_2]_t/[Br_2]_0 = f = 1 - 3k_1\frac{[A]}{[Br_2]_0}t \qquad (3)$$

Thus if simple zero-order kinetics is followed, a plot of the relative bromine concentration f (which varies between 1 and 0) against time should be a straight line of intercept 1 and slope $-3k_1[A]/[Br_2]_0$.

The kinetic scheme becomes more complex if a first-order bromine-consuming term is included in the kinetic scheme, e.g.:

$$CH_3COCH_3 + Br_2 \xrightarrow{?} CH_3COCH_2Br + HBr$$

The net result, without going into the mathematics, is that graphs of f against t should be curved, the reaction slowing down as the bromine concentration decreases ("tailing"). Qualitatively, the graph would resemble a superposition of a zero-order straight line and a first-order concentration/time curve. If the reaction is a rate-determining attack of a brominating agent on unenolized ketone, a normal first-order concentration/time curve

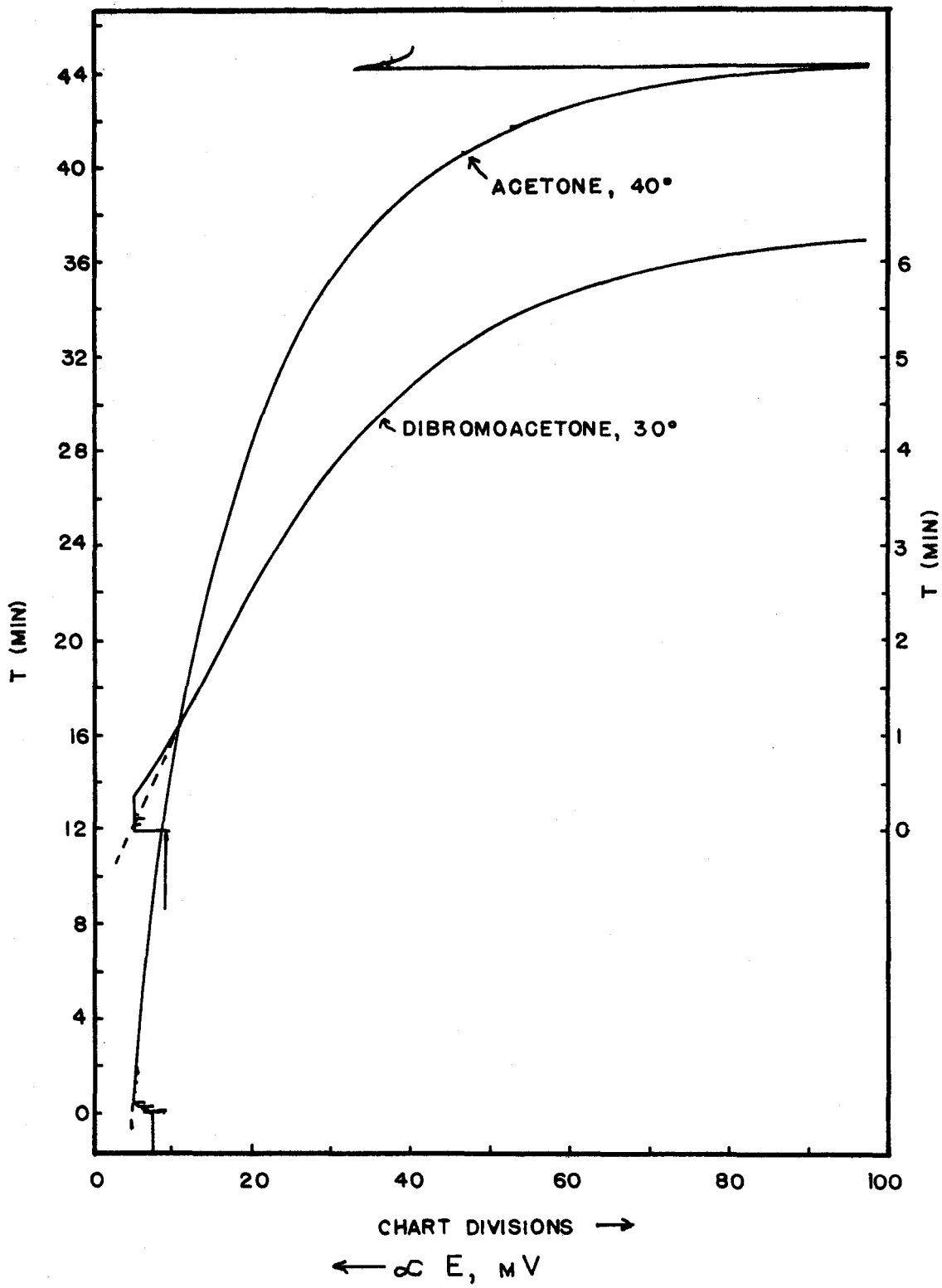
would be the result. The same result should be obtained with any other rate-determining step involving bromine.

There are two points to be considered before the above approach is used. One is that this analysis only applies if the ketone is in a large excess, so that its concentration is essentially time-invariant. For instance, if [A] decreases appreciably during the reaction, the rate of bromine removal will also decrease and the f *vs.* t graph will "tail". This was the behaviour observed in most of the cases to be described below where relatively insoluble bromoketones were studied; but soluble ketones (acetone, diethyl ketone, pinacolone) follow this analysis quite well. The second point is that bromination of the enol(ate) (assuming an enolization mechanism) must not be allowed to become rate-determining. In practice this means using initial bromine concentrations of 10^{-4} M or greater; this point is covered in detail in the experimental section (p 130). In the event it was possible to follow the reaction down to very low bromine concentrations and the point where enol bromination becomes rate-determining could be observed directly; when this point was reached observations were discontinued.

The experimental method used was to study the potential of a system containing buffer, bromine in potassium bromide, and ketone, at a platinum electrode, against a glass reference electrode[147]. The potential was recorded

FIGURE 2

Sample chart traces - acetone and dibromoacetone. See text.



on a pH-meter (reading millivolts), the reading of which was plotted continuously against time on a chart recorder. Typical chart traces are given in figure 2, p 72. Full experimental details are given in the experimental section.

The reagents and concentrations used in this study were:

NaOAc	1 M
HOAc	0.1 M
KBr	0.1 M
Br_2	$\sim 10^{-3}$–10^{-4} M as needed
acetone	~0.3 M (2% v/v)
other ketones	$\sim 10^{-2}$–10^{-4} M depending on solubility.

Total organic material (ketone + dioxane where needed for reasons of solubility) was 2% v/v.

The potentiometric method uses the Nernst equation as its basis of operation[145], which for this system is:

$$E = E^{o} - \frac{RT}{2F} \ln \frac{[Br^{\ominus}]^2}{[Br_2]}$$

Since $[Br^{\ominus}]$ was kept constant at 0.1 M throughout, this can be rewritten:

$$E = E' + \frac{RT}{2F} \ln [Br_2]$$

or $$[Br_2] = \exp\left(\frac{E - E'}{RT/2F}\right) \qquad (4)$$

From eq 4 it can be seen that if $[Br_2]$ decreases exponentially (as it will for a first order process) the potential should

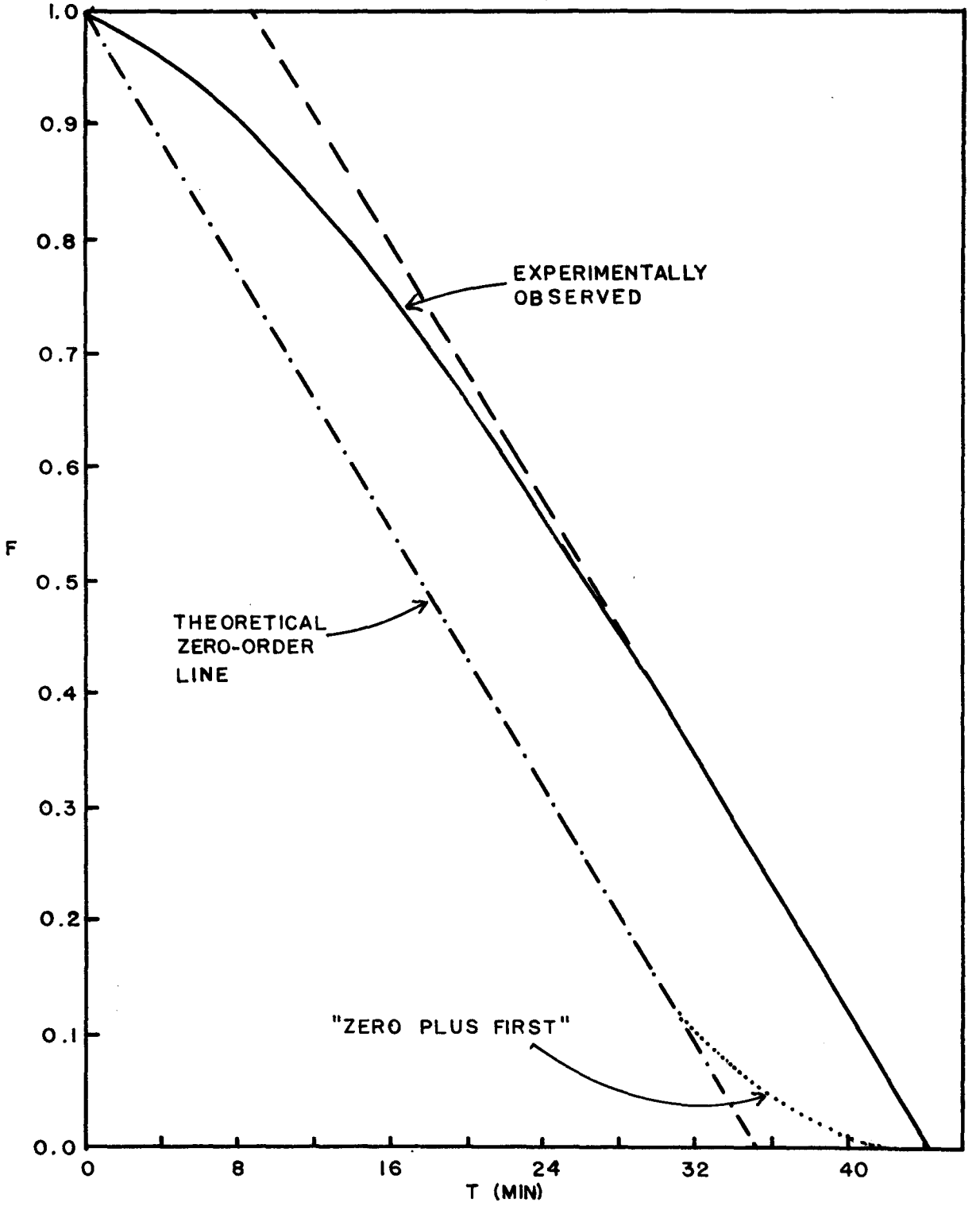
decrease linearly, and vice versa. Thus for a first-order bromine-consuming process the potential vs. time graphs drawn by the chart recorder should be straight lines. It is immediately apparent from a glance at figure 2, therefore, that we are not dealing with a simple first-order process in this reaction.

The method used for obtaining bromine concentrations from chart traces such as those shown in figure 2, using equations such as eq 4, is detailed in the experimental section (p 139). It was found to be simpler to derive the relative bromine concentration f (i.e. $[Br_2]_t/[Br_2]_0$), and the initial bromine concentration ($[Br_2]_0$) separately, and graphs of bromine concentration vs. time are plotted in terms of f. A typical graph of f vs. t obtained for the acetate-catalyzed bromination of acetone is shown in figure 3 (p 75).

Several points become apparent when figure 3 is examined: (i) the curve is not the expected zero-order straight line, but it does approach it; (ii) no sign of "tailing", as the curve approaches zero bromine concentration, is observed; (iii) the overall shape is sigmoid, i.e. the reaction accelerates as the bromine concentration diminishes. In other words no sign of first-order reaction is observable, but it is apparent that the approximation of treating brominations of acetone subsequent to the first one as all "fast" is inadequate. Graphs of this shape were

FIGURE 3

Concentration/time graph for the bromination of acetone at 40°.



obtained by Bell and Yates[50] during the chlorination of acetone. They found that the rates of chlorination of chloroacetone and dichloroacetone had to be included in the overall rate expression, and it is apparent that a similar treatment is necessary here.

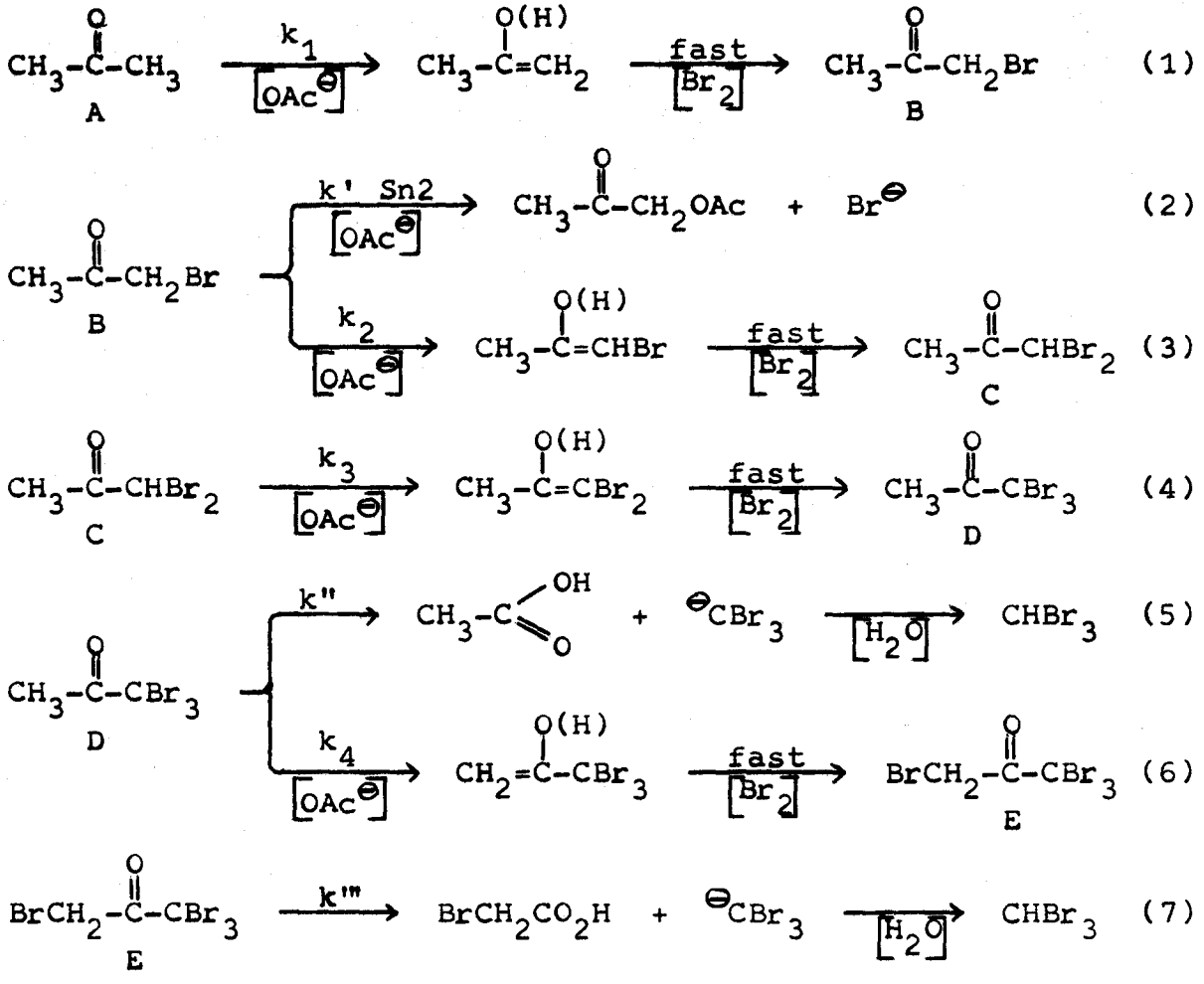
A modified scheme for the reactions involved when acetone is brominated (i.e. modified from Chart 2) is given as Chart 3, p 77. Before considering the rate expressions derivable from this scheme a few points about individual reactions in Chart 3 are worth noting.

Reactions 1, 3, 4 and 5 in Chart 3 are essentially the usual reactions considered in the haloform reaction. Reaction 2 represents the nucleophilic displacement of bromide by acetate in bromoacetone. Such reactions can be very fast for chloroacetone[119], and they are currently under investigation in our laboratories, as well as by other groups[148]. This reaction has been included in this scheme because it has been shown that acetoxyketones are important products in the acetate-catalyzed bromination of 2-butanone[128]; subsequently it has been found that reaction 2 in Chart 3 accounts for about 10% of the bromoacetone which reacts[149], so its inclusion in this scheme is necessary.

Reaction 6 in Chart 3 represents the bromination of 1,1,1-tribromoacetone. Now solutions of the bromoketones used in this work were made up by dissolving them

CHART 3

The Reactions Occurring During the Acetate-Catalyzed Bromination of Acetone



Notes: (i) A full discussion is given in the text.

(ii) The rate expressions derived in Appendix II involve reactions 1, 2, 3, 4 and 5 only.

(iii) Only those reactions considered most important are listed; other reactions may be possible.

in dioxane and diluting with water (eventually to 2% organic content). 1,1,1-Tribromoacetone was shown to survive unchanged under these conditions for at least 24 hours (by extracting into CCl_4 and examining the nmr spectrum), although it rapidly condenses in neat dioxane. Complete hydrolysis to bromoform occurs if the compound is stirred overnight in an acetate solution, but this reaction (5 in Chart 3) is slow enough to allow bromination to occur under the conditions used here, as was shown by the recovery of some unchanged starting material with 1,1,1,3-tetrabromoacetone and bromoform at the end of a normal potentiometric bromination run. It is not known whether or not this compound exists as $CH_3C(OH)_2CBr_3$ in solution, but it is thought unlikely because (i) it can be recovered as CH_3COCBr_3 by extraction into CCl_4, and (ii) it brominates at about the same rate as does bromoacetone (see below), which $CH_3C(OH)_2CBr_3$ would not be expected to do if its formation was essentially irreversible.

From the preceding evidence, it is quite likely that the bromination of tribromoacetone accounts for some of the bromine used in the bromination of acetone, and is thus included in Chart 3. It is possible that other bromination reactions of the compounds given in Chart 3 may account for some bromine, but only for a small fraction. Other studies[149] indicate that 1- and 3-acetoxy-2-butanone do not brominate rapidly under these conditions, so

acetoxyacetone is assumed to brominate slowly, if at all, in the presence of the reactive bromoketones.

Returning now to the rate expressions derivable from Chart 3; using reactions 1, 2, 3, 4 and 5 and with the notation in Chart 3, the following expression can be derived for the acetate-catalyzed bromination of acetone:

$$f = 1 - k_1A(1 + \frac{2k_2}{k_2'})t + \frac{k_1k_2(2k_3 - k_2')}{k_2'^2(k_3 - k_2')}.A(1 - e^{-k_2't}) - \frac{k_1k_2}{k_3(k_3 - k_2')}.A(1 - e^{-k_3t}) \quad (5)$$

where $k_2' = k_2 + k'$, $A = [A]/[Br_2]_0$ and $f = [Br_2]_t/[Br_2]_0$; a full derivation is given in Appendix II.

Reaction 6 in Chart 3 (k_4) is not included in this equation for two reasons: (i) its inclusion would make an already complex analysis even more so, without changing any of the conclusions reached, and (ii) it had not been discovered at the time this analysis was carried out. The net result of its inclusion would be an additional positive exponential term in $(1 - e^{-k_4t})$ in eq 5, and the term in t would have an additional $k_4/(k_4 + k'')$, i.e.:

$$f = 1 - k_1A(1 + \frac{2k_2}{k_2 + k'} + \frac{k_4}{k_4 + k''})t + ... \quad (6)$$

Eq 6, which is eq 5, with the addition of reaction 6, and the exponential terms left out, represents the case

when t is large and $(1 - e^{-kt})$ approaches zero, i.e. this is the equation to the straight line which the curve in figure 3 approaches. Thus the number of bromine atoms consumed per acetone molecule is not 3 as is assumed in the simple eq 3 (p 70), but is determined by the relative magnitudes of k_2, k', k_4 and k'' in eq 6. As it happens, the number turns out to be almost exactly 3, but this is the result of a fortuitous cancellation of terms resulting from the removal of bromoacetone by acetolysis, and the bromination of tribromoacetone.

Eq 5 is rather complex in form and cannot be used as it stands to determine the rate constant for acetone enolization, k_1. However, if eq 5 is differentiated with respect to time, and t is then set equal to zero, the initial slope of the curve in figure 3 is obtained:

$$\text{initial slope} = -k_1 A \ .$$

Qualitatively, this is the expected result, since acetone is the only compound present to react at zero time. Thus the curve in figure 3 starts out with this slope, and then accelerates to a line whose slope is given by eq 6.

A computer program was devised which enabled rate constants to be obtained from the initial slopes of graphs of the relative bromine concentration, f, against time; the entire experimental curve was fitted to a polynomial expression, of which the first coefficient corresponds to

the initial slope. Full details are given in the experimental section, and in Appendix I. For all the ketones studied the initial slope involves the first enolization rate constant only.

Reactions 2, 3, 4 and 5 in Chart 3 can be used to derive rate expressions for the bromination of bromoacetone (eq 7) and dibromoacetone (eq 8):

$$f = 1 - k_2B.\frac{2k_3 - k_2'}{k_2'(k_3 - k_2')}(1 - e^{-k_2't}) + k_2B.\frac{1}{k_3 - k_2'}(1 - e^{-k_3t}) \qquad (7)$$

$$f = 1 - C(1 - e^{-k_3t}) \qquad (8)$$

where $B = [B]_0/[Br_2]_0$ and $C = [C]_0/[Br_2]_0$.

It was not possible to have these ketones present in large excess over bromine when they were brominated (because of solubility requirements), and the above expressions (eqs 7 and 8) take this into account. Concentration/time graphs for these ketones will, therefore, be curved.

In order to check the above analysis, bromoacetone, 1,1-dibromoacetone and 1,1,1-tribromoacetone were prepared and brominated. It was essential for these compounds to be quite free of contamination by other bromoketones in order to obtain accurate rate constants, since quite small traces of higher bromoketones will remove

bromine rapidly and invalidate the use of the initial slope as a measure of the rate constant. All bromoketones were, therefore, purified by repeated preparative glpc.

Curves obtained in the bromination of bromoacetone and dibromoacetone are reproduced as figures 4 and 5, pps 83 and 84, in which the dashed lines illustrate the direction of curvature. Rate constants for the enolization of acetone, bromoacetone, 1,1-dibromoacetone and tribromoacetone are given in Table VIII, p 85. The values obtained at 30° were substituted into eqs 5, 7 and 8; the resulting theoretical curves are shown in figure 6, p 86, and they compare very well with the curves in figures 3, 4 and 5. In figure 5, the bromination of dibromoacetone, experimental points are compared with the theoretical curve; the agreement is excellent. This was the most convenient case for the comparison of theory with experiment as the rate expression is simple (eq 8) and subsequent bromination is slower for this ketone and thus does not cause complications.

A brief discussion of the estimated accuracy of all the data derived from potentiometric rate measurements is given next; this applies to the next section of the discussion also.

Insofar as the computer-calculated rate constants are as good as the input data provided, the estimated accuracy of the rate constants, and data derived from them, are based on their reproducibility, from repeat determinations.

FIGURE 4

Graph of f vs. t for the bromination of bromoacetone at 40°.

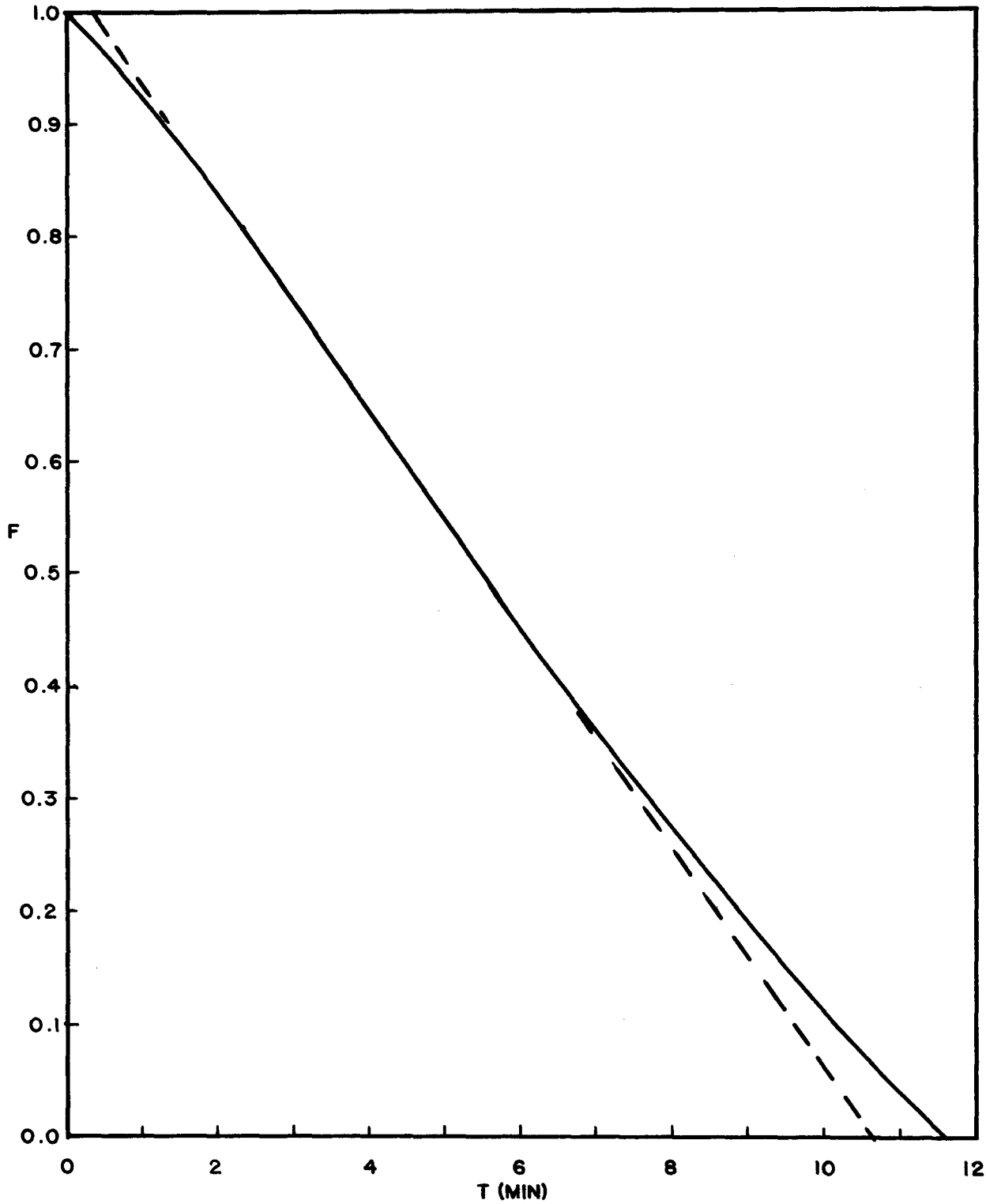


FIGURE 5

Graph of f vs. t for the bromination of dibromoacetone at 30°.

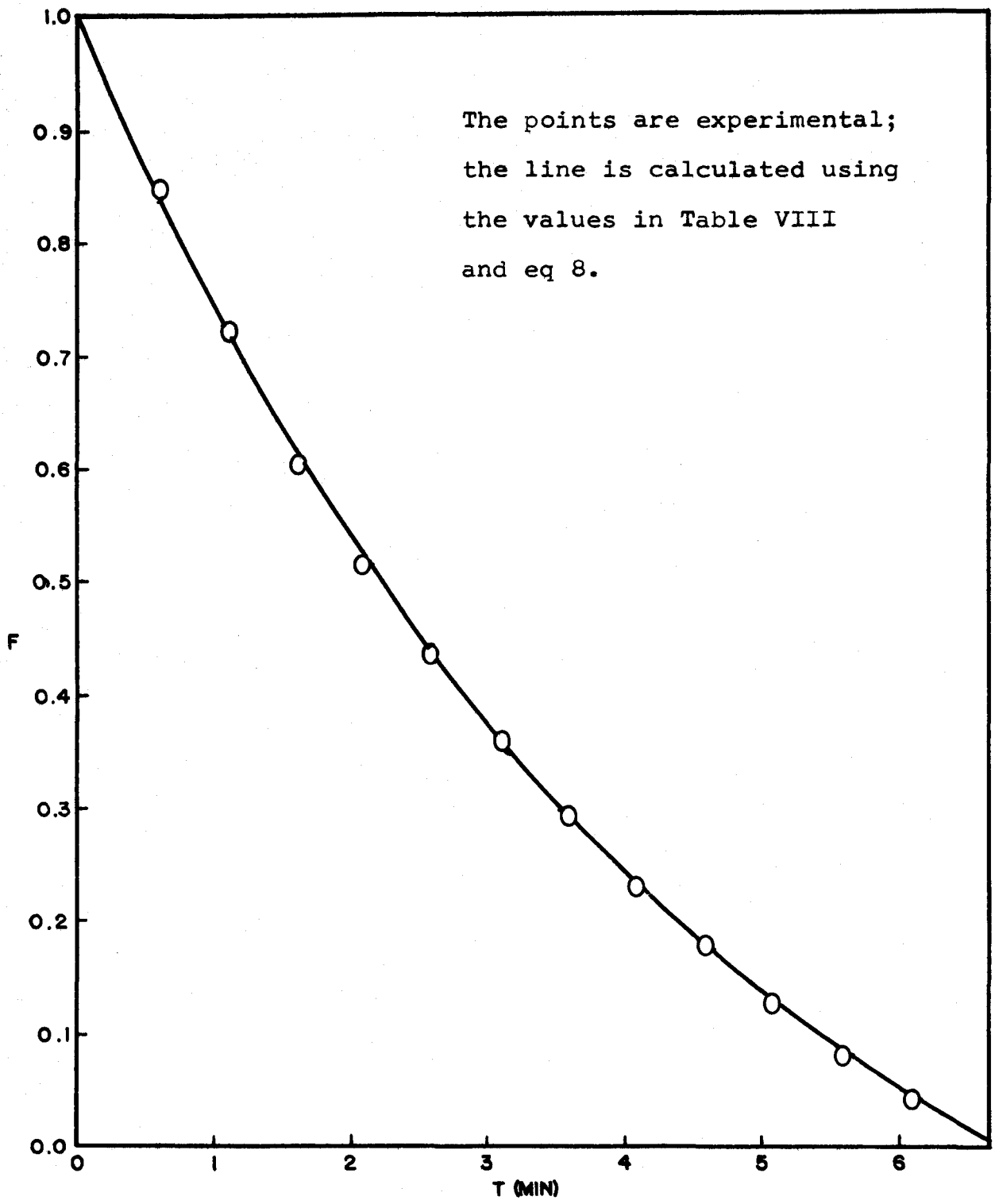


TABLE VIII

Enolization Rate Constants Derived from the Acetate-Catalyzed Bromination of Acetone and some Bromoacetones

Ketone	T, °C	k_1, sec.$^{-1}$ [a]	k_1^H, M^{-1}sec.$^{-1}$ [b,c]
CH_3COCH_3	20	1.18×10^{-7}	1.97×10^{-8}
"	25	2.37×10^{-7}	3.96×10^{-8}
"	30	4.43×10^{-7}	7.38×10^{-8}
"	35	8.03×10^{-7}	1.34×10^{-7}
"	40	1.43×10^{-6}	2.39×10^{-7}
CH_3COCH_2Br	20	1.81×10^{-4}	9.05×10^{-5}
"	30	6.54×10^{-4}	3.27×10^{-4}
"	40	1.66×10^{-3}	8.32×10^{-4}
$CH_3COCHBr_2$	20	1.68×10^{-3}	1.68×10^{-3}
"	30	5.05×10^{-3}	5.05×10^{-3}
"	40	1.49×10^{-2}	1.49×10^{-2}
CH_3COCBr_3	30	5.71×10^{-4}	1.90×10^{-4}

[a] Pseudo-first-order rate constants, derived from the initial slope of relative bromine concentration vs. time graphs.

[b] Statistically corrected second-order rate constants.

[c] Probably accurate to better than 5%; see text.

THEORETICAL CONCENTRATION/TIME GRAPHS

DERIVED USING EQUATIONS 5, 7 AND 8, AND THE RATE CONSTANTS AT 30° IN TABLE VIII.

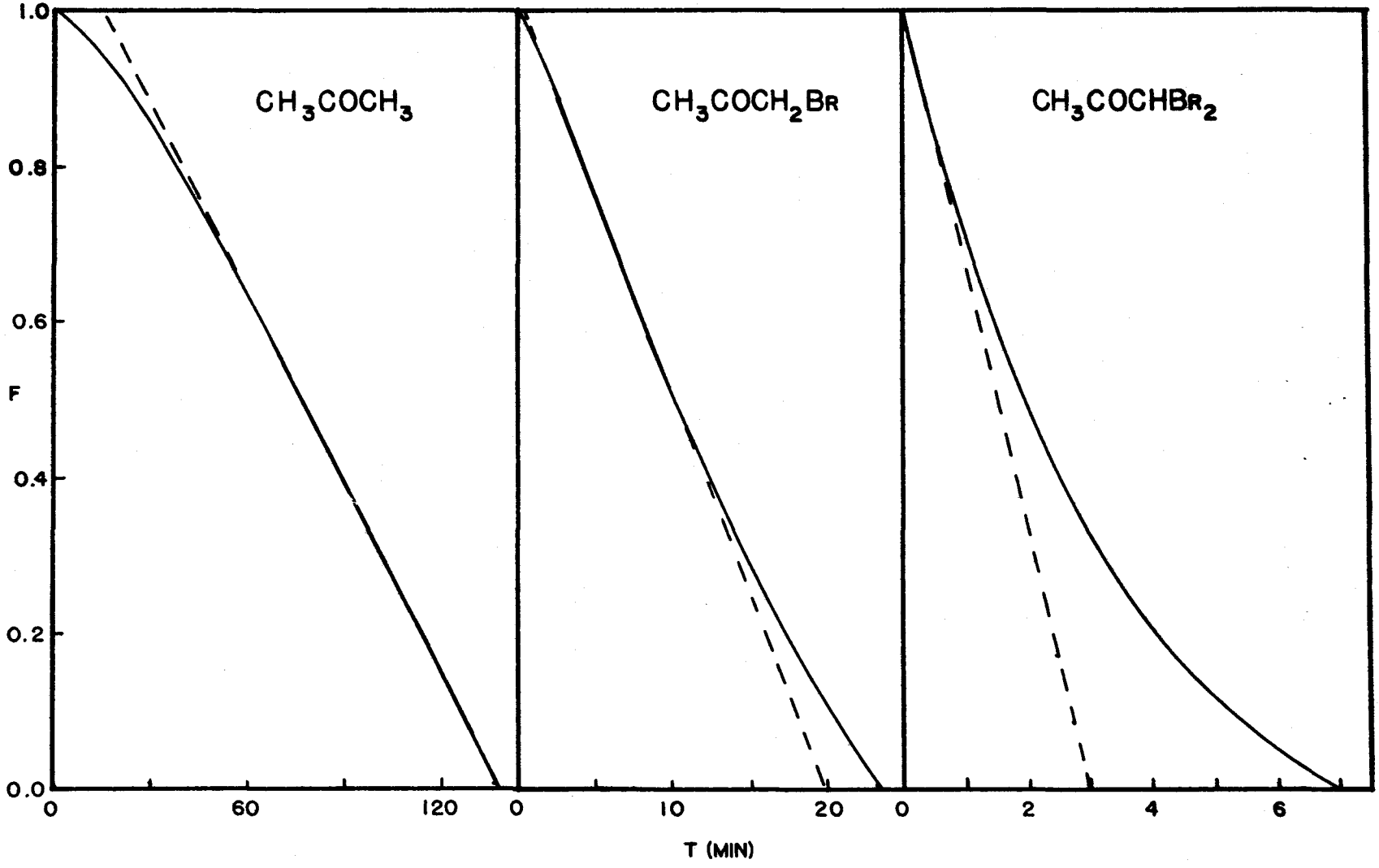


FIGURE 6

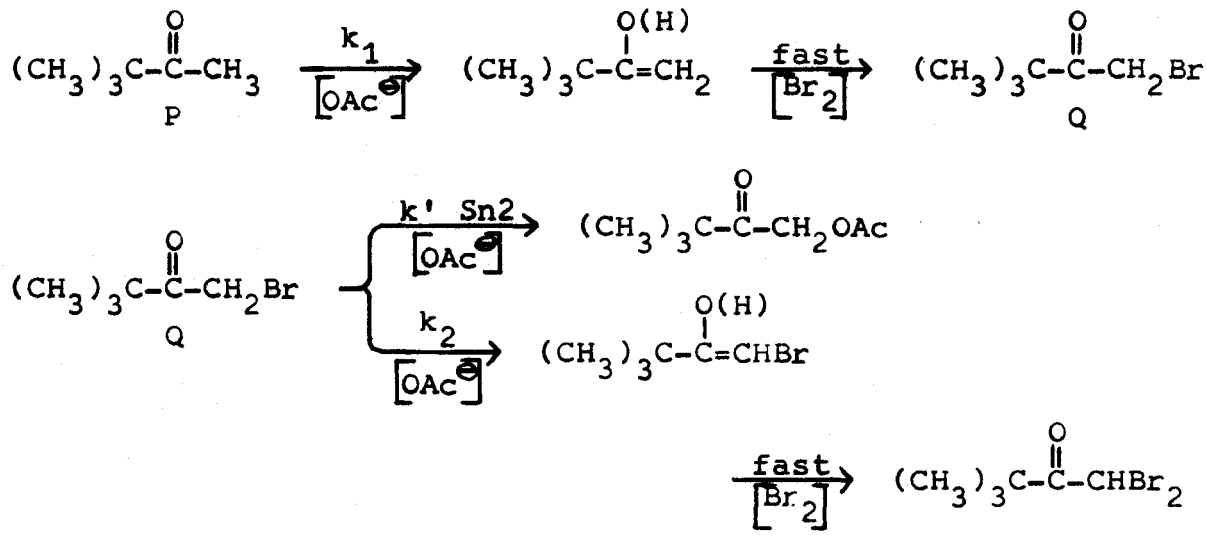
From the figures for each run provided in the experimental section it is possible to estimate a "mean accuracy" of about 5%, for rate constants derived from bromination data, using the "initial slope" method described above. (The accuracy of derived data (as the standard deviation) is given with the data - see the next section.) Where reliable literature values are available, for instance, for acetone at 25°,[115] the results quoted here are in agreement with them; see, however, the discussion of ketone iodination studies beginning on p 28 above.

If the computer analysis is used to try to derive more than one rate constant from a set of data (e.g. k_2 and k_3 as well as k_1 in eq 5), the values obtained tend to vary widely, by up to 100%, as the computer can vary these values within quite wide ranges to fit the observed data. Therefore, only the rate constant for the first enolization of each ketone is quoted here; these are quite reliable. Also, of course, the kinetic scheme must be quite correct in order to give meaningful values for these "secondary" rate constants; since the bromination of tribromoacetone was not included in the derivation of eq 5 for acetone, these "secondary" numbers will not be reliable in this case anyway (the first enolization rate constant is, of course, unaffected by this omission - see above). In simple cases, however, such as pinacolone, discussed next, meaningful values can be obtained.

Pinacolone

A discussion of the bromination of this ketone should help to clarify the rather complex situation described above, since this reaction is quite simple - simple enough, in fact, to be dealt with in a way which does not need computer analysis.

Bromopinacolone, $(CH_3)_3CCOCH_2Br$, gives the dibromo derivative $(CH_3)_3CCOCHBr_2$ on bromination using the acetate-catalyzed conditions described above. This compound then precipitates from solution and undergoes no further reaction. Therefore, the kinetic scheme for the bromination of pinacolone is:



$$\frac{d[Q]}{dt} = k_1[P] - k_2'[Q] \qquad (9)$$

where $k_2' = k_2 + k'$. The pinacolone concentration, [P], is essentially time-invariant, since pinacolone is present

in a large excess. Eq 9, therefore, is a standard expression, which can easily be integrated to give:

$$[Q]_t = \frac{k_1}{k_2'}[P](1 - e^{-k_2't})$$

Now the measured variable is the bromine concentration:

$$-\frac{d[Br_2]}{dt} = k_1[P] + k_2[Q]$$ (assuming all enol(ates) brominate immediately on formation)

$$= k_1[P] + \frac{k_1k_2}{k_2'}[P](1 - e^{-k_2't})$$

$$\therefore \quad -\int_{[Br_2]_0}^{[Br_2]_t} d[Br_2] = k_1[P]\int_0^t dt + \frac{k_1k_2}{k_2'}[P]\int_0^t dt - \frac{k_1k_2}{k_2'}[P]\int_0^t e^{-k_2't}dt$$

$$\therefore \quad [Br_2]_0 - [Br_2]_t = k_1[P]t + \frac{k_1k_2}{k_2'}[P]t - \frac{k_1k_2}{k_2'^2}[P](1 - e^{-k_2't})$$

$$\therefore \quad f = 1 - k_1Pt - \frac{k_1k_2}{k_2'}.Pt + \frac{k_1k_2}{k_2'^2}.P(1 - e^{-k_2't}) \qquad (10)$$

on dividing by $[Br_2]_0$ and writing $P = [P]/[Br_2]_0$.

Now if we assume k' to be negligible, which is not unreasonable in view of the steric crowding present in pinacolone, and if we make t large, in order to remove the exponential ($e^{-10} \propto 0$), eq 10 reduces to eq 11:

$$f = 1 - 2k_1Pt + \frac{k_1}{k_2}.P \qquad (11)$$

So it can be seen that at a late stage of the reaction the graph of f against t will be linear, with slope $-2k_1P$

and intercept $1 + k_1/k_2.P$. Thus it can be seen that both k_1 and k_2 can be obtained from the same graph.

The experimental graph of f against t for the bromination of pinacolone strongly resembles the graph for acetone given as figure 3, p 75, to which the reader is referred. From the linear portion a slope and an intercept can be obtained, and the use of eq 11 gives:

$$k_1 = 8.02 \times 10^{-8} \text{ sec.}^{-1} \; ; \; k_2 = 3.66 \times 10^{-5} \text{ sec.}^{-1}$$

The accurate values obtained from the computer analysis of the bromination of pinacolone, and the bromination of bromopinacolone, are:

$$k_1 = 6.34 \times 10^{-8} \text{ sec.}^{-1} \; ; \; k_2 = 5.79 \times 10^{-5} \text{ sec.}^{-1}$$

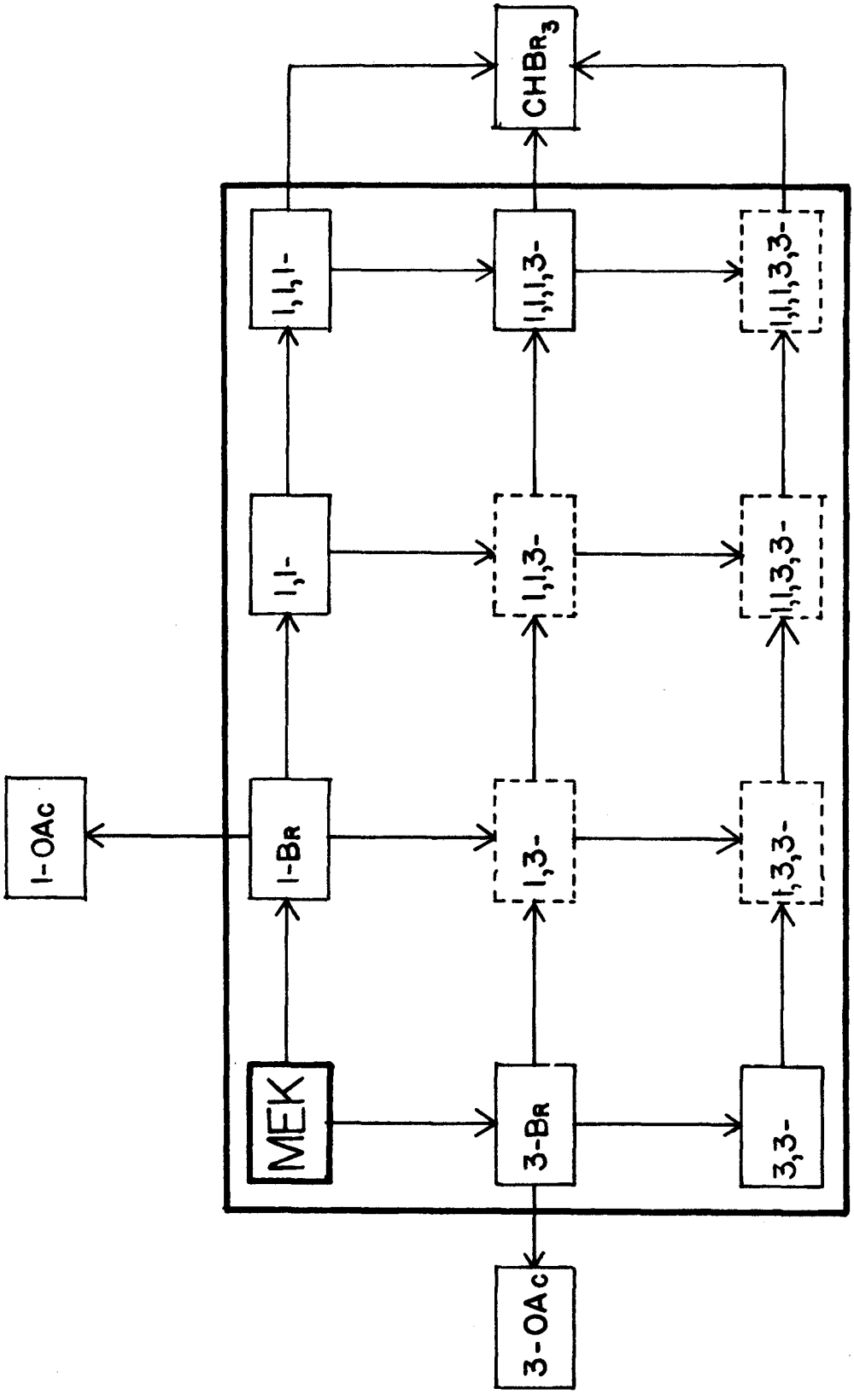
Considering the approximations and extrapolations which are involved in obtaining the simplified eq 11, the agreement between the two sets of figures is excellent.

2-Butanone

In contrast to the above simple situation, the reaction scheme for the bromination of 2-butanone is prohibitively complex, and no meaningful information can be obtained from f vs. t graphs for this ketone. An indication of the complexity can be obtained from Chart 4[128a], p 91, which is a schematic of the possible reaction products.

CHART 4

THE BROMINATION OF 2-BUTANONE



In Chart 4, the starting ketone, 2-butanone, is at the upper left, the box labelled MEK (methyl ethyl ketone). Reactions are indicated by arrows; those inside the large box all consume bromine, and reactions leading out of this box do not. The numbers indicate the positions of bromine atoms in the products which the smaller boxes represent; those in full outline have, in fact, been observed experimentally in this reaction[71,128]; those in dashed outline have not.

It may be noted here that Dubois and Panaye[152] have recently applied topological analysis to schemes of this type, which they obtain from a consideration of the possible base-catalyzed polyalkylations of aliphatic ketones.

Summary

It is evident from the above discussion that the acetate-catalyzed bromination of acetone goes by rate-determining enolization, followed by subsequent fast reaction with the enol. Despite the need to include reactions not usually considered in reaction schemes for ketone bromination in the overall kinetic analysis, all of the experimental results are explained using this assumption. No first-order bromine-consuming reactions were observed at any time - in particular graphs such as figure 3 always cut the time axis cleanly, with no sign of

"tailing". All the bromine consumption, or redox potential decrease, has been shown to be zero-order.

It remains to decide whether or not the reaction mechanism proposed by Rappe[3] could account for the observed results. This is "Hal B I", which occurs at pH 5-7; the pH of the bromination reaction mixture used here is 5.7. The mechanism is given on p 48, and is reproduced below for convenience:

$$X_2 + H_2O + B^{\ominus} \rightleftharpoons HXO + HB + X^{\ominus}$$

$$HXO + X^{\ominus} \longrightarrow \text{halogenating agent}$$

$$\text{halogenating agent} + \text{unenolized ketone} \longrightarrow \text{haloketone}$$

The first reaction cannot be rate-determining; if it were, the observed redox potential would be caused by X_2 in solution, and it would decrease in a first-order fashion. Similarly, if the second reaction were rate-determining, the potential would be caused by a mixture of X_2 and HOX, and would also show a first-order decrease. The same applies if the third reaction is rate-determining; the first two reactions would then be "fast", and the redox potential, whether caused by X_2, HOX or the halogenating agent, or by all three, must again show a first-order decrease.

It is concluded, therefore, that the non-enolic mechanism proposed by Rappe[3], for the weak-base-catalyzed

bromination of ketones in the pH-region 5-7, is wrong.

It now remains to determine whether the transition state for weak-base-catalyzed enolization resembles enol or enolate; studies bearing on this problem will be presented in the next section.

The Enolization of some Ketones and Bromoketones

Activation Parameters for the Bromoacetones

It will have been observed that acetate-catalyzed enolization rate constants for acetone, bromoacetone and 1,1-dibromoacetone were obtained at various temperatures in the previous section. It was possible to derive activation parameters for these ketones, using the standard equation derivable from transition-state theory[153]:

$$\ln \frac{k}{T} = \ln \frac{\varkappa k}{h} - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R}$$

The data from Table VIII, p 85, were used to obtain values of $\ln(k/T)$; these are plotted against $1/T$ in figure 7, p 95. The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, obtained from the slopes and intercepts of the graphs, are given in Table IX, p 96.

It is apparent from figure 7, and Table IX, that the rate differences between these compounds are caused

FIGURE 7

Graph of ln(k/T) vs. 1/T for acetone, bromoacetone and 1,1-dibromoacetone, to give activation parameters.

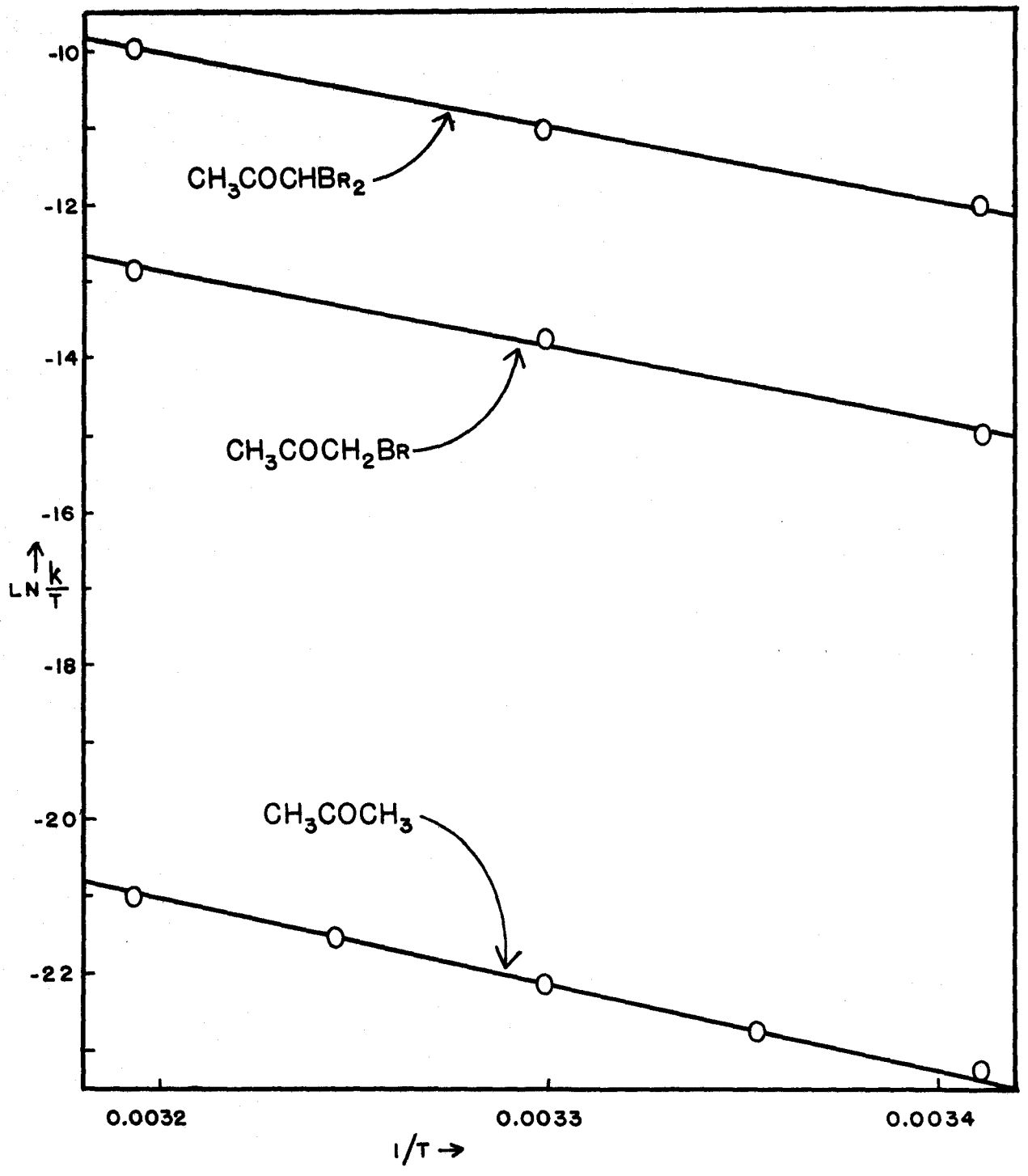


TABLE IX

Activation Parameters for the Enolization of Acetone, Monobromoacetone and 1,1-Dibromoacetone

Ketone	$\Delta H^{\ddagger}$ [a]	$\Delta S^{\ddagger}$ [b]
CH_3COCH_3	22.04 ± 0.28	- 18.54 ± 0.62
CH_3COCH_2Br	19.62 ± 0.72	- 10.00 ± 2.04
$CH_3COCHBr_2$	19.30 ± 0.37	- 5.39 ± 0.99

[a] In K.cals.mole^{-1}; from the slopes of the graphs in figure 7.

[b] In e.u. (cals.deg.$^{-1}$); from the intercepts of the graphs in figure 7 as given by computer calculation. (The numbers in Table VIII were used in deriving figure 7.)

by changes in the entropy term rather than in the activation enthalpies - a phenomenon similar to that noticed by Smith[154], who observed that the rate differences in the acid-catalyzed iodination of acetone caused by changing the acid were due almost entirely to the changing entropy of activation.

The difference in free energy of activation between acetone and bromoacetone has a contribution of 2.42 K.cals./mole from $\Delta H^{\ddagger}$, and 2.56 K.cals./mole from $T\Delta S^{\ddagger}$ (at 300°K). The difference between bromoacetone and dibromoacetone is 0.32 K.cals./mole from $\Delta H^{\ddagger}$, and 1.38 K.cals./mole from $T\Delta S^{\ddagger}$ - almost entirely due to the $T\Delta S^{\ddagger}$ term.

These differences can be rationalized as follows. The activation energy decrease in going from acetone to the bromoacetones is probably due to the increased proton acidity caused by bromine substitution. If this is the case two bromines are much less than twice as effective as one - this point will come up again later. Alternatively, the increase in steric crowding caused by two bromines could cause the difference between bromoacetone and dibromoacetone to be small.

The less negative entropies of activation found in going down the series can be explained if the transition state contains negative charge (enolate-like); in this case increasing bromine substitution will enable the negative charge to be more delocalized throughout the

molecule (due to the inductive electron-withdrawing powers of bromine) and hence the solvent will be less electrostricted as the charge does not need to be delocalized by solvation. This decrease in electrostriction means that fewer degrees of freedom are lost by the molecule/solvent complex at the transition state, and therefore the entropies of activation will be less negative.

The above argument does not apply if the transition state resembles enol, since the negative charge has been transferred to the solvent and there should be no differences due to electrostriction. It is more difficult to explain the entropy differences in this case, and thus the activation data are indicative of an enolate-like rather than an enol-like transition state. By itself, however, this data does not represent conclusive evidence.

Free-Energy Differences in Bromine- and Methyl-Substituted Ketones

It was mentioned in the historical introduction that many factors, inductive and steric effects, hyperconjugation and so on, can affect the rate and position of enolization in unsymmetrical ketones. It was therefore thought necessary to try to isolate one effect as far as possible in studying this process. Now bromine and methyl groups are known to be much the same effective size[155],

so a comparison of methyl ketones with ketones containing bromine atoms in the same positions as the methyl groups should minimize steric effects. Mesomeric effects are more difficult to prevent, but it was thought that in a series of compounds of formula $CH_3COCBr_x(CH_3)_{3-x}$ (x = 0-3) mesomeric effects should be minimized as the carbonyl group is between the substituent and the reaction site. Thus in these compounds the inductive effect should be operating almost alone, and would be expected to be more or less additive in its operation.

It was also of interest to study the effect of bromine on each side of the carbonyl group (e.g., see Table IV, p 43); this can be done using compounds such as $CH_3CH_2COCH_2CH_3$, $CH_3CH_2COCH_2Br$ and $BrCH_2COCH_2Br$, where, in the third compound, enolization should be accelerated by the bromine at the enolizing site and by the bromine on the other side of the molecule. (Compounds that are symmetrical, or those in which the enolizing site is obvious, must be used if the potentiometric method of following rates of bromine consumption, discussed above, is to be used.)

The bromoketones were synthesized using literature techniques, modified as necessary - see the experimental section. In particular the method of Rappe and Kumar[156] using N-bromo-succinimide[157] was found useful - this was extended to the bromination of methyl groups and bromo-

ketones (e.g. CH_3COCBr_3 could be prepared from CH_3COCH_3 and from $CH_3COCHBr_2$). The method shows a very high selectivity for the bromine- or alkyl-substituted side of a carbonyl group; this is in accord with what would be expected for a free radical reaction[158].

The bromoketones prepared, with their acetate-catalyzed enolization rates, are shown in Table X, p 101. From the rate constants the free energies of activation were calculated[153]; these are given in the table, together with the free-energy differences within each series.

The first series of compounds, $CH_3COCBr_x(CH_3)_{3-x}$, shows that the inductive effect of bromine can be transmitted through the carbonyl group - the enolization rates increase markedly with increasing bromine substitution. In fact tribromoacetone enolizes about as fast as bromoacetone, despite the fact that the latter is enolizing towards the bromine-substituted position rather than away from it.

However, in this series the overall effect of bromine is <u>not</u> additive - the $\Delta\Delta G^{\ddagger}$ column in Table X shows this clearly, with a 2.8 K.cals./mole difference between the first two members, but only a 0.5 K.cals./mole difference between the last two. This could mean that the above assumptions regarding the absence of steric and mesomeric effects are unjustified. However, it is also possible that the inductive effects of bromine in this system are

TABLE X

Average Rate Constants, and Free Energies of Activation, at 30°

Ketone	k_1^H [a]	$\Delta G^{\ddagger}$ [b]	$\Delta\Delta G^{\ddagger}$ [c]
$CH_3COC(CH_3)_3$	6.34×10^{-8}	27.74 ± 0.06	0.0
$CH_3COCBr(CH_3)_2$	6.99×10^{-6}	24.90 ± 0.03	2.8
$CH_3COCBr_2CH_3$	7.64×10^{-5}	23.46 ± 0.01	4.3
CH_3COCBr_3	1.90×10^{-4}	22.91 ± 0.05	4.8
$CH_3COC(CH_3)_3$	6.34×10^{-8}	27.74 ± 0.06	0.0
$BrCH_2COC(CH_3)_3$	5.79×10^{-5}	23.63 ± 0.04	4.1
$BrCH_2COCBr(CH_3)_2$	2.67×10^{-3}	21.32 ± 0.05	6.4
$CH_3CH_2COCH_2CH_3$	9.35×10^{-8}	27.50 ± 0.01	0.0
$CH_3CH_2COCH_2Br$	7.96×10^{-5}	23.44 ± 0.05	4.1
$BrCH_2COCH_2Br$	6.74×10^{-3}	20.78 ± 0.14	6.7
CH_3COCH_3	7.38×10^{-8}	27.64 ± 0.01	0.0
CH_3COCH_2Br	3.27×10^{-4}	22.59 ± 0.01	5.0
$CH_3COCHBr_2$	5.05×10^{-3}	20.94 ± 0.02	6.7

[a] In $M^{-1}sec.^{-1}$; average of the values in Table XVI, pps 150-2.

[b] In K.cals.$mole^{-1}$, calculated as described on p 155.

[c] Difference from the head of each sub-column.

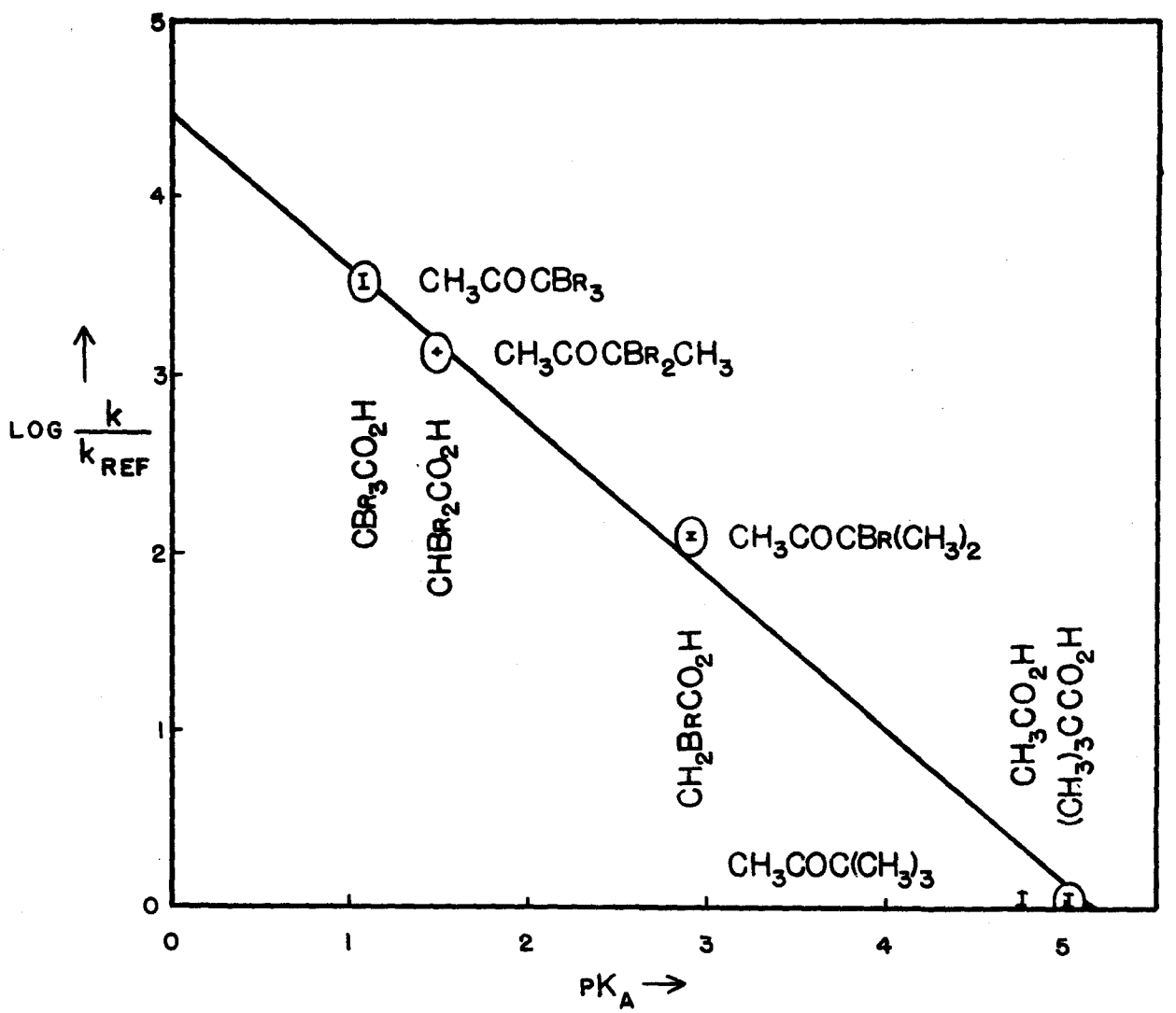
not additive. It has been suggested that the inductive effect acts through space rather than through the bonds of the molecule[179]. If this is so the non-additivity can be explained: since the electrostatic interaction between two charges decreases with the square of the distance between them, and since the distances between each of the bromines and the enolizing proton in, say, tribromoacetone, are not the same at the transition state, an equal contribution from each bromine would not be expected.

It was not possible to derive a linear free-energy relationship between the logarithms of the relative rates for these compounds and any of the standard parameters (e.g. plots vs. σ^* are curved); but a good correlation between these numbers and the pK_a's of some bromine-substituted acids was found - this is given in figure 8, p 103. (The acids corresponding directly to these ketones have not, apparently, had pK_a's reported, but the effect of changing CH_3 for H on the pK_a is seen to be small, since CH_3CO_2H and $(CH_3)_3CCO_2H$ are only about 0.25 pK_a units apart, and the acids used for the correlation should be much less different in pK_a than this from the directly corresponding ones.)

The correlation in figure 8 is excellent - a correlation coefficient[159] of -0.998 was calculated (negative since pK_a's are the negative logarithms of the acid ionization constants). Using acetic acid rather than trimethylacetic acid gave a less good correlation, -0.995.

FIGURE 8

Linear free energy correlation. Graph of the logarithms of the relative enolization rate constants for some of the compounds in Table X, against the pK_a's of the corresponding acids.



The slope of this line is -0.87 ± 0.02, but it is difficult to assign a meaning to this value, since no other correlations of this type are available for comparison. The fact that such a good correlation is observed between these enolization rates, and acid ionization constants, is, however, highly suggestive. Acids develop a full negative charge on ionization, so the implication is that the transition state for base-catalyzed enolization contains at least some negative charge. In other words this correlation is suggestive of a transition state resembling enolate and not one resembling enol.

The other series of compounds in Table X, apart from the acetone series, which was discussed above, show some interesting features. It is apparent that bromine substitution on the enolizing site causes a decrease in the free energy of activation of about 4.1 K.cals./mole, and on the other side from the enolizing site, a decrease of 2.3-2.8 K.cals./mole. In other words bromine substitution on the other side of the carbonyl group is somewhat more than half as effective at increasing rate as is substitution on the same side.

The above numbers indicate that the inductive effect of a bromine substituent is reduced by a factor of 1.3 to 1.8 by the interposition of a carbonyl group between it and the reacting site. Taft[160] estimates that interposition of a methylene group reduces the inductive effect

of a group by a factor of 2.8, so a carbonyl group would appear to be about half as effective as a methylene group in attenuating inductive effects.

General Conclusions

It has now been shown that the acetate-catalyzed bromination of ketones goes *via* enolization, and that the transition state for acetate-catalyzed enolization is probably enolate-like. The first conclusion supports the bulk of the previous studies given in the historical introduction, and the second supports the reasoning given by Bell[19] and others, and is quite consistent with the linear free-energy relationships detailed on pps 34 ff.

However, the acetate-catalyzed deuterium exchange study showed that methyl substitution increased the reactivity of the methylene protons in 2-butanone. This supports the previous work of Warkentin and Tee[133], but they concluded, on the basis of the accepted direction of the inductive effect of the methyl group, that the transition state was enol-like. Now if the transition state is really enolate-like, this means that the accepted direction of the inductive effect of methyl groups in these systems needs to be re-interpreted. This was suggested by Warkentin and Barnett[46], and several recent studies indicate that, although methyl is clearly inductively electron-donating

to sp^2-hybridized carbon[161,162] (for instance, in the benzene ring, as indicated by the sign of its σ constant[161]), it may in fact be inductively electron-withdrawing from sp^3-hybridized carbon[162-4]. This is probably the case in this reaction - methyl has a slight electron-withdrawing effect in 2-butanone, causing the observed slight accelerating effect of a methyl group on the acetate-catalyzed enolization rate at the methylene position. In other words, methyl, being polarizable, can accept or donate electron density as required.

With regard to the effects of fluorine and methoxyl groups, noted by Jullien and Nguyen[116], and Hine et al.[134], the reader is referred to the collection of the anomalous effects of these groups given in another paper by Hine et al.[165]. Hine does not, however, suggest why they should be anomalous. Streitwieser et al.[166] recently found no evidence for fluorine hyperconjugation, and Kaplan and Pickard[167] found that α-fluoro substituents destabilize sp^2-hybridized carbanions. Until further study elucidates the position, the explanation in terms of polarizability indicated by Jullien et al.[47] is probably the most reasonable - F and OMe, being almost non-polarizable, find it almost impossible to act inductively by accepting electron density from the rest of the molecule.

SUMMARY

(i) The acetate-catalyzed bromination of acetone has been shown to go by an enolization mechanism, and the non-enolic one suggested by Rappe[3] has been disproved. Some of this work has been presented at a recent conference[128a].

(ii) The transition state for this reaction has been shown to be enolate-like, from the linear free-energy correlation of enolization rates with acid ionization constants, and from a consideration of the activation parameters derived from the enolization rates of acetone and some bromoacetones.

(iii) The inductive effect of bromine has been shown to affect enolization rates at <u>both</u> sides of the carbonyl group quite strongly.

(iv) The results of Warkentin and Tee[133], concerning the relative rates of acetate-catalyzed enolization at the two sites of 2-butanone, are supported; this work has recently been published[142]. However, the results are interpreted in terms of a change in sign of the inductive effect of methyl groups, to become electron-withdrawing in saturated systems, and not in terms of an enol-like transition state.

EXPERIMENTAL

This section is divided into three parts. In part one the preparation and purification of the bromoketones, and all other materials used in the determination of rate constants, is described. The second part deals with the hydrogen-deuterium exchange studies on 2-butanone. In the third part the apparatus used for the potentiometric determination of rates of bromine consumption is described, together with its experimental use. Also described are the mathematical basis of operation of the potentiometric method, the methods used to treat the data obtained in order to obtain enolization rate constants, and the results obtained.

Bromoketones and Other Materials

Purification Procedures and Instrumental Analysis

For the reasons detailed above (p 81) it was necessary for the bromoketones used for kinetic measurements to be in a state of high purity, and especially not to be contaminated with higher bromoketones.

Fractional distillation under reduced pressure, the purification method almost invariably used previously[12,13,39,156,168,169], was found to be impractical for the purities needed. For instance, spinning band distillation of a mixture of CH_3COCH_2Br and $CH_3COCHBr_2$ in a ratio of about 5:1 resulted in several fractions which all proved to have the approximate composition: CH_3COCH_2Br, 45%; $CH_3COCHBr_2$, 45%; $BrCH_2COCH_2Br$, 10%. This is thought to be a result of some decomposition to HBr, and subsequent rearrangement, on the column. The following procedure was therefore adopted.

The crude bromination product, almost invariably a mixture in solution in CCl_4, was quickly distilled at reduced pressure, in order to remove excess CCl_4 and concentrate the product as far as possible. (Boiling-points are only recorded in those cases in which a reasonably steady boiling-point was observed.) The distillate shown to contain most of the desired product (by nmr) was

stabilized by the addition of magnesium oxide[12,168] (which removes any HBr present) and purified by preparative glpc. 1,1,1-Tribromoacetone, however, would not survive this procedure - it is thermodynamically unstable with respect to the 1,1,3- isomer, to which it readily rearranges on distillation. In this case MgO was added to the crude reaction product and the whole was purified by preparative glpc in 100 μl portions.

Preparative glpc was carried out using a Varian Aerograph A 90-P3 instrument, using a 10' x 3/8" silicone QF-1 (10%) column. The column support was 60/80 chromosorb W, non-acid-washed in order to cut down the possibility of rearrangement. This column proved to be ideal for the purpose, the only compounds not well separated being CH_3COCBr_3 and $BrCH_2COCH_2Br$, with retention times within a minute of each other; for this reason product mixtures containing both of these compounds were not used. Injection volumes were 20-100 μl; column temperatures were between 110° and 130°; and helium flow rates 50-100 ml/min, depending on the compounds. Generally several components of a product mixture were collected, in nmr (or similar) tubes cooled in ice. Compounds collected in this way were chromatographed at least once more; after this they all showed only one peak on available analytical glpc columns (10' x 1/8" QF-1 (12%), 5' x 1/8" FFAP (10%) and 10' x 1/8" SE-30 (20%), all on 60/80 chromosorb W) and

showed no extraneous signals in their nmr spectra. Pure compounds were all water-white, without traces of the yellow colour characteristic of less pure bromoketones. Pure compounds were stored in a freezer at about -10°, without MgO, and were all stable under these conditions[12].

Nmr spectra were recorded on a Varian T-60 instrument, in solution in CCl_4 containing tetramethylsilane as reference. Chemical shifts are recorded in parts per million downfield from TMS. Nmr was the technique of choice for routine identification, as most simple bromoketones have simple and characteristic nmr spectra[13]. The spectra obtained were in agreement with literature spectra where available[13,156], insofar as the literature spectra were recorded on the neat bromoketones against external TMS[13,156].

Densities, where listed, were obtained by weighing 100 µl or 500 µl samples, measured by micro-pipette, and should be regarded as approximate. Refractive indices were recorded on a Bausch and Lomb refractometer connected to a Haake constant temperature bath. Melting points were recorded on a Thomas Hoover Unimelt capillary melting point apparatus, and are not corrected for stem exposure.

Bromoacetone

This was prepared by the potassium chlorate

method of Catch et al.[12]:

$$6CH_3COCH_3 + 3Br_2 + KClO_3 \longrightarrow 6CH_3COCH_2Br + KCl + 3H_2O .$$

Potassium chlorate (12.25 g, 0.1 mole) was dissolved in water (100 ml) in a 250-ml flask fitted with a bypass addition funnel, a reflux condenser and a magnetic stirrer. Acetone (73.5 ml, 1 mole, excess) was added, and bromine (16.4 ml, 48 g, 0.3 mole) was placed in the addition funnel. A little bromine was added, and the reaction initiated by heating to 60° and illuminating with a 75-watt tungsten lamp. Once the initial bromine was decolorized, addition was continued at a rate sufficient to keep the reaction solution approximately colorless, and heating and illumination were discontinued. When all the bromine was added the solution was stirred for an hour, and then the heavy bromoketone layer which separated was shaken with MgO/water and dried over $CaCl_2$. The crude mixture, which contained some chloroacetone (presumably from displacement of $Br^{\ominus}$ by $Cl^{\ominus}$ in solution) and some 1,1-dibromoacetone, was purified as described on p 109. The product was bromoacetone: bp ~75° (65 mm); $n^{25}\underline{D}$ 1.4680 [lit.[12] bp 63.5-64° (50 mm), $n^{15}\underline{D}$ 1.4697; lit.[13] bp 38-39° (11 mm), $n^{25}\underline{D}$ 1.4739]; nmr (CCl_4) δ 2.30 (s, 3, $C\underline{H}_3CO$), 3.78 (s, 2, $BrC\underline{H}_2CO$).

1,1-Dibromoacetone

This compound was available in quantity as a by-product from the preparation of bromoacetone (p 111), and various preparations of tribromoacetone (p 115), and a separate preparation was not developed: $n^{25}\underline{D}$ 1.5232 [lit.[13] $n^{25}\underline{D}$ 1.5237]; d_4^{23} 2.063; nmr (CCl_4) δ 2.51 (s, 3, $C\underline{H}_3CO$), 5.67 (s, 1, $Br_2C\underline{H}CO$).

1-Bromo-3,3-dimethyl-2-butanone (Bromopinacolone)

This was prepared as the result of an investigation to see whether the N-bromo-succinimide (NBS) method of Rappe and Kumar[156] could be extended to methyl ketones; Rappe and Kumar found no methyl group bromination in the ketones they studied[156].

Pinacolone (10.02 g, 0.1 mole) was added to CCl_4 (100 ml) in a 250-ml 2-necked flask fitted for refluxing and magnetic stirring. NBS (17.8 g, 0.1 mole) was weighed in and the mixture was heated to boiling, with the light from a 75-watt tungsten spot-lamp directed at it. After 24 hours of refluxing, nmr monitoring indicated a mixture roughly 70% pinacolone, 15% bromopinacolone and 15% dibromopinacolone, with dibromination proceeding faster than monobromination. The reaction was stopped by cooling the mixture in ice; the insoluble solids were filtered off and most of the CCl_4 removed on a rotary evaporator. Distillation gave a fraction boiling at 55-60° (4 mm) which

was shown by nmr to be at least 50% bromopinacolone, with smaller amounts of $(CH_3)_3CCOCHBr_2$, $BrCH_2(CH_3)_2CCOCH_3$ and $BrCH_2(CH_3)_2CCOCH_2Br$. Preparative glpc as described on p 110 gave pure bromopinacolone: $n^{25}\underline{D}$ 1.4630 [lit.[170] $n^{25}\underline{D}$ 1.4659; lit.[171] $n^{20}\underline{D}$ 1.4640]; nmr (CCl_4) δ 1.21 (s, 9, $(C\underline{H}_3)_3CCO$), 4.01 (s, 2, $BrC\underline{H}_2CO$).

1,1-Dibromo-3,3-dimethyl-2-butanone

This is a white crystalline solid obtained as a byproduct in the preparation of bromopinacolone. Purification by sublimation gave the title compound: mp 73-74° [lit.[35] mp 69°]; nmr (CCl_4) δ 1.29 (s, 9, $(C\underline{H}_3)_3CCO$), 6.27 (s, 1, $Br_2C\underline{H}CO$).

3,3-Dibromo-2-butanone

This was prepared by the method of Rappe and Kumar[156] as described for bromopinacolone, using 2-butanone (7.2 g, 0.1 mole) and NBS (35.6 g, 0.2 mole) in CCl_4 (150 ml). Nmr monitoring indicated complete reaction after 1½ hours, when the reaction was stopped; the yield (by nmr) was about 95%, as compared to Rappe and Kumar's reported[156] 71% after 24 hours. The product was purified as described on p 109: bp ~45° (13 mm); $n^{25}\underline{D}$ 1.5053 [lit.[156] bp 47° (15 mm), $n^{25}\underline{D}$ 1.5050]; d_4^{22} 1.827; nmr (CCl_4) δ 2.50

(s, 3, $C\underline{H}_3CO$), 2.67 (s, 3, $C\underline{H}_3CBr_2CO$).

1,1,1-Tribromoacetone

Three preparative methods resulting in adequate yields were developed; existing preparative procedures are lengthy and start from dibromoacetone[13,17b], itself not too readily available.

(a) Base-catalyzed bromination

Anhydrous sodium acetate (16.4 g, 0.2 mole) was dissolved in glacial acetic acid (100 ml), in a 250-ml stoppered conical flask, by stirring and heating to about 50° on a combined hotplate/magnetic stirrer. Acetone (58 g, 1 mole) was added, followed by bromine (5.4 ml, 0.1 mole). (Larger quantities of bromine resulted in hexabromoacetone, a white crystalline solid, mp 107-8°.) The resulting red mixture was stirred until colourless (about one hour) at 50° - sodium bromide precipitated out during this time. Ice-cold water (about 300 ml) was added to the solution in a 500-ml separating funnel, and the resulting mixture was extracted with small portions of CCl_4. The CCl_4 layer was dried over $CaCl_2$, and most of the CCl_4 removed on a rotary evaporator, leaving a mobile yellow liquid to which MgO was added. Preparative glpc of this (see p 110) resulted in CH_3COCBr_3 (about 1 g) and $CH_3COCHBr_2$ (about 1.5 g).

(b) NBS and acetone

Acetone (3.22 g, 0.04 mole) was mixed with CCl_4 (250 ml) and reacted with NBS (29.7 g, 0.13 mole) as described for bromopinacolone (p 113). The reaction was stopped after 28 hours, when nmr monitoring indicated the products to be CH_3COCH_2Br, 40%; $CH_3COCHBr_2$, 20%; and CH_3COCBr_3, 40%. (Rappe and Kumar[156] could not brominate CH_3COCH_2Br using this method.) The CCl_4 solution was concentrated, treated with MgO and the components were separated by preparative glpc as before.

(c) NBS and dibromoacetone

1,1-Dibromoacetone (2.81 g, 0.013 mole) and NBS (2.32 g, 0.013 mole) were refluxed in CCl_4 (14 ml) under illumination as described above (p 113). The reaction was stopped after 12 hours, when the yield of CH_3COCBr_3 was 91% as indicated by nmr. This was the best of the three methods used. After purification (see p 110) pure tribromoacetone was obtained: bp ~54° (1 mm); $n^{25}\underline{D}$ 1.5708 [lit.[13] bp 90-91° (13 mm), $n^{25}\underline{D}$ 1.5689]; d_4^{20} 2.334; nmr (CCl_4) δ 2.76 (s, $C\underline{H}_3CO$).

1,3-Dibromo-3-methyl-2-butanone

This compound was prepared by the method of Wagner and Moore[169].

Methyl isopropyl ketone (43 g, 0.5 mole) was

placed in a 250-ml 3-necked flask, fitted with a gas inlet tube, a magnetic stirrer, a bypass addition funnel and a reflux condenser. Bromine (53 ml, 1 mole) was placed in the addition funnel and the flask and contents cooled to 0° in ice. A few drops of bromine were added and the reaction initiated with a 75-watt lamp; when the solution suddenly became colourless the rest of the bromine was added slowly over two hours. When addition was complete nitrogen was passed through the solution overnight in order to sweep out the HBr formed; the product was then distilled directly from the flask, and some was purified by glpc as described on p 110. This gave pure 1,3-dibromo-3-methyl-2-butanone: mp 13-14°; bp 68-72° (3 mm); $n^{25}\underline{D}$ 1.5154 [lit.[169] mp 10-12°, bp 111° (15 mm), $n^{25}\underline{D}$ 1.5178]; nmr (CCl_4) δ 1.94 (s, 6, $(C\underline{H}_3)_2CBrCO$), 4.31 (s, 2, $BrC\underline{H}_2CO$).

1,3-Dibromoacetone

This was prepared exactly as described for 1,3-dibromo-3-methyl-2-butanone, using acetone (29 g, 0.5 mole). The product proved to be $BrCH_2COCH_2Br$, 50%; $BrCH_2COCHBr_2$, 45%; other bromoketones, 5%. Pure 1,3-dibromoacetone was separated by preparative glpc: mp 28-28.5°; bp ~80° (9 mm) [lit.[13] mp 25.5-27.0°, bp 79.5-80.5° (9 mm)]; nmr (CCl_4) δ 4.10 (s, $BrC\underline{H}_2CO$).

3-Bromo-3-methyl-2-butanone

This compound, prepared from methyl isopropyl ketone by the method of Catch et al.[39], was kindly supplied by Mr. J. William Thorpe[149], and was purified by glpc as described on p 110. Bp 70-74° (100 mm); $n^{25}\underline{D}$ 1.4554 [lit.[39] bp 83-84° (150 mm), $n^{16}\underline{D}$ 1.4590; lit.[156] $n^{25}\underline{D}$ 1.4570]; d_4^{20} 1.334; nmr (CCl_4) δ 1.80 (s, 6, $(C\underline{H}_3)_2CBrCO$), 2.36 (s, 3, $C\underline{H}_3CO$).

1-Bromo-2-butanone

This compound, prepared from the corresponding diazo-ketone by the method of Catch et al.[168], was also supplied by Mr. Thorpe. Purification by preparative glpc (p 110) gave the pure compound: bp 44-45° (10 mm); $n^{25}\underline{D}$ 1.4670 [lit.[12] bp 49° (10 mm); lit.[168] $n^{20}\underline{D}$ 1.4670]; nmr (CCl_4) δ 1.08 (t, 3, J = 7 Hz, $C\underline{H}_3CH_2CO$), 2.64 (q, 2, J = 7 Hz, $CH_3C\underline{H}_2CO$), 3.76 (s, 2, $BrC\underline{H}_2CO$).

Pure Ketones

Acetone, reagent grade supplied by Mallinckrodt, was redistilled through a 20 x 2 cm column packed with 3 mm single-turn glass helices. The centre cut was glpc pure and showed no extraneous nmr signals.

2-Butanone was Fisher certified grade, purified as described for acetone.

3-Pentanone was Eastman reagent grade, purified as described for acetone.

Pinacolone, Aldrich reagent grade, was purified by preparative glpc, using the 10' x 3/8" QF-1 column described on p 110. The product collected showed no extraneous nmr signals, and gave only one peak on the analytical glpc columns (p 110).

Other Materials

Bromine, reagent grade, was used as supplied by Shawinigan or by B.D.H.

Water - ordinary lab distilled water was generally used, but for electrochemical concentration measurements at bromine concentrations below about 5×10^{-4} M, all water used was distilled from potassium permanganate prior to use[147].

Potassium Bromide, Shawinigan reagent grade, was dried overnight at 130° prior to use.

Sodium Acetate: the hydrated reagent grade material supplied by Shawinigan was dried for three days at about 130°, ground in a mortar, redried for one day and stored in a desiccator.

Acetic Acid, C.I.L. reagent grade, was redistilled before

use.

Dioxane, Fisher certified grade, was purified by refluxing with hydrochloric acid, and then with sodium, according to the procedure of Fieser[172]. The pure solvent was stored under nitrogen.

Deuterium Oxide, 99.5% D, was used as supplied by the Columbia Organic Chemicals Co.

Sodium Deuteroxide solutions were prepared by dissolving B.D.H. reagent grade sodium hydroxide in D_2O.

Chromic Acid cleaning solution, used for all volumetric apparatus, nmr tubes and so on, was prepared as described by Vogel[173] from sodium dichromate and concentrated sulfuric acid.

Sodium Chloride, B.D.H. reagent grade, was dried at 130° before use.

Acetate-Catalyzed Deuterium Exchange

The techniques used for measuring the relative exchange rates at two sites of simple unsymmetrical ketones by nmr have been described in the literature[46,132,133,142].

The stock solutions used, made up gravimetrically, were two acetic acid/sodium acetate buffers in D_2O of ratio 0.0936 and 0.0469; the acetate concentrations being in each case about 1.1 M. The hydrogen introduced by using HOAc rather than DOAc was negligible in comparison with the large deuterium pool. Aliquots of the stock solutions were diluted with a solution of sodium chloride in D_2O of equivalent molarity. By this procedure ten solutions with acetate concentrations ranging between about 1.1 and 0.11 M, at a constant buffer ratio of 0.0936 and a constant ionic strength of about 1, were obtained, as well as ten similar solutions at a buffer ratio of 0.0469. Addition of 0.1 ml of 2-butanone to 1 ml of the above solutions resulted in a 2-butanone concentration of 1.18 M, an ionic strength of 1.04, and the acetate concentrations shown in Table XI, p 124. After mixing, the solutions were sealed into standard nmr tubes which had been cleaned with chromic acid, thoroughly rinsed, and dried at 130°.

The samples were immersed in a thermostat at 54.8°,

together with a sample containing 2-butanone and 1.04 M sodium chloride, but no acetate. Integrations were performed every 1 or 2 days as necessary, after quenching exchange by chilling the tubes with ice. Reaction outside the bath was negligible, and time outside the bath was not counted.

Exchange was followed to at least one half-life by integrating the signals from the 1- and 3-positions, using the non-exchanging β-methyl group as internal standard, on a Varian A-60 instrument[132,133]. The methyl group signal from the acetate present did not interfere, being well separated from the α-CH_3 of 2-butanone. Each sample was integrated six times and an average was taken.

The integral from the β-methyl group was taken as representing three protons, and the areas for the 1- and 3-positions were converted into the average number of protons per molecule remaining at these positions. On plotting the logarithms of these numbers against time, good straight lines were obtained even for exchanges followed to over two half-lives. An example of a rate plot is given in figure 9, p 123. Each graph contained at least 15 points. A linear least-squares program for the IBM 7040 computer (see Appendix I, computer programs) was used to obtain pseudo-first-order rate constants and their standard deviations - these are given in Table XI, p 124, and plotted against the acetate concentration in

FIGURE 9

A typical rate plot. Buffer ratio 0.0469, acetate concentration 0.935 M.

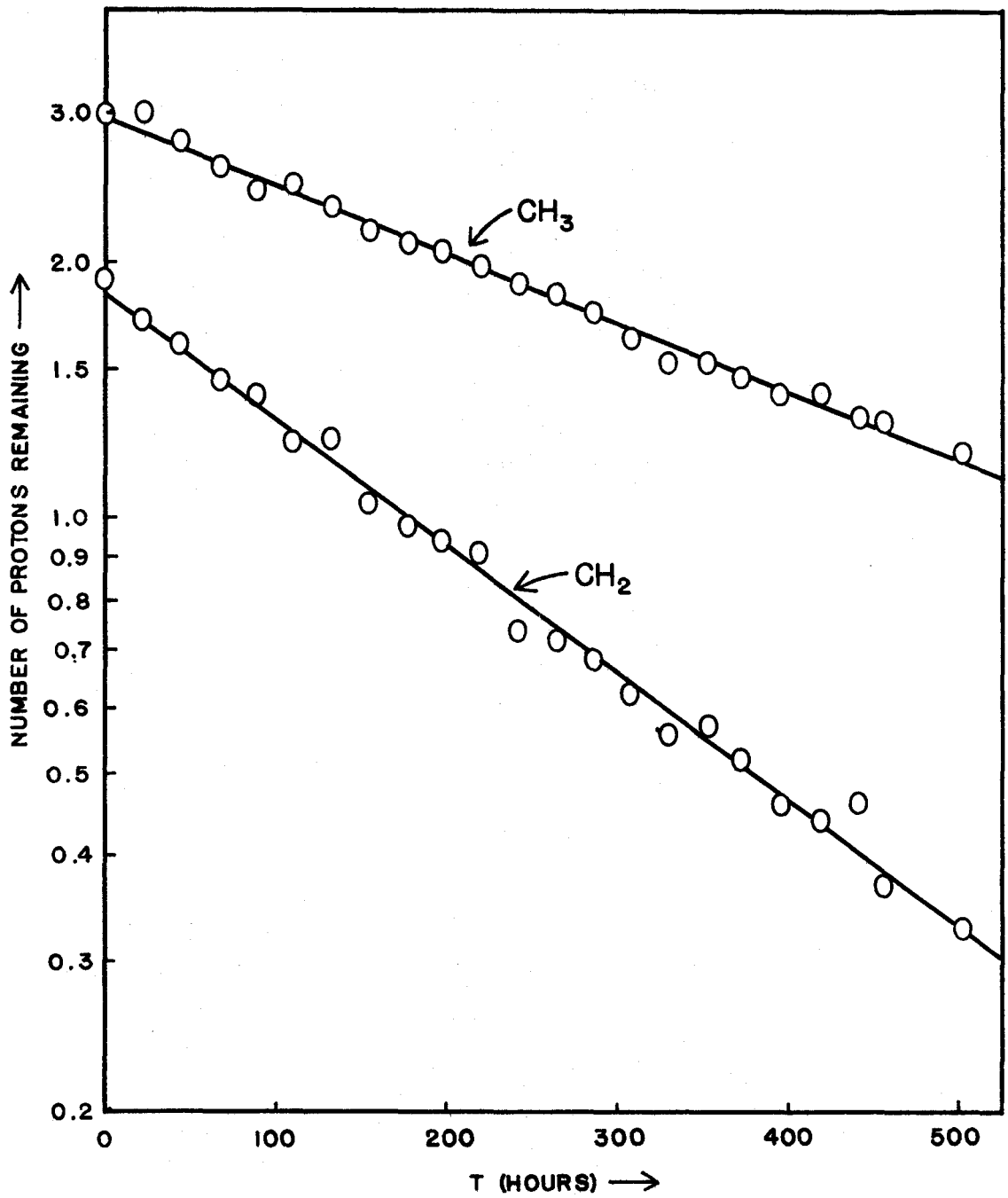


TABLE XI

Pseudo-First-Order Rate Constants for the H-D Exchange of 2-Butanone in Deuterium Oxide Acetate Buffers at 54.8°

Buffer Ratio 0.0936

$[OAc^{\ominus}]$, M	$k^{obsd} \times 10^7$ sec.$^{-1}$	
	CH_2	CH_3
1.039	11.60 ± 0.29	6.22 ± 0.09
0.935	10.97 ± 0.30	5.74 ± 0.11
0.831	9.54 ± 0.20	5.37 ± 0.11
0.727	7.67 ± 0.19	4.10 ± 0.05
0.623	6.82 ± 0.15	3.55 ± 0.06
0.520	5.46 ± 0.10	2.78 ± 0.04
0.416	4.58 ± 0.11	2.36 ± 0.03
0.312	3.31 ± 0.08	1.72 ± 0.02
0.208	2.37 ± 0.07	1.20 ± 0.02
0.104	1.31 ± 0.07	0.65 ± 0.04

Buffer Ratio 0.0469

$[OAc^{\ominus}]$, M	$k^{obsd} \times 10^7$ sec.$^{-1}$	
	CH_2	CH_3
1.039	11.52 ± 0.35	6.09 ± 0.14
0.935	9.53 ± 0.18	5.19 ± 0.10
0.831	11.03 ± 0.33	4.79 ± 0.14
0.727	9.35 ± 0.61	4.27 ± 0.15
0.623	6.56 ± 0.18	3.57 ± 0.05
0.520	5.97 ± 0.60	3.47 ± 0.10
0.416	4.23 ± 0.11	2.20 ± 0.03
0.312	3.37 ± 0.09	1.76 ± 0.03
0.208	2.15 ± 0.08	1.23 ± 0.02
0.104	1.31 ± 0.18	0.36 ± 0.15

FIGURE 10

Plot of observed pseudo-first-order rate constants against acetate concentration for H-D exchange of 2-butanone; buffer ratio 0.0469.

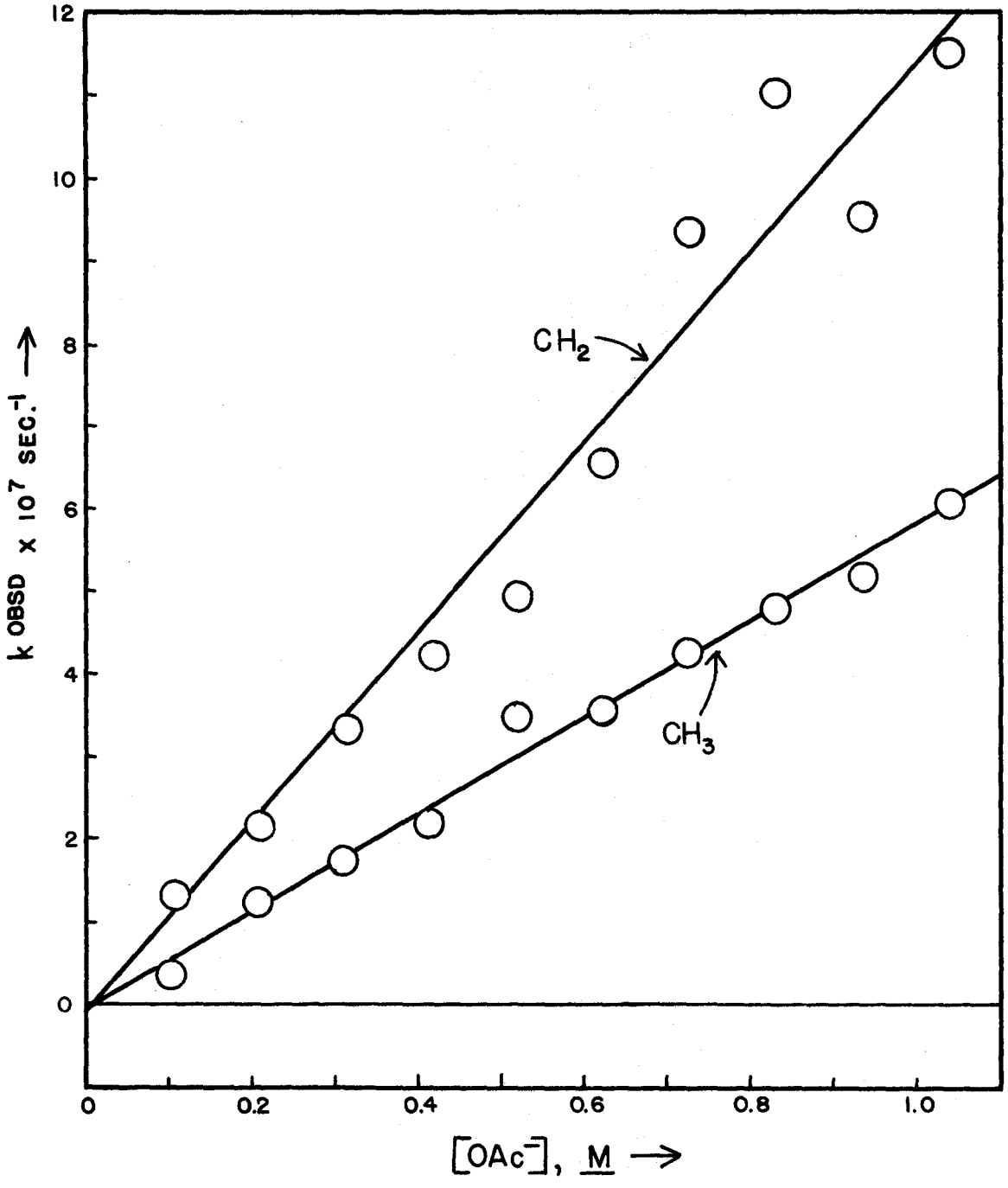


figure 1, p 59, and figure 10, p 125. The same computer program was used to obtain acetate catalysis constants from these figures; see Table VI, p 60.

For the study of deuteroxide catalysis at 54.8°, a deuteroxide stock solution of 1.962×10^{-3} M in D_2O was used. The probe temperature was set, using the variable-temperature controller, at 54.8 ± 0.5° (as determined from the ethylene glycol sample and calibration graph supplied with the instrument), and the deuteroxide solution equilibrated to that temperature by leaving it in the probe for a few minutes. 2-Butanone at the same temperature was then added, after which the tube was shaken and replaced in the probe. Integrations were performed every 150 sec over a 90-min period, which was over one half-life under the reaction conditions. The integral areas were used to obtain the rate ratio for deuteroxide catalysis at 54.8°, k_{CH_2}/k_{CH_3} = 0.88 ± 0.05 and 0.84 ± 0.08 for the two determinations, as described above.

Enolization Rate Constants

Theory

The enolization rates of the ketones and bromoketones were followed by monitoring the zero-order rates of bromine consumption by the enol(ate). Bromine concentrations were determined potentiometrically, after a method originally developed by Bell and Robinson[147].

The bromine/bromide half cell has a large oxidation potential, which can be measured on a voltmeter against a reference electrode. As the bromine concentration in the reaction mixture decreases, so does the redox potential, providing a method for following the reaction. The redox potential was measured at a platinum electrode, using as reference a glass electrode[147]. The potential was displayed on a pH-meter reading millivolts, and also on a chart recorder, giving a permanent trace of the kinetic run to be measured at leisure; this was felt to be a procedure superior to the stopwatch/tape recorder method used by Bell and Robinson[147].

The Nernst equation for a reaction

$$aA + bB \rightleftharpoons cC + dD$$ is[145]:

$$E = E^{o} - \frac{RT}{zF} \ln \frac{a_C^c a_D^d}{a_A^a a_B^b} \qquad (12)$$

where E = half-cell potential (Volts);

E° = standard emf (Volts);

R = gas constant (joules/$^{\circ}$K);

T = temperature ($^{\circ}$K);

$|z|$ = number of electrons involved in the electrochemical reaction;

F = Faraday's constant (coulombs = joules/volts);

a = activity.

The electrochemical reaction with which we are concerned is

$$Br_2 + 2\epsilon^{\ominus} \longrightarrow 2Br^{\ominus} \qquad (13)$$

If we replace activities by concentrations, and apply eq 13 to eq 12, we obtain

$$E = E^{\circ} - \frac{RT}{2F} \ln \frac{[Br^{\ominus}]^2}{[Br_2]}$$

Since $[Br^{\ominus}]$ is held constant at 0.1 M during the reaction, we can write

$$E = E^{\circ\prime} + \frac{RT}{2F} \ln [Br_2] \qquad (14)$$

The term $E^{\circ\prime}$ in eq 14 can also be used to accommodate the potential of the glass reference electrode, and any other activity coefficient or concentration terms which remain constant during the reaction (i.e. all except $[Br_2]$), and we can write

$$E = E' + \frac{RT}{2F} \ln [Br_2] \qquad (15)$$

Eq 15 was used to determine initial bromine concentrations, $[Br_2]_0$, by determining E' experimentally (see below, p 143):

$$E = E' + C_T \log_{10} [Br_2]_0$$

$$\text{where } C_T = 2.3026\frac{RT}{2F} ;$$

$$[Br_2]_0 = \text{antilog}\left(\frac{E - E'}{C_T}\right) \qquad (16)$$

Now the cell potential was recorded on both pH-meter and chart recorder. The pH-meter reading (E) was linearly related to the chart paper reading (ch) <u>via</u> the expression (see below, p 142):

$$E = -(0.760 \pm 0.001)ch + (73.79 \pm 0.03) \qquad (17)$$

Eq 15 can be written, using eq 17:

$$ch = ch' - \frac{1}{0.760}\cdot\frac{RT}{2F} \ln [Br_2]$$

$$= ch' - C_T' \ln [Br_2]$$

$$\therefore \quad [Br_2] = \exp\left(\frac{ch' - ch}{C_T'}\right)$$

If we now choose an arbitrary zero, ch_0, such that

$$[Br_2]_0 = \exp\left(\frac{ch' - ch_0}{C_T'}\right) ,$$

we can write

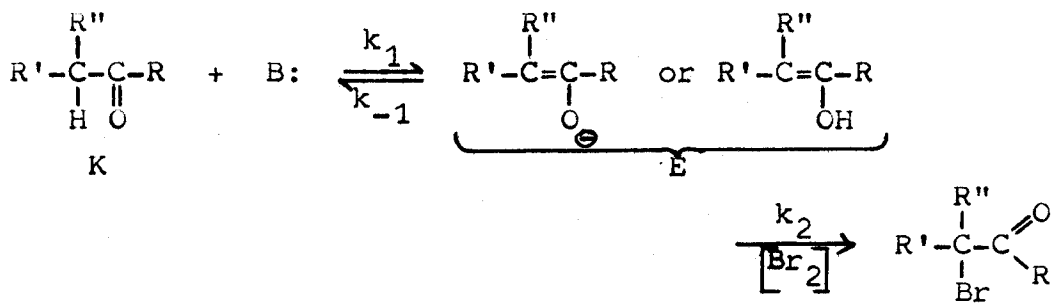
$$f = \frac{[Br_2]}{[Br_2]_0} = \exp\left(\frac{ch_0 - ch}{C_T'}\right) \qquad (18)$$

and eq 18 can be used to determine f, and hence $[Br_2]$ as long as $[Br_2]_0$ is known from eq 16, directly from the chart

traces.

From the form of eq 18 it can be seen that if bromine consumption is first-order (i.e. $f = f_0 \exp(-kt)$) the chart trace will be a straight line (of slope $C_T'.k$); but if bromine consumption is zero-order, the chart trace will be a curve, accelerating in the direction of increasing time. Sample chart traces are reproduced in figure 2, p 72, and figure 11, p 131.

Now considering the enolization reaction:



Assuming steady state conditions, we have

$$\frac{d[E]}{dt} = k_1[K][B:] - k_{-1}[E] - k_2[E][Br_2] = 0$$

$$\therefore \quad [E] = \frac{k_1[K][B:]}{k_{-1} + k_2[Br_2]}$$

$$\text{Now} \quad -\frac{d[Br_2]}{dt} = k_2[E][Br_2] = \frac{k_1 k_2 [K][B:][Br_2]}{k_{-1} + k_2[Br_2]} \qquad (19)$$

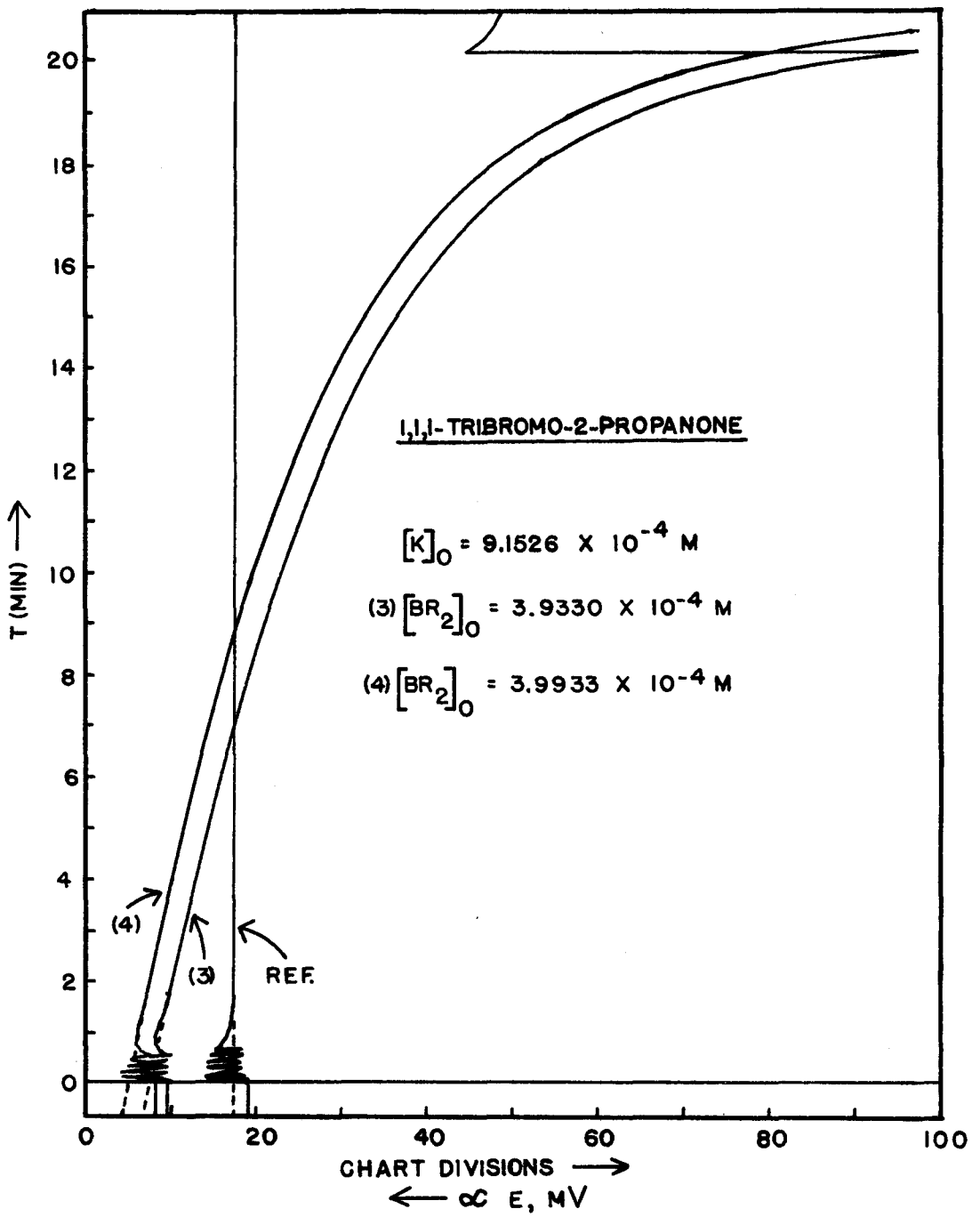
$$= \frac{k_1 k_2}{k_{-1}}[K][B:][Br_2] \quad \text{if} \quad k_{-1} \gg k_2[Br_2] \qquad (20)$$

$$= k_1[K][B:] \quad \text{if} \quad k_2[Br_2] \gg k_{-1} \qquad (21)$$

Eq 21, zero-order bromine consumption, holds if the

FIGURE 11

Sample chart traces - tribromoacetone.



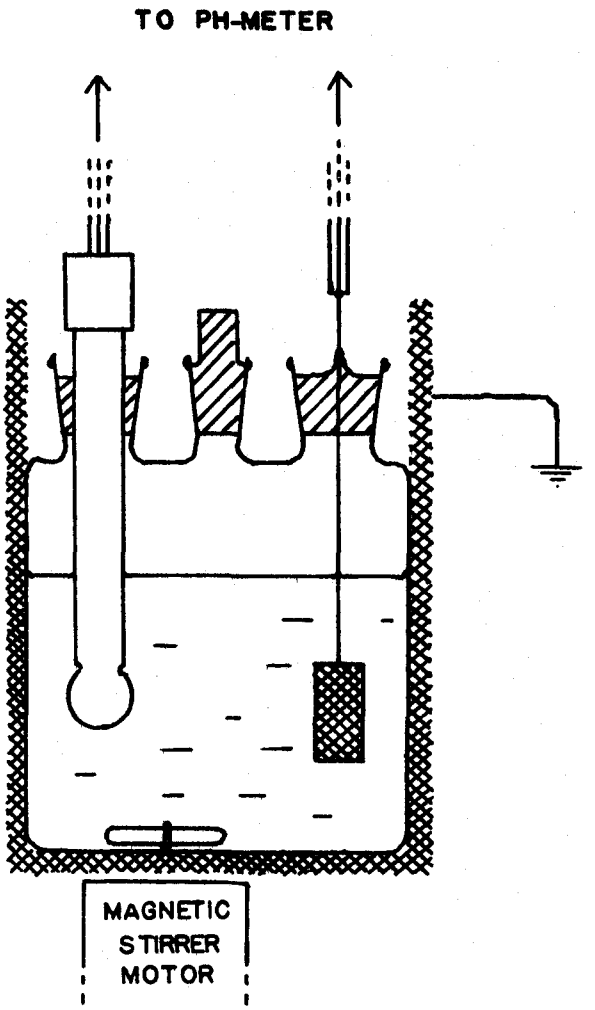
bromine concentration is high. From the figures of Dubois and Toullec[27] $k_2 \simeq 2 \times 10^5 k_1$ for the acid-catalyzed enolization of various alkyl ^{t}butyl ketones, so in this case $[Br_2]$ can approach 10^{-5} M before eq 21 ceases to hold. Assuming that this figure applies to the base-catalyzed bromination of bromoketones means that eq 21 should hold for the bromine concentrations used in this work (10^{-3} - 10^{-5} M). In any case it was possible to see at what stage bromine consumption ceased to be zero-order, and this was done. Others (for instance, see refs 24 and 26) have chosen to use eq 19 to determine both k_{-1} and k_2[24,27], and eq 20 for studying k_2 values[26].

Apparatus

A cylindrical glass cell of about 120 ml capacity, with two B-19 ground-glass necks and one B-14 neck, was constructed. A Fisher full-range glass electrode (cat. no. 13-639-1; silver-silver chloride internals) was sealed into a B-19 joint with epoxy resin and occupied one neck of the cell. A platinum electrode obtained from Johnson, Matthey and Mallory, Ltd., (JA 1331, cylinder 13 x 31 mm, type C Unimesh) was similarly sealed into a B-19 joint and occupied the second neck. The third neck was used to introduce reagents and was normally occupied by a standard B-14 ground-glass stopper. A diagram of the cell is given

FIGURE 12

Apparatus for potentiometric bromine concentration measurements.



as figure 12, p 133. Stirring was accomplished using an off-centre 1" teflon-coated bar magnet, driven by a TRI-R submersible magnetic stirrer obtained from TRI-R Instruments, Jamaica, N. Y. Thus the cell was sealed from the outside air, and bromine loss by evaporation during the course of a run (sometimes as long as six hours) was effectively prevented. The cell was immersed in a thermostatically-controlled water bath, which could be set at temperatures between 15° and 60°, ± 0.03° as determined by N.R.C.-calibrated thermometers.

The platinum electrode lead was connected to the input terminal of a Fisher Accumet model 310 expanded scale pH-meter, and the glass electrode lead connected to the reference terminal. The pH-meter was used to read positive millivolts, and was itself connected to a chart recorder in order to obtain a permanent trace of the kinetic run. The chart recorder was a Bristol Dynamaster recorder (the Bristol Co., Waterbury, Conn.).

Due to the very high resistance of the glass electrode it was found necessary to screen the entire apparatus very carefully from stray electrical fields - if this was not done it was not possible to obtain stable potential readings. To this end, the electrode leads, of screened cable, had their screening grounded to the pH-meter; itself grounded to the electrical ground <u>via</u> a three-pronged plug. The cell itself was entirely sur-

rounded by copper gauze, which, with the metal parts of the thermostatic bath, was grounded to a water pipe. An aluminum-foil-covered screen between the cell and passers-by ended the apparatus' sensitivity to nylon underwear.

When all these precautions were taken, it was possible to obtain stable and reproducible potentials which were quite independent of the speed of stirring the solution - which indicates the absence of polarization at the platinum electrode[147]. Between runs the platinum electrode was stored in a solution containing 10^{-3} M bromine in 10^{-1} M KBr; the glass electrode was stored in the same buffer solution (containing 10^{-1} M KBr) as was used for the kinetic runs.

Procedure

The stock solutions used for kinetic runs were: potassium bromide, 0.3333 M; sodium acetate, 2 M; acetic acid, 1 M; all in water; and bromine, about 5×10^{-2} M, in 0.3333 M potassium bromide solution. All were made up gravimetrically. Solutions of the ketones and bromoketones were made up by weighing them into volumetric flasks (25 or 100 ml), dissolving them in sufficient dioxane to bring the total organic content to 20% v/v (e.g. 5 ml dioxane for a 25 ml flask), and diluting with water. In the case of acetone, no added dioxane was needed. By this procedure

it was possible to produce true solutions of even the more insoluble ketones, and the ketones did not come out of solution when added to the buffer solution in the cell.

A typical kinetic run was carried out as follows. 50 Ml of the 2 M NaOAc, 25 ml of the 0.3333 M KBr and 10 ml of the 1 M HOAc were transferred to the cell by means of calibrated volumetric pipettes. The electrodes were then placed in the cell, and the cell set up in the thermostat and allowed to come to temperature equilibrium (10 or 15 min). The stock bromine solution (5 ml) was then pipetted in, and left to equilibrate until the potential was absolutely steady, with the pH-meter operation switch in the expanded mode position; i.e. the chart recorder drew a straight line parallel to the time axis. This generally took 0.5 to 1 hour. During this period the ketone solution was supported in the thermostat to come to temperature equilibrium. The initial steady potential was then recorded, and the initial bromine concentration calculated from it as described on p 143. A chart speed appropriate for the ketone under study was selected (one inch of chart could be 1, 2, 4, 8 or 16 min). The recorder pen was then placed at the far left of the chart, by adjusting the pH-meter's standardizing potentiometer.

The kinetic run was then started by pipetting 10 ml of the ketone solution into the cell, and simultaneously switching on the recorder chart drive motor. The

solution volume in the cell was now 100 ml, the concentrations being NaOAc, 1 M; HOAc, 0.1 M; and KBr, 0.1 M; with the ketone and bromine concentrations as listed in Table XV, p 147. The concentration of organic material (dioxane and ketone) was now 2% v/v.

The chart was allowed to run until the pen reached the far right of the chart - a range of bromine concentration of just over two powers of ten - with the pH-meter operation switch in the expanded mode. The operation switch was then set to normal mode, in order to check that bromine removal was still zero-order (i.e. that the rate of potential decrease was still increasing). (In this mode the chart represents over 20 powers of ten in bromine concentration.) This was to ensure that eq 21, p 130, still applied at the end of the run. Sample chart traces are reproduced as figure 2, p 72, and figure 11, p 131.

The run was then stopped. The cell was removed, and a small amount of carbon tetrachloride was added to the solution, in order to extract possible reaction products. The mixture was then stirred vigorously for a few minutes, and the CCl_4 was removed by a dropping pipette. The nmr spectrum of the CCl_4 layer was then recorded. By this means it was sometimes possible to identify reaction products directly - see Table XII, p 138.

The entire process was then repeated, using a second cell, for the duplicate determination; the chart

TABLE XII

Reaction Products from Ketone Brominations

Starting Material	Products Remaining after Kinetic Run [a]
$CH_3COC(CH_3)_3$	-
$CH_3COCBr(CH_3)_2$	-
$CH_3COCBr_2CH_3$	-
CH_3COCBr_3	CH_3COCBr_3, $BrCH_2COCBr_3$, $CHBr_3$
$BrCH_2COC(CH_3)_3$	$BrCH_2COC(CH_3)_3$ (w), $Br_2CHCOC(CH_3)_3$
$BrCH_2COCBr(CH_3)_2$	$BrCH_2COCBr(CH_3)_2$ (vw), $Br_2CHCOCBr(CH_3)_2$
$CH_3CH_2COCH_2CH_3$	-
$CH_3CH_2COCH_2Br$	$CH_3CH_2COCH_2Br$, $CH_3CH_2COCHBr_2$ (w), $CHBr_3$
$BrCH_2COCH_2Br$	$BrCH_2COCH_2Br$, $CHBr_3$
CH_3COCH_3	$CHBr_3$ (vw), CH_3COCH_3
CH_3COCH_2Br	CH_3COCH_2Br, CH_3COCBr_3 (vw), $CHBr_3$
$CH_3COCHBr_2$	$CH_3COCHBr_2$, CH_3COCBr_3, $CHBr_3$

[a] Identified by nmr spectra. w = weak, vw = very weak. Blanks indicate either not recorded or too weak to assign.

was wound back, usually, and the second run was traced out on the same chart as the first. This was repeated a third time, using a third cell; only this time instead of adding ketone solution, a 20% dioxane solution without ketone was used. This blank run was also traced out on the same chart; it was generally almost parallel to the time axis, except for runs of very long duration (very little blank reaction), but dioxane purified as described on p 120 had to be used at all times in order to achieve this. Thus, typically, for a particular ketone a chart resembling figure 11, p 131, was produced.

The chart traces were measured as follows. The early, almost straight, part of the curve was extrapolated back through the early irregularities (caused by the action of adding the ketone solution) to the zero time line (see figure 11). This value was taken as ch_0 (see eq 18, p 129). Values of ch were then read off at various times (between 15 and 30 points for each curve), correcting these values as necessary for any blank reaction. Values of $(ch - ch_0)$ and time (t) were then treated by computer, as explained below and in Appendix I, to obtain the enolization rate constants k_1.

Treatment of Data

Several rate expressions are derived in Appendix II.

A typical rate expression, of the form of that for acetone, will be used here, but the treatment is much the same whichever one is used.

A rate expression of the form

$$f = 1 + \alpha t + \beta(1 - e^{-k_2' t}) + \gamma(1 - e^{-k_3 t}) \qquad (22)$$

can be modified as follows. Expanding the exponential as a power series, i.e.:

$$e^{-kt} = 1 - kt + \frac{k^2t^2}{2!} - \frac{k^3t^3}{3!} + \frac{k^4t^4}{4!} - \ldots ,$$

leads to eq 23:

$$f = 1 + t\left\{\alpha + k_2'\beta + k_3\gamma\right\} + t^2\left\{-\beta\frac{k_2'^2}{2!} - \gamma\frac{k_3^2}{2!}\right\} + t^3\left\{\beta\frac{k_2'^3}{3!} + \gamma\frac{k_3^3}{3!}\right\} + \ldots \qquad (23)$$

This is of the form of a polynomial in t, i.e.:

$$f = a_1 + a_2 t + a_3 t^2 + a_4 t^3 + \ldots \qquad (24)$$

The coefficients a_1, a_2, a_3, etc., may be expressed in terms of rate constants by substituting appropriate values for α, β and γ from the rate expressions. For instance, for acetone, one can obtain (see Appendix II):

$$\begin{aligned} a_1 &= 1 \\ a_2 &= -k_1 A \\ a_3 &= -k_1 A \cdot \frac{k_2}{2!} \end{aligned} \qquad (25)$$

$$a_4 = -k_1A.\frac{k_2}{3!}(k_3 - k_2')$$

etc.

So, in theory, if eq 24 can be solved exactly, all the rate constants for a particular ketone bromination can be evaluated. In practice, however, after a_2 the cumulative errors become so bad that it is difficult to obtain better than order of magnitude values (see above, p 87).

The important coefficients are a_1 and a_2. The first coefficient, a_1, is invariably 1, due to the method used of working in terms of relative bromine concentrations f ($= [Br_2]/[Br_2]_0$). The second coefficient, a_2, since it only contains terms in t, is the mathematical equivalent of the value obtained by differentiating the rate expression and then setting t = 0. Thus a_2 is always the initial slope of the concentration (f) vs. time graph, and is always of the form in eq 25 above, only containing the first enolization rate constant. This holds whatever ketone is being treated and whatever subsequent reactions it undergoes, Sn2 displacements, hydrolyses, further brominations and so on.

Computer programs for solving polynomial expressions, using matrix algebra, are readily available. That used here (Appendix I) is a combination of two programs,

somewhat modified, from a standard text on FORTRAN IV programming[174]. It was designed to print out values of the polynomial coefficients (a), and the initial rate constants (k_1) directly. The program was for the IBM 7040 computer.

The data for the computer were presented on cards as follows. The first card was an identification number (NUM) and the second was used for further identification. The next card contained the number of polynomial coefficients to be computed (M, usually 7), and the number of data points following (N, usually 15-30). Values of t and ($ch - ch_0$) were then presented (T(J) and F(J)), the computer calculating f values (eq 18, p 129) from the ($ch - ch_0$) values given. The last data card was used for constants; the number of minutes between data points (Q); C_T' values for use in eq 18 (R); the initial bromine concentration (CBR2); and the initial ketone concentration (CKET). The computer calculated the polynomial coefficients and the initial rate constant - a typical printout is given in Appendix I.

Initial Bromine Concentrations and Apparatus Calibrations

Eq 17, p 129, the equation relating pH-meter readings (E) to chart paper readings (ch), was obtained as

follows. The standardizing potentiometer on the pH-meter was used to set standard readings on the meter, with the electrodes shorted out. These readings were also recorded on the chart, where the readings were noted. These data were then treated with the linear least-squares program (Appendix I) to obtain eq 17:

$$E = -(0.760 \pm 0.001)ch + (73.79 \pm 0.03) \qquad (17)$$

These values were checked periodically, and remained the same throughout the experimental work.

Values of C_T and C_T', listed in Table XIV, p 146, for use with eq 16 and eq 18 respectively, were calculated using the following values[175]:

$$C_T = 2.3026\frac{RT}{2F} \qquad C_T' = \frac{1}{0.760}\cdot\frac{RT}{2F}$$

$$R = 8.3143 \text{ joules}^{\circ}K^{-1}\text{mole}^{-1}$$

$$F = 9.6487 \times 10^4 \text{ coulombs mole}^{-1}$$

$$1 \text{ joule} = 10^3 \text{ mV coulombs}$$

$$T^{\circ}K = 273.16 + T^{\circ}C$$

Values of E', used for obtaining initial bromine concentrations, were obtained as follows. A stock bromine solution was titrated iodimetrically, by using it to oxidize $I^{\ominus}$, from excess KI, to I_2, and titrating with standard thiosulfate, starch indicator; thus its concen-

tration was known. This known solution was then placed in the cell with all the other reagents, except ketone. The steady potential reached was recorded, at each of the five temperatures used in this work. These values were used to calculate E' values from eq 16; these are tabulated in Table XIII, p 145. The average values of E', used for calculating $[Br_2]_0$ values using eq 16, are tabulated in Table XIV, p 146.

Values of $[Br_2]_0$ at any temperature could thus be obtained from the pH-meter reading before the start of a run; these values were multiplied by a factor of 0.9 to account for the dilution when the ketone solution was added.

Results

The initial ketone and bromine concentrations used for the kinetic runs are listed in Table XV, pps 147-9. The column "run#" is an identification number; missing numbers were used for trial runs or were otherwise unusable (for instance, CH_3COCBr_3 runs 1 and 2 were contaminated with $BrCH_2COCH_2Br$), and are not listed.

The enolization rate constants derived from the kinetic runs are listed in Table XVI, pps 150-2, together with the statistically corrected second-order rate constants derived from them. Average values for the various

TABLE XIII

Values of E', for Use in Determining Initial Bromine Concentrations

$[Br_2]_0$ [a]	$[Br_2]$ in cell [b]	T°C	E, mV	E', mV [c]
2.06 ± 0.01	1.144 ± 0.006	20	495.7 ± 0.1	581.23 ± 0.17
"	"	25	497.0 ± 0.1	584.00 ± 0.17
"	"	30	500.1 ± 0.1	588.54 ± 0.17
"	"	35	503.6 ± 0.1	593.49 ± 0.17
"	"	40	511.0 ± 0.1	602.37 ± 0.17
6.02 ± 0.01	3.344 ± 0.006	20	509.4 ± 0.1	581.41 ± 0.13
"	"	25	511.1 ± 0.1	584.34 ± 0.13
"	"	30	513.5 ± 0.1	587.95 ± 0.13
"	"	35	518.1 ± 0.1	593.80 ± 0.13
"	"	40	525.0 ± 0.1	601.94 ± 0.13
4.17 ± 0.01	2.317 ± 0.006	20	504.8 ± 0.1	581.43 ± 0.13
"	"	25	506.1 ± 0.1	584.04 ± 0.13
"	"	30	509.0 ± 0.1	588.24 ± 0.13
"	"	35	513.0 ± 0.1	593.55 ± 0.13
"	"	40	520.6 ± 0.1	602.47 ± 0.13

[a] Concentration of stock solution, determined by duplicate iodimetric titration; x 10^{-2} M.

[b] 5 Ml. of the stock solution diluted to 90 ml. in the cell; x 10^{-3} M.

[c] Calculated from the expression $E' = E - C_T.\log_{10}[Br_2]$

TABLE XIV

Values of C_T, C'_T and E', for Use in Calculations

T, °C	C'_T [a]	C_T [b]	E' [c]
20	16.6195	29.0835	581.36
25	16.9030	29.5796	584.13
30	17.1864	30.0756	588.24
35	17.4699	30.5716	593.61
40	17.7533	31.0677	602.26
54.8	18.5923	-	-

[a] In chart divisions; for use with eq 18.

[b] In mV; for use with eq 16.

[c] In mV; for use with eq 16; average of the values in Table XIII.

TABLE XV

Initial Ketone and Bromine Concentrations

Ketone	run#	T,°C	E, mV [a]	$[Br_2]_0$, M [b]	$[K]_0$, M
CH_3COCH_3	10	20	493.9	8.851×10^{-4}	0.2002
	11	20	491.0	7.036×10^{-4}	0.2002
	15	25	508.6	2.517×10^{-3}	0.2720
	16	25	508.5	2.497×10^{-3}	0.2720
	17	25	508.4	2.478×10^{-3}	0.2720
	12	30	511.9	2.606×10^{-3}	0.2720
	13	30	509.7	2.201×10^{-3}	0.2720
	14	30	512.4	2.708×10^{-3}	0.2720
	18	35	515.2	2.452×10^{-3}	0.2720
	19	35	515.5	2.507×10^{-3}	0.2720
	20	35	515.7	2.546×10^{-3}	0.2720
	7	40	518.6	1.826×10^{-3}	0.2002
	8	40	518.9	1.867×10^{-3}	0.2002
	9	40	518.4	1.798×10^{-3}	0.2002
CH_3COCH_2Br	9	20	502.2	1.708×10^{-3}	1.491×10^{-3}
	10	20	500.6	1.505×10^{-3}	1.491×10^{-3}
	11	20	501.0	1.553×10^{-3}	1.491×10^{-3}
	4	30	505.9	1.646×10^{-3}	1.491×10^{-3}
	5	30	506.0	1.660×10^{-3}	1.491×10^{-3}
	6	40	521.2	2.214×10^{-3}	1.491×10^{-3}
	7	40	521.9	2.331×10^{-3}	1.491×10^{-3}
	8	40	522.1	2.366×10^{-3}	1.491×10^{-3}

contd.

TABLE XV contd.

Ketone	run#	T°C	E, mV [a]	$[Br_2]_0$, M [b]	$[K]_0$, M
$CH_3COCHBr_2$	9	20	499.0	1.326×10^{-3}	2.110×10^{-3}
	10	20	500.9	1.541×10^{-3}	2.110×10^{-3}
	3	30	507.2	1.818×10^{-3}	2.110×10^{-3}
	5	30	507.9	1.918×10^{-3}	2.110×10^{-3}
	6	40	519.1	1.894×10^{-3}	2.110×10^{-3}
	7	40	519.6	1.966×10^{-3}	2.110×10^{-3}
	8	40	520.2	2.056×10^{-3}	2.110×10^{-3}
$CH_3COC(CH_3)_3$	1	30	469.9	1.046×10^{-4}	1.561×10^{-2}
	2	30	470.4	1.087×10^{-4}	1.561×10^{-2}
$CH_3COCBr(CH_3)_2$	3	30	472.0	1.228×10^{-4}	2.271×10^{-3}
	4	30	471.2	1.155×10^{-4}	2.271×10^{-3}
$CH_3COCBr_2CH_3$	3	30	470.3	1.078×10^{-4}	4.645×10^{-4}
	4	30	470.1	1.062×10^{-4}	4.645×10^{-4}
CH_3COCBr_3	3	30	487.2	3.933×10^{-4}	9.153×10^{-4}
	4	30	487.4	3.993×10^{-4}	9.153×10^{-4}

contd.

TABLE XV contd.

Ketone	run#	T°C	E, mV [a]	$[Br_2]_0$, M [b]	$[K]_0$, M
$BrCH_2COC(CH_3)_3$	1	30	503.0	1.318×10^{-3}	2.057×10^{-3}
	2	30	505.0	1.536×10^{-3}	2.057×10^{-3}
$BrCH_2COCBr(CH_3)_2$	2	30	500.9	1.122×10^{-3}	1.338×10^{-3}
	3	30	499.3	9.936×10^{-4}	1.338×10^{-3}
$CH_3CH_2COCH_2CH_3$	1	30	468.2	9.189×10^{-5}	3.810×10^{-2}
	2	30	468.4	9.324×10^{-5}	3.810×10^{-2}
$CH_3CH_2COCH_2Br$	1	30	511.9	2.606×10^{-3}	3.049×10^{-3}
	2	30	511.9	2.606×10^{-3}	3.049×10^{-3}
$BrCH_2COCH_2Br$	1	30	511.8	2.587×10^{-3}	3.313×10^{-3}
	2	30	511.9	2.616×10^{-3}	3.313×10^{-3}

[a] Initial steady pH-meter reading.

[b] Calculated using eq 16; see p 129.

TABLE XVI

Enolization Rate Constants

Ketone	run#	k_1, $sec.^{-1}$ a	b	k_1^H, $M^{-1}sec.^{-1}$ c
CH_3COCH_3	10	1.276×10^{-7}	6	2.127×10^{-8}
	11	1.083×10^{-7}	6	1.806×10^{-8}
	15	2.361×10^{-7}	6	3.934×10^{-8}
	16	2.399×10^{-7}	6	3.997×10^{-8}
	17	2.364×10^{-7}	6	3.941×10^{-8}
	12	4.387×10^{-7}	6	7.311×10^{-8}
	13	4.385×10^{-7}	6	7.308×10^{-8}
	14	4.519×10^{-7}	6	7.530×10^{-8}
	18	8.013×10^{-7}	6	1.336×10^{-7}
	19	7.975×10^{-7}	6	1.329×10^{-7}
	20	8.110×10^{-7}	6	1.352×10^{-7}
	7	1.430×10^{-6}	6	2.382×10^{-7}
	8	1.441×10^{-6}	6	2.402×10^{-7}
	9	1.432×10^{-6}	6	2.386×10^{-7}
CH_3COCH_2Br	9	1.830×10^{-4}	2	9.150×10^{-5}
	10	1.760×10^{-4}	2	8.802×10^{-5}
	11	1.840×10^{-4}	2	9.202×10^{-5}
	4	6.633×10^{-4}	2	3.316×10^{-4}
	5	6.443×10^{-4}	2	3.221×10^{-4}
	6	1.849×10^{-3}	2	9.245×10^{-4}
	7	1.665×10^{-3}	2	8.325×10^{-4}
	8	1.477×10^{-3}	2	7.385×10^{-4}

contd.

TABLE XVI contd.

Ketone	run#	k_1, $sec.^{-1}$ a	b	k_1^H, $M^{-1}sec.^{-1}$ c
$CH_3COCHBr_2$	9	1.651×10^{-3}	1	1.651×10^{-3}
	10	1.709×10^{-3}	1	1.709×10^{-3}
	3	4.912×10^{-3}	1	4.912×10^{-3}
	5	5.189×10^{-3}	1	5.189×10^{-3}
	6	1.405×10^{-2}	1	1.405×10^{-2}
	7	1.582×10^{-2}	1	1.582×10^{-2}
	8	1.469×10^{-2}	1	1.469×10^{-2}
$CH_3COC(CH_3)_3$	1	2.095×10^{-7}	3	6.984×10^{-8}
	2	1.708×10^{-7}	3	5.692×10^{-8}
$CH_3COCBr(CH_3)_2$	3	2.175×10^{-5}	3	7.249×10^{-6}
	4	2.021×10^{-5}	3	6.736×10^{-6}
$CH_3COCBr_2CH_3$	3	2.304×10^{-4}	3	7.680×10^{-5}
	4	2.283×10^{-4}	3	7.610×10^{-5}
CH_3COCBr_3	3	6.096×10^{-4}	3	2.032×10^{-4}
	4	5.326×10^{-4}	3	1.775×10^{-4}

contd.

TABLE XVI contd.

Ketone	run#	k_1, $sec.^{-1}$ [a]	[b]	k_1^H, $M^{-1}sec.^{-1}$ [c]
$BrCH_2COC(CH_3)_3$	1	1.079×10^{-4}	2	5.393×10^{-5}
	2	1.238×10^{-4}	2	6.191×10^{-5}
$BrCH_2COCBr(CH_3)_2$	2	5.722×10^{-3}	2	2.861×10^{-3}
	3	4.940×10^{-3}	2	2.470×10^{-3}
$CH_3CH_2COCH_2CH_3$	1	3.745×10^{-7}	4	9.363×10^{-8}
	2	3.739×10^{-7}	4	9.347×10^{-8}
$CH_3CH_2COCH_2Br$	1	1.464×10^{-4}	2	7.321×10^{-5}
	2	1.719×10^{-4}	2	8.593×10^{-5}
$BrCH_2COCH_2Br$	1	2.099×10^{-2}	4	5.247×10^{-3}
	2	3.295×10^{-2}	4	8.238×10^{-3}

[a] Pseudo-first-order rate constants, from the computer printout (see p 142).

[b] Statistical correction factor; the number of α-protons available for enolization.

[c] k_1 divided by the correction factor and the acetate concentration (1 M).

ketones are in Table X, p 101.

The data for the linear free-energy correlation, figure 8, p 103, is given in Table XVII, p 154.

The activation parameters for the acetone derivatives (see figure 7, p 95, and Table IX, p 96) were derived from the standard expression[153]:

$$k = \frac{\kappa k T}{h} . \exp(-\frac{\Delta H^{\ddagger}}{RT}) . \exp(\frac{\Delta S^{\ddagger}}{R}) \qquad (26)$$

Dividing eq 26 by T and taking logs, we obtain eq 27:

$$\ln \frac{k}{T} = \ln \frac{\kappa k}{h} - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} \qquad (27)$$

Values of k_1^H and T from Table VIII, p 85, were used to obtain $\ln (k_1^H/T)$, which is plotted against 1/T in figure 7, p 95. These graphs were treated using the linear least-squares computer program (Appendix I) to obtain the best values of slope and intercept. From these,

$$\Delta H^{\ddagger} = - \text{slope} . R$$

$$\Delta S^{\ddagger} = (\text{intercept} - \ln \frac{\kappa k}{h}) . R$$

The constants used were[175]:

$$R = 1.9872 \text{ cals.mole}^{-1}.{}^{o}K^{-1}$$

$$h = 6.62554 \times 10^{-27} \text{ erg}$$

$$\kappa = 1 \text{ (assumed)}$$

$$k = 1.38053 \times 10^{-16} \text{ erg.}{}^{o}K^{-1}$$

$$\ln \frac{\kappa k}{h} = 23.760$$

TABLE XVII

Linear Free Energy Correlation. Data for Figure 8

Ketone	k_1^H [a]	$\log_{10} k_{rel}$ [b]	pK_a [c]	Acid
$CH_3COC(CH_3)_3$	5.69×10^{-8}	0.0000	5.032	$(CH_3)_3CCO_2H$
"	6.98×10^{-8}	0.0889	5.032	"
$CH_3COCBr(CH_3)_2$	6.74×10^{-6}	2.0730	2.902	$BrCH_2CO_2H$
"	7.25×10^{-6}	2.1048	2.902	"
$CH_3COCBr_2CH_3$	7.61×10^{-5}	3.1262	1.48	Br_2CHCO_2H
"	7.68×10^{-5}	3.1300	1.48	"
CH_3COCBr_3	1.78×10^{-4}	3.4940	1.07	Br_3CCO_2H
"	2.03×10^{-4}	3.5527	1.07	"

[a] From Table XVI, in $M^{-1}sec.^{-1}$

[b] k_{rel} is k_1^H divided by the first k_1^H entry for pinacolone.

[c] Values from ref 176.

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ obtained are listed in Table IX, p 96.

The $\Delta G^{\ddagger}$ values listed in Table X, p 101, were obtained as follows. The standard expression[153] is:

$$k = \frac{\varkappa kT}{h} . \exp(- \frac{\Delta G^{\ddagger}}{RT}) \; ;$$

$$\ln k = \ln \frac{\varkappa kT}{h} - \frac{\Delta G^{\ddagger}}{RT} \qquad (28)$$

We can write:

$$\ln k_0 = \ln \frac{\varkappa kT}{h} - \frac{\Delta G_0^{\ddagger}}{RT} \qquad (29)$$

Combining eq 28 and eq 29:

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} - RT \ln \frac{k}{k_0} \qquad (30)$$

To obtain $\Delta G_0^{\ddagger}$ from eq 29, the values on p 153 were used:

for $k_0 = 1 \times 10^{-8}$ $\underline{M}^{-1}\text{sec.}^{-1}$, $\ln k_0 = -18.4207$ and

$\Delta G_0^{\ddagger} = 28.854$ K.cals./mole at 30°.

Eq 30 was then used to obtain the values given in Table X. The value listed there is the mean of that derived from each of the two k_1^H values obtained for each ketone, listed in Table XVI.

APPENDIX I

Computer Programs

Linear Least-Squares Program

This fits a series of data points (x and y) to the straight-line equation $y = mx + c$, using a standard method[177,178]. The input data is the number of points (N) and values of x and y. The program prints out the slope (m) and intercept (c), with their standard deviations. The program is on p 158.

Polynomial Coefficient Program

This fits a series of points f and t to the polynomial expression

$$f = a_1 + a_2 t + a_3 t^2 + a_4 t^3 + \ldots.$$

using standard methods[174]. The method of presenting data is described on p 142. Time values (t) are presented in the form of integers (1, 2, 3, etc.) to reduce round-off error - the numbers become very large (t^{10} being required for 7 coefficients) and double precision computation is required.

The program sets up a matrix of powers of t, and

of f multiplied by powers of t (C-MATRIX) and solves it by elimination[174]. It then prints out the coefficients, and corrects them by changing the t-values from integers back to minutes. The initial rate constant is then calculated from a_2; values of f and f_{new} (calculated using the coefficients) are printed out, and the root-mean-square deviation between f and f_{new} is also found. A typical printout is given on p 162; the program is on pps 159-161.

```
000538 RØBIN A CØX  ************************************************************

EXECUTE PRØGRAM LØADING

000MI 01SEC00900=
                                                                              $$
      $IBJØB          NØDECK                                                  $$
      $IBFTC                                                                  $$
      C-----LEAST SQUARES PRØGRAM.                                            $$
    1       DIMENSIØN X(40), Y(40)                                            $$
    2     100 READ 1, N                                                       $$
    3       1 FØRMAT(I3)                                                      $$
    4         DØ 2 J = 1,N                                                    $$
    5       2 READ 3, X(J), Y(J)                                              $$
    6       3 FØRMAT(2F10.0)                                                  $$
    7         A = N                                                           $$
   10         SIGX = 0.0                                                      $$
   11         SGDXY = 0.0                                                     $$
   12         SGDX2 = 0.0                                                     $$
   13         SIGY = 0.0                                                      $$
   14         SIGY2 = 0.0                                                     $$
   15         SIGXY = 0.0                                                     $$
   16         DØ 4 I = 1,N                                                    $$
   17       4 SIGX = SIGX + X(I)                                              $$
   20         XBAR = SIGX/A                                                   $$
   21         DØ 5 L = 1,N                                                    $$
   22         DELX = X(L) - XBAR                                              $$
   23         SGDXY = SGDXY + Y(L)*DELX                                       $$
   24         SGDX2 = SGDX2 + DELX**2                                         $$
   25         SIGY2 = SIGY2 + Y(L)**2                                         $$
   26         SIGY = SIGY + Y(L)                                              $$
   27         SIGXY = SIGXY + X(L)*Y(L)                                       $$
   30       5 CØNTINUE                                                        $$
   31         SLØPE = SGDXY/SGDX2                                             $$
   32         SYDX2 = (SIGY2 - ((SIGY**2)/A) - SLØPE*SIGXY + (SLØPE*SIGX*SIGY/A) $$
             1)/(A - 2.0)                                                     $$
   33         SB = SQRT(SYDX2/SGDX2)                                          $$
   34         YBAR = SIGY/A                                                   $$
   35         CEPT = YBAR - SLØPE*XBAR                                        $$
   36         SA = SQRT(SYDX2/A)                                              $$
   37         PRINT 6, SLØPE, SB                                              $$
   40       6 FØRMAT(1H0,4X,8HSLØPE  =,E14.6,5X,20HSTANDARD DEVIATIØN =,E13.6) $$
   41         PRINT 7, CEPT, SA                                               $$
   42       7 FØRMAT(1H0,12HINTERCEPT  =,E14.6,5X,20HSTANDARD DEVIATIØN =,E13.6) $$
   43         PRINT 8                                                         $$
   44       8 FØRMAT(1H0,15X,10H**********)                                   $$
   45         GØ TØ 100                                                       $$
   46         END                                                             $$
      $ENTRY
```

```
$JØB   WATFØR  000538 RØBIN A CØX                                          $$
$IBJØB         NØDECK                                                     $$
$IBFTC                                                                    $$
C-----MATRIX PRØGRAM FØR SØLVING  F = A(1) + A(2)T + A(3)T**2 + ....      $$
C-----M = DEGREE ØF PØLYNØMIAL, N = NØ. ØF PØINTS.                        $$
1           DØUBLE PRECISIØN ST(20), C(11,12), A(11), TEMP, CMAX, G, PA, SA, S $$
          1X, D, DØLD                                                     $$
2           DIMENSIØN T(30), F(30), FNEW(30), CK(11), LØC(11)             $$
3         100 READ 52, NUM                                                $$
4          52 FØRMAT(I2)                                                  $$
5             PRINT 53, NUM                                               $$
6          53 FØRMAT(1H1,60X,I3)                                          $$
7             IF(NUM.EQ.10) GØ TØ 50                                      $$
10            READ 1                                                      $$
11            PRINT 1                                                     $$
12             1 FØRMAT(55H                                             ) $$
13            READ 2, M, N                                                $$
14             2 FØRMAT(2I3)                                              $$
15            DØ 3 J = 1,N                                                $$
16             3 READ 4, T(J), F(J)                                       $$
17             4 FØRMAT(2F10.0)                                           $$
20            READ 5, Q, R, CBR2, CKET                                    $$
21             5 FØRMAT(4F10.0)                                           $$
22            DØ 6 J = 1,N                                                $$
23             6 F(J) = EXP(-F(J)/R)                                      $$
C-----FIRST THE C-MATRIX IS SET UP.                                       $$
24            MP = M + 1                                                  $$
25            M2 = 2*MP - 2                                               $$
26            XN = N                                                      $$
27            DØ 8 I = 1,MP                                               $$
30             8 C(I,M+2) = 0.0                                           $$
31            DØ 9 I = 1,M2                                               $$
32             9 ST(I) = 0.0                                              $$
33            DØ 10 J = 1,N                                               $$
34            TEMP = F(J)                                                 $$
35            DØ 10 I = 1,MP                                              $$
36            C(I,M+2) = C(I,M+2) + TEMP                                  $$
37         10 TEMP = TEMP*T(J)                                            $$
40            DØ 11 J = 1,N                                               $$
41            TEMP = T(J)                                                 $$
42            DØ 11 I = 1,M2                                              $$
43            ST(I) = ST(I) + TEMP                                        $$
44         11 TEMP = TEMP*T(J)                                            $$
45            DØ 12 I = 1,M                                               $$
46         12 C(1,I+1) = ST(I)                                            $$
47            DØ 13 I = 2,MP                                              $$
50            K = M - 1 + I                                               $$
51         13 C(I,MP) = ST(K)                                             $$
52            C(1,1) = XN                                                 $$
53            DØ 14 I = 2,MP                                              $$
54            DØ 14 J = 1,M                                               $$
55         14 C(I,J) = C(I-1,J+1)                                         $$
56            MX = MP + 1                                                 $$
C-----C-MATRIX IS NØW SET UP.                                             $$
C-----MATRIX IS NØW SØLVED BY ELIMINATIØN.                                $$
57            DØ 18 I = 1,MP                                              $$
60         18 CK(I) = 0.0                                                 $$
61            DØ 25 I = 1,MP                                              $$
```

```
62            IP = I + 1                                                    $$
63            CMAX = 0.0                                                    $$
64            DØ 21 K = 1,MP                                                $$
65            IF(CMAX - DABS(C(K,I))) 19, 21, 21                            $$
66         19 IF(CK(K)) 20, 20, 21                                          $$
67         20 LØC(I) = K                                                    $$
70            CMAX = DABS(C(K,I))                                           $$
71         21 CØNTINUE                                                      $$
72            IF(DABS(CMAX).LE.10.E-6) GØ TØ 48                             $$
73            L = LØC(I)                                                    $$
74            CK(L) = 1.0                                                   $$
75            DØ 24 J = 1,MP                                                $$
76            IF(L - J) 22, 24, 22                                          $$
77         22 G = -C(J,I)/C(L,I)                                            $$
100           DØ 23 K = IP,MX                                               $$
101        23 C(J,K) = C(J,K) + G*C(L,K)                                    $$
102        24 CØNTINUE                                                      $$
103        25 CØNTINUE                                                      $$
      C-----CØEFFICIENTS ARE NØW FØUND AND PRINTED ØUT.                     $$
104           PRINT 26                                                      $$
105        26 FØRMAT(1HO,5X,23HPØLYNØMIAL CØEFFICIENTS)                     $$
106           DØ 27 I = 1,MP                                                $$
107           L = LØC(I)                                                    $$
110           A(I) = C(L,MX)/C(L,I)                                         $$
111        27 PRINT 28, I, A(I)                                             $$
112        28 FØRMAT(1H ,5X,2HA(,I3,3H) =,E16.8)                            $$
113           A(2) = A(2)/Q                                                 $$
114           DØ 29 J = 2,M                                                 $$
115        29 A(J+1) = A(J+1)/(Q**J)                                        $$
      C-----CØRRECTED CØEFFICIENTS ARE NØW PRINTED ØUT.                     $$
116           PRINT 38                                                      $$
117        38 FØRMAT(1HO,33HCØRRECTED PØLYNØMIAL CØEFFICIENTS)              $$
120           DØ 39 J = 1,MP                                                $$
121        39 PRINT 40, J, A(J)                                             $$
122        40 FØRMAT(1H ,5X,2HA(,I3,3H) =,E16.8)                            $$
      C-----INPUT DATA ARE NØW CØRRECTED BY REMØVING FACTØRS USED TØ REDUCE $$
      C-----  ERRØR, AND FNEW AND IT'S SD CALCULATED.                       $$
123           RATE = (-1.*A(2)*CBR2)/(CKET*60.)                             $$
124           PRINT 51, CBR2, CKET, RATE                                    $$
125        51 FØRMAT(1HO,6HCBR2 =,E13.6,5X,6HCKET =,E13.6,5X,23HINITIAL RATE CØN $$
             3STANT =,E13.6,6H /SEC.)                                       $$
126           PRINT 41                                                      $$
127        41 FØRMAT(1HO,16X,1HT,16X,1HF,15X,4HFNEW)                        $$
130           DF = 0.0                                                      $$
131           DØ 43 J = 1,N                                                 $$
132           T(J) = T(J)*Q                                                 $$
133           FNEW(J) = A(1) + A(2)*T(J)                                    $$
134           DØ 42 I = 2,M                                                 $$
135        42 FNEW(J) = FNEW(J) + A(I+1)*T(J)**I                            $$
136           DF = DF + (F(J) - FNEW(J))**2                                 $$
137        43 PRINT 44, T(J), F(J), FNEW(J)                                 $$
140        44 FØRMAT(1H ,10X,E13.6,4X,E13.6,4X,E13.6)                       $$
141           DF = SQRT(DF/XN)                                              $$
142           PRINT 45, DF                                                  $$
143        45 FØRMAT(1HO,37HR.M.S. DEVIATIØN BETWEEN F AND FNEW =,E16.8)    $$
144           GØ TØ 100                                                     $$
145        48 PRINT 49                                                      $$
146        49 FØRMAT(1HO,25HNØ UNIQUE SØLUTIØN EXISTS)                      $$
```

```
147           GØ TØ 100                                                $$
150        50 STØP                                                     $$
151           END                                                      $$
         $ENTRY
```

1,1,1-TRIBRØMØ-2-PRØPANØNE 3.

PØLYNØMIAL CØEFFICIENTS
A(1) = 0.10116707E 01
A(2) = -0.85117364E-01
A(3) = 0.73422709E-02
A(4) = -0.10238080E-02
A(5) = 0.83852998E-04
A(6) = -0.34374667E-05
A(7) = 0.55261214E-07

CØRRECTED PØLYNØMIAL CØEFFICIENTS
A(1) = 0.10116707E 01
A(2) = -0.85117364E-01
A(3) = 0.73422709E-02
A(4) = -0.10238080E-02
A(5) = 0.83852998E-04
A(6) = -0.34374667E-05
A(7) = 0.55261214E-07

CBR2 = 0.393300E-03 CKET = 0.915260E-03 INITIAL RATE CONSTANT = 0.609602E-03 /SEC.

T	F	FNEW
0.100000E 01	0.932559E 00	0.932952E 00
0.200000E 01	0.864621E 00	0.863850E 00
0.300000E 01	0.801632E 00	0.800753E 00
0.400000E 01	0.738921E 00	0.741327E 00
0.500000E 01	0.685089E 00	0.684194E 00
0.600000E 01	0.627831E 00	0.628668E 00
0.700000E 01	0.575358E 00	0.574513E 00
0.800000E 01	0.524212E 00	0.521757E 00
0.900000E 01	0.469347E 00	0.470531E 00
0.100000E 02	0.419004E 00	0.420961E 00
0.110000E 02	0.372975E 00	0.373089E 00
0.120000E 02	0.327207E 00	0.326842E 00
0.130000E 02	0.282910E 00	0.282036E 00
0.140000E 02	0.238983E 00	0.238419E 00
0.150000E 02	0.195518E 00	0.195761E 00
0.160000E 02	0.153128E 00	0.153971E 00
0.170000E 02	0.113149E 00	0.113269E 00
0.180000E 02	0.750758E-01	0.743876E-01
0.190000E 02	0.385623E-01	0.388125E-01
0.200000E 02	0.908263E-02	0.907150E-02

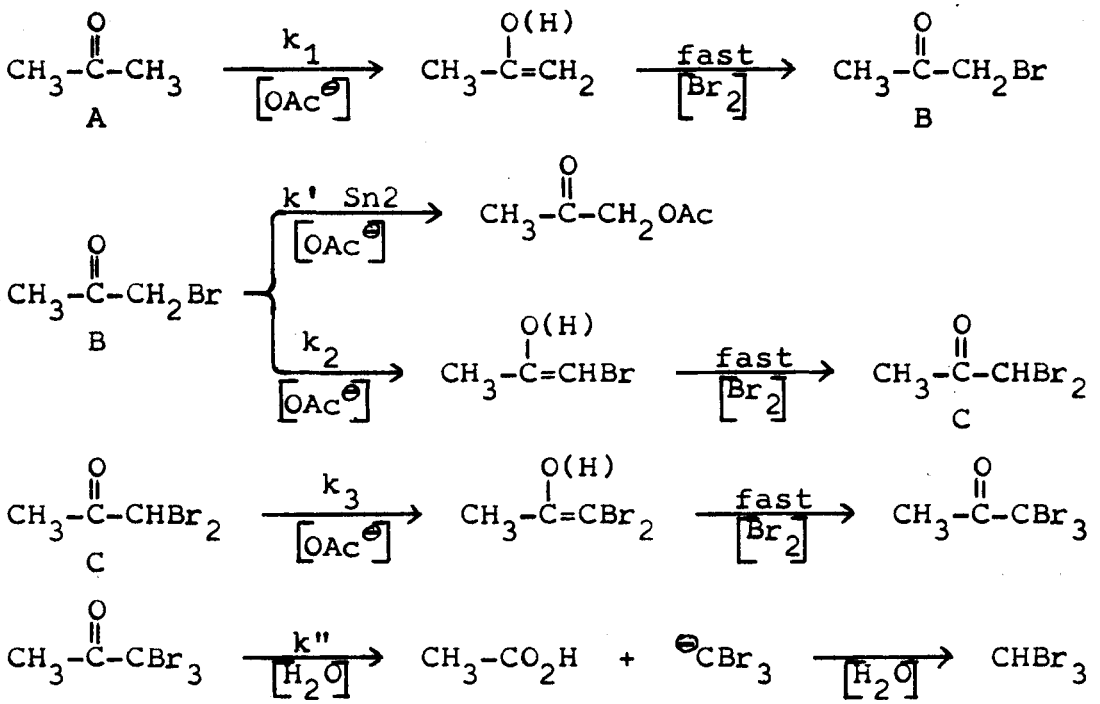
R.M.S. DEVIATIØN BETWEEN F AND FNEW = 0.10800402E-02

APPENDIX II

Rate Expressions

Acetone

The following kinetic scheme is assumed:



Assuming a steady state enol concentration (see p 130):

$$-\frac{d[Br_2]}{dt} = k_1[A] + k_2[B] + k_3[C] \qquad (A1)$$

Here $[OAc^{\ominus}]$ is constant and included in the k's; [A] is held constant.

$$\frac{d[B]}{dt} = k_1[A] - k_2[B] - k'[B] = k_1[A] - k_2'[B]$$

where $k_2' = k_2 + k'$

$$\therefore \int_0^t dt = \int_{[B]_0}^{[B]_t} \frac{d[B]}{k_1[A] - k_2'[B]}$$

$$\therefore \quad t = -\frac{1}{k_2'} \ln \left[(k_1[A] - k_2'[B]) \right]_{[B]_0}^{[B]_t} = 0$$

$$\therefore \quad -k_2't = \ln \frac{k_1[A] - k_2'[B]_t}{k_1[A]}$$

$$\therefore \quad k_1[A]e^{-k_2't} = k_1[A] - k_2'[B]$$

$$\therefore \quad [B] = \frac{k_1}{k_2'}[A](1 - e^{-k_2't}) \qquad \text{(A2)}$$

$$\frac{d[C]}{dt} = k_2[B] - k_3[C] = \frac{k_1k_2}{k_2'}[A](1 - e^{-k_2't}) - k_3[C] \qquad \text{(A3)}$$

This is a first-order differential equation, which can be solved by assuming a solution, differentiating it and equating coefficients:

Assume $[C] = \alpha e^{-k_2't} + \beta e^{-k_3t} + \gamma$ (A4)

then $\frac{d[C]}{dt} = -k_2'\alpha e^{-k_2't} - k_3\beta e^{-k_3t}$ (A5)

Multiplying eq A4 by k_3 gives eq A6:

$$k_3[C] = \alpha k_3 e^{-k_2't} + k_3\beta e^{-k_3t} + k_3\gamma \qquad \text{(A6)}$$

Eliminating $k_3\beta e^{-k_3 t}$ between eq A5 and eq A6 gives

$$\frac{d[C]}{dt} = - k_2'\alpha e^{-k_2' t} + k_3\alpha e^{-k_2' t} + \gamma k_3 - k_3[C]$$

$$= - e^{-k_2' t}(k_2'\alpha - k_3\alpha) + \gamma k_3 - k_3[C]$$

This is identical with eq A3 if

$$\frac{k_1 k_2}{k_2'}[A] = -\alpha(k_3 - k_2') \quad \text{and} \quad \frac{k_1 k_2}{k_2'}[A] = \gamma k_3$$

$$\therefore \quad \alpha = \frac{- k_1 k_2}{k_2'(k_3 - k_2')}[A] \quad \text{and} \quad \gamma = \frac{k_1 k_2}{k_2' k_3}[A]$$

β is evaluated from the limiting condition that $[C] = 0$ when $t = 0$; $[C]_0 = 0 = \alpha + \beta + \gamma \quad \therefore \beta = - \alpha - \gamma$

$$\therefore \quad \beta = \frac{[A]}{k_2'(k_3 - k_2')k_3}(k_1 k_2 k_3 - k_1 k_2 k_3 + k_1 k_2 k_2')$$

$$= \frac{k_1 k_2}{k_3(k_3 - k_2')}[A]$$

$$\therefore \quad [C]_t = - \frac{k_1 k_2}{k_2'(k_3 - k_2')}[A]e^{-k_2' t} + \frac{k_1 k_2}{k_3(k_3 - k_2')}[A]e^{-k_3 t}$$

$$+ \frac{k_1 k_2}{k_2' k_3}[A] \qquad \text{(A7)}$$

We now have $[B]$ and $[C]$, so we can evaluate $[Br_2]_t$, which is the measured variable, from eq A1, as follows:

$$- \frac{d[Br_2]}{dt} = k_1[A] + \frac{k_1 k_2}{k_2'}[A] - \frac{k_1 k_2}{k_2'}[A]e^{-k_2' t} + \frac{k_1 k_2 k_3}{k_2' k_3}[A]$$

$$- \frac{k_1 k_2 k_3}{k_2'(k_3 - k_2')}[A]e^{-k_2' t} + \frac{k_1 k_2 k_3}{k_3(k_3 - k_2')}[A]e^{-k_3 t}$$

$$\therefore \quad -\int_{[Br_2]_0}^{[Br_2]_t} d[Br_2] = k_1[A]\int_0^t dt + \frac{2k_1k_2}{k_2'}[A]\int_0^t dt + \frac{k_1k_2}{k_3 - k_2'}[A]\int_0^t e^{-k_3 t}dt$$

$$- \frac{k_1k_2(2k_3 - k_2')}{k_2'(k_3 - k_2')}[A]\int_0^t e^{-k_2' t}dt$$

$$\therefore \quad [Br_2]_0 - [Br_2]_t = k_1[A]t + \frac{2k_1k_2}{k_2'}[A]t$$

$$- \frac{k_1k_2(2k_3 - k_2')}{k_2'^2(k_3 - k_2')}[A](1 - e^{-k_2' t})$$

$$+ \frac{k_1k_2}{k_3(k_3 - k_2')}[A](1 - e^{-k_3 t})$$

Dividing by $[Br_2]_0$, and writing $A = [A]/[Br_2]_0$, gives eq A8:

$$f = 1 - k_1A(1 + \frac{2k_2}{k_2'})t + \frac{k_1k_2(2k_3 - k_2')}{k_2'^2(k_3 - k_2')}A(1 - e^{-k_2' t})$$

$$- \frac{k_1k_2}{k_3(k_3 - k_2')}A(1 - e^{-k_3 t}) \qquad \text{(A8)}$$

This gives $\left(\frac{df}{dt}\right)_{t=0} = -k_1A$ as it should;

and $\left(\frac{df}{dt}\right)_{t\to\infty} = -k_1A(1 + \frac{2k_2}{k_2'})$

$= -3k_1A$ if k' is negligible.

From p 140, we have, using eqs 23 and 24,

$$a_1 = 1$$

$$a_2 = \alpha + k_2'\beta + k_3\gamma$$

$$a_3 = -\beta\frac{k_2'^2}{2!} - \gamma\frac{k_3^2}{2!}$$

$$a_4 = \beta\frac{k_2'^3}{3!} + \gamma\frac{k_3^3}{3!}$$

and, from eq 22 and eq A8:

$$\alpha = -k_1A(1 + \frac{2k_2}{k_2'})$$

$$\beta = \frac{k_1k_2(2k_3 - k_2')}{k_2'^2(k_3 - k_2')}A$$

$$\gamma = -\frac{k_1k_2}{k_3(k_3 - k_2')}A$$

$$\therefore\ a_2 = -k_1A\left\{1 + \frac{2k_2}{k_2'} - \frac{k_2(2k_3 - k_2')}{k_2'(k_3 - k_2')} + \frac{k_2}{k_3 - k_2'}\right\}$$

$$= -k_1A\left\{\frac{k_2'k_3 - k_2'^2 + 2k_2k_3 - 2k_2k_2' - 2k_2k_3 + 2k_2k_2'}{k_2'(k_3 - k_2')}\right\}$$

$$= -k_1A\left\{\frac{k_2'k_3 - k_2'^2}{k_2'(k_3 - k_2')}\right\}$$

$$\therefore\ \underline{a_2 = -k_1A}$$

$$a_3 = -k_1A\frac{k_2}{2!}\left\{\frac{2k_3 - k_2'}{k_3 - k_2'} - \frac{k_3}{k_3 - k_2'}\right\}$$

$$\therefore\ \underline{a_3 = -k_1A\frac{k_2}{2!}}$$

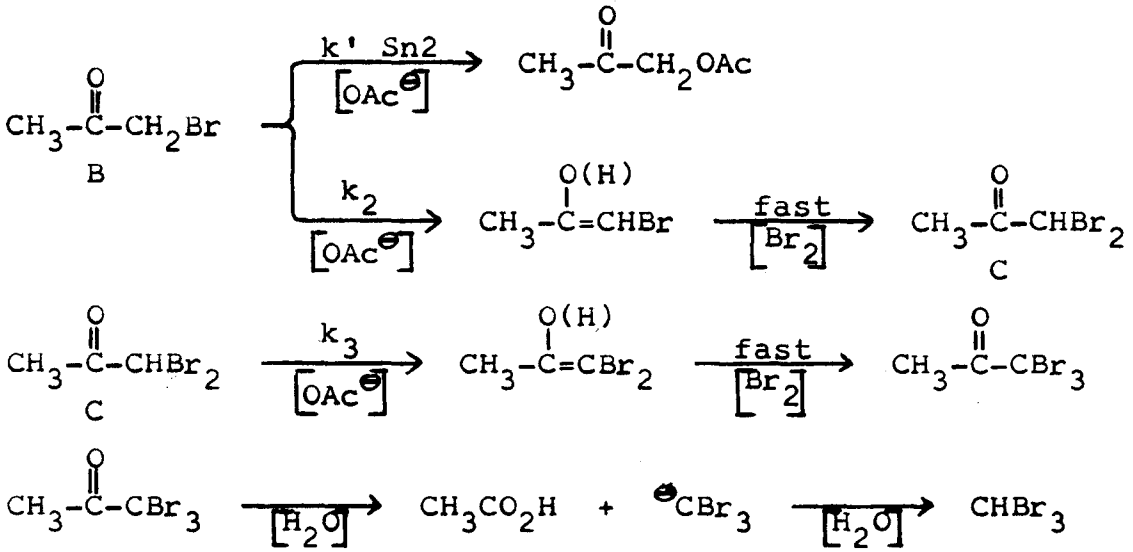
$$a_4 = -k_1A\frac{k_2}{3!}\left\{\frac{k_3^2}{k_3 - k_2'} - \frac{k_2'(2k_3 - k_2')}{k_3 - k_2'}\right\}$$

$$= - k_1 A \frac{k_2}{3!}\left\{\frac{(k_3 - k_2')^2}{k_3 - k_2'}\right\}$$

$$\therefore \quad \underline{a_4 = - k_1 A \frac{k_2}{3!}(k_3 - k_2')}$$

Bromoacetone

The following kinetic scheme is assumed:



Assuming a steady state enol concentration, the rate of bromine removal is given by eq A9. $[OAc^{\ominus}]$ is constant and included in the k's.

$$- \frac{d[Br_2]}{dt} = k_2[B] + k_3[C] \qquad (A9)$$

$$- \frac{d[B]}{dt} = (k_2 + k')[B] = k_2'[B]$$

$$\therefore \quad \int_{[B]_0}^{[B]_t} \frac{d[B]}{[B]} = - \int_0^t k_2' dt$$

$$\therefore \quad \ln\frac{[B]_t}{[B]_0} = -k_2't \qquad \therefore \quad [B]_t = [B]_0 e^{-k_2't}$$

$$\frac{d[C]}{dt} = k_2[B] - k_3[C] = k_2[B]_0 e^{-k_2't} - k_3[C]$$

This differential equation may be solved in a manner similar to that used above, to give:

$$[C]_t = \frac{k_2}{k_3 - k_2'}[B]_0 e^{-k_2't} - \frac{k_2}{k_3 - k_2'}[B]_0 e^{-k_3t}$$

$$\therefore \quad -\frac{d[Br_2]}{dt} = k_2[B]_0 e^{-k_2't} + \frac{k_2k_3}{k_3 - k_2'}[B]_0 e^{-k_2't} - \frac{k_2k_3}{k_3 - k_2'}[B]_0 e^{-k_3t}$$

$$\therefore \quad -\int_{[Br_2]_0}^{[Br_2]_t} d[Br_2] = k_2[B]_0\left\{1 + \frac{k_3}{k_3 - k_2'}\right\}\int_0^t e^{-k_2't}dt - k_2[B]_0 \cdot \frac{k_3}{k_3 - k_2'}\int_0^t e^{-k_3t}dt$$

$$\therefore \quad [Br_2]_0 - [Br_2]_t = k_2[B]_0 \cdot \frac{2k_3 - k_2'}{k_2'(k_3 - k_2')}(1 - e^{-k_2't}) - k_2[B]_0 \cdot \frac{1}{k_3 - k_2'}(1 - e^{-k_3t})$$

Dividing by $[Br_2]_0$, and putting $[B]_0/[Br_2]_0 = B$, we obtain:

$$f = 1 - k_2B \cdot \frac{2k_3 - k_2'}{k_2'(k_3 - k_2')}(1 - e^{-k_2't}) + k_2B \cdot \frac{1}{k_3 - k_2'}(1 - e^{-k_3t}) \qquad \text{(A10)}$$

Dibromoacetone

The following kinetic scheme is assumed:

$$CH_3\text{-}\overset{\overset{O}{\|}}{\underset{C}{C}}\text{-}CHBr_2 \xrightarrow[[OAc^{\ominus}]]{k_3} CH_3\text{-}\overset{O(H)}{\overset{|}{C}}=CBr_2 \xrightarrow[[Br_2]]{\text{fast}} CH_3COCBr_3$$

$$-\frac{d[C]}{dt} = k_3[C] \qquad \therefore \int_{[C]_0}^{[C]_t} \frac{d[C]}{[C]} = -k_3 \int_0^t dt$$

$$\therefore \ln\frac{[C]_t}{[C]_0} = -k_3 t \qquad \therefore [C]_t = [C]_0 e^{-k_3 t}$$

$$-\frac{d[Br_2]}{dt} = k_3[C] = k_3[C]_0 e^{-k_3 t}$$

$$\therefore -\int_{[Br_2]_0}^{[Br_2]_t} d[Br_2] = k_3[C]_0 \int_0^t e^{-k_3 t} dt$$

$$\therefore [Br_2]_0 - [Br_2]_t = [C]_0(1 - e^{-k_3 t})$$

Dividing by $[Br_2]_0$ and putting $[C]_0/[Br_2]_0 = C$ gives:

$$f = 1 - C(1 - e^{-k_3 t}) \qquad \text{(A11)}$$

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