BASE-CATALYZED HYDROGEN-DEUTERIUM EXCHANGE OF A SIMPLE KETONE

THE RELATIVE RATES OF BASE-CATALYZED HYDROGEN-DEUTERIUM EXCHANGE IN METHYL ETHYL KETONE

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SCOPE AND CONTENTS: The relative rates of hydrogen deuterium exchange at the α- and α'-positions in the simplest unsymmetrical ketone were determined by use of N.M.R. spectroscopy.

It has been long held that in base-catalyzed enolization processes the least alkyl substituted α-position is most reactive. However it was observed that in the exchange reaction of 2-butanone catalyzed by OD^- in D_2O, the α- and α'-positions are similarly reactive, while for weaker bases ($p\text{-}NO_2PhO^-$, AcO^-) the most substituted α-position is the more reactive.

The results are discussed in terms of a model for the transition state for enolization, and a continuity of mechanism between the acid-catalyzed, and base-catalyzed processes is proposed.

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TABLE OF CONTENTS

TABLE OF CONTENTS

GENERAL INTRODUCTION

The enolization of ketones is of fundamental interest, and is, moreover, important with respect to reactions of ketones such as halogenation, racemization and isotopic exchange, which are believed to involve the enol as the reactive species. It is pertinent to many synthetic reactions e.g., condensations and alkylations which, while not involving the enol, involve the enolate anion; the same ion proposed for the intermediate in base-catalyzed enolization.

An unsymmetrical dialkyl ketone has TWO different sites of enolization, and in a normal kinetic study it is not easy to differentiate between their reactivities. However the application of N.M.R. spectroscopy to hydrogen-deuterium exchange studies enables one to compare the reactivities of discrete sites within a molecule, rather than to observe the reactivity of the molecule as a whole.

This thesis concerns the exchange of a simple dialkyl ketone in deuterated media as followed by N.M.R. spectroscopy. The relative rates of base-catalyzed exchange of α-CH_2 and α'-CH_3 hydrogens in methyl ethyl ketone have been determined. Contrary to accepted views on the orientation of base-catalyzed enolization, the rates of exchange at the two positions are of the same magnitude for deuteroxide catalysis, and for weaker bases the <u>most</u> substituted site exchanges faster. The results are discussed in terms of the transition state for enolization, and previous evidence is reassessed.

HISTORICAL INTRODUCTION

The study of the enolization of ketones has been carried out largely by the extensive use of halogenation, racemization and deuterium exchange reactions. These areas of study will be presented in turn and correlated in a later section, together with mechanistic interpretations.

(i) Halogenation

(a) Acid-catalyzed

In 1904 Lapworth (1) made the basic discovery that the rate of bromination of acetone in acidic aqueous solution is proportional to the concentration of acetone and to that of hydrogen ion, but is independent of the concentration of bromine. His explanation was that the observed rate is the rate of acid catalyzed enolization of acetone, the bromine reacting rapidly with enol as it is formed.

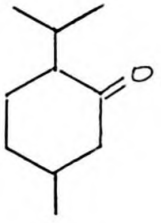
$$CH_3.COCH_3 \xrightarrow[\text{slow}]{H^+} CH_3C(OH):CH_2 \xrightarrow[\text{fast}]{Br_2} CH_3COCH_2Br$$

This explanation was adopted by Dawson and Leslie (2) for the analogous iodination of acetone, which is also zero-order in halogen. Rice and Fryling (3) confirmed that chlorine, bromine, and iodine all react with acetone at the same rate under the same conditions, and also showed that the reactions have the same temperature coefficient.

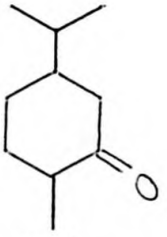
An unsymmetrical ketone $R.CH_2.COCH_3$ can enolize in two directions, viz.

$$R.CH{:}C(OH)CH_3 \longleftarrow R.CH_2COCH_3 \longrightarrow R.CH_2.C(OH){:}CH_2$$

Thus the products obtained from a reaction proceeding through enolization will depend upon which enol is formed preferentially. Kling (4) observed that the products from the monochlorination of methyl ethyl ketone in a slightly acid medium were ~ 80% 3-chloro-2-butanone, and ~ 20% 1-chloro-2-butanone. Similarly the chlorination or bromination of menthone(I) and carvomenthone(II) leads to tertiary halogen compounds as the only identified products (5). In a like manner



(I)



(II)

Dawson and Wheatley (6) found that the rates of iodination of methyl alkyl ketones in acidic solution increase with the size of the alkyl substituent. It is also reported (7) that the use of an acid catalyst in the condensation of methyl ethyl ketone with benzaldehyde leads to reaction at the methylene group, whereas a basic catalyst causes reaction at the methyl group.

These results suggest that for acid-catalyzed enolization the most alkyl substituted α-position enolizes preferentially. If, however, an α-substituent is present which inductively withdraws electrons, the reverse

effect might be observed. Thus Hughes, Watson and Yates found that halogen-substituted acetones react with bromine at slower rates than does acetone (8,9), the inductive effect of the halogen substituent being opposite in sense to that of an alkyl group. Similarly Watson and co-workers observed that the rate of bromination of acetophenone is accelerated by nuclear substituents which inductively release, and retarded by those which inductively withdraw electrons (10). Bartlett and Vincent (11) studied the concomitant acid-catalyzed iodination and racemization of l-menthone (see I, p. 3), and found that 78.7% of the enolic hydrogen came from the asymmetric centre. This corresponds to a ratio of rates of 3.68:1 in favour of the most substituted site.

In the light of such evidence Hughes (12) suggested the analogy between the effects of substituents in acid-catalyzed enolization and in Saytzeff oriented eliminations. It has thus become the accepted view (13-15) that in acid-catalyzed enolization it is the <u>most</u> alkyl substituted α-position which enolizes preferentially. There is evidence which seemingly conflicts with this view, but which is not mentioned in texts on Physical Organic Chemistry (14,15). In 1936 Evans studied the acid-catalyzed bromination of α-alkyl substituted acetophenones (16). In contrast to the earlier work he found that the rates <u>decrease</u> with increasing size of the α-substituent, and that the Arrhenius activation energy correspondingly increases. The significance of this result will be considered later in the discussion.

(b) Base-catalyzed

The first significant study of base-catalyzed halogenation is that of Bartlett. In 1934, he showed that enolization is the rate-determining step in the haloform reaction, and offered an explanation of the unsymmetrical halogenation of acetone observed in basic solutions (17). Bell and Longuet-Higgins obtained precise data (18) which confirmed the rate law observed by Bartlett, and the fact that the rate-determining step is the abstraction of an α-proton.

It became the accepted view that in base-catalyzed enolization the preferred site of attack is the α-position that is least substituted (14,15,19). This view was based upon relatively little data, but correlated well with the views of Hughes and Ingold on β-eliminations (ref. 14, p. 420 et seq.). It was Hughes (12) who suggested the analogy between base-catalyzed enolization and Hofmann oriented eliminations. Evidence for the view was provided by the bromination study of α-substituted acetophenones by Evans and Gordon (20). They found that increasing substitution at the α-carbon decreases the rate appreciably, and increases slightly the Arrhenius activation energy (cf. 16). It was thus concluded that inductive release by the alkyl substituents destabilizes the transition state for the rate-determining formation of the intermediate enolate anion (12,14,19). Similarly Morgan and Watson (21) observed the rate enhancement of the bromination of acetophenones bearing electron - withdrawing substituents on the ring (cf. ref. 10). Likewise haloacetones react faster than acetone itself (9,22). Further evidence quoted by Cardwell (19) is the excellent yields of R.COOH obtained from the action of hypobromite on RCOMe in the degradation of terpenes by Simonsen, and others (23). The author (19)

also quotes examples of the same Hofmann-type orientations (12) observed in condensations catalyzed by strong bases. Recently Cullis and Hasmi (24) have observed that for the hydroxide catalyzed iodination of methyl alkyl ketones, the overall rate decreases with size of the alkyl substituent.

The haloform reaction (23,25) of methyl ketones seemingly supports the hypothesis that base-catalyzed enolization occurs preferentially at the least substituted site. For a large number of methyl ketones R.COMe, the main products isolated are RCOOH, and CHX_3.(X = Hal)(23,25). However, several workers have shown that mixed products may be obtained with simple dialkyl ketones. Sukhevich and Chilingaryan (26) found that under the action of $Ca(OCl)_2$, methyl ethyl ketone gives acetic acid as well as propionic acid, and methyl isobutylketone gives acetic acid as well as iso-valeric acid. Cullis and co-workers have shown that the iodoform reaction is not quantitative (24,27), and that α-halo acids may be produced as well as the aliphatic acids anticipated (24,28). This evidence signifies that enolization at the most substituted site in the parent ketone may be competitive with that at the least substituted site.

It is well known that halogenation is subject to general acid-base catalysis (29), and for a series of homologous carboxylate anions one can obtain a reasonable Brönsted (22,30), or Taft relationship (30).

(ii) Racemization

By 1930 it was a well known fact that optically active ketones, esters and acids are racemized by alkaline reagents only if the α-carbon is the centre of asymmetry and possesses a hydrogen atom. The generally accepted explanation of this phenomenon was the formation of the enol, which, having a plane of symmetry, is as likely upon reketonization to give the d-isomer as

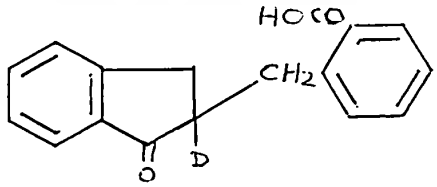
the 1. The investigations of McKenzie (31), and others (32-35) involving various substrates have provided numerous examples in support of this theory.

It was on this basis that Conant and Carlson (36) studied the base-catalyzed enolization of α-optically active, aryl ketones by following their rates of racemization. For catalysis by the alkoxide-alcohol systems they used, they found a linear dependence between the rate and the concentration of the base. No clear correlation between the rate of enolization and the structure of each ketone was apparent to the authors (36), though analysis of their data suggests that there is considerable development of negative charge, and of the enolic double-bond at the transition state.

It has already been mentioned (p. 4) that Bartlett and Vincent (11) used the rate of racemization of l-menthone (see I, p. 3), together with its rate of iodination, to find the relative rates of enolization at the two α-positions in that molecule. Using the same type of procedure Bartlett and Stauffer (37) studied the acid-catalyzed enolization of a series of optically active sec-butyl ketones. For RCOCHMeEt the rates, relative to that of the sec-butyl hydrogen taken as unity, are, for R = Me, Et, $PhCH_2$, cyclo-Hex, 1.56, 3.63, 13.2, and 0.42, respectively (statistically corrected). For the same order of substituents, the rates of enolization of the sec-butyl hydrogen are 0.248, 0.103, 0.0118, 0.0183 (at 25°). Thus the rates of enolization of sec-butyl ketones do not in any sense parallel the competitive rates of the groups introduced. For instance, the benzyl group reacts 5 times as fast as a methyl group, but the total rate of enolization of benzyl sec-butyl ketone is only one-fourth as fast as that of methyl s-butyl ketone. The authors (37) also point out the anomalous behaviour of the ketone having a cyclo-hexyl group.

(iii) Deuterium Exchange

With the discovery of deuterium (38), and the subsequent interest in reactions involving deuterated species, it was not long before the exchange of ketones was studied. Bonhoeffer and Klar (39) observed that exchange between acetone and heavy water was negligible, but that in the presence of a base exchange occurred readily. Subsequently it was shown that the velocity of introduction of deuterium into acetone is linearly dependent upon the concentration of the catalyst (40). Wilson studied the bromination 2-deutero,2-(o-carboxybenzyl)indan-1-one(III)



III

in acetic acid containing sodium acetate. Throughout any experiment the first-order rate constant remained sensibly constant, proving that no hydrogen-deuterium exchange with the medium could have occurred by any unknown mechanism ahead of the measured reaction (41).

Very recently Kursanov, and co-workers (42) have studied the exchange of various ring-substituted acetophenones in the EtO^- - EtOD system, and found that electron-withdrawing groups (p-NO_2,p-Br) cause rate enhancement, whereas electron-releasing groups (p-OMe,p-NMe_2) cause rate retardation (cf. refs. 10,21). Their results give a good Hammett σ-ρ plot, with $\rho = 1.43$. This indicates that the reaction is quite sensitive to a change of the p-substituent, and in particular there is considerable development of negative charge in the transition state (cf. p. 7, ref. 36). Dessy and co-workers (43) have studied the effect of ring size upon the base-catalyzed

exchange of homologous cyclic ketones in D_2O-DMF media. They rationalize their results in terms of the s-character of the carbon-orbital directed towards the enolizable hydrogen as a function of ring size.

It is only recently that N.M.R. spectroscopy has been used to study the rates of deuterium exchange of a ketone. Markentin and Lam (44) found the relative rates of exchange of vinylic and allylic hydrogens in 6,6-dimethyl cyclo-hex-2-en-1-one. The technique they employed has been further utilized in the work described in this thesis.

(iv) Correlation of Enolization Processes (i-iii).

Enolization was invoked to explain the halogenation, racemization, and deuterium exchange of ketones (vide supra), and in the mid-thirties it was clearly shown that these processes all have the same rate-determining step, both for acid- and base-catalysis.

For acid-catalysis, Ingold and Wilson (45) showed that the rates of racemization and bromination of 2-o-carboxybenzylindan-1-one are identical. The same was found to be true for d-phenyl sec-butyl ketone (37). Reitz (46) then demonstrated that the initial rate of bromination of acetone in heavy water, catalyzed by D_3O^+, is equal to the initial rate of uptake of deuterium by acetone in the absence of bromine. Thus the three processes are identically rate-controlled.

Using phenyl sec-butyl ketone Kau and Wilson (47) showed that base-catalyzed bromination and racemization have identical rates. The same ketone was also shown to racemize in a D_2O-dioxan medium at the same rate at which deuterium was incorporated, OD^- being the catalyst (48). Clearly then, for base-catalysis also, halogenation, racemization, and

deuterium exchange involve the same rate-determining step, and if enolization is invoked to explain one of the processes, it must be used for all of them.

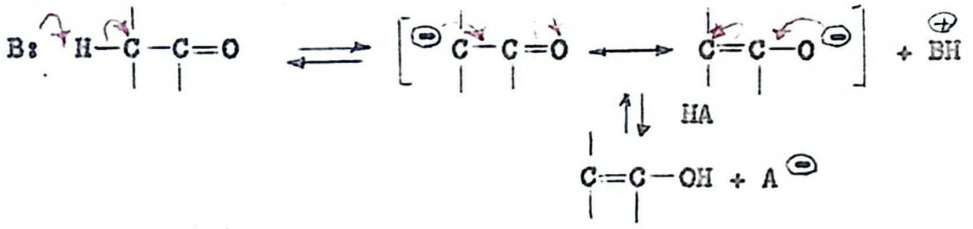
(v) Mechanistic Interpretations

Although the gross identity of the rate-determining step of the processes reviewed above was readily established to be enolization of the substrate, mechanistic details concerning enolization have been more difficult to obtain. In this section is summarized the historical development of ideas concerning the detailed mechanistic description of enolization.

The mechanism of enolization and other prototropic changes was discussed by Lowry (49), Ingold, Shoppee and Thorpe (50), and Baker (51) in terms of the electronic theory of valency. Lowry believed that prototropic changes are not spontaneous, but depend upon the presence of other molecules in the system. Experiments on the bromination of acetone, pyruvic acid, and laevulic acid in chloroform or carbon tetrachloride (52) confirmed Lowry's view. In aqueous solution these substances react with bromine at a slow rate, i.e., slow enolization takes place, but in anhydrous solvents there is a relatively rapid reaction after an initial latent period, the duration of which is not reproducible. The experimental facts point, therefore, to the conclusion that enolization takes place only when some outside agent is introduced or developed in the system.

Lowry proposed that prototropic changes are possible only in the presence of both a proton donor and a proton acceptor. The change consists of the release of a proton to the acceptor, and the gain of a proton from

the donor, rather than the transference of a proton from one point in the molecule to another. This theory, as applied to the mutarotation, was verified in a striking manner by the observation (53) that, although pyridine and cresol are individually poor catalysts for the mutarotation of tetramethyl glucose, the two acting in conjunction form a powerful catalyst. Lowry's view was, therefore, that two catalytic agents are necessary for the promotion of prototropic changes. As an extension of these ideas he postulated a mechanism which may be formulated as follows.



According to this scheme, the catalysts have no function other than that of proton acceptor or donor.

Baker (51) put forward a somewhat different view of the effects of catalysts on prototropic changes. On the basis of a mechanism suggested by Ingold, Shoppee and Thorpe to represent the interconversion of three carbon tautomerides (50), he suggested that catalysts are of two types:

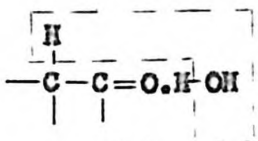
(a) those which attack the enolizable proton directly, and

(b) those which facilitate indirectly its liberation (by protonation of the carbonyl compound at oxygen, for example).

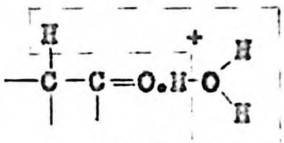
It was pointed out by Meyer (54) that acids catalyze enolization far more powerfully in non-ionizing than in ionizing media - i.e., the acid exerts a far greater influence when in the covalent state than when ionized. This

fact has further been demonstrated by the measurements of the speeds of halogenation of carbonyl compounds in different media (52), and particularly by the observation that, in moist chloroform, the bromination of acetone, pyruvic acid and laevulic acid (autocatalysed by HBr), is very much slower than in dry chloroform. To Watson (55) it was difficult to understand how this could be the case if catalysis required both a proton donor and a proton acceptor. He suggested that the observed effects of water and acids upon enolization might perhaps be interpreted by a scheme, which includes the ideas of both Lowry and Baker. Water was regarded as merely giving and accepting a proton, while acids combine these functions with that of facilitating the removal of the proton (Baker, second-type, p.10).

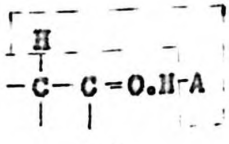
Watson argued as follows: in carbonyl compounds there is doubtless a partial appropriation of electrons by the carbonyl oxygen (55), which will result in the α-hydrogens being in a state of "incipient ionization" (50,57), i.e., the electrons forming the α C-H bond are not shared equally, but more in the "sphere of influence" of the carbon nucleus. Considering the case of enolization, (a) in pure water, (b) in acidic aqueous solution, (c) in non-ionizing media in the presence of acids, the agents by which the change is induced are respectively, (a) H_2O, (b) H_3O^+, (c) the covalent acid. He regarded these as co-ordinating with the carbonyl oxygen to give respectively,



(a)



(b)



(c)

The co-ordinated group thus provides a proton. In case (b) and (c), an additional influence comes into play, for the "inductive effect" (58) of the positive pole in (b) and of the electronegative atom A in (c) will augment the electron shifts which lead to the ionizing of the proton, and will thus facilitate enolization. The remainder of the co-ordinated group (OH^-,H_2O,A^-) will then withdraw the incipiently ionized hydrogen atom, and these processes, together with the concomitant reassembly of electrons within the molecule, will result in the formation of the enol.

On this scheme of Watson's (55), water acts only as a proton acceptor or donor, as in Lowry's mechanism, while acids, ionized or covalent, also accelerate the change by facilitating ionization of the α-hydrogen through an inductive effect. He thus attempted to explain the catalytic effect of acids, and, moreover, the superiority of covalent to ionized acids as catalysts, since the α-proton will clearly unite with a negative ion A^- to give a covalent acid more readily than with a neutral water molecule to give H_3O^+.

Lowry's mechanism, which involved synchronous participation of a proton donor, and an acceptor (49), was criticized by Baker (51,59) on the grounds that polar substituents did not affect the rate of mutarotation of certain sugar derivatives in the manner expected for such a mechanism. However, the synchronous mechanism is complicated enough not to be wholly unequivocal in requirements of this nature (*ref.* 14, p.551). Pedersen (60) objected to such a mechanism on the basis of an analysis of the kinetic data for the mutarotation of glucose, and the halogenation of acetone. The rate of prototropy of a system S in the presence of an acid

BH, and a base B^-, is given by

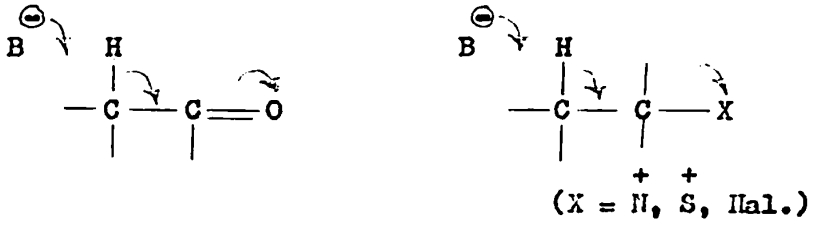
$$\text{rate} = [S]\left(k_1[BH] + k_2[B^-] + k_3[BH][B^-] \right) .$$

Each of the terms $k_1[S][BH]$, and $k_2[S][B^-]$ might represent either a two step, or synchronous mechanism. However Pedersen (60) argued that, since the observed rate does not contain a term of the expected magnitude corresponding to $k_3[S][BH][B^-]$, the synchronous mechanism is unimportant in those systems considered. However, Swain (61) has since pointed out that this objection was over-pressed, because kinetic ambiguities are present. It is not possible to distinguish between a term in $[S][BH][H_2O]$, and one in $[S][B^-][H_3O^+]$, or a term in $[S][B^-][H_2O]$, and one in $[S][BH][OH^-]$. Thus it is not certain that the diagnostic term $k_3[S][BH][B^-]$ is as important as Pedersen supposed. Pedersen's argument does not, therefore, exclude the synchronous mechanism. Neither, of course, does Swain's observation preclude a step-wise mechanism.

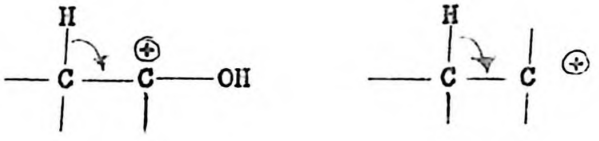
It has been mentioned earlier (p. 3-4) that α-alkyl substituents facilitate acid-catalyzed enolization (5-8), while α-halogen substituents are rate-retarding (8,9). When the bromination of haloacetones was commenced by Watson and co-workers (8,9), it was anticipated that the presence of the α-halogen would increase the ease of loss of the α-proton, and thus the rate should be faster than that for acetone itself. In aqueous solution, and without a catalyst, this was observed. However, in the presence of an acid catalyst, acetone reacted faster. To explain this result, the process was considered to be step-wise, the first step being co-ordination between the carbonyl oxygen and a hydroxonium ion (52,55).

Now clearly the presence of a -I substituent (14, p.71) alpha to the carbonyl opposes the appropriation of electrons by the carbonyl oxygen, and thus reduces its capacity for co-ordination (8). On the other hand a +I substituent (14, p.71) facilitate co-ordination with a positively charged species. The observed effects of ring substituents upon the rate of reaction of acetophenone (10) may also be explained in the same way.

For base-catalysis the effect of substituents is reversed, i.e., +I substituents are rate-retarding; -I substituents are rate-enhancing (9, 20-22). This being the case, Hughes (12) suggested that enolization might be considered as "internal" elimination, base-catalysis being analogous to a "Hofmann-type" elimination (E2),



the formal difference being only that the C=O group does not break up, whereas the C-X group does. Similarly acid-catalysis is analogous to a "Satyzeff-type" elimination from a carbonium ion (E1).



This being the case, the reasoning invoked to explain the orientations of β-eliminations (62), might be applied to acid- and base-catalyzed enolizations. Substituents influence eliminations both by the inductive and

the conjugative modes of electron displacement (ref. 14, p.420 et seq.). Either mode may become dominant and lead to Hofmann-type or Saytzeff-type orientation, as determined by the polarity and unsaturation of the substituents, or for alkyl substituents, by the polarity of the leaving group X (vide supra). The point of Hughes's comparison was that we might expect the same two types of structural effects to be operative in prototropic changes, and he showed, by examples of structural effects on both prototropic rates and equilibria (12), that this same concept of electronic dualism could describe the pattern of constitutional influences on prototropy.

Cardwell and Kilner (19,63) extended Hughes's hypothesis and pointed out that, while for acid-catalyzed substitution of ketones, orientation follows almost exclusively the Saytzeff rule (64), for base-catalyzed substitution both Hofmann and Saytzeff orientations may be observed (19). By analysis of kinetic data, Cardwell (19) suggested that the two opposing orientations may be due to the fact that alkyl groups inductively hinder the loss of the α-proton to a base, but once this has occurred they stabilize the resulting enolate anion in a hyperconjugative manner.(cf. p. 23)

For the particular case of methyl ethyl ketone, which can form two different enolates:

it was predicted (19) that a substituting agent which reacts with the enolate as soon as it is formed will give rise to $Et.CO.CH_2X$ (Hofmann-type). However, if conditions are used which allow equilibration of the

enolate ions before substitution takes place, the product will largely be MeCHXCOMe, the Saytzeff-oriented product.

Cardwell's hypothesis is not tenable, since hyperconjugative stabilization of the enolate anion (per se) is unlikely (see p. 21 ff, ref. (72)). However if the intermediate is enol, or a strongly solvated enolate it may be justifiable.

Analysis of kinetic data for the acid-catalyzed halogenation of dialkyl ketones consistently suggests hyperconjugative rate-control by the alkyl substituents (63). The relationships are, indeed, closely similar to those for bimolecular olefin elimination from alkyl bromides (ref. 14, p. 438, Table 31-8), a reaction of typical hyperconjugative rate-control, as summarized in the generalized Saytzeff rule (loc. cit.).

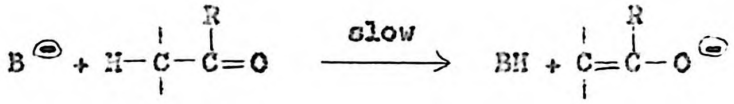
Concerning the reason why hyperconjugation is dominating in the control of acid-catalyzed enolization rates by alkyl groups, although the inductive effect assumes this role for base-catalyzed enolization, Cardwell and Kilner (63) suggested that much more unsaturation develops, through partial carbonium-ion formation, in the transition state of acid-catalyzed enolization, than in the base-catalyzed reaction. In the specific case of hydrogen-ion catalysis, the effective initial tautomer is not the ketone itself, as in base-catalysis, but the conjugate acid of the ketone.

$$\rangle CH-\overset{|}{C}=\overset{+}{O}H \longleftrightarrow \rangle CH-\overset{|}{\overset{+}{C}}-OH$$

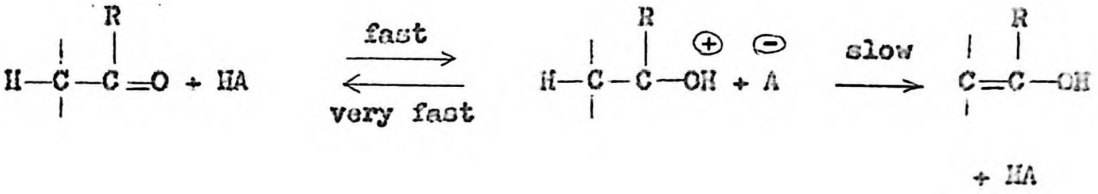
As in unimolecular olefin formation (31), which follows the generalized Saytzeff rule, such a development of carbonium-ion character would excite strong hyperconjugation by alkyl groups in the transition state for the

formation of the C=C double-bond (ref. 14, Chapter VIII, Section 3le).

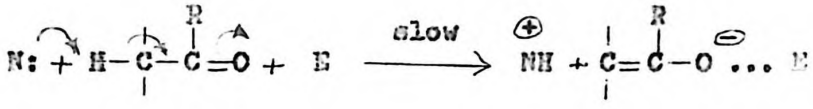
The question of the molecularity of enolizations was resurrected by Swain in 1950 (61). For the enolization of ketones it was currently accepted that there are two different mechanisms: base-catalyzed and acid-catalyzed (64,65). In the base-catalyzed mechanism only a base, or nucleophilic reagent, is involved.



In the acid-catalyzed mechanism only an acid, or electrophilic reagent, is involved in initiating enolization.



However instead of these two different mechanisms Swain suggested that there might be only a single mechanism, a concerted or push-pull mechanism, which holds in all cases, requiring the united action on the ketone in the rate-determining step of both a nucleophile and an electrophile (cf. Lowry, ref. 49).



The nucleophile N might be either uncharged (as shown) or negatively charged: it might be OH^-, AcO^-, H_2O or any other base. The electrophile E might be either uncharged (as shown) or positively charged:

it might be Cu^{++}, H_3O^+, HOAc, H_2O, or any other acid or species capable of solvating an anion. The product would be either the solvated enolate anion (as shown) or an enol, or enol derivative depending upon the nature of the electrophile E, i.e., on whether it (or a fragment of it such as H^+) covalently bonds to the oxygen atom. The strongest kind of pull would be one that does lead to the formation of a covalent bond between oxygen and the electrophilic reagent, but an electrostatic solvation (as shown) will suffice.

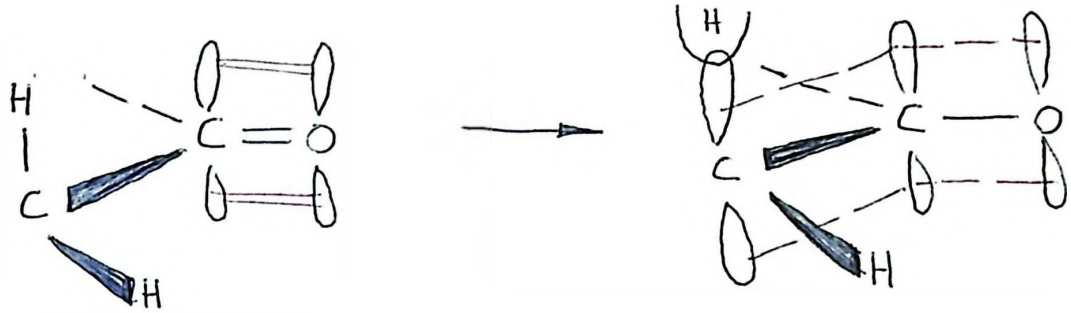
This hypothesis of Swain's is compatible with rate data for the enolization of ethyl acetoacetate, the mutarotation of glucose, and the enolization of acetone (61). As mentioned previously (p. 14), Swain disagreed with Pedersen's interpretations of rate data (60) on the grounds of failure to recognize the ambiguities of some of the kinetic terms. He concluded that the enolization of acetone catalyzed by acetic acid involves mainly acetate ion as the nucleophile, and hydroxonium ion as the electrophile. It was still in doubt whether their action was concerted or stepwise, although Swain (61) favoured the former by analogy with mutarotation.

Bell and Jones (66) confirmed the results of Dawson and Spivey, the same results which Pedersen (60) and Swain (61) had discussed in terms of their respective hypotheses, and maintained that from their rate data it was not possible to decide whether or not the main reaction was via a concerted mechanism. They examined some consequences of a concerted mechanism, on the basis of other available experimental evidence, and concluded, however, that such a mechanism is not of major importance in reactions of ketones catalyzed by acids and bases in aqueous solution.

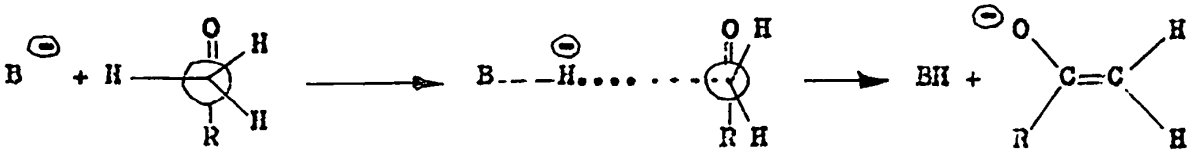
Subsequently, Swain and co-workers (67) showed, by use of isotope effects, that enolization catalyzed by acetic acid involves a pre-equilibrium proton transfer to the carbonyl oxygen, followed by a rate-determining abstraction of an α-proton by acetate ion. Catalysis by acetate ion alone involves a similar proton abstraction, assisted by hydrogen bonding of water to the carbonyl oxygen. Mineral-acid-catalyzed reactions are attributed to a mechanism analogous to that for acetic acid (67), but with water as the nucleophile (68).

In an attempt to gain further information regarding the transition state for enolization and ketonization, some workers have undertaken stereochemical studies. Zimmerman (69) found the stereochemistry of ketonization to be determined by preferential attack of a proton donor on the least hindered side of the enolic double-bond. In a subsequent paper (70), he presents further stereochemical evidence which supports the idea that the transition state for enolization or ketonization closely resembles the enol. A similar conclusion was reached by Corey and Snoen (71) who studied the acid-catalyzed enolization of a cholestanone. The magnitude of the isotope effect (k_H/k_D = 7.4) they observed for 3β-acetoxy-6-deuterocholestan-7-one indicated almost complete rupture of the α C-H bond in the transition state, and suggested a model for the transition state considerably more like the enol in structure than like the conjugate acid of the ketone. In further agreement with the stereochemical work of Zimmerman, they showed that there is stereoelectronic control of enolization in such systems, since axial α-hydrogens are preferentially abstracted, so as to allow the maximum π-overlap of the rupturing α C-H bond with the

carbonyl π-system.



In the general case this should mean that the α-hydrogen abstracted will be that which is most closely perpendicular to the nodal plane of the π-system.



transition state

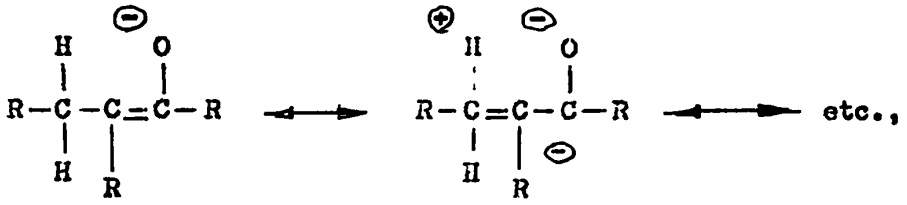
Emmons and Hawthorne (72) determined the primary and secondary isotope effects for acid-, and base-catalyzed enolization of phenyl cyclopentyl ketone, as summarized below.

Medium	k^H/k^D (primary)	k^H/k^D (secondary)
H_2O,ACOH,ACONa	6.17	1.24
H_2O,ACOH,HCl	3.96	1.21

The primary isotope effect of 6.17 for the base-catalyzed reaction indicated that the α C-H bond is quite loose in the transition state. The smaller value of 3.96 for the acid-catalyzed reaction is consistent with proton abstraction from the conjugate acid of the ketone. The rather large secondary isotope effects of 24% and 21% are particularly noteworthy. If the secondary deuterium isotope effect is a valid measure of hyperconjugation (73), it is reasonable to propose that the transition state for enol formation is very close to enol itself, and is stabilized to a very appreciable extent by hyperconjugation with β C-H bonds. Since an enol is a high energy species relative to ketone, Hammond's postulate (74) suggests that the transition state for enolization would be closer to enol in its geometry. The stereochemical evidence of Zimmerman (69,70) and the work of Corey and Sneen (71) confirm this hypothesis. Thus it is not surprising that hyperconjugation is the dominating factor in determining the direction of acid-catalyzed enolization in an unsymmetrical ketone (vide supra., pp. 16-18). The most striking fact is that the base-catalyzed reaction showed a secondary isotope of around 20%. This is far beyond the experimental error, and suggests that the postulate of an anion (14) as an intermediate in this reaction is incorrect, and that Swain's concerted mechanism (62) of ketone enolization more accurately represents the facts, at least under the experimental conditions that Emmons and Hawthorne employed.

It is highly improbable for an enolate anion, or a transition state leading to it to derive significant stabilization from hyper-

conjugation, since it would involve high-energy canonical forms



which violate the adjacent charge rule. Thus the existence of this significant secondary deuterium isotope effect in base-catalyzed enolization is inconsistent with an intermediate enolate ion, but may be explained using Swain's concerted mechanism (p.18). The concomitant action upon the substrate ketone precludes much development of negative charge in the ketonic body at the transition state, and thus any electrostatic inhibition of hyperconjugation is obviated.

In their paper which postulated the Alternate Rule, Swain and Thornton (75) devoted some space to enolization. From the relatively large magnitude of the solvent isotope effects (H_2O vs. D_2O), when H_2O or OH^- is the nucleophile (68,76), they inferred that the transition states for enolization are generally closer to products than to reactants. Accordingly, the shortest bond to the α-hydrogen at the transition state is the one to the oxygen of the nucleophile, and the α-hydrogen isotope effect should be affected most by changes in the length of this OH bond. (Furthermore, the $C_\alpha H_\alpha$ bond is further removed and so likely to be less affected by changes in the nucleophile.) Therefore, the stronger the base used, and the weaker the developing OH bond, the larger should be the primary isotope effect. Since hydroxide lacks the extra electron-attracting

proton of water, it should have a longer bond to the α-proton at the transition state, and thus give a larger α-hydrogen isotope effect.

A symmetrical transition state gives a maximum isotope effect because the α-hydrogen has no symmetric or asymmetric stretching frequencies, as it does in the initial state, and thus the difference in zero-point energies of the transition states for the protiated and deuterated substrates is minimal, and the difference in activation energy is maximal (77). With a stronger base the developing O-H bond will be less developed at the transition state, and the latter will be more symmetrical, and thus the primary isotope effect will be larger. There is in fact a progressive increase in this isotope effect from water to acetate ion to hydroxide ion for α-phenyl isocaprophenone (67a). Similary the k_H/k_T isotope effect for enolization of this substrate is larger for acetic acid catalysis (11.4) than for acetate ion catalysis (10.2), because the α C-H bond is shorter and the transition state more symmetrical with the electron-attracting proton on the carbonyl oxygen in place of no substituent.

Bunton and Shiner have suggested a model for predicting the solvent isotope effects for various reactions (78). For the abstraction of a proton by hydroxide ion, a hydrogen-bond between the base and a water molecule will be broken at the transition state, and they predict an effect of 0.79. In the case of base-catalyzed enolization, an effect greater than this is anticipated depending upon the extent that negative charge developes on the carbonyl oxygen. If the oxygen held a unit negative charge, k^{H_2O}/k^{D_2O} should equal 1.1. The experimental value is 0.69 (79), which suggests that either their model is inapplicable to this reaction, or more

probably that there is an error in assuming that a unit negative charge is located on the enolic oxygen in the transition state (78).

A theoretical treatment of proton transfer reactions has recently been published by Bader (80). He theoretically justified the conclusion that, in analogous transition states for proton abstractions, the stronger the base used, the less tightly bound to it will be the proton at the transition state (vide supra, refs. 67,75,78,81). For a system

$$A—H \cdots B \longrightarrow A \cdots H—B,$$

"the original A–H bond must be progressively lengthened to attain the transition state as the strength of the base (B) is decreased" (80). Thus in enolization, a weaker base will result in the transition state being farther along the reaction co-ordinate, i.e., closer to the product.

It is noted, in passing, that very recently Hulett has sought evidence for proton-tunnelling in enolization reactions. In the base-catalyzed bromination of di-isopropyl ketone, the Arrhenius plot shows a marked curvature, attributed to proton-tunnelling (81). At low temperatures the plot for acetone is also curved (82), but cannot be attributed to tunnelling, as the hydrogen-deuterium isotope effect on the Arrhenius parameters is small, and the Arrhenius plot for acetone-d_6 is also curved. Hulett ascribes these latter results to a specific medium effect (82). Such studies as this one by Hulett are useful in that they can afford values for the height and width of the potential barrier for the reaction concerned.

RESULTS AND DISCUSSION

The work presented in this thesis was begun in the hope that a clearer picture of the transition state for base-catalyzed enolization would be obtained by unequivocal determination of the preferred sites of attack in simple dialkyl ketones. In this section the observed results are discussed in the light of previously accepted beliefs, and a model for the transition state is proposed which is not unlike that of Swain's (61).

It has been long held that the preferred site of attack in base-catalyzed enolization is that which is less alkyl substituted (14,15). However the first observation made in this study contradicts this belief. In the exchange of MIK in D_2O, with OD^- as the catalyst, and at ambient temperatures, the α-methylene and α'-methyl protons are exchanged for deuterons at roughly <u>equal</u> rates. Kinetics conducted at 0^oC yield the same result.

Rates of Exchange for OD^- catalysis at various temperatures

Temp. °C	Conc. MEK	Conc. OD^-	$k^a.10^4$ sec.$^{-1}$	$k^{a'}.10^4$ sec.$^{-1}$	$k^a/k^{a'}$
~ 35°	1.67	.0406	24.0±1.0	22.7±0.6	1.06±.07
~35°	1.40	.0205	13.6±0.3	13.6±0.1	1.00±.02
~35	1.65	.0094	5.35±.10	5.23±.04	1.03±.03
~15	1.1	.0417	5.01±.27	4.33±.10	1.16±.09
0.00±.05	2.2	.03925	1.74±.07	1.82±.04	0.95±.06
0.00±.05	2.2	.03925	1.78±.12	1.71±.04	1.04±.09
0.00±.05	2.2	.03925	1.93±.18	1.88±.08	1.03±.12
0.00±.05	1.1	.03925	2.50±.15	2.09±.05	1.20±.10

The immediate inference from these results is that destabilization of the transition state, which is supposed to resemble enolate, by electron-releasing α-substituents is not important as was previously thought. Alternatively it can be concluded that the intermediate is not the enolate as such.

If we postulate that the transition state resembles enol*, electron-releasing substituents can be a stabilizing influence by inductive release to the more electronegative sp^2 carbon (84), and by hyper-conjugation with the incipient double-bond (cf. ref. 12). Increasing substitution can also have a deleterious effect in that approach to the α-positions becomes hindered, and the solvent shell of the carbonyl oxygen becomes disturbed (vide infra p.32). In the case of methyl ethyl ketone the

*It might also resemble a strongly hydrogen-bonded enolate. In either case there is negligible charge in the ketonic body at the transition state, which may thus be considered as enol-like.

α-methylene group should be favoured by virtue of electron-release, while the α'-methyl group should be favoured for steric reasons*. If this presents a true picture of the situation it seems that in the case of catalysis by OD^- (p. 27) the two effects cancel out.

The use of a weaker base necessitates greater rupture of the α C-H bond at the transition state** (80), which is accordingly farther along the reaction coordinate. Thus the transition state is even closer to the enol, and the incipient C=C double-bond is more developed. Any stabilization by electron-releasing substituents is thus greater (vide supra). It might therefore be expected that, in catalysis by weaker bases than OD^-, the α-methylene protons of MEK would exchange preferentially. This has been observed.

Variation of Rates with Base Strength

Base	Temp.	Catalytic constants† ($M.^{-1}sec.^{-1}$)		Ratio α:α'
(Na^+ salt)	(°C)	$\alpha\text{-}CH_2$	α'-Me	
OD^-	0.00±.05	$4.64\pm.23\times10^{-3}$	$4.59\pm.13\times10^{-3}$	1.01±.09
$p\text{-}NO_2PhO^-$	59.2±.03	$1.34\pm.07\times10^{-4}$	$8.93\pm.78\times10^{-5}$	1.50±.21
AcO^-	59.2±.03	$1.18\pm.05\times10^{-6}$	$5.47\pm.70\times10^{-7}$	2.16±.36

*It is unreasonable to invoke the different acidities of the α-methyl and the α-methylene protons, since the process is not considered to proceed via the enolate ion, and is also not an equilibrium process.

**This is consistent with the Swain-Thornton Rule (75).

†Those for OD^- are calculated from the average of the 3 values determined for 2.2M ketone (See Table p. 27). Those for the other two bases are derived in a manner described in the Experimental section.

As the base-strength decreases, OD^- to p-NO_2PhO^-, to AcO^-, the ratio of the rates (α:α') increases as 1.0 to 1.5 to 2.2. This is consistent with the postulation of an enol as the intermediate, but not with an enolate as such.

If the intermediate in the system studied were the charged enolate anion, and if the transition state resembled this, a change in the ionic strength of the medium should affect the rates noticeably* (cf. ref. 14, p. 360). The table below shows the effect of ionic strength upon the rates of catalysis by p-nitrophenoxide ion at 50.0°C.

Variation of Rates with Ionic Strength

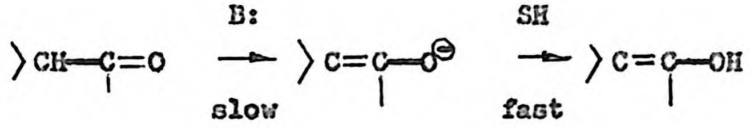
Conc. NaCl (M)	Total Salt (M)	$k^{\alpha}.10^2 hr.^{-1}$	$k^{\alpha'}.10^2 hr.^{-1}$
0	0.103**	2.45±.45	2.79±.13
0.052	0.155	2.75±.47	2.59±.04
0.104	0.207	2.87±.39	2.73±.61
0.208	0.311	2.48±.49	2.62±.20

Within the limits of the experimental error there is no change in the rates over the range of salt concentration used (0.1 M to 0.3 M). This is not conclusive evidence of the absence of an enolate intermediate, but the inference is strong.

*This is provided that changes in ΔH^*, and ΔS^* are not such as to completely cancel out. Such an event would be extremely fortuitous.

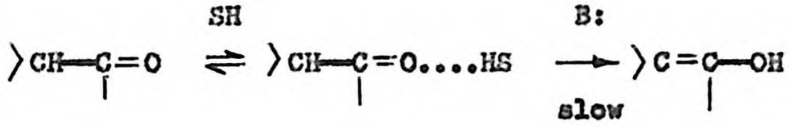
**Conc. of base used.

While base-catalysis has usually been depicted as involving the enolate anion (14,15,29(p. 140)64,65), the work presented here and other recent work suggests that there is strong participation of the solvent at the transition state (61,67,72). Clearly, in aqueous solution, the carbonyl oxygen of methyl ethyl ketone will be strongly solvated with water molecules, and, moreover, as negative charge develops on the carbonyl oxygen during base-catalysis the involvement of solvent molecules will become even greater. Therefore, instead, of the classical mechanism (14,15,29(p. 140)64,65)



(B1)

we should, perhaps, prefer the mechanism B_2, which is essentially concerted (61).



(B2)

Such a mechanism is expected to be operative in catalysis in protic media, and a change in the base-strength would serve only to change the position of the transition state along the reaction coordinate (vide supra p. 28). It is anticipated that enolization via a <u>true</u> enolate anion can only occur in aprotic media where any solvation of the carbonyl oxygen is electrostatic.

A change in the solvent medium by increasing proportions of an aprotic component might change the nature of the transition state towards that anticipated for an enolate intermediate. The data given below shows the effect of various percentages (v/v) of dioxane on the rates of catalysis

by OD^- on methyl ethyl ketone at 0°C.

Variation of Rates with % Dioxane

% dioxane	% D_2O	$k_\alpha.10^4$ sec.$^{-1}$	$k_{\alpha'}.10^4$ sec.$^{-1}$	$k_\alpha/k_{\alpha'}$
0	90*	2.51±.15	2.09±.05	1.20±.10
20	70	1.96±.12	2.14±.04	0.915±.073
40	50	1.71±.12	2.10±.07	0.814±.083
60	30	1.09±.11	1.79±.06	0.612±.083

The rate of reaction at the α-methylene group is markedly sensitive to the change in the medium, while that at the α'-methyl group is much less so. This is consistent with a transition state which has more enolate character as the hydrogen-bonding power of the medium decreases. The trend towards enolate may be due to a change in the solvation of the base such that its activity increases, or due to a change in the solvation of the carbonyl oxygen. It is likely that both occur, but it is difficult to decide, a priori, which might be the more important.

The medium effect observed when dioxane is added to the system is also observed if the concentration of the substrate is changed markedly**.

*10% (v/v) of the medium is MEK (=1.1 M). Conc. of OD^- = 0.03925 N.

**Since the reaction under study is well documented to be pseudo-first-order, the observed rate constant should be independent of the initial ketone concentration.

Variation of Rates with Conc. of MEK

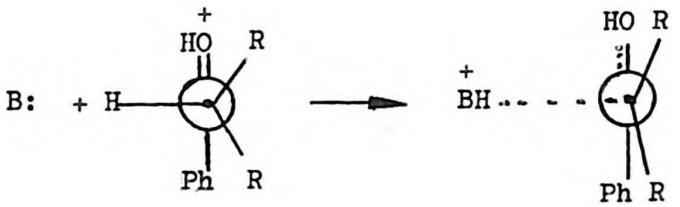
Conc. MEK (M)	$k_\alpha .10^4 sec.^{-1}$	$k_{\alpha'} .10^4 sec.^{-1}$	$k_\alpha / k_{\alpha'}$
1.1	2.51±.15	2.09±.05	1.20±.10
2.2	1.82±.12*	1.80±.05*	1.01±.09

In the light of the findings of this study, and that of previously cited evidence (See p. 27-30), it is proposed that the intermediate in base-catalyzed enolization in aqueous solution is the enol.

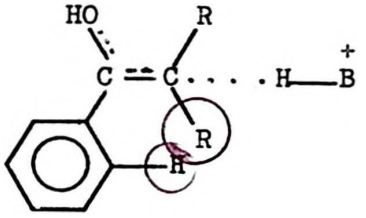
The observation, by Cullis and Hasmi (24), that the overall rate of hydroxide catalyzed iodination of methyl alkyl ketones decreases with the size of alkyl substituent seemingly supports a transition state resembling enolate. However, the consideration of scale models suggests that, as the size of the alkyl group on one side of the carbonyl group increases, the solvent shell of the carbonyl oxygen is disturbed and the approach of a base to either α-position is hindered. Thus the overall rate of base-catalyzed enolization of acetone is greater than that for MEK (2.8:1.8 - statistically corrected) but, as this work has shown, within MEK the α'-methyl group is not preferred. It was hoped to study higher ketones such as methyl isopropyl ketone, methyl sec-butyl ketone, etc., but of those immediately following MEK the majority are unsuitable for the method employed here, either by virtue of an unfavourable N.M.R. spectrum or a low solubility in aqueous solution.

*The average of the 3 values for 2.2 M MEK (See Table p. 27). For both: conc. OD^- = 0.03925 N, temperature = 0°C.

Earlier writers (12,14,19) have quoted the work of Evans and Gordon (20) as evidence for an enolate intermediate, but they omit to refer to earlier work of Evans (16). With Gordon, Evans found that the rates of base-catalyzed bromination of α-alkyl acetophenones decreased with increasing size of the substituent. This was taken to indicate destabilization by the inductive effect of the alkyl substituents upon a negatively charged activated complex. The reaction medium was 75% acetic acid to which 2 g/litre of sodium acetate was added. In the same medium containing 0.5 M HCl, Evans (16) had previously found that the same series of ketones showed the same downward trend in rates. Clearly the Evans and Gordon work is tenuous evidence for an enolate intermediate. That the two series of experiments show the same trend in the results, suggests a common factor is operative in the two cases. Increasing α-alkyl substituents could affect the rates of enolization for the reason that in the transition state eclipsing effects between the phenyl group and an α-alkyl substituent can become significant.



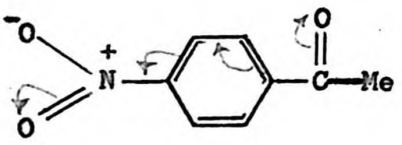
Since the phenyl group will "try" to retain maximum π-overlap with the keto-enol π-system, there is liable to be strong non-bonded repulsion between the o-hydrogen of the phenyl group and the cis-alkyl group(see overleaf).



While the trends described are in the same direction they differ in the magnitude of the rates differences, the reaction carried out in the medium containing 0.5 M HCl being less sensitive to a change in the substituent. In this medium there can be little doubt that the reactive species is the conjugate acid of the ketone (67,68), with H_2O, AcOH and AcO^- (by dissociation of AcOH) as the nucleophiles. Thus the transition state for the rate-determining step will be positively charged, and some stabilization by electron release from the alkyl substituents might accrue, this working in an opposite sense to the eclipsing effect. For the medium containing sodium acetate (equivalent to nearly 0.25 M), catalysis by the true acid-catalysed mechanism (67,68) will not be significant, and the majority will be via the concerted mechanism in which a weaker electrophile (than H^+) AcOH, or H_2O is involved at the transition state. This transition state will have no positive charge within it, and therefore will be less stabilized by electron-releasing substituents. Thus it is that the acetate catalyzed reaction is more retarded by the α-substituents than the acid-catalysed reaction.

Using the same two reaction media Watson and co-workers (10(b),21) had studied the effect of nuclear substituents upon the rate of bromination of acetophenones. For the reaction catalyzed by hydrogen-ion, electron-withdrawing groups at the meta- or para-positions reduced the rate (10(b)),

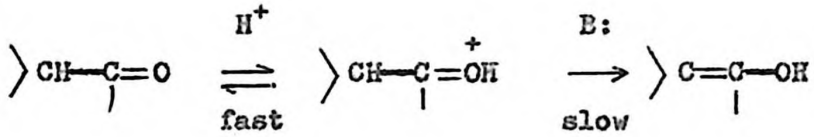
while for that catalyzed by acetate ion they were rate-increasing (21). For the acid-catalyzed process the reactant is the conjugate acid of the ketone and the transition-state in the rate-determing abstraction of a α-proton has some positive charge in the ketonic body. Thus electron-withdrawing substituents will destabilize this transition state. Moreover, in the ground state ketone, the presence of, say, a para-nitro group opposes the polarity of the carbonyl oxygen,



which accordingly will be less readily protonated in the equilibrium preceding the rate-determining proton abstraction. Therefore, the rate-retardations observed are readily rationalized.

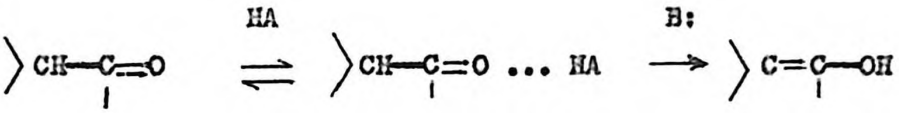
To explain why the electron-withdrawing groups increase the acetate-catalyzed rate, when it is proposed that the process does not involve an enolate (vide supra), the ground state ketone again is considered. If the process is essentially concerted, changes in the ground state energy of the ketone and in energy of the transition state are both important. With an enol-like transition state the effect of a nuclear substituent should be considerably smaller than the corresponding effect on the ground state, since the carbonyl group is more polar than the C=C bond of the enol. Consequently, the activation energy of the process is lowered, and the rate is increased, for electron-withdrawing substituents.

For catalysis of enolization by mineral and carboxylic acids, Swain and co-workers have shown that the rate-determining step is the removal of an α-proton from the conjugate acid of the ketone formed in a rapid pre-equilibrium (67,68).



(A1)

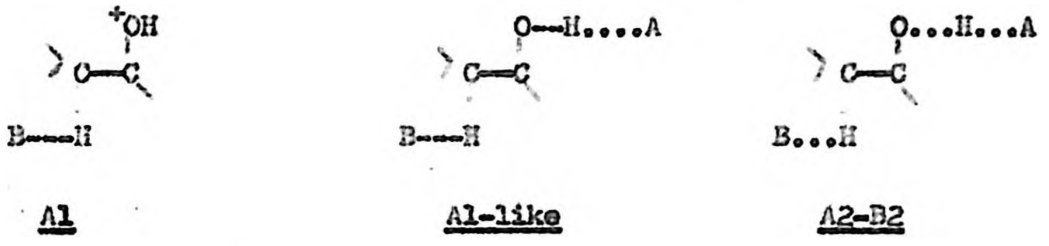
If, however, the acid used were much weaker, protonation of the carbonyl oxygen by the strong electrophile H^+ would not be important, and the weaker electrophile HA, itself, might be co-ordinated with the carbonyl oxygen (cf. Watson (55)), giving mechanism A2.



(A2)

Essentially this is a concerted mechanism since the electrophile, originally loosely bound to the ketone, only becomes strongly or covalently bound at the transition state (61). In aqueous solution, in the absence of stronger electrophiles, water can function as HA (61), and the process is exactly the same as the concerted base-catalyzed process (B2) proposed earlier (p. 30). Clearly there is no essential difference between acid- and base-catalysis if both are occuring via a concerted mechanism of the type suggested, since both have only strong involvement of both the nucleophile and the electrophile at the transition state. On the other hand the acid-catalyzed mechanism A1 has prior involvement of the electrophile, and

the base-catalyzed mechanism B1 has posterior involvement of the same species. Moreover, since there is no essential difference between the concerted mechanisms A2, and B2, there is a continuity between acid and base-catalyzed enolizations. For a concerted mechanism (A2-B2) we can envisage a whole spectrum of transition states which differ in the extent of involvement of the electrophile and the nucleophile at the transition state, and for which those appropriate for mechanisms A1 and B1 are but the extremes*.



A1 A1-like A2-B2

B1-like B1

The exact nature of the transition state will be dependent upon the strength of the acid and the base involved.

For the extreme A1, in which the reactant is the conjugate acid of the ketone, the nature of the transition state will be between that of the conjugate acid and the enol. Thus electron-release, whether by an inductive effect

*cf. Bunnett (85).

towards sp^2 carbon or by hyperconjugation, can be a directing influence in enolization by this mechanism.

For the concerted cases, the transition states resemble enol, and electron-release by α-substituents can be expected to effect the type of orientation as in the A1 case, particularly for A1-like transition states. However factors which cause a trend to a B1-like transition state, will result in electron-releasing substituents being less stabilizing, and in the extreme destabilizing. The main factor liable to cause this trend will be a change to a stronger nucleophile and/or a weaker electrophile. Such a trend has been observed in the work described here (See p. 28). As the stronger bases were used, the relative rates of exchange changed away from those anticipated for an A1-like transition state towards those for a B1-like transition state. A similar trend was observed when the nature of the solvent was changed towards an aprotic extreme, since the base becomes effectively stronger, and the electrophile effectively weaker (See p.31).

SUMMARY

(i) The transition state in catalysis of enolization by weak bases is not enolate-like but enol-like, since reaction at the least alkyl-substituted α-position of a ketone is not necessarily preferred.

(ii) There exists a continuity of mechanism between acid- and base-catalysis, and those mechanisms normally depicted in reference books are but the extremes of the continuum.

(iii) During the exchange studies described here it was possible to observe the effect of deuterium substitution upon the proton magnetic resonance spectrum of methyl ethyl ketone. The results of these observations have recently been published (86).

EXPERIMENTAL

(i) Reagents

Methyl ethyl ketone (Fisher Scientific Company - reagent grade) was purified by fractional distillation through a one foot column containing glass helices. The fraction distilling over at 78-79°C was collected (lit. 79.6°/760 mm).

Deuterium oxide (Merck, Sharpe & Dohme) was used as supplied.

p-Dioxane (Fisher-Purified) was used as supplied.

Solutions of sodium deuteroxide were prepared by dissolving a small quantity of sodium hydroxide (BDH-reagent) in heavy water. Their concentrations were determined by titration against a standard acid using 0.1% bromo-cresol green in ethanol as an indicator. The solutions were kept in small bottles sealed with rubber septa.

Anhydrous sodium acetate (BDH-reagent grade) was finely ground in a mortar and pestle, and then heated in an oven at 160°C for two days. The material was removed from the oven, allowed to cool in a desiccator, and stored in a sealed bottle.

Solutions of sodium acetate were prepared by weighing a known amount of the anhydrous material into a bottle, and making it up to a known volume. The bottle was sealed with a rubber septum.

p-Nitrophenol (Brickman & Co., Montreal) was recrystallized from hot benzene, filtered off, and dried in a vacuum desiccator. The resulting pale-yellow crystals were kept in a tightly stoppered bottle. (M.p. = 113-114°C; lit. 114°.)

Sodium p-nitrophenoxide was prepared as follows: p-Nitrophenol (13.9 g) was dissolved in 50 ml of ether in a separatory funnel. To this solution was added 50 ml of approx. 2N.NaOH solution. The mixture was shaken and allowed to stand. A yellow-orange curd formed in the aqueous layer, and this was filtered off at the pump, the ethereal layer being discarded. The precipitate was washed with 3 portions of fresh ether, and then with a portion of water. The material remaining was sucked dry at the pump, and then recrystallized three times from 95% ethanol. A large volume of solvent was required, and since p-nitrophenol is very soluble in the medium, a good separation was ensured. The bright-yellow crystals turned red when heated to about 120°C, and did not melt at > 200°C (c.f. M.p. of p-nitrophenol 114°). It was assumed that the yellow crystals were the tetrahydrate $p\text{-}NO_2PhONa.4H_2O$, and that the red powder was the anhydrous material (87). The yellow crystals were crushed and heated at 160°C for 2-3 hours to convert them to the red anhydrous material which was then stored in a sealed tube.

Solutions of sodium p-nitrophenoxide were prepared by dissolving rough weights in 5 ml of heavy water. The concentration was determined by titration against standard acid, using the bright-yellow p-nitrophenoxide anion as the indicator. The solutions were kept in bottles sealed with rubber septa.

(ii) Kinetic Procedures

(a) Integration of the N.M.R. Spectra of Samples

The extent of loss of hydrogen at the α- and α'-positions ($CH_3^{\alpha'}COCH_2^{\alpha}CH_3^{\beta}$) of methyl ethyl ketone (MEK) in the kinetic samples was determined using a Varian A-60 N.M.R. spectrometer.

The N.M.R. spectrum of MEK is quite simple, and in it the two types of enolizable hydrogen are clearly distinguished. In CCl_4, measured against internals TMS, the β-methyl triplet is centered at 9.00 τ, the α'-methyl singlet is at 7.93 τ, and the α-methylene quartet is centered at 7.60 τ. Theoretically these peaks should integrate as 3:3:2 respectively. The extent of deuteration into the α'-methyl and α-methylene positions was determined by integration of the spectrum, and by setting the integral of the β-methyl signal equal to 3. Integration was made using the following standard settings:

Frequency band width	1 c.p.s.
R.F. field	0.2 milligauss
Sweep time	50 sec.
Sweep width	250 c.p.s.
Sweep offset	0 c.p.s.

The settings of the spectrum amplitude and the integral amplitude were chosen to suit the concentration of the sample*, and the various peak intensities.

In the manual for the A-60, Varian claim no better than a 2% accuracy in integrating spectra, thus the error in the results is at least this.

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*The concentration of the ketone was usually around one molar, or greater in order to give good integrations.

(b) Calculation of Rate Constants from the Kinetic Data

The integrated spectrum of a sample was measured, and from the heights of the integrals, the average number (N_H^t) of protons remaining at time t at the α- and α'-positions was calculated, assuming the height of the integral of the β-methyl signal to be equivalent to 3 protons. From the values N_H at different times the pseudo-first-order rate constant can be calculated by getting the best fit of the data to the equation

$$N_H^t = N_H^o \, e^{-kt} \qquad \ldots\ (1)$$

where N_H^t is the number of protons remaining at time t, N_H^o is those present initially, and k is the desired rate constant. Equation 1 is a rearranged form of

$$kt = \ln \frac{N_H^o}{N_H^t} \qquad \ldots\ (2)$$

which corresponds to the familar first-order rate law

$$kt = \ln \frac{a}{a-x}$$

The data were fitted to Equation 1 using a Non-Linear Least Squares Program for an IBM 7040 computer. (See Appendix, and rate plot overleaf.)

(c) Catalysis by Deuteroxide Ion at Ambient Temperatures

To approx. 0.1g of MEK, weighed accurately into an N.M.R. tube, were added 0.8 ml of a solution of sodium deuteroxide of known concentration from a syringe. The tube was shaken, a stop-watch started, and the tube

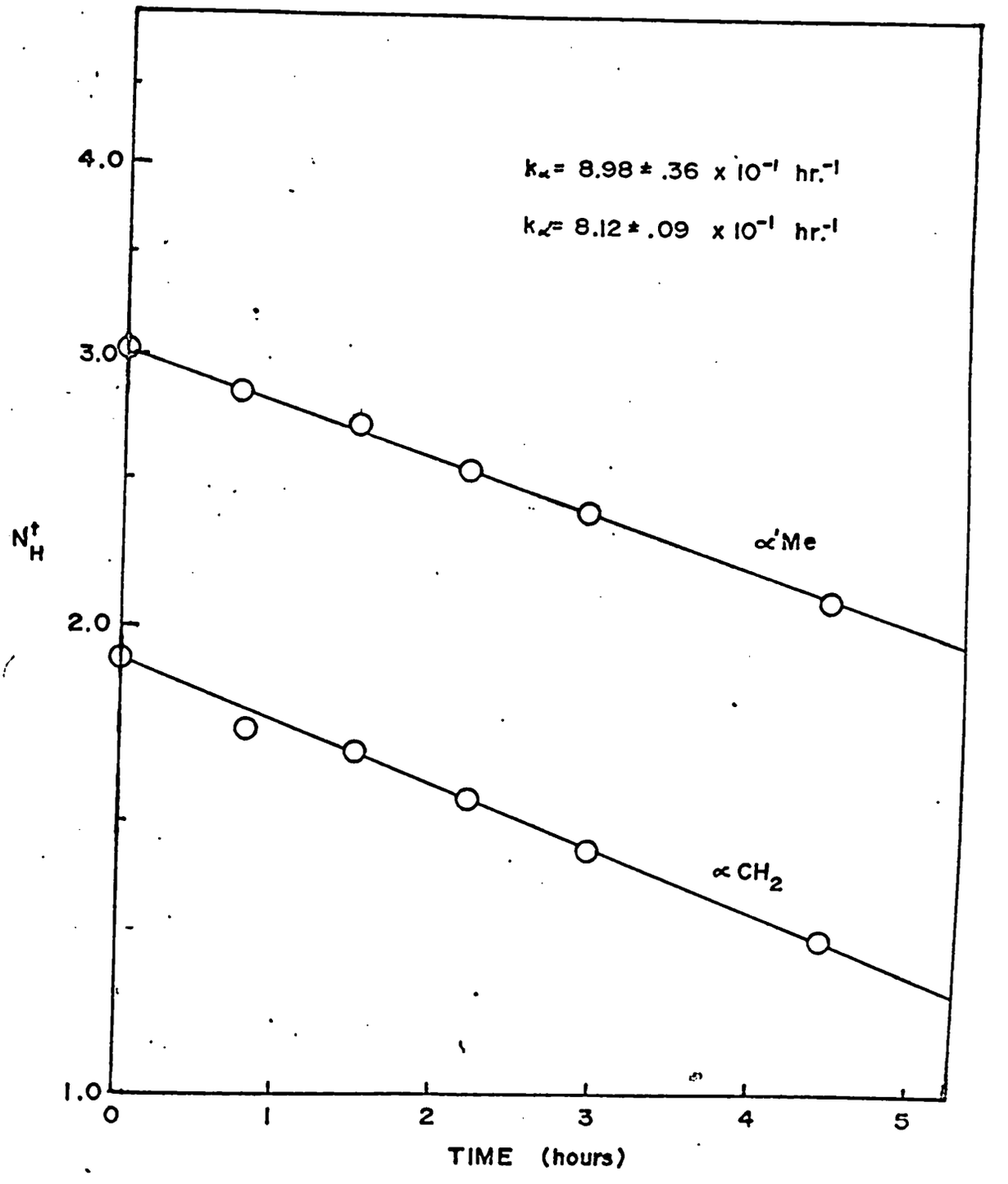

Fig. 1. AN EXAMPLE OF A RATE PLOT

EXCHANGE OF M.E.K. IN .103M $pNO_2PhONa-D_2O$ AT 59.2° C.

then placed into the probe* of the A-60. Successive integrations were then taken until the sample had become about 50% deuterated.

During the scanning (~30 sec/scan) the amount of exchange occurring was not negligible, thus it was necessary to apply a time correction. To the time at which the scan was commenced, 5 sec., and 10 sec. were added to give the times for the α-methylene, and the α'-methyl integrals respectively (Results pp. 53 - 56).

A similar kinetic run was carried out at roughly 15°C, using 0.1 ml MEK, 0.1 ml 0.417N.NaOD-D_2O, and 0.8 ml D_2O (Result p. 56).

(d) Catalysis by Deuteroxide Ion at 0°C

The basis of this procedure was to allow a sample to exchange at ice-water temperature, with aliquots being removed at known times and exchange killed by introduction into a buffer solution. The removed aliquots could then be integrated on the A-60 at comparative leisure.

A molar solution of potassium dihydrogen phosphate KH_2PO_4 (Fisher-reagent) was prepared by dissolving 6.8046 g of the salt in 40 ml of boiling water. When all the crystals had dissolved the solution was allowed to cool and then was transferred to a 50 ml volumetric flask. The total volume was then made up to the mark.

*The temperature in this probe was about 35°C.

A molar solution if disodium hydrogen phosphate $Na_2HPO_4 \cdot 7H_2O$ was similarly prepared using 13.4040 g of that salt.

A buffer solution of pH ~ 7 was prepared by mixing 30 ml of 1M KH_2PO_4 solution and 45 ml of 1M. Na_2HPO_4 solution.(cf. ref. 88)

The procedure for a kinetic run was as follows: To a 5 ml volumetric flask were added 0.5 ml of 0.3925 N NaOD in D_2O by syringe, and 3.5 ml of heavy water by graduated pipette. The resulting solution was shaken and then placed in a stirred ice-bath for 30 minutes to equilibrate to 0°C. After this time, 1.0 ml* of ice-cold MEK was injected by syringe, the flask was shaken twice, and a stop-watch started. The reaction flask was kept in a stirred ice-bath.

An aliquot (about 0.5 ml**) was removed by pipette every 5 minutes or so, and was quickly run into 0.5 ml of the phosphate buffer solution. The resulting solution was shaken and the majority** transferred to an N.M.R. tube. The spectrum of this sample was integrated three times in the A-60, and from the heights of the integrations the numbers of α- and α'-protons remaining were calculated. The average of these three determinations was taken as N_H^t. The results are presented below, pp. 58-59.

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*This gives a ketone concentration of 2.2 M in the reaction medium.

**N.B. Since we are not concerned here with concentrations, but with the average number of α- and α'-protons in the ketone molecule, this quantity does not need to be accurate.

That the buffer solution was an effective quencher of the reaction is shown by the results on p. 57, in which 0.1 ml MEK, 0.1 ml of 0.417 N.NaOD solution and 0.3 ml D_2O were allowed to react in an N.M.R. tube in the A-60 probe. The rapid exchange was terminated by injection of 0.5 ml buffer solution after 7 minutes. The resulting solution had not shown significant exchange on standing overnight (See Result p. 57).

A sample containing 50% dioxane was studied in a similar manner, the original solution in the reaction flask containing 0.5 ml of 0.3925 N.NaOD solution, 1.0 ml D_2O and 2.5 ml dioxane prior to injection of the ketone (Result p. 59).

Solutions containing various percentages of dioxane were exchanged in a similar manner. The reaction media had the compositions given below (Results pp. 60-62).

ml MEK	ml 0.3925 N NaOD	ml D_2O	ml dioxane	% dioxane (v/v)
0.5*	0.5	4.0	0.0	0
0.5	0.5	3.0	1.0	20
0.5	0.5	2.0	2.0	40
0.5	0.5	1.0	3.0	60

*This gives a ketone concentration of 1.1 M in the reaction medium.

(e) Catalysis by Acetate Ion at 59.2°C

Into an N.M.R. tube were placed 0.1 ml MEK, a volume of a sodium acetate solution of known concentration and a volume of D_2O such that the total volume was 1.0 ml. By varying the volumes of the base solution and the D_2O, different concentrations of the base in the reaction medium were obtained.

The sample tubes were sealed and kept in a constant temperature bath at 59.2 ± .05°C. As the reaction time was long - up to a ten day duration - the amount of time (2-3 minutes) for which the samples were removed for integration is negligible. Each kinetic point in these long runs was the average of three determinations, which were made about every 10 hours, depending upon the duration of the particular run. Minimum number of kinetic points was six. (Results pp. 63 -70.)

The use of a weak base in aqueous solution presents a problem in that hydrolysis occurs which affords other catalytic species. Thus the observed rate constants are not those due to the weak base alone. A method was divised, however, to circumvent this difficulty.

Consider the deuterolysis of acetate ion in heavy aqueous solution.

$$AcO^- + D_2O \overset{K_d}{\rightleftharpoons} OD^- + AcOD$$

and

$$K_d = \frac{[OD^-][AcOD]}{[AcO^-]} \qquad \ldots\ (1)$$

If α = the degree of deuterolysis, and c = initial concentration of AcO^-, equation 1 may be rewritten as

$$K_d = \frac{(\alpha c)(\alpha c)}{(1-\alpha)c} = \frac{\alpha^2 c}{1-\alpha} \qquad \ldots\ (2)$$

For the concentrations used in this work $\alpha \ll 1$, thus $1 - \alpha \simeq 1$, and equation 2 becomes

$$K_d = \alpha^2 c$$

Therefore $\alpha = \left(\frac{K_d}{c}\right)^{\frac{1}{2}}$ $\qquad \ldots\ (3)$

Since enolization is general acid, and base-catalyzed (ref. 29, p.109 ff.).

$$k_{obs} = \sum_{i}^{n} k_i[B_i] + \sum_{j}^{m} k_j[HA_j] .$$

In this case*

$$k_{obs} = k_1[AcO^-] + k_2[OD^-] + k_3[AcOD] . \qquad \ldots\ (4)$$

---

*This neglects any catalysis by water molecules. From the data of Dawson and Key (89) in aqueous solution, it is estimated that the contribution to the rate constant at 60° due to such catalysis is about 3×10^{-9}, sec.$^{-1}$, whereas, for the range of acetate concentrations used here, k_{obs} = $3\times10^{-7} \longrightarrow 3\times10^{-6}$, sec.$^{-1}$. Therefore such catalysis may contribute $\sim$ 1% reaction at most, which is smaller than the standard errors in the rate constants.

But $[AcO^-] = (1-\alpha)c \simeq c$, and $[OD^-] = [AcOD] = \alpha c$, and thus equation 4 becomes

$$k_{obs} = k_1 c + (k_2+k_3)\alpha c$$

and

$$\frac{k_{obs}}{c} = k_1 + (k_2+k_3)\alpha \qquad \ldots\ (5)$$

Substitute α from equation 3 in equation 5, and obtain

$$\frac{k_{obs}}{c} = k_1 + \frac{(k_2+k_3)(K_d)^{\frac{1}{2}}}{c^{\frac{1}{2}}} \qquad \ldots\ (6)$$

Therefore a plot of k_{obs}/c <u>versus</u> $c^{-\frac{1}{2}}$ should give a straight line whose intercept is k_1, the catalytic constant of acetate ion. Such a plot is shown overleaf.

The results were fitted to the equation $Y = mX + C$, with $Y = k_{obs}/c$, and $X = c^{-\frac{1}{2}}$, using a least-squares computer program, see Appendix. (Results pp. 71 -72.)

<u>(f) Catalysis by p-Nitrophenoxide Ion at 59.2°C</u>

The procedure used was exactly similar to that for acetate catalysis, except that since the reaction is faster, samples were only run for up to 8 hours, with a minimum of six kinetic points recorded (Results pp.73 -75).

The catalytic constants for attack of the $p\text{-}NO_2PhO^-$ at the α- and α'-positions were isolated using the same equation ((e)...6) and the same least-squares analysis (Results pp.76 -77).

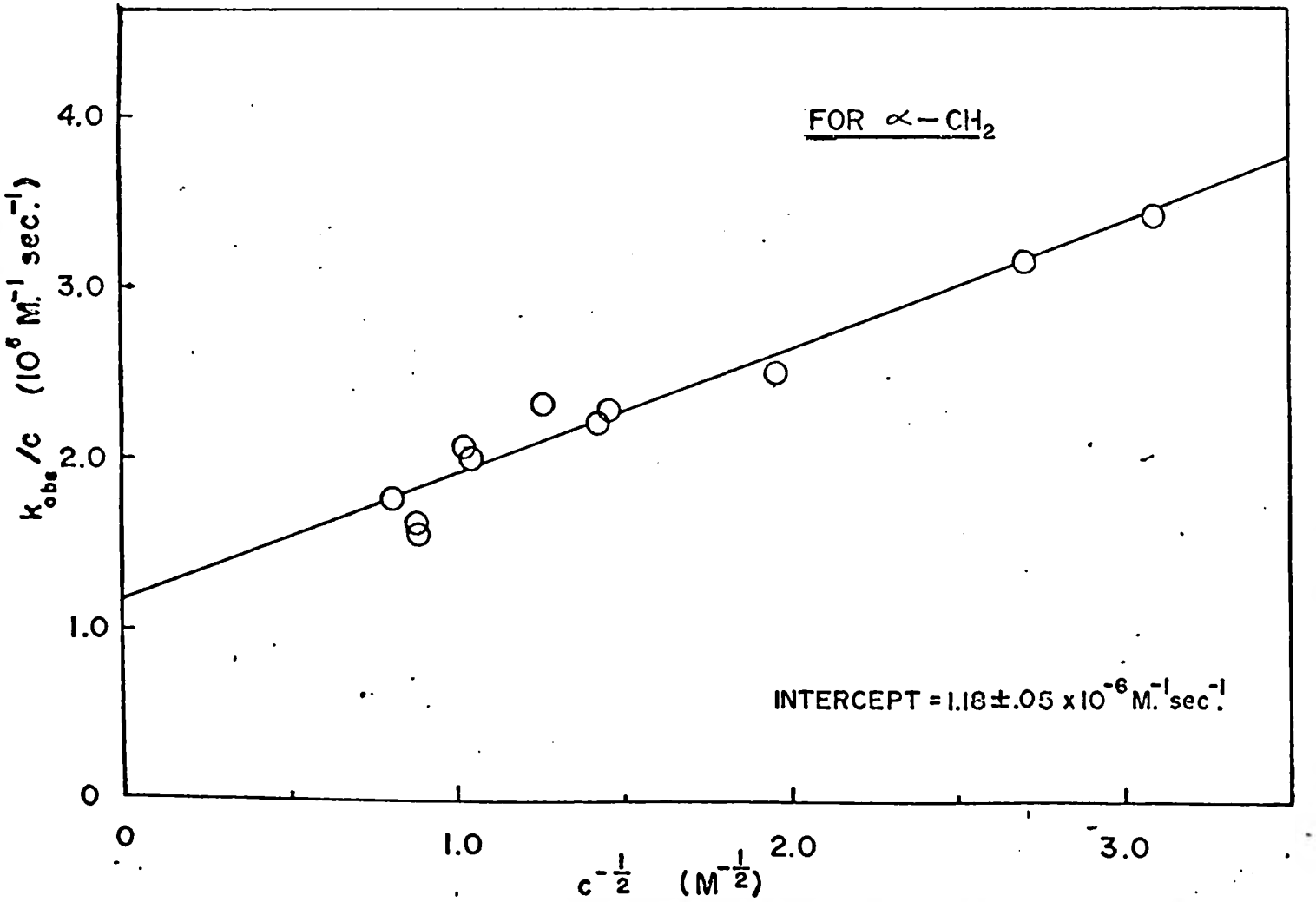

Fig. 2 . PLOT OF (k_{obs}/c) vs $(c^{-\frac{1}{2}})$ FOR AcO^- CATALYSIS AT 59.2°C.

(g) Catalysis by p-Nitrophenoxide at Different Ionic Strength

A solution of 0.521 M NaCl in D_2O was prepared by dissolving 0.060 g of salt (Mallinckrodt, A.R.) in 2 ml D_2O. Sample tubes were made up according to the table below, sealed and placed in a constant temperature bath at 50.0 ± 0.03°C. Their N.M.R. spectra were integrated roughly every 2 hours (Results pp. 78-79).

ml MEK	ml 0.206 M. pNO_2PhO^-	ml D_2O	ml 0.521 M NaCl	Conc. NaCl in M
0.1	0.5	0.4	0.0	0.000
0.1	0.5	0.3	0.1	0.052
0.1	0.5	0.2	0.2	0.104
0.1	0.5	0.0	0.4	0.208

(h) Rate data and Kinetic Results

Exchange of 1.67 M MEK in 0.0406 M.NaOD-D_2O at ~35°C

α'-Me		α-CH_2	
Time (sec.)	N_H^t	Time (sec.)	N_H^t
100	2.77	95	1.85
160	2.30	155	1.42
220	1.90	215	1.37
280	1.80	275	1.08
325	1.69	320	0.97
370	1.38	365	0.87
415	1.34	410	0.74
460	1.26	455	0.74
520	1.02	515	0.67
565	0.89	560	0.61
610	0.86	605	0.57
655	0.82	650	0.46
700	0.61	695	0.43
740	0.64	735	0.43
820	0.55	815	0.32

$k_{\alpha'} = 2.27 \pm .06 \times 10^{-3}$ sec.$^{-1}$ $\quad k_{\alpha} = 2.40 \pm .10 \times 10^{-3}$ sec^{-1}

$k_{\alpha}/k_{\alpha'} = 1.06 \pm .07$

Exchange of 1.65 M.MEK in 0.0094 N.NaOD-D_2O at ~ 35°C

α'-Me		α-CH_2	
Time (mins.)	N_H^t	Time (mins.)	N_H^t
1.42	2.97	1.33	1.93
2.92	2.94	2.83	1.86
3.58	2.81	3.50	1.81
4.45	2.75	4.37	1.74
5.30	2.72	5.22	1.71
5.92	2.64	5.83	1.64
6.67	2.54	6.58	1.60
7.42	2.54	7.33	1.58
9.17	2.42	9.08	1.48
9.83	2.31	9.75	1.40
11.17	2.26	11.08	1.35
11.92	2.18	11.83	1.36
12.67	2.12	12.58	1.35
13.25	2.02	13.17	1.28
13.92	1.97	13.83	1.23
14.50	1.98	14.42	1.20
15.17	1.98	15.08	1.20
15.83	1.93	15.75	1.20
16.50	1.88	16.42	1.20
17.08	1.80	17.00	1.10
17.67	1.78	17.58	1.08
18.20	1.75	18.12	1.00
19.08	1.78	19.00	1.08
23.42	1.53	23.33	1.01
24.18	1.48	24.08	0.91
24.92	1.45	24.83	0.89
26.17	1.40	26.08	0.87
27.17	1.33	27.08	0.85
28.17	1.33	28.08	0.86
29.67	1.27	29.58	0.77
31.17	1.21	31.08	0.80
32.17	1.19	32.08	0.75
33.17	1.12	33.08	0.68
34.17	1.13	34.08	0.68
35.17	1.06	35.08	0.67

$k_{\alpha'} = 3.12 \pm .02 \times 10^{-2}$ min.$^{-1}$ $k_{\alpha} = 3.21 \pm .06 \times 10^{-2}$ min.$^{-1}$

$= 5.23 \pm .04 \times 10^{-4}$ sec.$^{-1}$ $= 5.35 \pm .10 \times 10^{-4}$ sec.$^{-1}$

$k_{\alpha}/k_{\alpha'} = 1.03 \pm .03$

Exchange of 1.4 N.MeK in 0.0205 N.NaOD-D_2O at ~ 35°C

α'-Me		α-CH_2	
Time (min.)	N_H^t	Time (min.)	N_H^t
1.17	2.89	1.08	1.71
2.67	2.65	2.58	1.56
3.41	2.47	3.33	1.44
4.00	2.34	3.92	1.37
4.67	2.20	4.58	1.29
5.25	2.14	5.17	1.24
5.83	2.03	5.75	1.16
6.50	1.93	6.41	1.06
7.08	1.86	7.00	1.04
7.76	1.71	7.58	1.02
8.17	1.60	8.08	0.95
8.83	1.58	8.75	0.93
9.50	1.50	9.41	0.90
10.08	1.40	10.00	0.80
11.92	1.25	11.83	0.75
12.67	1.18	12.58	0.69
13.17	1.08	13.08	0.67
13.67	1.02	13.58	0.60
14.25	1.02	14.17	0.59
14.92	0.96	14.83	0.57
15.50	0.94	15.41	0.54
16.08	0.87	16.00	0.51
16.58	0.81	16.50	0.47
17.25	0.80	17.17	0.48

$k_{\alpha'} = 8.17 \pm .07 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha} = 8.14 \pm .19 \times 10^{-2}$ min.$^{-1}$

$= 1.36 \pm .01 \times 10^{-3}$ sec.$^{-1}$ $\quad = 1.36 \pm .03 \times 10^{-3}$ sec.$^{-1}$

$k_{\alpha}/k_{\alpha'} = 1.00 \pm .02$

Accumulated Rate Data for OD^- Catalysis at Ambient Temperatures ($\sim 35^\circ C$)

conc. MEK (M)	conc. OD^- (N)	$k_{obs} \cdot 10^4$ sec.$^{-1}$ α'-Me	$k_{obs} \cdot 10^4$ sec.$^{-1}$ α CH_2	$k_\alpha / k_{\alpha'}$
1.67	0.0406	22.7 ± .6	24.0 ± 1.0	1.06 ± .07
1.40	0.0205	13.6 ± .1	13.6 ± .3	1.00 ± .02
1.65	0.0094	5.23 ± .04	5.35 ± .10	1.03 ± .03

Exchange of 1.1 M.MEK in 0.0417 N.NaOD-D_2O at $\sim 15^\circ C$

α'-Me Time (sec.)	α'-Me N_H^t	α-CH_2 Time (sec.)	α-CH_2 N_H^t
100	2.91	95	1.85
145	2.82	140	1.82
190	2.77	185	1.81
235	2.68	230	1.73
265	2.68	260	1.68
310	2.61	305	1.73
355	2.55	350	1.70
400	2.46	395	1.62
430	2.48	425	1.59
460	2.44	455	1.59
490	2.34	485	1.47
535	2.34	530	1.41
565	2.27	560	1.39
610	2.32	605	1.52
670	2.30	665	1.47
700	2.23	695	1.40
730	2.20	725	1.32
760	2.17	755	1.30
790	2.12	785	1.33
835	2.10	830	1.33

$k_{\alpha'} = 4.33 \pm .10 \times 10^{-4}$ sec.$^{-1}$ $\quad k_\alpha = 5.01 \pm .27 \times 10^{-4}$ sec.$^{-1}$

$k_\alpha / k_{\alpha'} = 1.16 \pm .09$

Exchange Study to Show the Effectiveness of the Buffer

Time (min., sec.)		N_H^t α-CH_2	α'-Me
3.30		0.89	1.18
4.00		0.75	1.11
4.30		0.59	1.01
5.00		0.59	0.89
5.30		0.58	0.81
6.00		0.55	0.68
7.00	Buffer injected		
8.00		0.49	0.76
8.30		0.57	0.68
9.00		0.57	0.74
9.30		0.54	0.73
10.00		0.56	0.78
10.30		0.56	0.78
11.00		0.61	0.74
12.00		0.43	0.72
13.00		0.40	0.74
14.00		0.45	0.73
15.00		0.44	0.71
20.00		0.41	0.70
25.00		0.41	0.70
30.00		0.41	0.73
After 16 hours		0.48	0.75

Exchange of 2.2 M MEK in 0.03925 N $NaOD-D_2O$ at 0°C

Run 1

Time (min.)	N_H^t α-CH_2	N_H^t α'-Me
5.08	1.76	2.76
10.00	1.68	2.59
15.00	1.56	2.41
20.00	1.48	2.30
25.00	1.38	2.20
30.00	1.35	2.07
35.00	1.30	1.97
40.00	1.23	1.89

$k_\alpha = 1.04 \pm .04 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.09 \pm .02 \times 10^{-2}$ min.$^{-1}$

$= 1.74 \pm .07 \times 10^{-4}$ sec.$^{-1}$ $\quad = 1.82 \pm .04 \times 10^{-4}$ sec.$^{-1}$

$k_\alpha/k_{\alpha'} = 0.95 \pm .06$

Run 2

Time (min.)	N_H^t α-CH_2	N_H^t α'-Me
7.67	1.67	2.67
15.08	1.55	2.39
22.50	1.44	2.23
30.00	1.25	2.13
37.58	1.18	1.93
45.17	1.05	1.77
52.50	1.08	1.66
60.00	0.99	1.36

$k_\alpha = 1.07 \pm .07 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.02 \pm .02 \times 10^{-2}$ min.$^{-1}$

$= 1.78 \pm .12 \times 10^{-4}$ sec.$^{-1}$ $\quad = 1.71 \pm .04 \times 10^{-4}$ sec.$^{-1}$

$k_\alpha/k_{\alpha'} = 1.04 \pm .09$

Run 3

Time (min.)	N_H^t α-CH_2	α'-Me
6.00	1.79	2.82
12.08	1.51	2.51
18.00	1.45	2.40
24.08	1.41	2.25
30.00	1.25	2.03
36.00	1.17	1.93
42.08	1.15	1.84
48.00	1.09	1.78

$k_\alpha = 1.16 \pm .09 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.13 \pm .05 \times 10^{-2}$ min.$^{-1}$

$= 1.93 \pm .18 \times 10^{-4}$ sec.$^{-1}$ $\quad = 1.88 \pm .08 \times 10^{-4}$ sec.$^{-1}$

$k_\alpha / k_{\alpha'} = 1.03 \pm .12$

Exchange of 2.2 M.MEK in 0.03925 N.NaOD-D_2O - 50% dioxane at 0°C

Time (min.)	N_H^t α-CH_2	α'-Me
5.00	1.93	2.79
10.08	1.88	2.65
15.00	1.82	2.50
20.00	1.66	2.41
25.00	1.63	2.25
30.00	1.55	2.16
35.00	1.54	2.12
40.00	1.54	2.05

$k_\alpha = 7.52 \pm .64 \times 10^{-3}$ min.$^{-1}$ $\quad k_{\alpha'} = 9.18 \pm .32 \times 10^{-3}$ min.$^{-1}$

$= 1.25 \pm .11 \times 10^{-4}$ sec.$^{-1}$ $\quad = 1.53 \pm .05 \times 10^{-4}$ sec.$^{-1}$

$k_\alpha / k_{\alpha'} = 0.819 \pm .098$

Exchange of 1.1 M.MEK in 0.03925 N.NaOD-D_2O-dioxane at 0°C

Run 1 — 0% dioxane - 90% D_2O - (10% is MEK)

Time (min.)	α-CH_2 N_H^t	α'-Me
5.00	1.77	2.86
10.00	1.69	2.63
15.00	1.55	2.45
20.00	1.38	2.31
25.00	1.26	2.20
30.08	1.18	2.09
35.00	1.17	1.90
40.00	1.09	1.85

$k_\alpha = 1.50 \pm .09 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.25 \pm .03 \times 10^{-2}$ min.$^{-1}$

$= 2.50 \pm .15 \times 10^{-4}$ sec.$^{-1}$ $\quad = 2.09 \pm .05 \times 10^{-4}$ sec.$^{-1}$

$k_\alpha / k_{\alpha'} = 1.20 \pm .10$

Run 2 — 20% dioxane - 70% D_2O

Time (min.)	α-CH_2 N_H^t	α'-Me
5.00	1.88	2.81
10.08	1.79	2.68
15.00	1.65	2.51
20.00	1.56	2.35
25.00	1.43	2.16
30.00	1.48	2.04
35.10	1.30	1.90
40.10	1.24	1.84

$k_\alpha = 1.18 \pm .07 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.28 \pm .03 \times 10^{-2}$ min.$^{-1}$

$= 1.96 \pm .12 \times 10^{-4}$ sec.$^{-1}$ $\quad = 2.14 \pm .06 \times 10^{-2}$ min.$^{-1}$

$k_\alpha / k_{\alpha'} = 0.915 \pm .073$

Run 3 — 40% dioxane - 50% D_2O

Time (min.)	α-CH_2	N_H^t α'-Me
9.00	1.95	2.63
14.00	1.84	2.43
21.00	1.61	2.24
28.08	1.69	2.13
35.08	1.48	1.82
42.00	1.35	1.68
49.08	1.28	1.57
56.00	1.20	1.50

$k_\alpha = 1.02 \pm .07 \times 10^{-2}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.26 \pm .04 \times 10^{-2}$ min.$^{-1}$

$= 1.71 \pm .12 \times 10^{-4}$ sec.$^{-1}$ $\quad = 2.10 \pm .06 \times 10^{-4}$ sec.$^{-1}$

Run 4 — 60% dioxane - 30% D_2O

Time (min.)	α-CH_2	N_H^t α'-Me
9.08	2.08	2.69
14.00	1.83	2.52
21.00	1.77	2.32
28.00	1.69	2.13
35.00	1.65	1.95
42.00	1.59	1.86
49.00	1.48	1.72
56.10	1.51	1.67

$k_\alpha = 6.56 \pm .68 \times 10^{-3}$ min.$^{-1}$ $\quad k_{\alpha'} = 1.07 \pm .03 \times 10^{-2}$ min.$^{-1}$

$= 1.09 \pm .11 \times 10^{-4}$ sec.$^{-1}$ $\quad = 1.79 \pm .05 \times 10^{-4}$ sec.$^{-1}$

Accumulated Rate Data for OD^- Catalysis in D_2O-Dioxane

(Conc. of MEK = 1.1 M, Conc. NaOD = .03925 N)

		$k_{obs} \cdot 10^4$ sec.$^{-1}$		
% dioxane	% D_2O	α-CH_2	α'-Me	$k_\alpha / k_{\alpha'}$
0	90*	2.50 ± .15	2.09 ± .05	1.20 ± .10
20	70	1.96 ± .12	2.14 ± .04	.915 ± .073
40	50	1.71 ± .12	2.10 ± .07	.814 ± .083
60	30	1.09 ± .11	1.79 ± .06	.612 ± .083

*10% of the medium v/v is MEK.

Exchange of 1.1 M.MEK in AcO^- - D_2O Solutions at 59.2°C

1) Acetate conc. = 0.930 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.00	1.93	3.00
5.00	1.82	2.82
11.67	1.75	2.79
26.40	1.56	2.50
31.07	1.51	2.48
35.55	1.53	2.47
39.17	1.52	2.42
50.63	1.34	2.26
57.22	1.24	2.24
63.13	1.23	2.15
76.00	1.14	2.02
81.70	1.09	2.01
100.67	0.96	1.81

$k_\alpha = 6.86 \pm .18 \times 10^{-3} hr.^{-1}$ $\quad k_{\alpha'} = 4.834 \pm .10 \times 10^{-3} hr.^{-1}$

$= 1.91 \pm .05 \times 10^{-6} sec.^{-1}$ $\quad = 1.34 \pm .03 \times 10^{-6} sec.^{-1}$

2) Acetate conc. = 0.946 M

N_H^t

Time (hrs.)	α-CH_2	α'-Me
0.00	1.74	2.97
13.07	1.52	2.67
18.03	1.41	2.46
24.07	1.35	2.34
29.07	1.41	2.47
29.50	1.35	2.46
33.00	1.20	2.33
44.25	1.17	2.19
50.17	1.20	2.16
64.05	1.05	2.05
87.13	0.96	1.94

$k_\alpha = 7.10 \pm .61 \times 10^{-3}$ hr.$^{-1}$ $\quad k_{\alpha'} = 5.00 \pm .37 \times 10^{-3}$ hr.$^{-1}$

$= 1.97 \pm .17 \times 10^{-6}$ sec.$^{-1}$ $\quad = 1.39 \pm .10 \times 10^{-6}$ sec.$^{-1}$

3) Acetate conc. = 1.31 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.00	1.94	3.00
5.00	1.73	2.77
10.29	1.74	2.77
25.12	1.59	2.53
29.52	1.55	2.46
34.21	1.52	2.48
37.59	1.46	2.42
49.26	1.24	2.24
56.00	1.19	2.15
61.55	1.12	2.08
74.47	1.06	1.97
80.30	1.01	1.90
99.30	0.94	1.84

$k_\alpha = 7.66 \pm .34 \times 10^{-3} hr.^{-1}$ $\quad k_{\alpha'} = 5.13 \pm .14 \times 10^{-3} hr.^{-1}$

$= 2.13 \pm .09 \times 10^{-6} sec.^{-1}$ $\quad = 1.43 \pm .04 \times 10^{-6} sec.^{-1}$

4) Acetate conc. = 1.31 M

Time (hrs.)	N_H^t α-CH_2	α'-He
0.00	1.80	3.00
5.07	1.81	2.83
10.05	1.74	2.80
24.75	1.59	2.56
29.42	1.55	2.53
33.90	1.47	2.46
37.53	1.41	2.35
48.97	1.24	2.21
55.55	1.19	2.13
61.47	1.17	2.08
74.33	1.08	2.00
80.15	1.02	1.95
99.08	0.91	1.80

$k_\alpha = 7.42 \pm .22 \times 10^{-3} hr.^{-1}$ $\quad k_{\alpha'} = 5.32 \pm .13 \times 10^{-3} hr.^{-1}$

$= 2.06 \pm .06 \times 10^{-6} sec.^{-1}$ $\quad = 1.48 \pm .03 \times 10^{-6} sec.^{-1}$

5) Acetate conc. = 1.50 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
13.10	1.52	2.36
20.28	1.51	2.12
23.88	1.39	2.01
26.20	1.38	2.14
41.47	1.17	1.90
61.17	0.93	1.60
66.80	0.89	1.44
87.35	0.77	1.29
91.82	0.77	1.27
108.25	0.63	1.11

$k_\alpha = 9.60 \pm .35 \times 10^{-3} hr.^{-1}$ $k_{\alpha'} = 7.74 \pm .30 \times 10^{-3} hr.^{-1}$

$= 2.67 \pm .10 \times 10^{-6} sec.^{-1}$ $= 2.15 \pm .08 \times 10^{-6} sec.^{-1}$

6) Acetate conc. = 0.49 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
1.55	1.92	2.94
14.82	1.76	2.77
19.95	1.68	2.63
25.80	1.70	2.64
39.45	1.59	2.56
64.12	1.48	2.63
68.72	1.41	2.46
89.22	1.28	2.32
93.70	1.29	2.26
110.22	1.29	2.30

$k_\alpha = 3.97 \pm .23 \times 10^{-3} hr.^{-1}$ $k_{\alpha'} = 2.13 \pm .18 \times 10^{-3} hr.^{-1}$

$= 1.10 \pm .06 \times 10^{-6} sec.^{-1}$ $= 5.94 \pm .51 \times 10^{-7} sec.^{-1}$

7) Acetate conc. = 0.63 M

Time (hr.)	N_H^t α-CH_2	N_H^t α'-Me
12.95	1.68	2.76
17.43	1.68	2.62
23.48	1.61	2.57
37.45	1.59	2.51
62.12	1.27	2.15
66.70	1.25	2.14
87.20	1.15	2.05
91.72	1.10	1.93
109.20	1.09	1.77

$k_\alpha = 5.24 \pm .32 \times 10^{-3} hr.^{-1}$ $\quad k_{\alpha'} = 4.30 \pm .15 \times 10^{-3} hr.^{-1}$

$= 1.46 \pm .09 \times 10^{-6} sec.^{-1}$ $\quad = 1.20 \pm .04 \times 10^{-6} sec.^{-1}$

8) Acetate conc. = 0.104 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
3.92	1.89	2.85
28.88	1.74	2.72
45.40	1.83	2.67
70.67	1.71	2.64
96.53	1.67	2.54
119.03	1.64	2.55
170.35	1.55	2.33
215.25	1.39	2.26
247.58	1.36	2.09

$k_\alpha = 1.30 \pm .09 \times 10^{-3} hr.^{-1}$ $\quad k_{\alpha'} = 1.15 \pm .05 \times 10^{-3} hr.^{-1}$

$= 3.60 \pm .24 \times 10^{-7} sec.^{-1}$ $\quad = 3.19 \pm .13 \times 10^{-7} sec.^{-1}$

9) Acetate conc. = 0.260 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
4.17	1.78	2.84
29.15	1.50	2.50
45.67	1.55	2.43
70.92	1.47	2.31
96.82	1.37	2.19
119.30	1.34	2.23
170.63	1.14	1.90
215.48	1.06	1.76
247.87	0.94	1.66

$k_\alpha = 2.36 \pm .15 \times 10^{-3}$ hr.$^{-1}$ $k_{\alpha'} = 2.07 \pm .10 \times 10^{-3}$ hr.$^{-1}$

$= 6.56 \pm .41 \times 10^{-7}$ sec.$^{-1}$ $= 5.75 \pm .28 \times 10^{-7}$ sec.$^{-1}$

10) Acetate conc. = 0.468 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
4.25	1.83	2.90
29.22	1.61	2.64
45.77	1.55	2.47
71.02	1.37	2.34
96.90	1.27	2.13
119.20	1.15	1.99
170.70	0.96	1.73

$k_\alpha = 3.89 \pm .10 \times 10^{-3}$ hr.$^{-1}$ $k_{\alpha'} = 3.13 \pm .07 \times 10^{-3}$ hr.$^{-1}$

$= 1.08 \pm .03 \times 10^{-6}$ sec.$^{-1}$ $= 8.68 \pm .19 \times 10^{-7}$ sec.$^{-1}$

11) Acetate conc. = 0.136 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
12.93	1.76	2.89
25.77	1.75	2.85
36.08	1.70	2.79
49.38	1.64	2.75
59.27	1.65	2.70
74.25	1.60	2.68
98.50	1.55	2.56
109.05	1.51	2.55
120.10	1.50	2.47

$k_\alpha = 1.56 \pm .06 \times 10^{-3} hr.^{-1}$ $\quad k_{\alpha'} = 1.40 \pm .04 \times 10^{-3} hr.^{-1}$

$= 4.34 \pm .18 \times 10^{-7} sec.^{-1}$ $\quad = 3.88 \pm .10 \times 10^{-7} sec.^{-1}$

Analysis of Acetate Ion Catalysis at 59.2°C

1) For the α'-methyl group

$c=[AcO^-]$ (M)	$k_{obs}.10^7$ sec.$^{-1}$	$Y=(k_{obs}/c).10^6$ M.$^{-1}$ sec.$^{-1}$	$X=c^{-\frac{1}{2}}$	calc Y	Y-calc Y
0.104	3.19	3.07	3.101	3.11	-0.04
0.136	3.88	2.85	2.712	2.78	0.07
0.260	5.75	2.21	1.961	2.16	0.05
0.468	8.68	1.86	1.462	1.75	0.11
0.490	5.94	1.21	1.429	1.73	-0.52
0.630	12.0	1.91	1.260	1.59	0.32
0.930	13.4	1.44	1.037	1.40	0.04
0.946	13.9	1.47	1.028	1.40	0.07
1.310	14.3	1.09	0.874	1.27	-0.18
1.310	14.8	1.13	0.874	1.27	-0.14
1.500	21.5	1.43	0.816	1.22	0.21

Fitted to $Y = mX + C$, gives

$$C = 5.47 \pm .70 \times 10^{-7} \text{ M.}^{-1}\text{sec.}^{-1}$$

$$m = 8.25 \pm .95 \times 10^{-7} \text{ M.}^{-\frac{1}{2}}\text{sec.}^{-1}$$

2) For the c-CH_2 group

$c=[AcO^-]$ (M)	$k_{obs}.10^7.sec.^{-1}$	$Y=(k_{obs}/c).10^6.M.^{-1}sec.^{-1}$	$X=c^{-\frac{1}{2}}$	calc Y	Y-calc Y
0.104	3.60	3.46	3.101	3.50	-0.04
0.136	4.34	3.19	2.712	3.21	-0.02
0.260	6.56	2.52	1.961	2.65	-0.13
0.468	10.8	2.31	1.462	2.27	0.04
0.490	11.0	2.43	1.429	2.25	0.18
0.630	14.6	2.32	1.260	2.12	0.20
0.930	19.1	2.05	1.037	1.96	0.09
0.946	19.7	2.08	1.028	1.95	0.13
1.310	21.3	1.63	0.874	1.83	-0.20
1.310	20.6	1.57	0.874	1.83	-0.26
1.500	26.7	1.78	0.816	1.79	-0.01

Fitted to $Y = mX + C$, gives

$$c = 1.18 \pm .05 \times 10^{-6}\ M.^{-1}sec.^{-1}$$

$$m = 7.47 \pm .65 \times 10^{-7}\ \overline{M}^{\frac{1}{2}}.sec.^{-1}$$

Thus the catalytic constants are:

$$k_1^{\alpha} = 11.8 \pm .5 \times 10^{-7}\ M.^{-1}sec.^{-1}$$

$$k_1^{\alpha'} = 5.47 \pm .70 \times 10^{-7}\ M.^{-1}sec.^{-1}$$

and $k_1^{\alpha}/k_1^{\alpha'} = 2.16 \pm .36$

(See Fig 2, P. 51)

Exchange of 1.1 M.MEK in $p\text{-}NO_2PhO^-\text{-}D_2O$ Solutions at 59.2°C

1) p-Nitrophenoxide conc. = 0.185 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
0.00	1.89	2.92
0.70	1.62	2.58
1.22	1.46	2.45
1.67	1.40	2.33
2.17	1.38	2.27
2.68	1.25	2.12

$k_\alpha = 1.50 \pm .14 \times 10^{-1}\,hr.^{-1}$ $\quad k_{\alpha'} = 1.16 \pm .06 \times 10^{-1}\,hr.^{-1}$

$= 4.18 \pm .39 \times 10^{-5}\,sec.^{-1}$ $\quad = 3.21 \pm .17 \times 10^{-5}\,sec.^{-1}$

2) p-Nitrophenoxide conc. = 0.144 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
0.00	1.86	3.02
0.75	1.65	2.69
1.47	1.53	2.49
2.20	1.41	2.40
2.97	1.28	2.22
4.48	1.15	1.98

$k_\alpha = 1.11 \pm .06 \times 10^{-1}\,hr.^{-1}$ $\quad k_{\alpha'} = 9.33 \pm .47 \times 10^{-2}\,hr.^{-1}$

$= 3.09 \pm .17 \times 10^{-5}\,sec.^{-1}$ $\quad = 2.59 \pm .13 \times 10^{-5}\,sec.^{-1}$

3) p-Nitrophenoxide conc. = .103 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.00	1.90	3.01
0.75	1.72	2.83
1.47	1.67	2.71
2.18	1.56	2.53
2.93	1.44	2.38
4.47	1.26	2.09

$k_\alpha = 8.98 \pm .36 \times 10^{-2}$ hr.$^{-1}$ $k_{\alpha'} = 8.11 \pm .09 \times 10^{-2}$ hr.$^{-1}$

$= 2.50 \pm .10 \times 10^{-5}$ sec.$^{-1}$ $= 2.25 \pm .03 \times 10^{-5}$ sec.$^{-1}$

(See Fig. 1, P. 44)

4) p-Nitrophenoxide conc. = 0.082 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.00	1.90	2.98
2.32	1.46	2.41
2.86	1.43	2.33
3.70	1.36	2.25
4.55	1.33	2.23
5.45	1.22	2.00
6.45	1.17	1.97
7.93	0.99	1.75

$k_\alpha = 7.71 \pm .48 \times 10^{-2}$ hr.$^{-1}$ $k_{\alpha'} = 6.47 \pm .31 \times 10^{-2}$ hr.$^{-1}$

$= 2.14 \pm .13 \times 10^{-5}$ sec.$^{-1}$ $= 1.80 \pm .09 \times 10^{-5}$ sec.$^{-1}$

5) p-Nitrophenoxide conc. = 0.062 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.00	1.89	2.99
2.32	1.58	2.58
2.85	1.50	2.47
3.68	1.50	2.43
4.53	1.45	2.37
5.43	1.37	2.31
6.48	1.32	2.23
7.92	1.19	2.03

$k_\alpha = 5.52 \pm .34 \times 10^{-2} hr.^{-1}$ $k_{\alpha'} = 4.55 \pm .23 \times 10^{-2} hr.^{-1}$

$= 1.53 \pm .10 \times 10^{-5} sec.^{-1}$ $= 1.26 \pm .06 \times 10^{-5} sec.^{-1}$

6) p-Nitrophenoxide conc. = 0.041 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.00	1.93	3.04
2.28	1.63	2.62
2.82	1.57	2.50
3.65	1.53	2.47
4.52	1.47	2.39
5.42	1.48	2.37
6.47	1.39	2.24
7.92	1.32	2.19

$k_\alpha = 4.67 \pm .39 \times 10^{-2} hr.^{-1}$ $k_{\alpha'} = 4.15 \pm .29 \times 10^{-2} hr.^{-1}$

$= 1.30 \pm .11 \times 10^{-5} sec.^{-1}$ $= 1.15 \pm .08 \times 10^{-5} sec.^{-1}$

Analysis of p-Nitrophenoxide Catalysis at 59.2°C

1) For the α'-methyl group

$c=[pNP^-](M)$	$k_{obs}.10^5 sec.^{-1}$	$Y=(k_{obs}/c).10^4 M.^{-1} sec.^{-1}$	$X=c^{-\frac{1}{2}}$	calc Y	Y-calc Y
0.185	3.21	1.74	2.325	1.73	0.01
0.144	2.59	1.80	2.635	1.84	-0.04
0.103	2.25	2.19	3.114	2.02	0.17
0.082	1.80	2.19	3.492	2.15	0.04
0.062	1.26	2.04	4.016	2.34	-0.30
0.041	1.15	2.81	4.938	2.67	0.14

Fitted to $Y = mX + C$, gives

$C = 8.93 \pm .78 \times 10^{-5}\ M.^{-1} sec.^{-1}$

$m = 3.60 \pm .89 \times 10^{-5}\ M.^{-\frac{1}{2}} sec.^{-1}$

2) For the α-methylene group

$c=[pNP^-](M)$	$k_{obs}.10^5.sec.^{-1}$	$Y=(k_{obs}/c).10^4.M.^{-1}sec.^{-1}$	$X=c^{-\frac{1}{2}}$	calc Y	Y-calc Y
0.185	4.18	2.26	2.325	2.14	0.12
0.144	3.09	2.15	2.635	2.24	-0.09
0.103	2.50	2.42	3.114	2.41	0.01
0.082	2.14	2.61	3.492	2.54	0.07
0.062	1.53	2.47	4.016	2.72	-0.25
0.041	1.30	3.17	4.938	3.03	0.14

Fitted to Y = mX + C, gives

$$C = 1.34 \pm .07 \times 10^{-4}\ M.^{-1}sec.^{-1}$$

$$m = 3.43 \pm .78 \times 10^{-5}\ M.^{-\frac{1}{2}}sec.^{-1}$$

Thus the catalytic constants are:

$$k_1^{\alpha} = 1.34 \pm .07 \times 10^{-4}\ M.^{-1}sec.^{-1}$$

$$k_1^{\alpha'} = 8.93 \pm .78 \times 10^{-5}\ M.^{-1}sec.^{-1}$$

and $k_1^{\alpha}/k_1^{\alpha'} = 1.50 \pm .21$

Exchange of MEK in NaCl-D_2O Solutions Catalyzed by p.NO_2PhO^- at 50°C

conc. of MEK = 1.1 M conc. p-NO_2PhO^- = .103 M

1) Conc. NaCl = 0.00 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
1.27	1.73	2.79
2.87	1.68	2.72
4.17	1.56	2.58
5.23	1.69	2.54
7.90	1.49	2.38
10.15	1.37	2.16

$k_\alpha = 2.45 \pm .45 \times 10^{-2} hr.^{-1}$ $k_{\alpha'} = 2.79 \pm .13 \times 10^{-2} hr.^{-1}$

2) Conc. NaCl = 0.052 M

Time (hrs.)	N_H^t α-CH_2	N_H^t α'-Me
1.15	1.76	2.81
2.75	1.71	2.68
4.07	1.54	2.58
5.12	1.68	2.53
7.78	1.45	2.37
10.03	1.38	2.22

$k_\alpha = 2.75 \pm .47 \times 10^{-2} hr.^{-1}$ $k_{\alpha'} = 2.59 \pm .04 \times 10^{-2} hr.^{-1}$

3) Conc. NaCl = 0.104 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
1.12	1.75	2.90
2.70	1.57	2.66
4.03	1.52	2.28
5.08	1.57	2.42
7.73	1.43	2.42
9.98	1.31	2.19

$k_\alpha = 2.87 \pm .38 \times 10^{-2} hr.^{-1}$ $k_{\alpha'} = 2.73 \pm .61 \times 10^{-2} hr.^{-1}$

4) Conc. NaCl = 0.208 M

Time (hrs.)	N_H^t α-CH_2	α'-Me
0.80	1.78	2.88
2.37	1.67	2.73
3.68	1.54	2.61
4.73	1.66	2.55
7.38	1.43	2.32
9.63	1.44	2.33

$k_\alpha = 2.48 \pm .49 \times 10^{-2} hr.^{-1}$ $k_{\alpha'} = 2.62 \pm .20 \times 10^{-2} hr.^{-1}$

APPENDIX

(i) Non-Linear Least Squares Program

The program uses a method involving successive iterations, and requires the insertion of reasonalbe estimates of the parameters to be calculated, viz., N_H^o ($\equiv$C(1)), and k ($\equiv$C(2)). The values of N_H^t, and t are read in as Y(I,J), and XX(I) respectively. The program prints out the calculated parameters at the end of each interation, and terminates when the desired number of iterations is reached. It then prints out the standard errors in the parameters, as well as the calculated parameters themselves.

(ii) Linear Least Squares Program

This gives the best fit to a line Y = mX + C, using standard formulae (90). The subroutine FLEAS calculates the slope m (SMITH), the intercept C (SUE), and the respective errors in these (SB,SA). The values of k_{obs}, and c are read in as RK(I), and CONC(I), the program calculating k_{obs}/c, and $c^{-\frac{1}{2}}$ itself. To give an indication of the scatter of the points on the plot, the program was made to calculate Y-values on the calculated line that correspond to the inserted values of c (CONC(I)), and the difference (DIFF Y(I)) between these and the corresponding observed values (Y(I)).

```
=240STEE        SUSAN 100                    FØRTRAN SØURCE LIST
    ISN         SØURCE STATEMENT

      0 $IBFTC          NØDECK
        C       NØN-LINEAR LEAST SQUARES
        C
        C       INSERT MAX. DATA DIMENSIØNS, E.G. DIMENSIØN Y(30,30)
      1         DIMENSIØN Y(1,1000)
      2         DIMENSIØN XX(1000)
        C       END ØF INSERT
      3         DIMENSIØN C(12),F(12),DEL(12),S(12),SIG(12),A(12,12)
      4         READ 1,NREP
      6       1 FØRMAT (1I3)
      7         DØ 120 IREP=1,NREP
     10         READ 13,NPAR,ITERM,IM,JM
     15      13 FØRMAT(4I3)
     16         READ 2,(C(I),I=1,NPAR)
     23       2 FØRMAT(3F8.4)
     24         READ 3,((Y(I,J),J=1,JM),I=1,IM)
     35       3 FØRMAT(16F5.2)
     36         READ 151,(XX(I),I=1,JM)
     43     151 FØRMAT(13F6.2)
     44         PRINT 150,((Y(I,J),J=1,JM),I=1,IM)
     55     150 FØRMAT (11H-INPUT DATA/(1H+,5E13.6)
     56         PRINT 150,(XX(I),I=1,JM)
     63         ITER=0
     64         PRINT 4,IREP
     65       4 FØRMAT (15H-DATA GRØUP NØ=,I3)
     66         PRINT 5,ITER
     67       5 FØRMAT (14HOITERATIØN NØ=,I3)
     70         PRINT 6,IM,JM
     71       6 FØRMAT (11HOMAXIMUM I=,I3/11H+MAXIMUM J=,I3)
     72         PRINT 7,(C(I),I=1,NPAR)
     77       7 FØRMAT (17H+INPUT PARAMETERS/(1H+,6E16.7))
    100      60 CØNTINUE
    101         DØ 10 K=1,NPAR
    102         S(K)=0.0
    103         DØ 10 L=1,NPAR
    104      10 A(K,L)=0.0
    107         DØ 20 I=1,IM
    110         DØ 20 J=1,JM
    111         X=I
    112         Z=XX(J)
        C
        C       INSERT G=F(X,Z,C(1),C(2),...C(NPAR))
        C
    113         G=C(1)*EXP(-C(2)*Z)
        C
        C       END ØF INSERT
        C
        C       INSERT F(I) = DF/DC(I), I=1 TØ NPAR
        C
    114         F(1)=EXP(-C(2)*Z)
    115         F(2)=-Z*C(1)*EXP(-C(2)*Z)
        C
        C       END ØF INSERT
        C
    116         DØ 20 K=1,NPAR
```

```
5.240STEE        SUSAN 100                          FØRTRAN SØURCE LIST
    ISN          SØURCE STATEMENT

     117           S(K)=S(K)+F(K)*Y(I,J)-G*F(K)
     120           DØ 20 L=1,NPAR
     121           A(K,L)=A(K,L)+F(K)*F(L)
     122        20 CØNTINUE
          C        INSERT   CALL INVSP(A,N,0,IERR)      WHERE N IS INTEGER=NPAR
     127           CALL INVSP(A,2,0,IERR)
          C        END ØF INSERT
     130           DØ 30 K=1,NPAR
     131           DEL(K)=0.0
     132           DØ 30 L=1,NPAR
     133        30 DEL(K)=DEL(K)+A(K,L)*S(L)
     136           DØ 40 I=1,NPAR
     137        40 C(I)=C(I)+DEL(I)
     141           ITER=ITER+1
     142           PRINT 8,ITER
     143         8 FØRMAT (14H-ITERATIØN NØ=,I3)
     144           PRINT 9,(C(I),I=1,NPAR)
     151         9 FØRMAT (22HØCALCULATED PARAMETERS/(1H+,6E16.7))
     152           IF(ITER-ITERM)60,70,70
     153        70 CØNTINUE
     154           IFREE=IM*JM-NPAR
     155           FREE=IFREE
     156           RES=0.0
     157           DØ 110 I=1,IM
     160           DØ 110 J=1,JM
     161           X=I
     162           Z=XX(J)
          C        INSERT G=F(X,Z,C(1),C(2),...C(NPAR))
     163           G=C(1)*EXP(-C(2)*Z)
          C        END ØF INSERT
     164        90 RES=RES+(Y(I,J)-G)**2/Y(I,J)
     165       110 CØNTINUE
     170           CHISQ=RES/FREE
     171           DØ 50 I=1,NPAR
     172        50 SIG(I)=(A(I,I)*CHISQ)**0.5
     174           PRINT 11,(SIG(I),I=1,NPAR)
     201        11 FØRMAT (16HØSTANDARD ERRØRS/(1H+,6E16.7))
     202           PRINT 12,CHISQ
     203        12 FØRMAT (13HØCHI SQUARED=,E14.7)
     204       120 CØNTINUE
     206           END
```

```
INPUT DATA
 0.195000E 01 0.176000E 01 0.168000E 01 0.170000E 01 0.159000E 01
 0.148000E 01 0.141000E 01 0.128000E 01 0.129000E 01 0.129000E 01

INPUT DATA
 0.155000E 01 0.148200E 02 0.199500E 02 0.258000E 02 0.394500E 02
 0.641200E 02 0.687200E 02 0.892200E 02 0.937000E 02 0.110220E 03

DATA GRØUP NØ=  1

ITERATIØN NØ=  0

MAXIMUM I=  1
MAXIMUM J= 10
INPUT PARAMETERS
   0.20CCC00E 01   0.40C0CCCE-02

ITERATIØN NØ=  1

CALCULATED PARAMETERS
   0.1883600E 01   0.3973816E-02

ITERATIØN NØ=  2

CALCULATED PARAMETERS
   0.1883569E 01   0.3971840E-02

ITERATIØN NØ=  3

CALCULATED PARAMETERS
   0.1883566E 01   0.3971811E-02

ITERATIØN NØ=  4

CALCULATED PARAMETERS
   0.1883566E 01   0.3971811E-02

ITERATIØN NØ=  5

CALCULATED PARAMETERS
   0.1883566E 01   0.3971811E-02

ITERATIØN NØ=  6

CALCULATED PARAMETERS
   0.1883566E 01   0.3971810E-02

ITERATIØN NØ=  7
```

```
CALCULATED PARAMETERS
   0.1883566E 01   0.3971811E-02

ITERATIØN NØ=  8

CALCULATED PARAMETERS
   0.1883566E 01   0.3971811E-02

ITERATIØN NØ=  9

CALCULATED PARAMETERS
   0.1883566E 01   0.3971810E-02

ITERATIØN NØ= 10

CALCULATED PARAMETERS
   0.1883566E 01   0.3971811E-02

STANDARD ERRØRS
   0.2388617E-01   0.2312223E-03

CHI SQUARED= 0.1500987E-02

005240STEE        SUSAN 100   001MIN 22SEC CØST$004.95 REM. TIME 0049MIN 32S
```

```
2240STEE        MARY  100                    FØRTRAN SØURCE LIST
   ISN          SØURCE STATEMENT
     0 $IBFTC
       C
       C      ANALYSIS ØF CATALYSIS BY A WEAK BASE USING A LEAST SQUARES METHØD
       C
       C      DATA FITTED TØ RATE CØNST/CØNC VS 1.0/SQRT(CØNC)
       C
     1         DIMENSIØN RK(100), CØNC(100), Y(100),X(100),CALCY(100),DIFFY(100),
              1TITLE(12)
     2   200 READ 20,(TITLE(J),J=1,12)
     7    20 FØRMAT(12A6)
    10       READ 1,N
    12     1 FØRMAT(I3)
    13       READ 2,(RK(J),J=1,N)
    20     2 FØRMAT(16F5.2)
    21       READ 3,(CØNC(J),J=1,N)
    26     3 FØRMAT(16F5.3)
    27       DØ 4 I=1,N
       C
       C      DEFINE Y(I)=RATE CØNST/CØNC, X(I)=1.0/SQRT(CØNC)
       C
    30       Y(I)=RK(I)/(CØNC(I)*10.0)
    31       X(I)=1.0/SQRT(CØNC(I))
    32     4 CØNTINUE
    34       CALL FLEAS (N,Y,X,SMITH,SB,SUE,SA)
    35       DØ 5 I=1,N
    36       CALCY(I)=SMITH*X(I)+SUE
    37       DIFFY(I)=Y(I)-CALCY(I)
    40     5 CØNTINUE
    42       PRINT 6,(TITLE(J),J=1,12)
    47     6 FØRMAT(1HO/1HO12A6/1HO)
    50       PRINT 7
    51     7 FØRMAT(1HO9X,7HCØNC(I),3X,5HRK(I),5X,4HY(I),6X,4HX(I),6X,8HCALCY(I
             1),2X,8HDIFFY(I))
    52       PRINT 8,((CØNC(I),RK(I),Y(I),X(I),CALCY(I),DIFFY(I)),I=1,N)
    63     8 FØRMAT(1HO5X,6F10.3)
    64       PRINT 9, SUE
    65     9 FØRMAT(1HO/1HO9X,19HCATALYTIC CØNSTANT=,E15.6)
    66       PRINT 10, SA
    67    10 FØRMAT(1H+9X,19HERRØR IN CAT CØNST=,E15.6)
    70       PRINT 11, SMITH
    71    11 FØRMAT(1HO9X,20HLEAST SQUARES SLØPE=,E15.6)
    72       PRINT 12, SB
    73    12 FØRMAT(1H+9X,15HERRØR IN SLØPE=,E15.6/1HO)
    74       GØ TØ 200
    75       END
```

ANALYSIS ØF CATALYSIS BY PARANITRØPHENØXIDE IØN (METHYLENE)

CØNC(I)	RK(I)	Y(I)	X(I)	CALCY(I)	DIFFY(I)
0.185	4.180	2.259	2.325	2.137	0.122
0.144	3.090	2.146	2.635	2.244	-0.098
0.103	2.500	2.427	3.116	2.409	0.018
0.082	2.140	2.610	3.492	2.538	0.072
0.062	1.530	2.468	4.016	2.718	-0.250
0.041	1.300	3.171	4.939	3.035	0.136

CATALYTIC CØNSTANT= 0.133891E 01
ERRØR IN CAT CØNST= 0.680413E-01

LEAST SQUARES SLØPE= 0.343384E 00
ERRØR IN SLØPE= 0.779266E-01

ANALYSIS ØF CATALYSIS BY PARANITRØPHENØXIDE IØN (METHYL)

CØNC(I)	RK(I)	Y(I)	X(I)	CALCY(I)	DIFFY(I)
0.185	3.210	1.735	2.325	1.731	0.005
0.144	2.590	1.799	2.635	1.842	-0.044
0.103	2.250	2.184	3.116	2.015	0.169
0.082	1.800	2.195	3.492	2.151	0.044
0.062	1.260	2.032	4.016	2.340	-0.307
0.041	1.150	2.805	4.939	2.672	0.133

CATALYTIC CØNSTANT= 0.893328E 00
ERRØR IN CAT CØNST= 0.776274E-01

LEAST SQUARES SLØPE= 0.360109E 00
ERRØR IN SLØPE= 0.889055E-01

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