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Very Slow Reactions, Rates, and Isotope Effects in the Bromination of 2-Benzoylbutane[1]

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The application of a method for following very slow reactions using an isotopic dilution method is described. The particular case studied is the bromination of 2-benzoylbutane and 2-benzoylbutane-2-*d* in acetic acid containing sodium acetate. The reaction is not particularly well suited to the method, and the successful application thus illustrates the generality of the method. The rates measured are consistent with those measured at a higher temperature by a gas chromatographic method, which is also applicable to rather slow reactions. Several rates measured by this latter method are also presented. The limitations of various techniques for slow reactions are discussed. Second-order rate constants of less than 10^{-8} M^{-1} sec^{-1} are measured. The deuterium isotope effect is given by the equation $k_H/k_D = 0.99 \exp(1280/RT)$, which does not suggest that tunneling is important. The measured rate at the lowest temperature is greater than predicted by the Arrhenius equation for both protium and deuterium compounds; the source is not tunneling but may be mechanistic or experimental error.

The study of proton-transfer reactions has been a subject of interest for many years, in part because it appears to be the simplest example of the nucleophilic substitution reaction. It is also a reaction in which tunneling can contribute to the reaction rate to a significant extent. An approach to this problem is to study the temperature dependence of the reaction rate, for a simple model for tunneling has predicted that there would be significant deviations from the Arrhenius equation at low temperatures.[4] Most experimental tests of this prediction have been limited to reactions with low activating energy, which allows the measurement of the reaction rate over a wide range of temperatures and allows the measurement of reasonable rates at quite low temperatures.[5] Nevertheless, the above model for tunneling shows that, for a given barrier curvature, the tunnel correction will be larger for a high barrier.[4,6] High activation energy proton-transfer reactions have not been studied much at a variety of temperatures, largely because different techniques are necessary since the rate is so sensitive to temperature. It seemed worthwhile therefore to explore methods for studying very slow reactions to enable rates to be measured at temperatures well below those at which the rate is convenient.

Reactions can be followed by studying the concentration of product or reagent as a function of time, and slow reaction can be followed merely by making the times longer. For purposes of this paper we shall consider that we can spend no more than 3 months on a reaction. We further assume that limitations of analytical precision require us to have at least a factor of 2 change in the measured concentration during the course of the measurement. If the concentration of a reagent is followed, we can say that the half-life must be at least 3 months. A bimolecular reaction with the second reagent in excess at 1 M would then have a rate constant measurable by this method of not less than 10^{-7} M^{-1} sec^{-1}; the rates of transfer of tritium from 2-nitropropane-2-*t* to 2,4,6-trimethylpyridine of this order of magnitude have been followed this way.[7] When the reaction is followed by observing the increase in concentration of a product there is no such limitation, and if a satisfactory analysis for 1% of product is available a second-order rate constant of 10^{-9} M^{-1} sec^{-1} is measurable under the above restrictions; an accurate analysis for one part per million of product can give rate constants of 10^{-13} M^{-1} sec^{-1}. This is clearly a promising direction.

Occasionally, but not generally, the immediate product from the reaction of A and B is highly reactive, and if a reagent C is added at very low con-

(1) From the Ph.D. Theses of (a) J. D. Allen, 1962, and (b) E. T. Wallick, 1966, Rice University, Houston, Texas.

(2) Robert A. Welch Foundation Predoctoral Fellow, 1960–1962.

(3) Robert A. Welch Foundation Predoctoral Fellow, 1963–1965. National Institutes of Health Predoctoral Fellow, 1965–1966.

(4) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 210.

(5) E. F. Caldin and M. Kasparian, *Discussions Faraday Soc.*, **39**, 25 (1965); J. R. Hulett, *J. Chem. Soc.*, 430 (1965).

(6) R. P. Bell, *Trans. Faraday Soc.*, **55**, 1 (1959).

(7) E. S. Lewis and J. K. Robinson, *J. Amer. Chem. Soc.*, **90**, 4337 (1968).

centration which reacts rapidly and selectively with this reactive species then the reaction will be zero order in C, and the rate of disappearance of a very small amount of C will correspond to the rate of reaction of A with B which may proceed only to a very small extent. Thus the ionization of 2-nitropropane by pyridine bases was followed spectrophotometrically by the disappearance of iodine, which reacts very rapidly with the carbanion, and measurements of a few hours' duration afforded rate constants down to as low as 10^{-7} M^{-1} sec^{-1} in the extreme.[8] This method in practice is limited by the selectivity of the added iodine, which disappeared slowly by other routes; slower reactions could thus not be measured. Similar limitations may be quite general for this method; it is therefore less promising than the sensitive product analysis above.

The analysis for a substance in the presence of several orders of magnitude higher concentration of other substances needs to be both very sensitive and very specific. Isotopic dilution analysis is extremely sensitive, and the specificity is limited only by the extent to which radioactive contaminants can be removed by purification procedures. We present in this paper a gas chromatographic method for following a few per cent reaction and an isotopic dilution analysis which we use to follow about 1% reaction but which is easily extended to far slower reactions.

The isotopic dilution analysis method for rate measurement is not new, but most previous applications have been to cases in which the separation of radioactive reagent and radioactive product have been relatively facile. Thus Conway and Libby[9] separated carbon dioxide from alanine to measure rates of decarboxylation with half-lives of 10^5 years, Manno and Johnson[10] separated iodobenzene from inorganic iodide to measure exchange rate constants as slow as 10^{-12} M^{-1} sec^{-1}, and Kresge and Chiang[11] separated water and 1,3,5-trimethoxybenzene, measuring exchange rates as slow as 5×10^{-9} M^{-1} sec^{-1}; this last work was reported in a paper illustrating strikingly the value of measurement of very slow reaction rates.

The ionization of carbonyl compounds by bases can be a very rapid reaction or a slow one, and the rate may be roughly estimated from considerations of basicity and acidity of the two reagents.[12] Thus the transfer of a proton from ketone free from further acid-strengthening substituents to a weak base can be expected to be quite slow. The ionization of phenyl *sec*-alkyl ketones by acetate ion in acetic acid was chosen for this study because earlier work[13] showed that several such reactions are slow, and because the presence of only one ionizable proton simplifies the kinetics and the interpretation of the isotope effect. Part of the slowness might be a consequence of steric hindrance toward proton transfer, examples of which are now well established.[8,14]

(8) E. S. Lewis and L. H. Funderburk, *J. Amer. Chem. Soc.*, **89**, 2322 (1967).
(9) D. Conway and W. F. Libby, *ibid.*, **80**, 1077 (1958).
(10) P. J. Manno and W. H. Johnson, *ibid.*, **79**, 807 (1957).
(11) A. J. Kresge and Y. Chiang, *ibid.*, **83**, 2877 (1961).
(12) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953).
(13) W. D. Emmons and M. F. Hawthorne, *ibid.*, **78**, 5593 (1956).
(14) (a) R. G. Pearson and F. V. Williams, *ibid.*, **75**, 3073 (1953); (b) E. S. Lewis and J. D. Allen, *ibid.*, **86**, 2022 (1964); (c) J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

Results and Discussion of Results

The rates of some brominations of phenyl alkyl ketones are given in Table I, measured by one of two methods. Method I is the spectrophotometric measurement of disappearance of bromine as described by Emmons and Hawthorne,[13] except that sodium bromide was added to keep the bromine–tribromide extinction coefficient constant (660 at 390 nm) as recommended elsewhere.[15] This method is of adequate sensitivity to measure far slower reaction rates than given here, but the solvent system slowly reduces the bromine, so that method I (see Table I) is unsuitable for slower reactions or reactions at much higher temperatures. Method II allows for this complication by using a large excess of bromine. The extent of reaction is measured by a gas chromatographic determination of the bromo ketone–ketone ratio. This method is quite adequate if the bromo ketone survives both the reaction conditions and the gas chromatography, both of these are limiting under various circumstances, and special precautions are always necessary to get any bromo ketones through the gas chromatograph.

The first three entries show that the spectrophotometric method is on the verge of having uncertain stoichiometry, since the second bromine can go in 33 times faster than the first. For extents of bromination of well under 1%, as in this work, the assumption of one bromine per molecule of acetophenone is fairly good, but di- or tribrominations become quite important and at 3% completion the rates of dibromination and monobromination are equal. In our work on this compound and on propiophenone, the zero-order plots were quite good straight lines; so there is no reason to suspect serious error from this possibility of dibromination. It may, however, distort the isotope effect a little.

A clear result from the table is the retarding effect of alkyl groups on the rate, most striking with the second one. The relatively minor effect on k_H on changing from one secondary alkyl to another suggests that most of the retardation from propiophenone is a consequence of the acid-weakening character of the alkyl group, although some steric effect may be present and is probably responsible for most of the variations in k_H of the last four entries. It is possible that the case R = $CH(CH_3)CH(CH_3)_2$ shows an unusually large isotope effect due to a steric retardation which does not interfere with tunneling, analogous to that found earlier,[8] but the evidence is hardly convincing.

The values of k_D and the isotope effect are less precise than we would like, almost entirely because of the rather large light hydrogen content. Unfortunately, this is associated with isotope effects higher than we had anticipated, so that the corrections are quite large and quite sensitive to the mole fraction of light hydrogen, f_H, at the position in question. These compounds were made as we were beginning to learn about the use of nmr for these analyses; the precision is lower than that which we now achieve on this sort of analysis. Even so, the determination of f_H by nmr is more positionally specific than mass spectral analysis and is much more precise than a routine deuterium analysis by mass spectrometry. Analysis by density measure-

(15) E. S. Lewis and M. D. Johnson, *J. Amer. Chem. Soc.*, **81**, 2070 (1959).

TABLE I

RATES OF BROMINATION OF C_6H_5COR IN AQUEOUS ACETIC ACID–SODIUM ACETATE

R	Registry no.	T, °C	Method[a]	k_H,[b] 10^6 sec^{-1}	k_D(obsd),[b,c] 10^6 sec^{-1}	k_H/k_D (cor)[d]
CH_3	98-86-2	27.5	I	2.36	0.354	(10.5)[e,f]
CH_2Br	70-11-1	27.5	I	78.8		
$CHBr_2$	13665-04-8	27.5	I	82		
CH_2CH_3	93-55-0	38.5	I	1.83	0.339	7.0[e]
$CH(CH_3)_2$	611-70-1	100	II	19.8	4.26	6.8
$CH(CH_3)C_2H_5$	938-87-4	100	II	6.5	1.5	5.6
$CH(CH_3)CH(CH_3)_2$	18321-24-9	100	II	6.2	(0.643)[g]	(10)[g]
Cyclohexyl	712-50-5	100	II	(8.2)[h]	*h*	

[a] Method I, spectrophotometric; method II, gas chromatographic; see text. [b] Pseudo-first-order rate constants in 1.83 *M* sodium acetate solution. [c] Measured rate constants for largely deuterated material. [d] Isotope effects corrected for incomplete deuteration by the relation $k_D = [k_D(\text{obsd}) - k_H f_H]/(1 - f_H)$, where k_D is corrected for contamination of the reagent by a mole fraction f_H of protium compound. [e] This number includes an unestablished secondary isotope effect of the other deuterium atoms. [f] The correction for protium contamination is quite large, so that we do not believe that this number is very precise. [g] Application of the correction yields $k_H/k_D = 22$, but the correction is large and there is only one determination of k_D; the isotope effect probably is fairly large and lies between $k_H/k_D(\text{obsd}) = 9.7$ and this "corrected" value of 22. [h] The gas chromatograph showed a variety of peaks, which we attribute to decomposition products of the bromo ketone. This was so serious with the deuterated ketone that no meaningful rate constant could be calculated.

ment on water produced by combustion is much better for finding the difference between 0 and 1% D in the molecule than the difference between 99 and 100% at some position. In our hands the combustion analysis is better than the nmr only under the most favorable circumstances (*i.e.*, large ratio of deuterated to unchanged positions) and only when the analyst is doing these analyses regularly.

The methods used for Table I seemed unlikely to be applicable to much slower reactions, nor could we hope for improved accuracy, which is necessary for a good interpretation of the results. We have therefore developed a third method based upon an isotopic dilution analysis for the bromo ketone. We did not try using radioactive bromine, because the short half-life (for ^{82}Br, $t_{1/2}$ = 35.7 hr) limits studies to those which can be completed in a few half-lives, and because the method lacks generality. We prepared 2-benzoylbutane-4-*t* and 2-benzoylbutane-2-*d*-4-*t*, added this to the brominating medium, and after various times stopped the reaction and added 2-benzoyl-2-bromobutane in known amount. Reisolation of the 2-benzoyl-2-bromobutane in pure form and counting then allowed the calculation of the yield from the bromination reaction. The pseudo-zero-order rates were measured from the slope of a line of extent of completion *vs.* time. A typical run is illustrated in Figure 1. The results are presented in Table II.

TABLE II

RATES OF BROMINATION OF 2-BENZOYLBUTANE AND 2-BENZOYLBUTANE-2-*d* BY ISOTOPIC DILUTION ANALYSIS

T, °C	$k_H \times 10^6$ sec^{-1}	k_D(obsd) $\times 10^6$ sec^{-1}	k_H/k_D (cor)
100[a]	650[a]	150[a]	5.4[a]
79.8	146.7	23.8[b]	6.5[b]
48.50	9.86	1.47[b]	7.1[b]
32.10	3.53	0.458[b]	8.3[b]

[a] Entry from Table I by gas chromatography; the deuterated compound contained 5.7% protium compound. [b] The sample contained 1% protium compound.

The error in the entries in Table II is not readily calculated, especially since the most obvious source of error is a systematic error tending to give high results due to contamination of the bromo ketone counted with radioactive impurities. An idea may be obtained from the Arrhenius plot of Figure 2. The points for k_H at the two higher temperatures and the one at 100° by the gas chromatographic method give a respectable Arrhenius plot, with $k_H = 10^{6.25} \exp(-19{,}520/RT)$. The deviation at the lowest temperature can not be attributed to tunneling, since the deuterium compound also deviates, and the isotope effect, also shown in Figure 2, obeys the Arrhenius equation reasonably well. There is insufficient precision to exclude tunneling and Arrhenius plot curvature due to it entirely, but a further reason to question its importance comes from the iso-

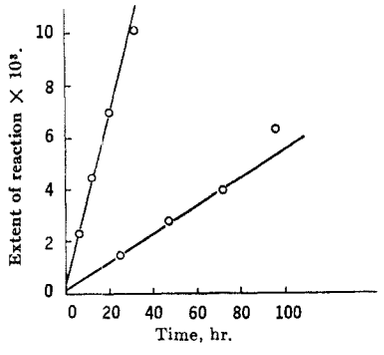


Figure 1.—Plot of extent of completion *vs.* time for two runs by isotopic dilution analysis. Upper points give k_H, lower points k_D.

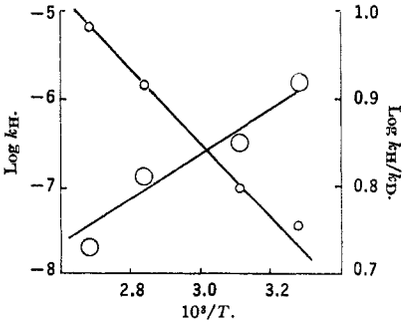


Figure 2.—Arrhenius plot for k_H (left scale, small circles), and k_H/k_D (right scale, large circles corresponding to 3% error in k_H/k_D. Left-most points by gas chromatography, others by isotopic dilution.

tope effect temperature dependence, fitted by the equation $k_H/k_D = 0.99 \exp(1280/RT)$. Neither the essentially unit A_H/A_D factor nor the reasonable $E_{a_d} - E_{a_H}$ term, although both are rough, suggests any major contribution to the isotope effect other than zero-point energy loss.[4]

The deviation of the lowest point from the Arrhenius equation could be caused by the intrusion of a new mechanism with a similar isotope effect, such as a radical[16] bromination, or a low A factor low E_a ionic mechanism, such as the concerted termolecular mechanism rejected as a major contributor under most circumstances.[17] An alternative explanation is that it is the result of experimental error. These run at the lowest temperatures were chronologically the first, and the execution of the chromatographic separations may have been less effective in these cases. Furthermore, the smaller extent of reaction due to the slower reactions exaggerates the effect of imperfect separations. There seems under these circumstances to be no reason to pursue explanations for the Arrhenius equation deviations.

Discussion of the Isotopic Dilution Method.—Isotopic dilution analyses in general depend only on the ability to isolate a pure sample of the substance in question and to determine its specific activity. The latter usually presents no problem, although in the present work dealing with difficultly volatile liquids in small amounts made the determination of the total amount of material counted impractical by weighing. The concentration of the material to be counted was therefore determined by the ultraviolet absorption of a toluene solution before adding scintillators. We estimate a minimum random error of $\pm 1\%$ in the specific activities from this source, and believe that this level of precision was very nearly attained. Statistical errors can be reduced by taking enough counts, and there was no evidence of drifts in counting efficiency over the times necessary to get at least 10^4 counts. Thus the determination of specific acitivity is not a likely source of major error.

The major problem is associated with the purity of the isolated material. Errors are of two sorts, depending on whether the contaminants are radioactive or not. The latter case is the least troublesome; thus, if the material isolated has only the fraction g ($g < 1$) of the desired substance, then the true specific activity a is related to that measured, a_{obsd}, by the relation $a = a_{obsd}/g$.[18] Thus a few per cent contamination will only produce a few per cent error in a, and, if g is reproducible, there will be no error in rate constant.

The more difficult problem is that of contamination by radioactive impurities. Thus, if we allow the reaction to go to 1% completion, and add an amount of cold carrier compound (Y) equal to that of the unreacted material, the specific activity of the product (Y) will only be 1% of that of the reagent (X). If we then isolate Y contaminanted by only 1% X, the specific activity measured will be too high by a factor of 2! For smaller extents of completion this error of contamination is even more serious. In the above case example, the error may be reduced by purification to a level of 99.99%; then the error due to contamination is only 1%, but small scale routine purification to this level is generally impossible. The problem is attacked by the so-called "hold-back carrier" technique.[19] If the above 99% pure Y is mixed with an equal amount of nonradioactive X and then repurified to a mixture 99% Y and 1% of X, X has now been reduced in specific activity by a factor of 100, and counting of Y now is in error by only 1%. The efficacy of this procedure can be followed by counting the X fraction, and in our studies this process was repeated until the specific activity of the X fraction was negligible.

This error can thus be overcome so long as there is a reasonably efficient separation of X and Y, and the number of powerful separation methods now available suggests that one can rely upon this being quite general.

A further problem is associated with unwanted radioactive impurities in the reagent X, which may be difficultly separable from Y, or converted into difficultly separable materials under the reaction conditions. Clearly the number of these is related to the synthetic procedure for preparing X and to the point at which the radioactivity is introduced. The hazards of introducing very high levels of activity followed by dilution with carrier in introducing very high activity impurities have been pointed out[19] and taken into consideration. Clearly the optimum experimental design is to introduce the activity in the last step of the synthesis by a process that minimizes side reactions. Known contaminants can be rendered inactive by the "hold-back carrier" technique, and a rigorous purification, unaccompanied by any dilution with cold X, will then complete the process. We were unable to achieve this optimum design, but the application to a less than ideal system illustrates better the generality of the method.

The steps used in the synthesis of the radioactive reagents are illustrated in Scheme I, starting with the introduction of the radioactivity. Scheme II illustrates the purification and analysis to determine the extent of reaction. The preparation of the starting materials and some of the details are described in the Experimental Section. We were unsuccessful at preparing the Grignard reagent from 2-phenyl-2-(1-methyl-3-bromopropyl)-1,3-dioxolane, thus requiring this more devious process of introduction of the label before the methylation. We neglected to apply the "hold-back carrier" technique to the removal of active 2-benzoyl-2-methylbutane (**5**) from our sample of 2-benzoylbutane, and this oversight is probably re-

(16) All systems were protected from strong light to inhibit any photochemically initiated chain reactions, but a low level of ordinary light could account for a very slow reaction if the kinetic chain length is long. Similarly, only a very long chain length radiation induced reaction could account for the discrepancy, since the level of activity has fairly low. We can not calculate this radiation-induced rate, but by analogy with other work it must be very small.

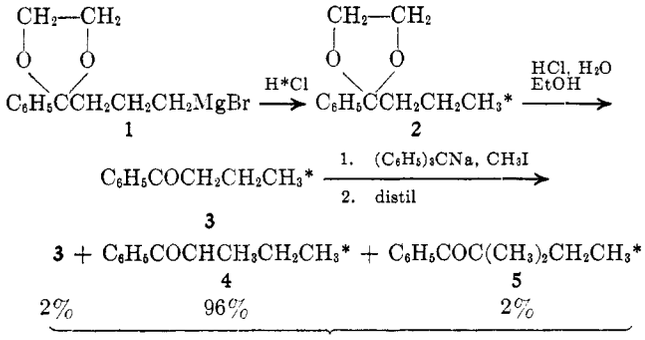
(17) Reference 4, p 151.

(18) This is true if g is a weight fraction and the amount of substance is measured by weights, but in our case amounts are measured by uv absorption. If there is a nonradioactive contaminant Z with a mole fraction n_Z in with the desired substance Y with a mole fraction n_Y, then the appropriate g to put in is $g = \epsilon_Y n_Y/(\epsilon_Y n_Y + \epsilon_Z n_Z)$ where ϵ_Y and ϵ_Z are the extinction coefficients of Y and Z. Thus no error results from a transparent contaminant ($\epsilon_Z = 0$), but serious errors can result from contaminants with $\epsilon_Y > \epsilon_Y$, even if n_Z is small. Fortunately, compounds with high ϵ are usually strongly adsorbed on a chromatographic column, so that our purification renders such a contamination unlikely.

(19) E. J. Dewitt, C. T. Lester, and G. A. Ropp, *J. Amer. Chem. Soc.*, **78**, 2101 (1956).

SCHEME I

PREPARATION OF 2-BENZOYLBUTANE-4-*t* AND 2-BENZOYLBUTANE-2-*d*-4-*t*



sample A

(all specific activities about same as that of **4**)

1. $C_6H_5COCH_2CH_2CH_3$ (inactive)
2. column chromatography
3. repeat "hold-back" three times
4. preparative glpc

Sample B of **4** (3.2×10^4 dps/mmol)
<0.1% $C_6H_5COCH_2CH_2CH_3$ of negligible specific activity
≪0.1% **5**, undetectable by glpc, specific activity as in sample A

1. D_2O, $SOCl_2$
2. repeated exchange

$C_6H_5COCDCH_3CH_2CH_3$*

6

(containing 1% **4** and other impurities as in sample B)

SCHEME II

DETERMINATION OF EXTENT OF BROMINATION OF **4**

4 (sample B) or **6**
~80 mg (m_1 mol)

HOAc, H_2O
NaOAc, NaBr, Br_2
for measured time t

4 + $C_6H_5COCBrCH_3CH_2CH_3$*
(~99%) **7** (~1%)

1. partition between petroleum ether and aqueous $Na_2S_2O_3$
2. add ~40 mg (m_2 mol) of $C_6H_5COBrCH_3CH_2CH_3$ (inactive)
3. discard aqueous layer
4. wash and dry organic layer
5. chromatograph on Florisil

fraction (mostly **4**)

fraction C (mostly **7**)

1. $C_6H_5COCHCH_3CH_2CH$ (**8**)
2. chromatograph

fraction E (mostly **7**)

fraction D (mostly **8**) count

if count of D is significant, repeat C → D + E process; if not, rechromatograph to remove residual **8**

7 (in petroleum ether)

1. replace solvent with toluene
2. determine uv spectrum (A)
3. add scintillation solution (count rate = c)
4. determine specific activity (a_{obsd})

sponsible for a good bit of the remaining kinetic uncertainties, even though this contamination of the sample used was undetectable by gas chromatography, and all low-level samples had been subjected to further column chromatography several times. Apparently the bromo ketone and the completely methylated ketone are not easily separated by the column chromatography. The removal of the labeled unmethylated ketone **3** was done very carefully, since it would be brominated rapidly, and possibly the product would be difficult to separate from the bromination product of **4**.

The specific activity a_{obsd} of the sample of bromo ketone was determined by combining the absorbance of the solution (ϵ = 153 at 327 nm) with the count rate, making suitable allowance for the volume of sample taken to count. The specific activity of the starting material, a_0, was counted under the same conditions by converting it quantitatively into bromo ketone using a rapid acid-catalyzed reaction before counting. The extent of completion (x) is then given by the equation $x = am_2/a_0m_1$. The pseudo-first-order rate constant was then calculated from the slope of a plot of x *vs.* t. These plots sometimes had intercepts greater than zero at $t = 0$. Although some of this could be attributed to a real effect of a small, rapidly brominated amount of enol in the ketone, which might easily be different from the equilibrium content, we believe that a reasonably reproducible contamination by **5** is a more likely source of this intercept. In either case the use of the slope rather than the extent of completion at any one time eliminates or reduces the error. When a bromination reaction is this slow, both steric or electronic explanations for the slowness would also suggest that bromine would not compete as well for the enolate ion (or enol) as it does in more familiar systems. If this competition were really unfavorable, bromine would enter the rate expression. This was not checked for 2-benzoylbutane, but the gas chromatographic results on 2-benzoylpropane and the spectrophotometric results on propiophenone were both independent of bromine concentration. In the latter case the use of very dilute bromine solutions (using 10-cm cells) allowed a study of the region of bromine dependency, and it was found that bromine reacted about 3×10^6 times faster than acetic acid with the reactive intermediate.[20] Since the bromine concentrations in the present work are high, it is likely that the enolate is efficiently trapped, and that the rates are genuine ionization rate measurements.

The choice of nature and position of the label calls for some comment. Either tritium or ^{14}C is required for generality for organic reactions, and tritium was chosen both because it is easier to introduce and because it is cheaper and offers minimal health hazards, even at levels far higher than we used. The label was not put in the ring, because of the (rather far-fetched) possibility of exchange. The α position was avoided since we were interested in measuring isotope effects. We avoided a label at the 1 or 3 position of the butyl group because it might be lost by β elimination from the bromo ketone. The further advantage of a label in the 4 position was that secondary isotope effects would be reduced to a trivial amount, so that the rate on the tritium compound could be compared directly with that of ordinary 2-benzoylbutane.

We conclude that we have successfully measured a slow reaction rate by this isotope dilution analysis, and that the inherent limitations have not been ap-

(20) Reference 1a.

proached, so that far slower reactions could be studied. The only practical limitation is the tedium of the numerous chromatographic separations,[21] so that the method should not be applied unless there is some real reward for the considerable effort.

Experimental Section

Materials.—Acetophenone, propiophenone, 2-benzoylpropane, and phenacyl bromide were commercially available materials. Repeated exchange of the first two with deuterium oxide in dioxane containing potassium carbonate gave acetophenone-d_3, 94% deuterated (by combustion), and propiophenone-α-d_2, 95% deuterated (by combustion). 2-Benzoylbutane was made following Bartlett and Stauffer.[22]

2-Benzoyl-3-methylbutane.—Following the plan of Nunn and Henze,[23] benzonitrile (69 g, 0.66 mol) in dry toluene (800 ml) was added to the Grignard reagent from 2-bromo-4-methylbutane (0.6 mol) in refluxing ether (700 ml). The ether was removed and the toluene solution was allowed to stand for 9 hr. The mixture was then boiled for 6 hr, cooled, and treated with 450 ml of cold saturated ammonium chloride solution. The toluene layer was extracted with cold dilute sulfuric acid, and this extract was boiled under reflux for 2.5 hr, cooled, and extracted with ether. The ketone was isolated by distillation and gave a 2,4-dinitrophenylhydrazone, mp 121–122° (lit.[24] mp 118–119°). Fractional distillation gave a compound containing only 1% contaminant by gas chromatography.

2-Benzoylpropane-2-*d*, 2-benzoylbutane-2-*d*, and 2-benzoyl-3-methylbutane-2-*d* were made by boiling the ketones with about a twofold excess of sodium hydride in suspension in tetrahydrofuran. After hydrogen evolution had ceased, usually in excess of 12 hr, deuterium oxide (in twofold excess) was added and distillation yielded the ketone in good recovery, but the deuterium contents were, respectively, 92 (nmr) (93% by combustion), 94 (nmr), and 94% (nmr) (95% by combustion). This method is not recommended. The acid-catalyzed exchange described below used for 2-benzoylbutane-4-*t* is superior. Benzoyldibromomethane was prepared following Evans and Brooks[25] by the bromination of phenacyl bromide.

2-Benzoyl-2-bromopropane.—The bromination of the ketone led to this compound.[26] Similarly, 2-benzoyl-2-bromobutane and 2-benzoyl-2-bromo-3-methylbutane, all used for gas chromatographic references, were prepared by brominating the ketone in acetic acid solution. Adsorption chromatography on alumina and Florisil, respectively, was needed to get a sample pure enough for use. The same method was used to convert 2-benzoylbutane-4-*t* into 2-benzoyl-2-bromobutane-4-*t*.

Butyrophenone-4-*t* (3).—The Grignard reagent from 2-phenyl-2-(3-bromopropyl)-1,3-dioxolane (54 g) was prepared following the procedure of House and Blaker[27] starting from ethyl benzoylacetate. Tritiated water (1 g, 10 mCi) was added slowly to boiling thionyl chloride, and the gases were passed over the ethereal solution of the Grignard reagent. Ordinary water was used to complete the transfer of the tritiated water 1 hr after the radioactive water had been added. After 5 hr, the residual magnesium was removed by filtration, and the ether was washed with water, 5% sodium carbonate, water, and saturated brine. Since the ketal is only partially hydrolyzed at this stage, isolation should not be attempted. The ether was concentrated to a total volume of 150 ml, then added to a mixture of 1 l. of 1 *M* hydrochloric acid and 400 ml of ethanol, and heated overnight on the steam bath. After conventional work-up, distillation gave 13.29 (44%) of 1-benzoylpropane-3-*t*, to which was added 5 g of ordinary butyrophenone distilled through the same apparatus to scavenge column holdup, etc.

2-Benzoylbutane-4-*t* (4).—In a flask protected from the atmosphere, equipped with a magnetic stirrer, a reflux condenser and an addition funnel was placed 10.2 g of 1-benzoylpropane-3-*t*. An ethereal solution of triphenylmethylsodium was added until the red color persisted; then methyliodide (100 ml) was added with stirring. A precipitate of sodium iodide was observed in 10 min, but the solution was stirred for 6 hr, then poured on 500 ml of water, and the layers were separated. Conventional work-up gave 8.32 g (82%) of 2-benzoylbutane-4-*t*, and a further 2.35 g of less active material was obtained by scavenging with cold material. Analytical scale glpc showed, about 2% each, peaks with retention times identical with those of the unmethylated and dimethylated ketones (**3** and **5**, respectively).

Further purification was accomplished by adding an equal amount of unlabeled butyrophenone and chromatographing on Woelm activity I alumina, with the unmethylated compound more strongly adsorbed. This treatment was repeated twice, so that only about 1 part in 10^7 of the activity was attributable to contamination by **3**, and preparative scale glpc on a silicone fluid column showed that the product contained 0.1% butyrophenone (essentially devoid of activity) and no detectable amount of the active dimethylated ketone **5**.

2-Benzoylbutane-2-*d*-4-*t* (6).—Thionyl chloride (0.8 ml) was added to deuterium oxide (10 ml, 99.5%), and the mixture heated to 90° for 1 hr to complete the hydrolysis; then 1.01 g of 2-benzoylbutane-4-*t* was added and the heating continued for 24 hr. The mixture was then extracted with petroleum ether, which was then washed and dried and the solvent evaporated. The exchange was repeated as before and the product was distilled, yielding 0.5 g of material with a deuterium content 99.0 ± 0.1 by an nmr method. This analysis involves rather difficult comparisons either of peaks of very different size, or of unestablished origin. The analysis was facilitated by the availability of a sample of intermediate deuterium content. With this sample, it was possible to integrate the relative intensities of the signal at δ 3.38 (sextet, the tertiary hydrogen) with the multiplet at 8.0 of two of the aromatic hydrogens. A protium content of 5.7% was calculated. The rough factor of 40 difference in integral was reduced to a factor of 4 by sweeping the intense one ten times as fast, a technique depending only on the constancy of speed of a synchronous motor and the number of teeth on gears, rather than relying on the precision of resistors in attenuators. This analysis was unsuitable for the more highly deuterated species since the signal to noise level was very poor on the smaller peaks of the sextet. When the sample which contained 5.7% protium compound was studied with the higher resolution and greater sensitivity of a 100-Mc instrument, a small peak was found at δ 8.19, which is presumably a ^{13}C satellite of a portion of the aromatic proton spectrum. This peak, although not rigorously assigned to any proton, was used in a peak height analysis, by comparing its height to that of the largest peak of the sextet from the tertiary hydrogen.[28]

Kinetics.—The solvent for all runs was prepared by diluting a mixture of 150 g of anhydrous sodium acetate, 15.5 g of sodium bromide, and 85 ml of water to 1 l. with glacial acetic acid. The sodium bromide is called for in the spectrophotometric runs, it was included in the others merely to keep the conditions uniform.

Spectrophotometric Kinetics.—The method of Emmons and Hawthorne[13] was followed, except that a Cary Model 14 spectrophotometer was used. The problems of temperature control in this method have been discussed elsewhere.[14b]

Gas Chromatographic Kinetics.—A weighed sample of ketone was diluted to 25 ml with the solvent and 0.4–0.8 ml of bromine was added. About 4 ml of this solution was placed in each of six ampoules, which were then sealed and placed in an oil thermostat at 100° in a darkroom. In the presence of light the results were nonreproducible. At various times an ampoule was removed and immediately cooled in ice. The ampoule was then opened and the contents were transferred to a separating funnel and partitioned between 25 ml of 0.01 *M* sodium thiosulfate solution and petroleum ether. Most of the petroleum ether was evaporated on a water bath and the residue was subjected to gas chromatographic analysis. Columns were made of glass and were packed with Chromosorb W containing 10% Dow-Corning 550 silicone oil. The bromo ketones were rather sensitive on gas chromatography and did not survive metal columns.

Blank runs showed that the bromo ketone–ketone ratio was

(21) Professor R. V. Stevens has suggested that these separations could well be carried out by preparative scale thin layer chromatography, with a great reduction in time.

(22) P. D. Bartlett and C. H. Stauffer, *J. Amer. Chem. Soc.*, **57**, 2580 (1935).

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(26) A. Faworsky and N. Mandryka, *J. Prakt. Chem.*, **88**, 691 (1913).

(27) H. O. House and J. W. Blaker, *J. Org. Chem.*, **23**, 334 (1958).

(28) We thank Professor M. R. Wilcott for the 100-Mc nmr spectra.

unaffected by the isolation procedure, and the analysis was calibrated by known mixtures frequently.

Rate constants were calculated from the slope of a plot of bromo ketone–ketone against time, since the reactions were not carried to a large enough extent of completion to consider the variation of ketone concentration with time.

Isotopic Dilution Analysis Kinetics.—A weighed amount (≤ 80 mg) of the tritiated ketone was mixed with the heated solvent and an excess of bromine (five- to tenfold) was added and the vessel placed in the thermostat. At the desired time (1–8 days) the reaction was quenched by cooling and dilution with petroleum ether (bp 30–60°); then a weighed amount (40–50 mg) of the inactive bromo ketone was added. Successive washings with water, 0.05 *M* sodium thiosulfate, water, 10% sodium carbonate, water, and saturated brine gave a colorless solution which was concentrated to about 1–2 ml at not greater than 50° on a rotary evaporator. Further concentration or higher temperatures sometimes led to discoloration. The concentrate was then subjected to chromatography on Florisil, from which the bromo ketone was eluted with petroleum ether and then the unchanged ketone with toluene. The bromo ketone rich fractions were mixed with inactive ketone and rechromatographed, and the ketone fraction was counted; if the activity was low enough the bromo ketone fraction was chromatographed once more before uv and radioassay, but if the activity was significant, the "holdback" separation was repeated.

After the final chromatographic separation the petroleum ether was mostly removed and replaced with toluene, again taking precautions not to overheat or remove all solvent. When the volume reached about 6 ml the uv spectrum was taken and the concentration calculated [λ_{max} 327 nm (ϵ 153) in toluene]. A 5-ml sample of the same solution was transferred to a counting vial, 15 ml of scintillator solution [4 g of 2,5-diphenyloxazole and 0.1 g of 2,2-*p*-phenylenebis(5-phenyloxazole) in 1 l. of toluene] was added and the sample was counted. Efficiency of counting was determined by automatic external standardization, and varied little except when much higher concentrations of bromo ketone were used, when some quenching appeared.

Registry No.—2-Benzoylbutane-2-*d*, 18321-26-1.

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The Mass Spectra of Cyclobutyl and Cyclopropylcarbinyl Methyl Ethers and the Methanolysis of Bicyclobutane[1]

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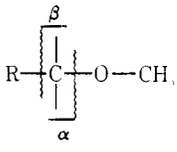
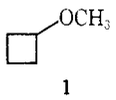
The mass spectral fragmentation patterns of cyclobutyl and cyclopropylcarbinyl methyl ethers were found to be similar and the mechanisms of the fragmentations were evaluated by use of deuterium-labeled material and by means of high-resolution mass spectrometry. In both materials the base peak was *m/e* 58, corresponding to the loss of ethylene. The mechanism of the acid-catalyzed addition of methanol to bicyclobutane was studied using the above mass spectral results. The addition was not concerted but proceeded *via* protonation to yield a bicyclobutonium ion (or equivalent activated complexes) which partially equilibrated before the nucleophilic attack of methanol occurred. When 1,3-butadiene in methanol was irradiated with ultraviolet light, cyclobutyl and cyclopropylcarbinyl methyl ethers were formed in low yield. These ethers were shown to be derived in a dark reaction of methanol with bicyclobutane.

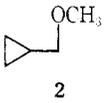
Alkyl ethers undergo two major fragmentation reactions upon electron impact in the mass spectrometer. These are "α" cleavage of the carbon–oxygen bonds leading to carbonium ions and "β" cleavage leading to oxonium ions.[3,4] The oxonium ions of ethers where both groups are larger than methyl undergo further rearrangements[3,4] which are of no concern to the present study. Generally, β cleavage has been found to yield the base peak of methyl ethers.[3]



In the course of a study of the photochemistry of 1,3-butadiene in methanol,[5] it was discovered that the mass spectra of cyclobutyl methyl ether (CBME), **1**, and cyclopropylcarbinyl methyl ether (CPCME), **2**, have one main feature which distinguishes them from the spectra reported for other methyl ethers. The



1



2

base peaks for **1** and **2** are at *m/e* 58, corresponding neither to α cleavage nor to β cleavage, but to the loss of the elements of ethylene. It was considered that these fragmentations involve cleavage of the cyclobutane and cyclopropane rings as shown in eq 1–2. In accord with eq 1 are the mass spectra of several cyclobutane derivatives which were recently reported.[6] In each case it was found that fission of the cyclobutane ring leads to the most abundant ion. Similarly it has been suggested that fission of the cyclopropane ring gives rise to the M − 28 peak in the mass spectrum of benzylcyclopropane.[7] It is of interest, however,

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