[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Carbon-14 Kinetic Isotope Effects. IV. The Effect of Activation Energy on Some Carbon-14 Kinetic Isotope Effects[1,2]

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Carbon-14 kinetic isotope effects have been determined in the reactions of methyl iodide-C^{14} with N,N-dimethyl-*p*-toluidine, N,N-diethylaniline and N,N-dimethyl-*o*-toluidine in methanol solution. The activation energies of these three similar reactions are 14.5, 18.0 and 21.1 kcal./mole, respectively, and the kinetic isotope effects of these three processes are 1.117 ± 0.011, 1.120 ± 0.001 and 1.134 ± 0.047, respectively. These results are consistent with but not definitive proof that kinetic isotope effects increase with increasing activation energy. These results together with other results in the literature indicate a linear relationship between activation energy and kinetic isotope effect in a given family of reactions. The reversibility of the reaction of methyl iodide-C^{14} with N,N-dimethyl-*o*-toluidine and its effect on the kinetic isotope effect of the forward reaction is demonstrated.

Introduction

The difference in the reaction rates of two related compounds with a series of similar reactants is generally greater the higher the activation energies. It is of interest to see whether this relationship also applies to kinetic isotope effects. In the reactions of formic-C^{13} acid in which the rate-determining steps involve extraction of hydrogen by either bromine or chlorine atoms, a difference in kinetic isotope effects was found in the direction that the slower reaction showed the greater degree of isotope fractionation.[3] In this report the authors presented a semi-quantitative discussion of the effect of the reaction rate on the carbon-13 isotope effects in terms of the absolute reaction rate theory. Kinetic isotope effects in the alkaline hydrolysis of six *m*- and *p*-substituted ethyl benzoates-α-C^{14} in 90% ethanol also have been studied.[4] The activation energies of these reactions have been determined by other workers.[5] A comparison of k/k^* and E indicates that the relative order of values of k/k^* is the same as that of the values of E, with one exception. Another series in which kinetic isotope effects can be compared with activation energies is the decomposition of five substituted ureas in propionic acid studied by Magee and Daniels.[6] Again the relative order of values of k/k^* is the same as that of the values of the activation energy.

In studies of deuterium isotope effects[7] a similar relationship has been found. For instance the kinetic isotope effect in the removal of an α-hydrogen (or deuterium) atom of toluene and substituted toluenes has been investigated.[8] The relative magnitudes of the kinetic isotope effect of five free radicals and atoms (and of the selectivity of the free radicals) followed the order of activation energies.

A favorable series to examine in order to test the relationship between kinetic isotope effect and activation energy would be one in which the same labeled compound reacts with different reagents in the same solvent. Furthermore, the attacking atom in each of the reagents could be kept constant, so that effects due to different masses of the atoms directly concerned in the transition state would be ruled out. The only results of this type so far available are those of Bender and Hoeg[9] for the reaction of methyl iodide-C^{14} with triethylamine and pyridine in benzene. Here the reaction possessing the highest activation energy (pyridine) is the one exhibiting the greatest isotope effect. This relationship is to be expected in such a reaction series; the greater the activation energy (*i. e.*, the weaker the nucleophile) the looser is the transition state and therefore the smaller the zero point energy difference between the transition states of the carbon-12 and carbon-14 molecules. Hence, the greater is the k/k^*. However, the two amines do not constitute an optimum series because of large electronic and steric differences. If a reaction series is imagined in which the nucleophiles are made successively weaker, the activation energies would increase until the nucleophile becomes too weak to participate in the transition state, *i. e.*, the mechanism changes from SN2 to SN1 (assuming that the solvent and the structure of the compound allow an appreciable SN1 reaction). The isotope effect would therefore be expected to increase in the SN2 series, and then reach a maximum value with the SN1 reaction.[10] Practical considerations in the determination of kinetic isotope effects limit the choice of a suitable reaction series, and the best that could be found satisfying these considerations was the reaction of methyl iodide-C^{14} with aromatic amines in methanol. In this case the SN1 reaction is not realizable, but a wide range of activation energies is covered by the SN2 reaction. The amines investigated in the present work and their respective activation energies were N,N-dimethyl-*p*-toluidine,[11] 14.5 kcal./mole; N,N-diethylaniline,[12] 18.0 kcal./mole; and N,N-dimethyl-*o*-toluidine,[11,13] 21.1 kcal./mole.

Since the isotopic analysis was carried out on one of the reactants, methyl iodide, it was necessary to show in each case that the reaction goes substantially to completion. N,N-Dimethyl-2,6-dimeth-

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[1] This research was supported by Contract At(11-1)295 of the U. S. Atomic Energy Commission.

[2] Previous paper, M. L. Bender and G. J. Buist, THIS JOURNAL, **80**, 4304 (1958).

[3] G. A. Ropp, C. J. Danby and D. A. Dominey, *ibid.*, **79**, 4944 (1957).

[4] G. A. Ropp and V. F. Raaen, *J. Chem. Phys.*, **22**, 1223 (1954).

[5] C. K. Ingold and W. S. Nathan, *J. Chem. Soc.*, 222 (1936); D. P. Evans, J. J. Gordon and H. B. Watson, *ibid.*, 1430 (1937).

[6] E. M. Magee and F. Daniels, THIS JOURNAL, **79**, 829 (1957).

[7] K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

[8] G. A. Russell, THIS JOURNAL, **79**, 3871 (1957).

[9] M. L. Bender and D. F. Hoeg, *ibid.*, **79**, 5649 (1957).

[10] See, however, reference 2.

[11] D. P. Evans, H. B. Watson and R. Williams, *J. Chem. Soc.*, 1345 (1939); 1348 (1939).

[12] D. P. Evans, *ibid.*, 422 (1944).

[13] W. G. Brown and S. Fried, THIS JOURNAL, **65**, 1841 (1943).

ylaniline, $E = 25.6$ kcal., was considered as a fourth member of the series.[13] However, the reverse reaction in the case of N,N-dimethyl-*o*-toluidine, the third member of the series (see later), was of sufficient magnitude to prevent accurate determination of the isotope effect by the method used, so it is evident that the determination of the isotope effect for a tertiary amine containing two *o*-methyl groups would be at best very approximate.

Experimental

Materials.—Absolute methanol was prepared by treating commercial acetone-free methanol with magnesium.[14] Commercial methyl iodide was distilled through a fractionating column, b.p. 42.0°. Isotopic dilution of 500 μc. of methyl iodide-C^{14} (Nuclear-Chicago Corp.) with the purified methyl iodide was carried out in the vacuum line. The diluted material was stored over a globule of mercury in the freezer compartment of a refrigerator. Eastman Kodak Co. "mono-free" N,N-diethylaniline was distilled twice under vacuum, the second time through a fractionating column; b.p. 53° (1.3 mm.), $n^{20.5}\mathrm{D}$ 1.5414 (lit. $n^{22.3}\mathrm{D}$ 1.5411), purity by acid–base titration, 99.4%. N,N-Dimethyl-*p*-toluidine (Matheson Co.) was refluxed with excess acetic anhydride followed by fractional distillation under vacuum; b.p. 48–58° (1.0–1.4 mm.), $n^{20}\mathrm{D}$ 1.5463 (lit. $n^{20}\mathrm{D}$ 1.5469), purity by acid–base titration, 99.3%. N,N-Dimethyl-*o*-toluidine (Eastman-Kodak Co.) was refluxed with excess acetic anhydride with concd. sulfuric acid as catalyst followed by fractional distillation under vacuum; b.p. 37–40° (1.7–2.0 mm.), $n^{25}\mathrm{D}$ 1.5230 (lit. $n^{23.3}\mathrm{D}$ 1.5244), purity by acid–base titration, 99.8%. The amines were stored under nitrogen. N,N,N-Trimethyl-*p*-tolylammonium iodide and the corresponding *ortho* compound were prepared in the following manner. The respective amines were allowed to stand with a twofold excess of methyl iodide until the mixture became solid. The salts were then recrystallized from 95% ethanol; *para* compound, m.p. 222° (lit. 220°); *ortho* compound m.p. 223° (lit. 223°).

Kinetics.—Previous workers[11,13] used the determination of iodide ion by a silver nitrate titration in order to follow the reactions of methyl iodide with the various tertiary amines. This procedure is satisfactory up to about 50% reaction but beyond this point the end-point could not be determined accurately. The region from 50–90% is the most important for the determination of the isotope effect; moreover it is necessary to take an infinity reading to find out how closely the reaction reaches completion. Therefore, a procedure was devised for following the amine concentration by acid–base titration. Preliminary experiments showed that good second-order kinetics could be obtained up to 90% reaction; titration of infinity samples showed that the reaction reached 96–98% completion in all cases. Combined kinetic and isotope effect experiments were then carried out as described below.

N,N-Diethylaniline and N,N-Dimethyl-*o*-toluidine.—The amine, nitrogen-saturated absolute methanol, methyl iodide-C^{14} and finally methanol were added to a volumetric flask. Portions of the reaction mixture were pipetted into nitrogen-filled ampoules, cooled in ice, flushed with nitrogen and sealed. The ampoules were suspended in a 62.7° thermostat for various lengths of time. After an appropriate amount of time the ampoule was cooled and a 5.00-ml. portion removed and pipetted into a known volume of standard hydrochloric acid. The remainder of the sample was used for the isotopic analysis (see below). The titration was carried out against standard sodium hydroxide, using a Beckman model G *p*H meter. The point of inflection of the *p*H titer curve determined by inspection was taken as the end-point. The methyl iodide concentration at each point was calculated from the amine concentration using the theoretical infinity. This value did not differ by more than 4% from the experimental infinity. The second-order rate constant, k_2, was calculated from the slope of a plot of log $([\mathrm{amine}_t]/[\mathrm{MeI}_t])$ *versus* time.

N,N-Dimethyl-*p*-toluidine.—The technique used with this amine was different due to its faster reaction. Nitrogen-saturated methanol solutions of methyl iodide-C^{14} and amine were placed in the two compartments of a double compartment reaction tube, equilibrated at 48.5°, and mixed. Solutions were freshly made for each point. The reaction was stopped after a suitable amount of time and the amine analysis was carried out as described above except that the titration was continued until a *p*H of 3.27 was reached; this *p*H had been shown to be the end-point by preliminary experiments. The methyl iodide concentration was calculated as above and the second-order rate constant calculated for each point by using the integrated second-order rate equation. The reaction with this amine was particularly sensitive to the presence of oxygen and the liberation of iodine could not be entirely avoided.

Isotopic Analysis.—After a portion of each sample had been withdrawn for the amine titration, the remainder was poured into a 5–10-fold excess of 1 *M* hydrochloric acid. The methyl iodide was extracted 4 times with ether and converted to the β-methoxynaphthalene derivative according to the established procedure.[9] The crude derivative was first purified by chromatography on alumina: the product was dissolved in hot petroleum ether and eluted with 50:50 petroleum ether–benzene mixture. This process yielded an almost colorless material which was recrystallized about 9 times from ethanol–water. A sample of an earlier recrystallization was kept and its activity determined so that it could be shown whether constant activity had been reached. Sufficient of the derivative was weighed out approximately and combusted to carbon dioxide so that three aliquots of carbon dioxide could be measured out in the vacuum line (by means of a constant volume manometer) and the specific activity of each aliquot determined. The kinetic isotope effect was determined from a plot of log S against log $(1 - f)$ where S is the specific activity at fraction of reaction f. The slope of this plot is $(1 - k^*)/k$.[15]

Results

Kinetics.—The kinetics of the reactions of methyl iodide-C^{14} with N,N-diethylaniline, N,N-dimethyl-*o*-toluidine and N,N-dimethyl-*p*-toluidine in absolute methanol are shown in Fig. 1. The respective second-order rate constants are 9.95×10^{-5} (62.7°), 2.11×10^{-5} (62.7°) and 8.6×10^{-4} (48.5°) l./mole sec., corrected for the expansion of the solvent. From previous work the calculated values at these temperatures are 9.95×10^{-5}, 3.24×10^{-5} and 8.4×10^{-4} l./mole. sec., respectively.[11,13] The experimental infinities were 96.5, 96.7 and 97.2% of the theoretical values, respectively. The previous workers reported slight autocatalysis with the first two amines,[11,12] but none was apparent in the present work. Since there is a slight scatter of points in the N,N-dimethyl-*o*-toluidine and the N,N-dimethyl-*p*-toluidine results, the values of the fraction of reactions (for the determination of the kinetic isotope effects) were recalculated using the values of k_2 given above.

Kinetic Isotope Effects.—The results of the determinations of the carbon-14 kinetic isotope effects in the three displacement reactions described above are shown in Fig. 2. The kinetic isotope effects calculated from these plots using a least squares treatment of the data are given in Table I.

The data for N,N-dimethyl-*o*-toluidine in Fig. 2 show a tendency toward a downward curvature. If the kinetic isotope effect is calculated point by point, the regular decrease in the kinetic isotope effect with increasing fraction of reaction is immediately apparent. This result may be explained if it is assumed that the reverse reaction is appreciable in this case. Initially the methyl

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(14) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1955, p. 198.

(15) A. M. Downes and G. M. Harris, *J. Chem. Phys.*, **20**, 196 (1952).

(16) A. G. Worthing and J. Geffner, "Treatment of Experimental Data," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 249.

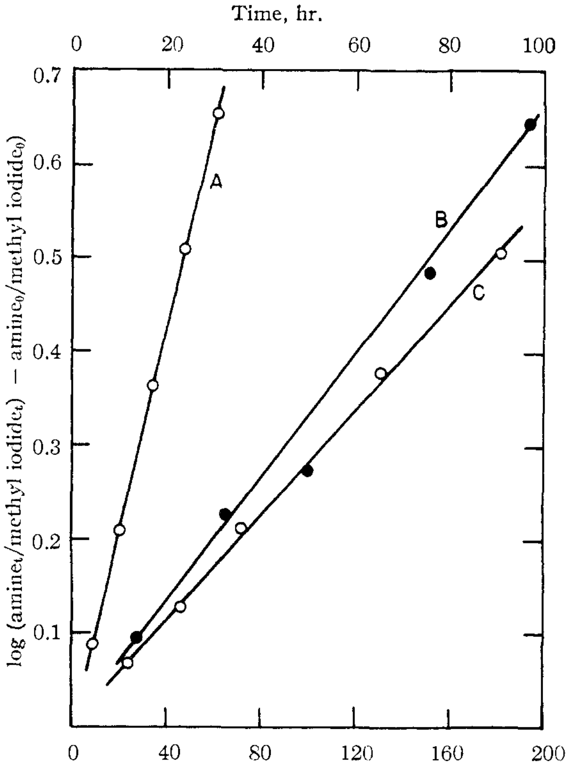

Fig. 1.—The kinetics of the reactions of methyl iodide-C^{14} with some substituted anilines: A, N,N-diethylaniline, 62.7° (top scale); B, N,N-dimethyl-*p*-toluidine, 48.5° (bottom scale); C, N,N-dimethyl-*o*-toluidine, 62.7° (top scale).

iodide-C^{14} becomes enriched in the normal manner, but later the enrichment is opposed by a dilution due to non-radioactive methyl iodide derived from the product. Confirmation of an appreciable reverse reaction was obtained from an exchange experiment described below. The value of the kinetic isotope effect given in Table II is therefore the value calculated from the lowest fraction of reaction.

TABLE I

CARBON-14 KINETIC ISOTOPE EFFECTS IN THE REACTIONS OF METHYL IODIDE-C^{14} WITH SOME TERTIARY AMINES IN ABSOLUTE METHANOL

Amine	Temp., °C.	Activation energy, kcal./mole	log *A*	k/k^*
N,N-Dimethyl-*p*-toluidine	48.5	14.5	6.8	1.117 ± 0.011[a]
N,N-Diethylaniline	62.7	18.0	7.7	1.120 ± .001[b]
N,N-Dimethyl-*o*-toluidine	62.7	21.1	9.3	1.134 ± .047[c]

[a] That part of the error due to the error in the specific activity was calculated according to the usual formulas,[16] but in allowing for the error in the fraction of reaction, the error was assumed to be systematic, not random (the probable error of k_2 was calculated, then k/k^* calculated for the two extreme values of k_2). [b] In calculating the error it was assumed that there was negligible error in the fraction of reaction. [c] A random selection of ten determinations of the specific activity gave ±0.7% as the mean deviation of the individual counts from the mean; this error was used to calculate the error in k/k^*.

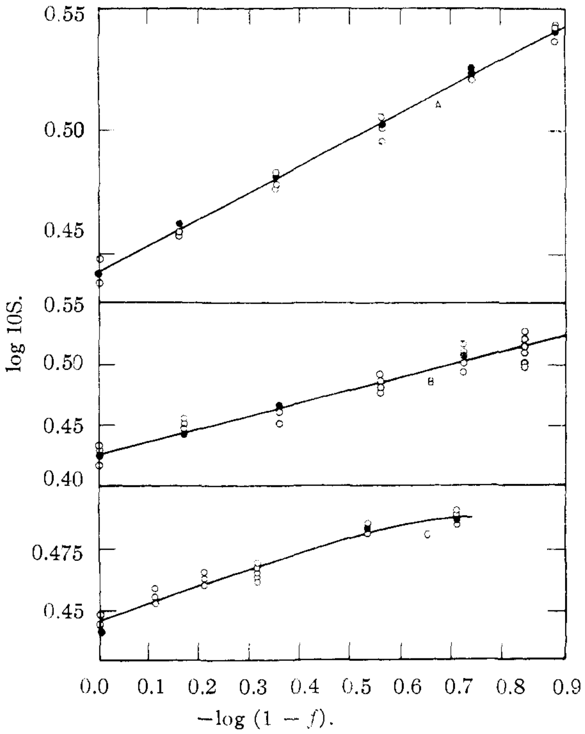

Fig. 2.—Kinetic isotope effects in the displacement reactions of methyl iodide-C^{14} in absolute methanol with: A, N,N-diethylaniline (62.7°); B, N,N-dimethyl-*p*-toluidine (48.5°), and C, N,N-dimethyl-*o*-toluidine (62.7°); ○, one determination; ●, two determinations.

Exchange between Quaternary Ammonium Salts and Methyl Iodide-C^{14}.—In these experiments, the normal quaternary ammonium salt was mixed with methyl iodide-C^{14} and allowed to stand under conditions comparable with those of the kinetic isotope effect runs. The results of these experiments are shown in Table II. It is seen that in the first case no appreciable dissociation of the ammonium iodide into amine and methyl iodide occurred, whereas appreciable dissociation of the am-

TABLE II

ISOTOPIC EXCHANGE BETWEEN METHYL IODIDE-C^{14} AND QUATERNARY AMMONIUM IODIDES

Sample	Specific activity, amp./cm. CO_2 (300°K.) × 10^{14}
N,N,N-Trimethyl-*p*-tolylammonium iodide[a]	
Initial methyl iodide	0.2770
Final methyl iodide	.2763, 0.2775[c]
Final methyl iodide	.2771, 0.2767[d]
N,N,N-Trimethyl-*o*-tolylammonium iodide[b]	
Initial methyl iodide	0.2770
Final methyl iodide	.1681, 0.1700[c]
Final methyl iodide	.1707, 0.1707[d]

[a] 0.149 *M* ammonium iodide and 0.0430 *M* methyl iodide-C^{14} in absolute methanol at 48.5° for 185 min. No amine could be detected by titration at the end of this time. [b] 0.055 *M* ammonium iodide and 0.0315 *M* methyl iodide-C^{14} in absolute methanol at 62.7° for 95 hr. No amine could be detected by titration at the end of this time. The time in each of the two runs was chosen to be comparable with the longest time a sample was left in the thermostat during the kinetic isotope run. [c] Seven recrystallizations of the β-methoxynaphthalene derivative. [d] Nine recrystallizations of the β-methoxynaphthalene derivative.

monium iodide occurred in the latter case even though the formation of amine could not be detected. This dissociation of N,N,N-trimethyl-*o*-tolylammonium iodide is a reflection of the reverse reaction that apparently occurs in the reaction of methyl iodide with N,N-dimethyl-*o*-toluidine and is consistent with the fact that the kinetic isotope effect in this reaction decreased with increasing fraction of reaction. No exchange run was performed with the methiodide of N,N-diethylaniline, but it is reasonable to assume that the reverse reaction is inappreciable in this case as the amine has no ortho substituent. Moreover, the plot of log *S versus* log $(1-f)$ is of great precision and shows no sign of curvature.

Discussion

A theoretical calculation of k_{12}/k_{14} may be made for the kinetic isotope effects of the three reactions studied by use of the equation for reactions involving three-center transition states developed by Bigeleisen and Wolfsberg.[17] If molecular fragments are used in the calculation of the temperature-independent factor and if the usual assumption is made that the carbon–iodine bond is broken in the transition state,[8] the theoretical value of k_{12}/k_{14} for all three reactions is about 1.09. The value for the reaction of methyl iodide-C^{14} with triethylamine, another tertiary amine investigated previously, is also about 1.09.[8] In all these cases, the effect of the activation energy on the kinetic isotope effect is not predicted by the simplified application of the Bigeleisen–Wolfsberg equation made above, although if a more complete model were used presumably this equation would have taken the differences in activation energy into account.

The values of k_{12}/k_{14} obtained in this investigation for the reactions of methyl iodide-C^{14} with the three tertiary amines overlap with one another because of rather extensive errors associated with two of the measurements. Furthermore, the relatively small change in the kinetic isotope effect with rather substantial changes in the activation energies of this family of reactions suggests that a relatively large (and presumably constant) temperature-independent kinetic isotope effect is the major contributor to the kinetic isotope effect. Therefore no definitive relationship can be demonstrated in the present instance between the activation energy and the k_{12}/k_{14} of this family of reactions. However, the mean values are consistent with a linear relationship and this relationship is reinforced by comparison of the present results with that of the reaction of methyl iodide-C^{14} with triethylamine, another tertiary amine, as well as by comparison of the results of this family of reactions with results of other investigators for the kinetic isotope effects of other families of reactions. In Fig. 3 is shown the relationship between the activation energy and the kinetic isotope effect of four families of reactions. In each family it is probable that the temperature-independent kinetic isotope effect is constant if it is of finite value. One family involves carbon-13 kinetic isotope effects,[6] two involve carbon-14 kinetic isotope effects[3] and one involves deuterium isotope effects.[8] The cumulative evidence definitely indicates a linear relationship between the activation energy of a process and its kinetic isotope effect, within a restricted family of reactions.

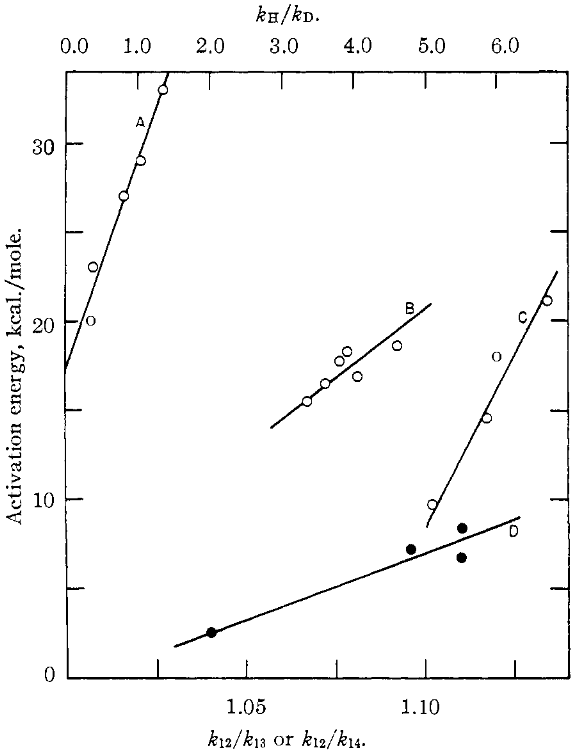

Fig. 3.—The relationship between activation energy and kinetic isotope effect: A, k_{12}/k_{13} for decomposition of substituted ureas (*sym*-dimethylurea, urea, phenylurea, *sym*-diphenylurea and 3,3′-dimethylcarbanilide); B, k_{12}/k_{14} for hydrolysis of substituted ethyl benzoates (*p*-OCH$_3$, *p*-CH$_3$, H, *p*-Cl, *m*-Cl, *m*-NO$_2$); C, k_{12}/k_{14} for reaction of methyl iodide with various tertiary amines (N,N-dimethyl-*o*-toluidine, N,N-diethylaniline, N,N-dimethyl-*p*-toluidine and triethylamine); D, k_H/k_D for the attack of various radicals on substituted toluenes (CH$_3$·, Br·, ROO·, Cl·). Individual reactions are listed in order of decreasing activation energy.

It is seen that the reversibility of a reaction has a very profound effect on the determination of the kinetic isotope effect as was demonstrated in the case of N,N-dimethyl-*o*-toluidine. It was found that this reaction proceeds to at least 96.7% completion, and that no amine can be detected from decomposition of the quaternary iodide; yet the kinetic isotope effect is in serious error, at least at large fractions of reaction. An attempted determination of the kinetic isotope effect in a reversible reaction (by following the specific activity of the reactant) could lead to an incorrect low value, or the isotope effect could even be overlooked entirely, particularly if only one point is taken. In such a case, the isotope effect would be best determined from the specific activity of the product isolated at the lowest possible fraction of reaction.

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[17] J. Bigeleisen and M. Wolfsberg, *J. Chem. Phys.*, **21**, 1972 (1953); **22**, 1264 (1954).