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ISOTOPE AND STERIC EFFECTS ON PROTON TRANSFERS

by

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INTRODUCTION

A method for the investigation of reaction mechanism which has
come to be used quite extensively is the determination of the hydrogen
isotope effect.

Wiberg has collected many examples of this effect in a review.\textsuperscript{1}
In this review he shows how to understand a large isotope effect in
terms of the difference in vibrational zero-point energy between a
bond to deuterium and the corresponding bond to hydrogen. The fol-
lowing three paragraphs show briefly how the zero-point energy can
contribute to the isotope effect. The arguments follow the same
lines as those of Wiberg.

The lowest energy level for any normal vibrational mode of any
molecule is the zero-point energy which for a harmonic oscillator
is \( 1/2 \hbar \nu \) where \( \hbar \) is Planck's constant and \( \nu \) is the classical
frequency of the vibration. This lowest energy level is the
vibrational energy of a molecule at absolute zero. At room temper-
ature most of the bonds to hydrogen are in this vibrational energy
level. This can be demonstrated for a carbon-hydrogen stretching
vibration by assuming a Boltzmann distribution of energies, a
stretching frequency of 3000 cm\(^{-1}\) and a temperature of 25\(^\circ\) C. The
ratio of the concentration of molecules in a singly excited state,
\( n_\nu \), to those in the lowest vibrational level, \( n_0 \), can be calculated
using the equation:

\[
\frac{n_\nu}{n_0} = e^{-\frac{-E_\nu}{kT}}
\]  

(1)

where \( E_\nu = \hbar \nu \), \( k \) is Boltzmann's constant and \( T \) is temperature.
Equation (1) yields an \( n_\nu/n_0 \) ratio of \( 0.6 \times 10^{-6} \) which shows that
only about 0.0001 \% of the molecules are in the next highest stretch-
ing vibrational level.
Because of the effect of the difference in mass on the stretching frequencies, a bond to hydrogen and the corresponding bond to deuterium have a different zero-point energy. This is made clearer by considering the Hooke's Law relation between the stretching frequency and the force constant for the stretching vibration. Equation (2).

\[ \gamma = \frac{1}{2\pi} \sqrt{\frac{k}{\mu}} \]  

(2)

In this expression \( \gamma \) is the frequency, \( k \) is the force constant and \( \mu \) is the reduced mass. For most hydrogen and deuterium containing bonds the reduced mass is 1 and 2. Equation (2) predicts a \( v_H/v_D \) ratio of 1.41 which is somewhat higher than the generally observed value of 1.35 because of the contribution of the mass of the group attached to hydrogen or deuterium to the reduced mass and the anharmonicity of the vibration.

The zero-point energy, calculated on the above basis, of a typical carbon-hydrogen stretching vibration of 3000 cm\(^{-1}\) is about 4.2 kcal/mole. Using the experimental frequency ratio 1.35, the corresponding carbon-deuterium stretching frequency is about 2200 cm\(^{-1}\), and the zero-point energy is 3 kcal/mole. The difference in zero-point energy is 1.2 kcal/mole. If we assume that the stretching vibration is lost on going to the transition state by becoming translation along the reaction coordinate, this difference will result in an activation energy 1.2 kcal/mole greater for the deuterium compound than for the hydrogen compound. At 25° C. this difference in activation energy amounts to a \( k_H/k_D \) ratio of 6.9.
Ratios of $k_H/k_D$ which are less than 6.9 at 25°C have been observed in reactions which are thought to proceed by way of non-linear transition states. One such reaction is that of pyridine diphenylborane with water which has been studied by Hawthorne and Lewis and in more detail by Lewis and Grinstein. In a non-linear transition state, the stretching vibration is unrelated to the reaction coordinate and is therefore not lost.

Westheimer has given an explanation for a range of values for the ratio $k_H/k_D$, even with a linear transition state. His discussion considers the vibrations present in a one-dimensional three-particle transition state. A treatment similar to Westheimer's has been given by Melander.

In the manner of Westheimer consider the reaction:

$$A-H + B \xleftrightarrow{\text{A-H-B}} \rightarrow A + H-B$$

where A-H-B is a linear transition state. In order for A-H-B to be a good model for a transition state the masses of A and B are assumed large compared to the mass of either hydrogen or deuterium. Now if A-H-B were an ordinary linear three-atom molecule, it would have two normal modes of vibration which are linear or stretching vibrations. Westheimer calls one of these "symmetric" and the other "antisymmetric."

$$\xleftrightarrow{\text{A-H-B}} \quad \xleftrightarrow{\text{A-H-B}}$$

"Symmetric"  "Antisymmetric"

Obviously the doubly degenerate bending mode $\downarrow A-H-B \downarrow$ is neglected in this treatment since the model is one-dimensional. The theory of absolute reaction rates demands that one of the vibrations of A-H-B become translation along the reaction coordinate. The
illustration of the "antisymmetric" vibration, with the A-H distance increasing and the B-H distance decreasing, clearly shows that it is the vibration which becomes translation along the reaction coordinate. If the retained vibration is really symmetrical the hydrogen atom will not move and the frequency of the vibration will not depend on the mass of the central atom. On going to the transition state the previously mentioned change in zero-point energy of 1.2 kcal/mole will occur. However, when the masses of A and B are different or especially when the force constants for the bonds of H to A and B are not equal, a change in the mass of the central atom will alter the vibration frequency. The zero-point energy for the "symmetric" vibration in the transition state will be different for hydrogen and deuterium. Therefore, the difference in activation energy for the hydrogen and deuterium compound will decrease.

Bell\(^7\) has considered zero-point energy in the transition state as arising from the effect of the mass of the central atom on the bending vibration of A\(\cdots\)H\(\cdots\)B. He does not consider the very unsymmetrical "symmetric" linear vibration. It is clear from either point of view that the value of the ratio, \(k_H/k_D\), obtained from consideration of differences in zero-point energy in the reactant molecules only, represents a maximum value to be expected from loss of stretching vibrations.

To obtain values of a kinetic isotope effect which can be given a quantitative interpretation, Bell\(^7\) suggests that several precautions should be taken.

One of these is that the solvent for the system under investigation should be kept constant. For instance, in the bromination of
nitromethane and nitromethane-\textsubscript{d3} catalyzed by chloroacetate ion the $k_{H}/k_{D}$ ratio changes from 4.3 to 5.2 on going from water to deuterium oxide as the solvent. An explanation offered for this difference by Bell\textsuperscript{7} is that the water does a better job than deuterium oxide of solvating the transition state or the reactants.

Secondly, isotopic substitution of atoms other than the one being transferred should be avoided since these will sometimes retard the reaction. This retardation is called a secondary isotope effect and some of these are large. For example, Emmons and Hawthorne\textsuperscript{9} found $k_{H}/k_{D} = 1.24$ in the bromination of cyclopentyl phenyl and cyclopentyl-2,2,5,5-\textsubscript{d4} phenyl ketones catalyzed by acetate ions. Also, Streitwieser, Jagow, Fahey and Suzuki\textsuperscript{10} have determined the effect of substitution of deuterium for $\alpha$-hydrogen in the acetylation of cyclopentyl $p$-toluenesulphonate which was found to solvolyze 15\% faster than cyclopentyl-1-\textsubscript{d1} $p$-toluenesulphonate.

A discussion of the possibility of "tunneling" in proton transfer reactions is appropriate in this thesis. Quantum theory predicts that a small particle like hydrogen has a perceptible probability of penetrating a barrier which it does not have enough energy to surmount. Bell\textsuperscript{7} gives a fairly detailed account of this concept and further discussion is available in Grinstein's thesis.\textsuperscript{11}

When applied to a hydrogen isotope rate effect the concept of tunneling has several consequences. One is that a proton will tunnel more than a deuterium atom because it is lighter. The rate constant for the hydrogen compound is increased relative to the rate constant for the deuterium compound and the $k_{H}/k_{D}$ ratio is increased. Also, the difference in apparent activation energies will be larger than expected from the difference in zero-point energies.
Another effect of tunneling is to cause a low value for $A_H/A_D$ where $A$ is the pre-exponential factor in the Arrhenius equation. The reason for this has been pointed out by Bell. Bell, Fendley and Hulett have determined the $k_H/k_D$ ratio, the $A_H/A_D$ ratio and $\Delta E_a$ for the fluoride ion catalyzed bromination of 2-carboethoxycyclopentanone-2-$d_1$. The main point of interest is the $A_H/A_D$ value of 0.042 which is strong evidence for extensive tunneling. Other examples of low $A_H/A_D$ ratios occur in the base catalyzed elimination of 1-bromo-2-phenylpropane investigated by Shiner and Smith with an $A_H/A_D$ of 0.366 and the reaction of leuco crystal violet with chloranil studied by Grinstein which exhibited an $A_H/A_D$ ratio of 0.345.

In order to gain more information about isotope effects in general, and with the idea of finding out what changes in isotope effect would be derived from modification of steric requirements around the reaction site, the acetate ion catalyzed bromination of a series of ketones was studied. Also, the iodination of nitroethane, nitroethane-2-$d_2$, 2-nitropropane and 2-nitropropane-2-$d_1$ catalyzed by pyridine and some of its derivatives was studied. It was possible with this series to obtain information about the behavior of the isotope effect with changing base strength since the pyridine bases differed in basicity.
METHODS

The mechanism of the base-catalyzed halogenation of ketones has been known for a long time. The rate of the reaction depends on the concentration of ketone and base but not on the concentration of halogen. This means that the halogen becomes involved after completion of the rate-determining step. A simple mechanism which satisfies these conditions is the following:

\[
\begin{align*}
\text{O} & \quad \xrightarrow{k_{\text{slow}}} \quad \text{O} \\
R_1\text{-C-C-H} + B & \quad \xrightarrow{k_{-1}} \quad R_1\text{-C-C}^- + BH^+
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \xrightarrow{k_2} \quad \text{O} \\
R_1\text{-C-C}^- + X_2 & \quad \xrightarrow{\text{fast}} \quad R_1\text{-C-C-X} + X^-
\end{align*}
\]

The rate of change of the concentration of halogen is given by the differential equation:

\[
- \frac{d(X_2)}{dt} = \frac{k_2 k_{\text{1}} (\text{Ketone})(B)(X_2)}{k_2(X_2) + k_{-1}(BH^+)}
\]  

(3)

Now at reasonable \((X_2)\), \(k_2(X_2) \gg k_{-1}(BH^+)\) and then

\[
- \frac{d(X_2)}{dz} = k_{\text{1}} (\text{Ketone})(B).
\]

A convenient method of determining \(k_{\text{1}}\) for this reaction is to measure the rate of disappearance of halogen when a large excess of ketone and base are present. Then \(k_{\text{1}}\) will be given by the equation:
\[
\frac{k_1 - (X_2)_{t_2} - (X_2)_{t_1}}{(K)_0(B)_0(t_2 - t_1)} - \frac{A_{t_2} - A_{t_1}}{\varepsilon(K)_0(B)_0(t_2 - t_1)}
\]

where \( t \) is time, \((K)_0\) and \((B)_0\) are the essentially constant concentrations of ketone and base \( (X_2) \) is halogen concentration. \( A \) is optical density and \( \varepsilon \) is the extinction coefficient.

Emmons and Hawthorne\(^9\) determined the rate of disappearance of bromine spectrophotometrically for the acid- and base-catalyzed reaction of phenyl cyclopentyl and phenyl cyclohexyl ketones and their deuterated analogs. They obtained rate constants from the slope of optical density vs. time plots and the isotope effects were given by the ratio of the protium and deuterium rate constants. The same procedure was followed in this thesis.

A modification of the Emmons and Hawthorne procedure, suggested by Lewis and Johnson,\(^{15}\) is the addition of excess bromide ion which prevents a change in the apparent extinction coefficient of bromine due to the reaction:

\[
\text{Br}_2 + \text{Br}^- \rightleftharpoons \text{Br}_3^-.
\]

This reaction produces a significant change in the extinction coefficient (more than double the value found by Emmons and Hawthorne). However, an error in the extinction coefficient has no effect on an isotope effect since \( \varepsilon \) cancels in the ratio of the protium and deuterium rate constants.

The following variation on the spectrophotometric method to obtain the isotope effect is interesting. A cell containing hydrogen compound and bromine was placed in the reference compartment of the spectrophotometer. Another cell, containing the same
concentrations of deuterium compound and bromine as the one above, was placed in the sample compartment. The plot obtained for acetophenone is shown below.

![Graph showing optical density vs. time](image)

**Figure 1**

Kinetics and Isotope Effect for the Acetate Catalyzed Bromination of Acetophenone by a Differential Method

The dotted portion of line 1 is due to the time lag between the beginning of the reaction and the time when the spectrophotometer was started. The slope, $s_1$, of line 1 is $k_H - k_D$ and the slope, $s_2$, of line 2 is $-k_D$. The ratio $k_H/k_D$ can be calculated from the equation given below.

$$\frac{k_H}{k_D} = 1 - \frac{s_1}{s_2}$$

Alternatively, $k_H/k_D$ can be determined from the ratio $t_2/t_1$. This method was not used again because the temperature was difficult to control.
Aliphatic nitro compounds undergo a base-catalyzed halogenation \textsuperscript{16} and the rate of reaction can be determined in a similar manner.

Bromine reacts with the pyridine bases used in this study possibly by the reaction

\[
\text{[Nitro Compound]} + \text{Br}_2 \rightleftharpoons \text{[Nitrato Compound]} + \text{Br}^-
\]

Iodine exhibits a similar behavior but to a smaller extent and the reaction does not interfere with the kinetic studies if an excess of iodide ion is added to convert iodine extensively to tri-iodide.

Pearson and Williams \textsuperscript{17} have determined conductimetrically the rates of iodination of nitroethane catalyzed by pyridine bases in aqueous ethanol. The equilibrium

\[
\text{[Nitro Compound]} + \text{H}_2\text{O} \rightleftharpoons \text{[Nitrato Compound]} + \text{OH}^-
\]

produces hydroxide ions which will also catalyze the iodination. This catalysis can be suppressed with a small amount of perchloric acid. In this thesis the perchloric acid concentration was usually 0.003 M.

The spectrophotometric method has two serious drawbacks. One is the stringent requirement on the purity of the reactants. Usually about one to three per cent of the reaction was followed, and the presence of a contaminant which reacts with halogen could invalidate the results. However, with the aid of vapor phase chromatography one can be reasonably sure of having high purity starting materials.
When clean kinetics of the type expected (zero order in halogen) were obtained, it seemed reasonable to assign significance to the data. The fact that isotope effects were observed also indicates that the reaction being followed was not that of halogen with an impurity.

A more fundamental limitation is the disappearance of halogen by side reactions i.e. reaction with solvent or with base. With dialkylacetophenones the desired path of reaction was not the main path for disappearance of bromine, so the spectrophotometric method was not used.

The rate constant, k₁, could be alternatively determined from a gas chromatographic analysis of the product after various time intervals. The rate constants were obtained from the slope of plots of mole ratio of bromo-ketone to ketone (P/K) vs. time. The best straight line was calculated by the method of least squares. Usually only about the first 5-10% of the reaction was followed, making a logarithmic plot unnecessary.

A typical plot is shown in Figure 2 on the following page.

One alarming feature of these plots was an intercept corresponding to an initial P/K ratio of 0.02-0.22. It was thought that this might be due to the presence of a small amount of ketone in the enol form, but since samples isolated a few minutes after addition of bromine to the reaction mixture did not show a bromo-ketone peak on the vapor phase chromatogram this conclusion seemed incorrect. The intercept also varied widely from run to run on the same material (0.02-0.10 in the case of isobutyrophenone).

The vapor chromatographic method of following the rate requires frequent calibration, preferably before each analysis, and the precision of determinations is not particularly good. about ± 5%.
Figure 2

Determination of the Rate Constant for the Acetate Catalyzed Bromination of Isobutyrophenone
The bromination of phenyl cyclohexyl ketone could not be followed in this way since many unidentified peaks presumably derived from the bromoketone, appeared on the chromatogram.

One important source of error in the rate constants determined for the deuterated substrates (and in the isotope effects obtained from a ratio of the rate constants) is protium contamination of the deuterated compound. A correction can be made using the relation given in Grinstein's thesis which is applicable to reactions carried to small extents of completion:

\[ k_D = \frac{k_{\text{obs}} \cdot k_H}{1 - f_H} \quad (1) \]

where \( k_{\text{obs}} \) is the measured deuterium rate constant, \( k_D \) the true deuterium rate constant, \( k_H \) the observed hydrogen rate constant, and \( f_H \) the fraction of protium contamination. For instance if the measured deuterium rate constant \( k_{\text{obs}} \) is 0.1 \( k_H \) and the fraction of protium, \( f_H \), is 0.05 the true deuterium rate constant \( k_D \), calculated from the equation above will be 0.05 \( k_H \). Thus \( k_{\text{obs}} \) is twice \( k_D \) for a mere 5% protium in the deuterated sample. Methods of determining the extent of deuteration are naturally of prime importance.

Two methods of deuterium analysis were used. One was the standard technique of combustion over hot copper oxide purification of the water, and analysis for deuterium content by the technique known as the density gradient method.

This method of analysis can be made very precise but is prone to be inaccurate because small amounts of water can easily be picked
up in the procedure. Therefore, a sample of at least 200 mg. was required to get reproducible analyses. Also the results are dependent on the atom fraction of deuterium in the molecule of interest. For example, acetophenone-\text{d}_3 with an atom fraction of deuterium of 0.375 can be analyzed more satisfactorily than 2.4-dimethylvalerophenone-\alpha-\text{d}_1 where the atom fraction of deuterium is about 0.0556.

The second method was the use of an NMR spectrometer to observe the disappearance of hydrogen from the position exchanged. The most successful way of following the disappearance especially when most of the hydrogen had been exchanged was a comparison of the peak height of the partially exchanged material to that of unexchanged material under constant instrument conditions. This technique must be applied with caution in cases when there is more than one equivalent exchangeable position since the peak for the residual hydrogen will be split by the deuteron. For instance in extensively deuterated nitroethane each peak in the quartet for the methylene group is split into a triplet.

An analysis of partially exchanged propiophenone mixtures for non-, mono- and di-deuterated species was possible from the NMR spectrum. The spectrum of the methyl group showed five peaks, two assignable to the non-deuterated species, two assignable to the mono-deuterated species, and one assignable to the sum of non-deuterated and di-deuterated species. From a comparison of the peak heights of the methyl group of unexchanged propiophenone to the peaks corresponding to the non-deuterated species in the mixture, the fraction of this species, \( f_0 \), was obtained. Knowledge of the total hydrogen content in the methylene group, \( f_M \), from its
integrated NMR intensity, permitted calculation of \( f_1 \), the fraction of the mono-deuterated species by the equation

\[
I_H = 2 f_0 + f_1.
\]

The fraction of the di-deuterated species, \( f_2 \), was then obtained from the equation

\[
f_0 + f_1 + f_2 = 1.
\]

Figure 3 shows the NMR spectrum of the methyl group in partially exchanged propiophenone, extensively exchanged propiophenone and unexchanged propiophenone.
The chemical shift of the peak for the methyl hydrogens by deuterium substituted in the methylene group, $\delta_{\text{HD}}$, is about 0.01 p.p.m. For the two peaks due to mono-deuterated propiophenone a $J_{\text{HD}}$ value of about 1 cycle/sec. can be calculated by use of the relation:

$$J_{\text{HD}} = \frac{\gamma_D J_{\text{HH}}}{\gamma_H}$$

where $\gamma_H$ and $\gamma_D$ are the gyromagnetic ratios for hydrogen and deuterium respectively and $J_{\text{HD}}$ and $J_{\text{HH}}$ are the splitting constants. This calculation was suggested by E. Grunwald. The spectrum shown in Figure 3 does not show this splitting because it was scanned at less than optimum resolution. A spectrum of partially exchanged nitroethane taken under conditions of higher resolution does show the predicted spin-spin splitting. The preceding method of analysis for the species present in a partially exchanged mixture is the only known non-destructive general method to get this kind of information.

With the information discussed in the previous paragraph available, a secondary isotope effect, caused by the presence of a deuterium atom on the same carbon atom from which a proton is being removed, can be calculated. The observed rate of bromination can be expressed in terms of the observed total rate constant, $k_{\text{obs.}}$, which is

$$k_{\text{obs.}} = k_0 f_0 + k_1 f_1 + k_2 f_2$$

$$k'_{\text{obs.}} = k'_0 f'_0 + k'_1 f'_1 + k'_2 f'_2$$

where $k_0$ is the rate constant for the non-deuterated species, $k_1$ the rate constant for the mono-deuterated species, $k_2$ the rate constant for the di-deuterated species and where the primes indicate the analogous quantities for a different mixture.
If we define $E_s$ as the secondary isotope effect and $E_p$ as the primary isotope effect (both in the direction $k_D/k_H$) and we assume that each is independent of the isotope present at the other position, the equations become

$$k_{obs.}/k_0 = f_0 + 0.5 (E_s + E_p) f_1 + f_2 E_s E_p$$

$$k'_{obs.}/k_0 = f'_0 + 0.5 (E_s + E_p) f'_1 + f'_2 E_s E_p$$

when $k_0/2$ is the rate per hydrogen. The solution of the simultaneous equations, in which $k_{obs.}$, $k'_{obs.}$, and $k_0$ were independently measured, and the $f$'s were measured by the NMR method described, for one mixture of propiophenone about 40% and another about 95% deuterated gave $E_s$ and $E_p$.

An attempt to determine the secondary isotope effect using acetophenone, with the assumption that partially deuterated mixtures had a statistical distribution of the species containing 0 to 3 deuterium atoms per molecule was unsuccessful. It is not known whether the nonsensical results (i.e., $E_s < 0$) result from a failure of one of the assumptions, or from the error characteristic of attempts to solve three simultaneous equations using data of limited accuracy.

The tritium isotope effect for the acetic acid catalyzed bromination of phenyl cyclohexyl ketone was determined. The isotope effect was calculated using the equation

$$k_H/k_T = \frac{\log(1-X)}{\log[(1-X)a_2/a_1]}$$

where $X$ is the extent of completion of the reaction, $a_1$ is the specific activity of the starting material, and $a_2$ is the specific activity after $X$ amount of reaction.
The extent of completion, $X$, was determined two ways. One was
the determination of the amount of unreacted ketone by vapor phase
chromatography; the second used an isotopic dilution analysis.

To understand the second let us start with $N^0$ g. of ketone
which has an initial specific activity $a_1$, measured by solution-
scintillation counting. After $X$ amount of reaction two equal parts
each containing $N'$ g. of ketone with specific activity $a_2$ are taken.
To one of these is added $M$ g. of untritiated ketone. If $a_3$ is the
specific activity of this sample, then

$$a_3 = a_2 \frac{N'}{N' + M},$$

or

$$N' = \frac{Ma_3}{a_2 - a_3}.$$

and

$$X = N^0 - 2N'/N^0.$$
RESULTS AND CONCLUSIONS

The results of the study of the acetate catalyzed bromination rates of the phenyl alkyl ketones are shown in Table 1.

One interesting result is the order of reactivity acetophenone ≪ α-bromoacetophenone ≳ α-α-dibromoacetophenone. The bromo compounds were studied to make sure that the rate measured was that of the removal of only one proton. Addition of an electron-attracting bromine could be expected to enhance the rate of removal of an adjacent proton and in accord with this idea α-bromoacetophenone was found to react about 33 times faster than acetophenone. However, α,α-dibromoacetophenone reacts at approximately the same rate as the mono-bromo compound suggesting that introduction of the second bromine atom causes steric retardation of the proton removal. Bell, Gelles and Møller found an analogous situation in the base catalyzed bromination of benzoylaceton and bromobenzoylaceton where the rate of reaction of benzoylaceton was twice that for the bromo-compound.

The isotope effect for 2,4-dimethylvalerophenone attracts attention but is unreliable. For one reason the correction using equation (4) is very large and probably excessive. Also, the F/K vs. time plots for this compound show considerable curvature, i.e., a change in slope of about 40-50% which is far beyond that attributable to the neglect of change in ketone concentration. The F/K vs. time plots for isobutyrophenone and phenyl sec-butyl ketone are not entirely free of this curvature but the effect is not nearly as serious. Reaction of isobutyrophenone was shown to be zero-order in bromine but this was not demonstrated for phenyl sec-butyl ketone and 2,4-di-methylvalerophenone. The curvature in the plots becomes more pronounced
Table 1

Pseudo First-Order Rate Constants and Isotope Effects for the Acetate Catalyzed Bromination of Phenyl Alkyl Ketones in Aqueous Acetic Acid

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>R(^a)</th>
<th>(k_H^b) (\times 10^6) sec(^{-1})</th>
<th>(k_D) (\times 10^6) sec(^{-1})</th>
<th>((k_H/k_D)^c) corr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.5</td>
<td>Methyl</td>
<td>2.36 ± 0.04 (2)</td>
<td>0.354 (1)</td>
<td>10</td>
</tr>
<tr>
<td>27.5</td>
<td>Bromomethyl</td>
<td>78.8 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27.5</td>
<td>Dibromomethyl</td>
<td>82 ± 2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.5</td>
<td>Ethyl</td>
<td>1.83 ± 0.03 (4)</td>
<td>0.339 ± 0.001 (2)</td>
<td>6.7</td>
</tr>
<tr>
<td>100</td>
<td>i-Propyl</td>
<td>19.8 ± 1 (6)</td>
<td>4.26 ± 0.01 (2)</td>
<td>6.8</td>
</tr>
<tr>
<td>100</td>
<td>sec-Butyl</td>
<td>6.5 ± 3 (3)</td>
<td>1.5 ± 1 (3)</td>
<td>6.2</td>
</tr>
<tr>
<td>100</td>
<td>4-Methyl-2-pentyl</td>
<td>6.2 ± 5 (3)</td>
<td>0.643 (1)</td>
<td>22</td>
</tr>
<tr>
<td>100</td>
<td>Cyclohexyl</td>
<td>8.2 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\) R represents the alkyl group in \(\Phi-\text{C-R}\).

\(b\) Rate constants given are pseudo first-order constants for the disappearance of ketone in 1.83 M sodium acetate in aqueous acetic acid. The numbers in parentheses are the number of runs and the errors indicated are average deviations.

\(c\) The values shown in this column were obtained by applying equation (4) given in the methods section, to correct for the protium content of the deuterated species.
on going from isobutyrophenone to phenyl sec-butyl ketone to 2,4-dimethylvalerophenone and could mean that for the hindered cases the condition $k_2(Br_2) > k_1(BH)$ is not appropriate even at reasonable bromine concentrations. If this were true the reaction rate would depend on bromine concentration. Examples of the dependence of reaction velocity on halogen concentration have been observed by Bell and Spiro\textsuperscript{21} in the base-catalyzed bromination of ethyl malonate and by Bartlett and Vincent\textsuperscript{22} in the halogenation of acetone and other ketones in alkaline hypochlorite solutions.

A tritium isotope effect of 3 was observed for the acetate catalyzed bromination of phenyl cyclohexyl ketone at 100°C. This is much smaller than the value of 11.5 expected from zero-point energy considerations.\textsuperscript{6} The reaction was shown to be first order in acetate ion but the order with respect to bromine was not determined. Vapor phase chromatography showed that phenyl 1-bromocyclohexyl ketone was only a minor reaction product. The products of the reaction were not identified but are probably the $\alpha,\beta$-unsaturated ketone, phenyl 1-cyclohexenyl ketone, and phenyl 2-bromocyclohexyl ketone formed from the reaction of hydrogen bromide with the $\alpha,\beta$-unsaturated ketone. Reaction of bromine with the $\alpha,\beta$-unsaturated ketone could also produce phenyl 1,2-dibromocyclohexyl ketone.

Kevill, Hess, Foster and Cromwell\textsuperscript{23} have recently shown that the tetraethylammonium bromide catalyzed elimination of 4-biphenyl-1-bromocyclohexyl ketone at about 91°C in acetonitrile yields the $\alpha,\beta$-unsaturated ketone and 4-biphenyl-1,2-bromocyclohexyl ketone.

In view of the complications mentioned, and bearing in mind that the
condition \( k_2(\text{Br}_2) \gg k_{-1}^+(\text{BH}) \) may not be applicable in this case, the \( k_H/k_T \) ratio of 3 for phenyl cyclohexyl ketone is of doubtful significance.

Inspection of a typical plot of optical density vs. time, Figure 4, for propiophenone reveals that the reaction is no longer zero-order in bromine at very low bromine concentrations. Figure 5 shows the region of curvature enlarged a factor of ten. This was accomplished by using a 10 cm. rather than a 1 cm. spectrophotometer cell.

Let us return to equation (3) and recall that \( k_1^+(\text{K})(\text{BH}) \) is the rate of bromination at reasonable concentrations of bromine. Now when the concentration of bromine becomes very low and specifically when the slope of the optical density vs. time plot becomes one-half the slope for the strictly zero-order plot the following equation will hold:

\[
\frac{k_2(\text{Br}_2)^{1/2}}{k_{-1}^+(\text{BH}) + k_2(\text{Br}_2)^{1/2}} = 1/2
\]  

(5)

where \((\text{Br}_2)^{1/2}\) is the concentration of bromine at the point on the curve where the slope becomes one-half that for the zero-order plot. Equation (5) readily simplifies to equation (6).

\[
k_{-1}^+(\text{BH}) = k_2(\text{Br}_2)^{1/2}
\]  

(6)

For the acetate stock solution (BH) represents neutral acetic acid and is about 16 and for propiophenone at 38.5° C. \((\text{Br}_2)^{1/2}\) was about \(4.6 \times 10^{-6}\) M. Therefore, \(k_2/k_{-1} \approx 3 \times 10^6\) showing that reaction of halogen with enolate and enol (\(k_2\) includes reaction via enol) is about three million times as fast as the reversion to ketone.
Figure 4
Zero-Order Plot for Acetate Catalyzed Bromination of Propiophenone (1 cm. cells)

Figure 5
Zero-Order Plot for Acetate Catalyzed Bromination of Propiophenone (10 cm. cells)
It is difficult to draw clear-cut conclusions from the data in Table 1 because the isotope effects were determined at different temperatures. The isotope effects could all be calculated at one temperature by using the Arrhenius Equation in the following form:

$$\log \left( \frac{k_1}{k_2} \right)_{T_2} = \frac{T_1}{T_2} \log \left( \frac{k_1}{k_2} \right)_{T_1} \quad (7)$$

where 1 and 2 refer to hydrogen and deuterium respectively. In the derivation of equation (7) it was necessary to assume that the ratio $A_1/A_2$, where the A's are the pre-exponential factors in the Arrhenius Equation, was unity. By Bell's argument this assumption is not valid if there is appreciable proton tunneling and we will see later that it is certainly not applicable in the iodination of nitroethane and 2-nitropropane catalyzed by certain pyridine bases.

Before applying equation (7) to the data the secondary isotope effect and the primary isotope effect for propiophenone need to be discussed. By the method described earlier the secondary isotope effect was found to be 1.18 and the primary effect 5.71 at 38.5° C. Observation of secondary isotope effects in reactions which have a transition state with carbanion character are quite limited. Streitwieser and Sickle found that substitution of two deuteriums on the methyl group of toluene-$\alpha$-$d_1$ diminished the rate of exchange of the third deuterium with lithium cyclohexylamide. The $k_H/k_D$ ratio was 1.31. This so-called "$\alpha$-deuterium isotope effect" has generally been thought to arise because a hydrogen-bending vibration becomes an out-of-plane bending vibration of lower frequency on going to the transition state. A smaller frequency change occurs for deuterium because of its larger mass and an isotope effect results.
Streitwieser and Sickle argue that an "inductive effect" should be considered in transition states with carbanion character since deuterium can more effectively donate electrons than hydrogen. From the \( k_H/k_D \) value 1.31 an isotope effect of about 1.16 would be expected for each deuterium. The value 1.18 determined for propiophenone is about the magnitude expected.

Returning to Table 1 and applying equation (7) to the \((k_H/k_D)_{corr.}\) ratio of 10 for acetophenone at 27.5\(^\circ\) C., an isotope effect of 4.9 at 100\(^\circ\) C. for the primary isotope effect only, can be calculated if it is assumed that the secondary isotope effect is the same in acetophenone and propiophenone. The value of 5.71 at 38.5\(^\circ\) C. for the primary isotope effect for propiophenone corrected to 100\(^\circ\) C. is 4.30. These values (4.9 and 4.3) are noticeably smaller than those for the more hindered ketones isobutyrophenone and phenyl \textit{sec}-butyl ketone (6.8 and 6.2 respectively). A possible explanation of this difference is that for the more hindered ketones proton tunneling is becoming important, as is discussed more convincingly in connection with the following nitro compounds.

The rate constants for the iodination of nitroethane given in Table 2 are to be compared with those determined by Pearson and Williams. Table 3 shows some of their results. Except possibly for pyridine the agreement is not too good. Pearson and Williams reported that a rapid reversible reaction occurred between iodine and the bases with formation of a complex only slightly soluble in water, but which was said to be soluble in 30% ethanol. When an attempt was made to prepare an iodine stock solution in 30% ethanol with the same iodine and pyridine concentrations that they used,
a precipitate, presumably N-iodo pyridinium tri-iodide, was formed almost immediately. This complication was avoided in this thesis by working with lower concentrations of iodine and by adding an excess of iodide ion.

The solvent used in this study was prepared by diluting 700 ml of water to one liter with ethanol. Heat was evolved and the volume contracted when the water and ethanol were mixed. After cooling to about 25° C, ethanol was added to bring the contents to the mark. The solvent used by Pearson and Williams was said to be 30% ethanol by volume, but no indication of the method of its preparation was given. It does not seem unreasonable that the solvents used were not identical. Perhaps theirs contained more ethanol thus explaining the solubility of the complex. Considering the possibility of a difference in solvent and the fact that an excess of iodide ion was used in this work and not by Pearson and Williams, the agreement among rate constants is probably as good as could be expected.

The order of the reactions was determined by measuring the rates at different concentrations of nitro compound and pyridine base. The reactions were found to be first order in each reactant. It was also demonstrated that variation in the initial concentration of perchloric acid (usually 0.003 M) did not change the second-order rate constants.

The temperatures given for the rate constants in Tables 2 and 4 are the temperatures measured inside the thermostated cell holder for the Cary. This is an important point since at temperatures much above room temperature, ca. 40° C., the reading inside the cell holder was as much as three degrees below that in the thermostat.
Table 2

Second-order Rate Constants and Isotope Effects for the Iodination of Nitroethane in Aqueous Ethanol

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>Pyridine Substituent</th>
<th>pK\textsubscript{a} \textsuperscript{a} in H\textsubscript{2}O</th>
<th>k\textsubscript{H} \times 10\textsuperscript{3} b l. mole min.</th>
<th>k\textsubscript{D} \times 10\textsuperscript{3} c l. mole min.</th>
<th>k\textsubscript{H} / k\textsubscript{D} c</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.9</td>
<td>2,6-Dimethyl</td>
<td>6.75</td>
<td>33.7± .5 (2)</td>
<td>3.24± .08 (2)</td>
<td>10.4</td>
</tr>
<tr>
<td>30.8</td>
<td>2,6-Dimethyl</td>
<td>6.75</td>
<td>50.1± .7 (3)</td>
<td>5.32± 0.7 (2)</td>
<td>9.4</td>
</tr>
<tr>
<td>36.3</td>
<td>2,6-Dimethyl</td>
<td>6.75</td>
<td>71.6± .6 (2)</td>
<td>8.30± 0.5 (2)</td>
<td>8.6</td>
</tr>
<tr>
<td>24.9</td>
<td>2-Methyl</td>
<td>5.97</td>
<td>26.6± .5 (2)</td>
<td>3.0± 0.1 (2)</td>
<td>8.8</td>
</tr>
<tr>
<td>24.9</td>
<td>2-Et-Butyl</td>
<td>5.76</td>
<td>2.07± .07 (3)</td>
<td>0.22± 0.1 (3)</td>
<td>9.5</td>
</tr>
<tr>
<td>36.3</td>
<td>2-Et-Butyl</td>
<td>5.76</td>
<td>5.3± .3 (2)</td>
<td>0.7± 0.0 (2)</td>
<td>7.4</td>
</tr>
<tr>
<td>24.9</td>
<td>4-Methyl</td>
<td>6.02</td>
<td>19.7± .1 (2)</td>
<td>2.3± 0.1 (2)</td>
<td>8.4</td>
</tr>
<tr>
<td>24.9</td>
<td>3-Methyl</td>
<td>5.68</td>
<td>15.0± .3 (-)</td>
<td>1.6± 0.2 (2)</td>
<td>9.0</td>
</tr>
<tr>
<td>24.9</td>
<td>None</td>
<td>5.17</td>
<td>6.95± .08 (-)</td>
<td>0.860± .01 (2)</td>
<td>8.1</td>
</tr>
<tr>
<td>36.3</td>
<td>None</td>
<td>5.17</td>
<td>16.0± .2 (2)</td>
<td>2.3± 0.1 (2)</td>
<td>6.9</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by Brown and Mihm.

\textsuperscript{b} The numbers in parentheses are the number of runs and the errors indicated are average deviations.

\textsuperscript{c} Uncorrected for about 2% protium.
Table 3

Pearson and Williams Second-Order Rate Constants for Iodination of Nitroethane in 30% Ethanol at 25°C

<table>
<thead>
<tr>
<th>Base</th>
<th>$k \times 10^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>l/mole min</td>
</tr>
<tr>
<td>2,6-Lutidine</td>
<td>20.8 ± 0.6</td>
</tr>
<tr>
<td>2-Methylpyridine</td>
<td>24.5 ± 0.9</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>18.2 ± 3</td>
</tr>
<tr>
<td>3-Methylpyridine</td>
<td>13.2 ± 2</td>
</tr>
<tr>
<td>Pyridine</td>
<td>6.5 ± 0.2</td>
</tr>
</tbody>
</table>

Table 4

Second-Order Rate Constants and Isotope Effects for the Iodination of 2-Nitropropane in Aqueous Ethanol

<table>
<thead>
<tr>
<th>Temp °C</th>
<th>Pyridine Substituent</th>
<th>$k_H \times 10^3$</th>
<th>$k_D \times 10^3$</th>
<th>$k_H/k_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.9</td>
<td>2,6-Dimethyl</td>
<td>0.517 ± 0.007 (3)</td>
<td>0.0567</td>
<td>9.2</td>
</tr>
<tr>
<td>36.3</td>
<td>2,6-Dimethyl</td>
<td>1.31 ± 0.07 (2)</td>
<td>0.20 ± 0.02 (2)</td>
<td>6.5</td>
</tr>
<tr>
<td>24.9</td>
<td>3-Methyl</td>
<td>1.10 ± 0.04 (2)</td>
<td>0.124</td>
<td>8.9</td>
</tr>
<tr>
<td>24.9</td>
<td>None</td>
<td>0.50 ± 0.02 (4)</td>
<td>0.057 ± 0.003 (2)</td>
<td>8.8</td>
</tr>
<tr>
<td>24.9</td>
<td>2-ɛ-Butyl</td>
<td>0.0307</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Uncorrected for ca. 1% protium in deuterated species.
Close inspection of Table 2 reveals a trend to a large isotope effect with increasing basicity of the catalyst. The differences in the isotope effect for 2-, 3-, and 4-methylpyridine and 2-\textsuperscript{t} butylpyridine are probably too small to be given any quantitative interpretation, but the general trend from the weakest base, pyridine, to the strongest base, 2,6-lutidine, is one of increasing $k_H/k_D$ ratio. Reitz\textsuperscript{8} observed this trend in the bromination of nitromethane where the values of the isotope effect are 3.8, 4.3 and 6.5 for catalysis by H\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}-CO\textsubscript{2} and CH\textsubscript{3}CO\textsubscript{2} respectively and Swain, Stivers, Reuwer and Schaad\textsuperscript{26} have used this trend to identify the attacking nucleophile in the catalysis of enolization of \textalpha{}-phenylisocaprophanone by acetic acid.

Because the rate constant for 2,6-lutidine catalyzed iodination of nitroethane did not fall on the log $k$ vs. $\alpha K_H$ plot determined by the other bases, Pearson and Williams concluded that for this base there was steric inhibition to proton removal. The rate constant obtained for 2,6-lutidine in this thesis does not alter that argument. In fact for 2-nitropropane where there are two methyl groups to interfere with attack by the base the steric inhibition is even more noticeable. Table 4 shows that the rates of proton removal are roughly the same for 2,6-lutidine and pyridine in spite of the fact that 2,6-lutidine is a stronger base by about 1.6 $pK_a$ units. Even more noticeable is the 2-\textsuperscript{t} butylpyridine catalysis of 2-nitropropane iodination in which the rate constant is only about 1/36 that for 3-methylpyridine even though the $pK_a$'s are almost the same. In fact the 2-\textsuperscript{t} butylpyridine catalysis in the nitroethane case also displays this steric effect. Table 2 shows that the rate for 2-\textsuperscript{t} butylpyridine is only about 1/7 that for 3-methylpyridine.
The results shown in Table 5 are particularly interesting. In all the cases shown the activation energy difference is well above the 1.2 kcal/mole derivable from consideration of differences in zero-point energy in stretching frequencies. Even the rather extreme assumption that bending as well as stretching frequencies will be lost on going to the transition state gives an expected activation energy difference of only about 1.7 kcal/mole. Coupled with the values of the pre-exponential ratio \( \frac{A_R}{A_D} \) which are far below the theoretical limit \(^7\) these activation energy differences give strong indication of proton tunneling in these reactions.

An interesting trend shown in Table 5 is that of larger differences in activation energy and lower values of the \( \frac{A_R}{A_D} \) ratio as steric hindrance toward proton removal increases, i.e., on going from pyridine to 2,6-dimethylpyridine to 2-\( \pi \)-butylpyridine for iodination of nitroethane and then to 2,6-dimethylpyridine for 2-nitropropane.

Attempts at theoretical treatment of tunneling have shown that this phenomenon is strongly dependent on the height and width of the barrier and this is not generally known with any accuracy. Bell\(^{27}\) has used a parabolic barrier as an approximation. Shavitt\(^{28}\) and Johnson and Rapp\(^{29}\) have used an Eckart barrier\(^{30}\) which is considered to have a more satisfactory physical shape than a parabola. Also the function giving the permeability of this barrier has an exact expression whereas that of Bell requires approximate solution.

The implication drawn from these treatments is that for the reactions described in Table 5 the barrier is becoming higher faster than it is widening.
Table 5
Arrhenius Parameters for the Ionization of Nitro Compounds by Pyridine Bases

<table>
<thead>
<tr>
<th>Nitro Compound</th>
<th>Pyridine Substituent</th>
<th>( E_a ) (kcal/mole)</th>
<th>( A_H ) (kcal/mole)</th>
<th>( \Delta E_a )</th>
<th>( A_H/A_Q )</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-Propyl</td>
<td>2,6-Dimethyl</td>
<td>14.9</td>
<td>( 4.7 \times 10^7 )</td>
<td>5.5</td>
<td>( 7.6 \times 10^{-4} )</td>
</tr>
<tr>
<td>Ethyl</td>
<td>None</td>
<td>13.3</td>
<td>( 4.7 \times 10^7 )</td>
<td>2.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Ethyl</td>
<td>2,6-Dimethyl</td>
<td>12.0</td>
<td>( 2.6 \times 10^7 )</td>
<td>3.0 ± 1</td>
<td>0.06 ± 0.01</td>
</tr>
<tr>
<td>Ethyl</td>
<td>2-Butyl</td>
<td>15.0</td>
<td>( 2.2 \times 10^8 )</td>
<td>4.1</td>
<td>( 8.4 \times 10^{-3} )</td>
</tr>
</tbody>
</table>
A. Purification of Compounds

Table 6

Materials Obtained from Commercial Sources

<table>
<thead>
<tr>
<th>Compound</th>
<th>Impurities a (mole %)</th>
<th>Method of Purification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetophenone</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Phenacyl bromide</td>
<td>1</td>
<td>Sublimation</td>
</tr>
<tr>
<td>Propiophenone</td>
<td>0.5</td>
<td>None</td>
</tr>
<tr>
<td>Isobutyrophenone</td>
<td>0.5</td>
<td>None</td>
</tr>
<tr>
<td>Nitroethane</td>
<td>4º</td>
<td>Distillation</td>
</tr>
<tr>
<td>2-Nitropropane</td>
<td>0.5</td>
<td>Distillation</td>
</tr>
<tr>
<td>Pyridine</td>
<td>2º</td>
<td>Distillation</td>
</tr>
<tr>
<td>2-Methylpyridine</td>
<td>0.5</td>
<td>Distillation</td>
</tr>
<tr>
<td>3-Methylpyridine</td>
<td>2º</td>
<td>Distillation</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>1º</td>
<td>Distillation</td>
</tr>
<tr>
<td>2,6-Dimethylpyridine</td>
<td>0.5</td>
<td>Distillation</td>
</tr>
</tbody>
</table>

a Analyses were obtained by vapor phase chromatography (v.p.c.) and unless otherwise indicated a 2-meter Carbowax column was used. The instrument was equipped with a thermal conductivity detector and calculations of purity are based on peak heights since the peaks were usually well shaped and had comparable retention times.

b M.p. 48-49º (lit. 50º).

c About 0.5 mole % of this was water.

d Analysis was made using a 2-meter silicone oil column and the 2-meter Carbowax column.

e Distillation after refluxing for several hours with barium oxide.

f Distillation on a Nester and Faust spinning band column of a fraction collected from the reduced pressure distillation of 54 g. of 2,6-dimethylpyridine to which had been added 71 g. of boron trifluoride etherate.

B. Preparation of Compounds

Acetophenone-d₃ -- To 12 g. (0.10 mole) of acetophenone in 25 ml. of dioxane which was purified by Fieser's method a. ³¹ was added 9 ml. of 99.5% deuterium oxide and 0.1 g. of potassium carbonate. This
mixture was refluxed for 12 hrs., cooled, and the dioxane and deuterium oxide were removed by distillation. This procedure was repeated four times.

The dioxane and deuterium oxide from each of the exchanges on the first portion were added in succession to another 12 g. portion of acetophenone containing 0.1 g. of potassium carbonate. Each exchange time was about 12 hours. Finally fresh deuterium oxide and dioxane were added and the mixture refluxed about 12 hrs., cooled, and the deuterium oxide and dioxane removed. This material was combined with the first material exchanged and the combined portions distilled giving 20 g. of deuterated acetophenone. This material was 98 mole % pure by v.p.c. Combustion analysis showed the acetophenone to contain 2.83 D/molecule. Attempts to increase the deuterium content by this method were not successful.

2,2-Dibromoacetophenone -- α,α-Dibromoacetophenone was prepared by a method analogous to that used by Evans and Brooks

To 15.5 g. (0.078 mole) of phenacyl bromide in 100 ml. of boiling chloroform was slowly added 13 g. (0.081 mole) of bromine in 30 ml. of chloroform. The bromine color disappeared rapidly during the early part of the addition but upon completion of the addition a persistent bromine color remained even after refluxing overnight. About three ml. of 48% hydrobromic acid was added and the mixture refluxed several more hours. During this time the bromine color disappeared. The chloroform was evaporated and the yellow oil remaining was dissolved in ether. The ether solution was washed with dilute sodium carbonate, dried, and the ether evaporated. A yellow
oil was obtained which crystallized on cooling. Recrystallization
from ether-petroleum ether gave yellow needles, m.p. 33-34° (lit.
35-36°). The yield was 11.8 g. (55% based on phenacyl bromide).

Propiophenone-α-d₂ -- Propiophenone-α-d₂ was prepared in the same
manner as acetophenone-d₃ by multiple exchanges with deuterium
oxide in dioxane catalyzed by potassium carbonate. The resulting
deuterated material was recrystallized from petroleum ether. It
was 99 mole % pure by v.p.c. Combustion analysis gave 190 D/mole-
cule.

Partially Deuterated Propiophenone -- Five grams of propiophenone
in 25 ml. of dry dioxane containing 1 g. of anhydrous potassium
carbonate and 7.7 g. of 49.5 mole % deuterium oxide was refluxed
for 144 hours. The mixture was cooled, extracted with ether and
the ether evaporated. The partially deuterated propiophenone was
sublimed. Vapor phase chromatography showed the material to con-
tain less than 1 mole % of impurities. Analysis of the partially
deuterated mixture by the NMR method described earlier gave the
following: \( T_H = 1.21 \) H/molecule, \( f_0 = 0.38 \), \( f_1 = 0.45 \), and
\( f_2 = 0.17 \) where \( T_H \) is the total average hydrogen content in the
methylene group, \( f_0 \) is the fraction of non-deuterated species,
\( f_1 \) the fraction of the mono-deuterated species and \( f_2 \) the fraction
of the di-deuterated species.

Isobutyrophenone-α-d₁ -- An attempt was made to prepare isobutyro-
phenone-α-d₁ by multiple exchanges with deuterium oxide in dioxane
with potassium carbonate as the catalyst. However, this procedure
failed to incorporate deuterium in the molecule.
A satisfactory procedure was the addition of 3.4 g. (0.14 mole) of sodium hydride to 10 g. (0.068 mole) of isobutyrophenone dissolved in 25 ml. of dry tetrahydrofuran followed by 3.3 g. (0.17 mole) of deuterium oxide after hydrogen evolution ceased. The mixture was cooled and the deuterated isobutyrophenone recovered by distillation. Analysis by v.p.c. showed that the isobutyrophenone-α-d₁ used for kinetic runs was about 98 mole % pure. NMR analysis at Shell Oil Company gave 0.92 D/molecule compared to 0.93 D/molecule by combustion analysis.

α-Bromoisobutyrophenone -- α-Bromoisobutyrophenone was prepared by the method of Faworsky and Mandryka. A yield of 26.5 g. (90%, based on ketone) was obtained with b.p. 147-148° at 30 mm.

One gram of α-bromoisobutyrophenone was oxidized with alkaline potassium permanganate according to the procedure in Shriner, Fuson and Curtin. The material obtained was identified as benzoic acid by m.p. 121° and mixed m.p. 121°. This shows that the bromine was not in the ring.

Phenyl Cyclohexyl Ketone -- By a method analogous to that of Nunn and Henze, phenyl cyclohexyl ketone was prepared by the drop-wise addition of 42 g. (0.39 mole) of benzonitrile in 600 ml. of anhydrous toluene to 0.34 mole of cyclohexyl magnesium bromide in 500 ml. of refluxing ether. The ether was removed and the toluene solution refluxed for five hours. The toluene solution was cooled and hydrolyzed with 150 ml. of cold saturated ammonium chloride. The aqueous layer was separated from the toluene and the toluene extracted with cold dilute sulfuric acid. The acid extract was
refluxed for one hour, cooled, and extracted with ether. The ether extract was washed with water, saturated sodium carbonate and saturated sodium chloride. Evaporation of the ether gave 42.4 g. (56.5% yield based on nitrile). The ketone was recrystallized from petroleum ether and dried. This material showed one peak on the vapor phase chromatograph and had a carbonyl absorption at 5.93μ and a m.p. of 56-57° (lit. 57-58°).

**Tritiated Phenyl Cyclohexyl Ketone** -- This compound was prepared by a method similar to that of Emmons and Hawthorne for the preparation of cyclohexyl-1-d₄ phenyl ketone.

To 20 ml. of acetic anhydride containing 2 ml. of acetyl chloride was added 5 g. (0.027 mole) of phenyl cyclohexyl ketone. To this mixture was added 3 ml. of tritiated water which had an activity of 25μc/ml. After 48 hours under reflux the volatile solvents were removed by distillation, and the tritiated ketone was recrystallized from petroleum ether. The material was sublimed at 50° and 1 mm. This material had an activity of about 120 counts per minute per milligram after correction for background.

Oxidation of 500 mg. of the tritiated ketone with alkaline potassium permanganate gave benzoic acid which had no activity above that of background, proving that tritium was not introduced into the aromatic nucleus by the exchange procedure.

**α-Bromocyclohexyl Phenyl Ketone** -- α-Bromocyclohexyl phenyl ketone was prepared by the method of Stevens and Farkas. A yield of 4.7 g. (33% based on the ketone) was obtained. Recrystallization
from petroleum ether gave light yellow flakes, m.p. 50-51° (lit. 50-51°). Vapor phase chromatography revealed no detectable impurities.

Phenyl sec-Butyl Ketone -- Phenyl sec-butyl ketone was prepared by the method used by Bartlett and Stauffer. The yield was 25 g. (75%). Vapor phase chromatography showed the ketone to be about 95 mole % pure. I.R. showed a carbonyl peak at 5.95μ.

The combined product from several runs was distilled using a spinning band column giving material which showed only one peak by v.p.c. analysis.

2-Bromo-2-methylbutyrophenone -- To 13 g. (0.080 mole) of phenyl sec-butyl ketone in 50 ml. of acetic acid was added dropwise with stirring 12.8 g. (0.080 mole) of bromine. The reaction mixture was stirred for 1 1/2 hours after addition of the bromine. One hundred ml. of water was added and the bromo-ketone extracted with petroleum ether. The petroleum ether was evaporated and the residue distilled. The yield was 14.8 g. (77%), b.p. 89-93° at 2 mm. About 1 g. of this material was purified by adsorption chromatography on alumina and showed less than 1 mole % impurity by vapor phase chromatography.

Phenyl sec-Butyl Ketone-α-d1 -- To 9.5 g. (0.059 mole) of phenyl sec-butyl ketone in 25 ml. of dry tetrahydrofuran was added 3.5 g. (0.146 mole) of sodium hydride. The mixture was refluxed until hydrogen evolution ceased, about 13 hours. Deuterium oxide, 6 g. (0.30 mole), was added through the reflux condenser. The mixture
was cooled and 6.7 g. of deuterated material recovered by distillation; b.p. 127-128° at 28 mm. This procedure was repeated several times and the products combined and distilled through a spinning band column to give material which was 99 mole % pure by vapor phase chromatography. NMR analysis at Shell Oil Company gave 0.92 D/molecule.

2,4-Dimethylvalerophenone -- 2,4-Dimethylvalerophenone was prepared in the same way as phenyl cyclohexyl ketone. To the Grignard reagent of 2-bromo-4-methylpentane (0.6 mole) in 700 ml. of refluxing anhydrous ether was added 69 g. (0.66 mole) of benzonitrile in 800 ml. of anhydrous toluene. The ether was removed and the toluene solution allowed to stand for 9 hours. The mixture was then refluxed for 6 hours, cooled, and hydrolyzed with 450 ml. of cold saturated ammonium chloride solution. The aqueous layer was separated and the toluene layer extracted with cold dilute sulfuric acid. The acid extract was refluxed for 2 1/2 hours, cooled, and extracted with ether. The ether extract was washed with water, sodium carbonate solution, and saturated sodium chloride. The ether was evaporated and the residue distilled. The yield was 49 g. (43% based on the nitrile). The 2,4-dinitrophenylhydrazone was prepared by the method in Shrinier, Fuson and Curtin; 38 m.p. 121-122°. Nielsen, Gibbons and Zimmermann 39 give m.p. 118-119° for this derivative.

The 2,4-dimethylvalerophenone was distilled through a spinning band column giving material which was 99 mole % pure by vapor phase chromatography.
Interestingly, when the toluene layer was evaporated on the water pump 4 g. of crystalline material was obtained. The material was sparingly soluble in water, ethanol, dilute sulfuric acid, or dilute sodium hydroxide. It could be recrystallized from acetone to give pale yellow crystals, m.p. 236-237°. I.R. (Nujol mull) gave bands at 3.45 (Nujol), 6.25, 6.56, 6.84 (Nujol), 7.31 (Nujol), 13.47, and 14.68 μ. When heated with calcium oxide the material gave vapors basic to pH paper indicating the presence of nitrogen. A small amount of the material was refluxed for 24 hours with dilute sulfuric acid but was seemingly unaffected by this treatment. It was possible to obtain an NMR spectrum of the material by dissolving a small amount in hot carbon tetrachloride and taking the spectrum hurriedly. The only protons detectable were those in the region where benzene hydrogens absorb. A compound compatible with the data is 2,4,6-triphenyl-1,3,5-triazine. This compound has been known for a long time 40 and was obtained by Frankland and Evans 41 by refluxing benzonitrile with diethyl zinc. These authors give a melting point of 229° for the compound.

2,4-Dimethylvalerophenone-α-d1 -- 2,4-Dimethylvalerophenone was exchanged using the same procedure employed in the exchange of isobutyrophenone and phenyl sec-butyl ketone. The deuterated material was distilled through a spinning band column. Vapor phase chromatography showed the distillate to be 98 mole % pure. NMR analysis at Shell Oil Company gave 0.94 D/molecule compared to 0.95 D/molecule by combustion analysis.
2-Bromo-2,4-dimethylvalerophenone -- To a refluxing solution of 10 g. (0.05 mole) of 2,4-dimethylvalerophenone in 25 ml. of acetic acid was added 10 g. (0.06 mole) of bromine in 10 ml. of acetic acid. After addition of the bromine the mixture was refluxed for two hours and allowed to stand overnight. One hundred ml. of water was added and the resulting solution extracted with ether. The ether was evaporated and the residue distilled; b.p. 110-120° at 1 mm. The yield was 10.4 g. Vapor phase chromatography revealed that about 14 mole % was unreacted ketone. Enough 2-bromo-2,4-dimethylvalerophenone was prepared for the standards for the kinetic runs by adsorption chromatography on Florisil. A typical experiment involved 0.4 g. of the bromo-ketone on 20 g. of Florisil with petroleum ether as the solvent and gave about 0.2 g. of pure bromo-ketone.

Nitroethane-d₂ -- According to the method of Leitch, a mixture of 10.5 g. (0.14 mole) of nitroethane, 10 g. (0.50 mole) of deuterium oxide and 0.20 g. of anhydrous sodium acetate was refluxed for 20 hours. The reaction mixture was cooled and the partially deuterated nitroethane separated from the deuterium oxide. This procedure was repeated two more times and the nitroethane distilled. Vapor phase chromatography indicated that the distillate was 97 mole % pure. NMR analysis was complicated by the spin-spin splitting of the hydrogen signal by the deuteron but there was at least 1.94 D/molecule.

2-Nitropropane-d₁ -- The procedure for the nitroethane exchange would not bring about appreciable exchange of 2-nitropropane. A procedure found to be satisfactory was the addition of 0.2 g. of sodium to a mixture of 15 g. (0.17 mole) of 2-nitropropane and 17.6 g. (0.88 mole)
of deuterium oxide. After refluxing for 17 hours the mixture was cooled and the 2-nitropropane separated. The exchange was repeated two more times and the deuterated 2-nitropropane distilled. Vapor phase chromatography indicated that the material was 98 mole % pure. NMR analysis gave 0.99 D/molecule.

2-t-Butylpyridine -- According to the method of Brown and Murphy, 284 g. of methyl iodide was added in 1 hour to 93 g. (1 mole) of 2-methylpyridine in 700-800 ml. of liquid ammonia containing 2 moles of sodium amide. After the ammonia had evaporated (overnight) the mixture was treated dropwise with 50 ml. of water. The liquid was separated from the solid and the solid dissolved in 100 ml. of water. The resulting suspension was extracted twice with 50 ml. portions of ether. The ether was removed and the residue combined with the liquid reaction product and dried over potassium hydroxide pellets. The product was distilled giving 95 g. of material, b.p. 62-68° C. at 33 mm. Vapor phase chromatography showed that less than 1 mole % of 2-methylpyridine was present. NMR analysis revealed that the product was a mixture of 2-ethyl- and 2-isopropylpyridine containing a small amount of 2-t-butylpyridine.

To 53 g. of this mixture in 700 ml. of liquid ammonia containing 2 moles of sodium amide was added 218 g. (1.5 mole) of methyl iodide. The methyl iodide was added slowly so that the deep red color of the solution did not disappear during the addition. This required about 8 hours. The product was worked up in the same manner as before and distilled, giving 38 g. of material, b.p. 69-73° at 28 mm. NMR showed that this product was 2-t-butylpyridine.
containing a small amount of 2-isopropylpyridine. Distillation on the spinning band column at atmospheric pressure gave 2-ethylpyridine which contained no detectable 2-isopropylpyridine by NMR analysis.

C. Typical Rate Determinations

The following is a typical run for bromination of ketones using the Cary Model 14 recording spectrophotometer:

A stock solution was prepared consisting of 150 g. of anhydrous sodium acetate, 15.5 g. of sodium bromide and 85 ml. of water diluted to one liter with glacial acetic acid. This is identical to the stock solution used by Emmons and Hawthorne except for the sodium bromide.

Weighed samples of each ketone were diluted to known volume with the stock solution. Then 3 ml. of this solution was introduced into two matched silica cells (1.0 cm. light path). At this point 20\(^{\circ}\) of bromine stock solution (100\(^{\circ}\) of bromine per 5 ml of stock solution) was added to one of the cells and mixed by shaking. The cells were stoppered and placed in the thermostated cell compartment of the Cary and the optical density recorded. The reactions were all run under zero-order conditions in the presence of large excesses (30 to 100 fold) of ketone and acetate ion. Under these conditions the plot of optical density vs. time was linear. The measurements were made at 390 m\(\mu\). The extinction coefficient of bromine in the stock solution was 660 as compared to 278 determined by Emmons and Hawthorne in the absence of bromide ion. Blanks were
determined and in the absence of ketone the consumption of bromine was negligible. The bromine light absorption followed Beer's Law at the concentrations used.

The following is a typical run for bromination of ketones using the Perkin-Elmer gas chromatograph to follow the reaction: Weighed samples of each ketone were diluted to 25 ml. with the acetate stock solution. Bromine (0.4-0.8 ml) was added and the mixture shaken. About 4 ml. of the reaction mixture was placed into each of six 5-ml glass ampoules and the ampoules sealed. The run began by immersing the ampoules in a mineral oil thermostat which was located in a dark room equipped with a safe light. Ampoules were removed at the desired time intervals and chilled in an ice bath to stop the reaction. The ampoules were opened and the contents transferred to a separatory funnel. Twenty-five ml. of 0.01 M sodium thiosulfate was added to destroy the unreacted bromine and the bromo-ketone--ketone mixture was extracted with petroleum ether. The petroleum ether was evaporated on a water bath and the samples analyzed.

Copper and stainless steel vapor chromatographic columns catalyzed the decomposition of the bromo-ketone at the temperatures necessary for analysis. To prevent this a 1-meter glass column was packed with Chromosorb W containing 10% Dow Corning silicone oil 550 as the stationary phase. This column gave adequate resolution of the ketone and bromo-ketone without decomposition.

Erratic results were obtained when these runs were not made in a dark room. This may have been due to a light catalyzed reaction of the bromine with the ketone.
It was demonstrated that the isolation procedure had no effect on the composition of the bromo-ketone-ketone mixtures by submitting a known mixture to the procedure.

The procedure for a typical iodination of nitro compounds follows: Weighed samples of pyridine base were made up to known volume with a 30% ethanol in water stock solution which was 0.100 M in sodium iodide, 0.003 M in perchloric acid and about 3 x 10⁻⁴ M in iodine. This solution was allowed to come to temperature equilibrium with the thermostat while samples of the nitro compound were weighed. The weighed nitro compound samples were made up to volume with the thermostated solution. The mixture was transferred quickly to a 10-cm. cell which was stoppered and placed in the cell compartment of the Cary. The change of optical density with time was followed at 471 nm. The extinction coefficient at this wave length in the stock solution described was 666. Flanks were determined in all cases and whenever necessary a correction for reaction with solvent was made.

The reactions were run under zero or low concentrations in the presence of large excesses (30-100 fold) of nitro compound and pyridine base. Under these conditions the plot of optical density vs. time was linear.

D. Tritium Isotope Effect for Phenyl Cyclohexyl Ketone

Tritiated ketone (0.5187 g.) was made up to 50 ml with the sodium acetate stock solution previously described. The mixture was transferred to a 100 ml. flask and 0.8 ml of bromine added. The stoppered flask was immersed in a thermostat located in a dark room.
Twenty-four hours later 0.8 ml. of bromine and 2.5 g. of sodium acetate were added. Twelve hours later the reaction mixture was removed from the thermostat and cooled. It was made up to 100 ml with acetate stock solution and divided into 50 ml portions. To one of these portions was added 0.125 g. of untritiated ketone. Twenty ml. of 0.01 M sodium thiosulfate was added to each of the portions to destroy unreacted bromine. Each portion was extracted with petroleum ether and the petroleum ether evaporated leaving an oil. The oil from each portion was sublimed at 50° and 1 mm. giving crystalline materials which were then recrystallized from petroleum ether, m.p. 54-56° for material from both portions. Solution scintillation counting gave the following specific activities in counts min. mg.: \( a_1 = 1179\), \( a_2 = 1981\), \( a_3 = 967\). In this sequence \( a_1 \) is the specific activity of the starting material, \( a_2 \) that of the portion containing no added ketone and \( a_3 \) that of the portion containing added ketone. All activities were corrected for background. The extent of completion, \( X \), calculated from this data is 0.54 compared to 0.53 obtained by v.p.c. analysis.
SUMMARY

The primary deuterium isotope effect was measured in the aceta
ton catalyzed bromination of some phenyl alkyl ketones. On the basis of the data obtained proton tunneling is considered but not demonstrat
ed. A secondary deuterium isotope effect is calculated for pro
propriophenone bromination.

The deuterium isotope effect was determined for the iodinatin
de of nitroethane and 2-nitropropane catalyzed by pyridine and some substi
stituted pyridines. A trend toward a larger isotope effect with increasing basicity is noted. Proton removal is sterically inhibi
ited when accomplished by some 2-substituted pyridines. On the basis of the abnormal relative magnitudes of the Arrhenius parameters on isotopic substitution, a large activation energy difference ($\Delta E_A$) and a small pre-exponential term ratio ($A_H/A_D$), an argument for proton tunneling is advanced.
REFERENCES


4. E.S. Lewis and R H Grinstein. ibid. 84, 1158 (1962).


38. Reference 34, p.219.
