The Beckmann Rearrangement in Concentrated Sulfuric Acid. Studies by Means of NMR and Kinetic Isotope Effect

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(Received June 14, 1978)

The mechanism of the Beckmann rearrangement of acetophenone (a) and 1-phenyl-2-propanone (b) oximes in concd sulfuric acid was elucidated by means of NMR spectroscopy and the carbon-14 kinetic isotope effect. For (a), the postulated reactive species acetophenone oxime hydrogensulfate was detected, the absence of hydrolysis of the oxime during the course of the reaction being verified. Positive carbon-14 kinetic isotope effect at the phenyl-1, $k^{12}/k^{14}=1.026$ at 40 °C and 1.019 ± 0.005 at 60 °C, confirmed a definite change in bonding of the phenyl-1 carbon in the transition state of the reaction. Concertedness of the rearrangement was thus established. For (b), sulfonation of the benzene ring prior to the rearrangement was observed, kinetic isotope effect study being found to be useless.

The Beckmann rearrangement, the reaction of ketoximes to give amides by the action of many kinds of acidic reagents, has been extensively studied for many years.[1,2] Stereochemical studies showed that the reaction is an intramolecular trans rearrangement. The kinetics of the reaction of *O*-picryl ethers of substituted benzophenone[3] and acetophenone oximes[4] in organic solvents revealed the nucleophilic nature of the rearrangement; electron-donating groups accelerate the reaction. However, the actual rearranging species are still not clear in many cases. Concertedness of the reaction has also not been verified completely. Gregory *et al.* reported a kinetic study on the rearrangement of substituted acetophenone oximes in sulfuric acid.[5] They proposed that the reactive species in concd sulfuric acid (>70%) is an oxime hydrogensulfate and that the transition state has a phenonium ion-like structure in which the leaving hydrogensulfate ion is still partially bonded to the nitrogen atom. This mechanism is substantially similar to the one postulated by Huisgen *et al.*[4] for the rearrangement of acetophenone oxime *O*-picryl ethers in 1,4-dichlorobutane.

On the other hand, studies on kinetic isotope effects give the most decisive information on the structure of transition state. A study on the Beckmann rearrangement along these lines was reported in the reaction of acetophenone and *anti*-1-phenyl-2-propanone oximes labeled with carbon-14 in concd sulfuric acid.[6] However, reverse isotope effects in both cases of acetophenone-*phenyl*-1-^{14}C oxime ($k^{12}/k^{14}=0.893$) and *anti*-1-phenyl-2-propanone-1-^{14}C oxime ($k^{12}/k^{14}=0.951$) were disproved by Glover and Raaen.[7] They claimed that acetophenone oxime is partially hydrolyzed to acetophenone during the course of the reaction, and that kinetic isotope effect study is meaningless under these conditions.

In this paper, evidence for the absence of hydrolysis under the reaction conditions is presented.[8] The mechanism of the rearrangement is discussed using the revised data of carbon-14 kinetic isotope effects.

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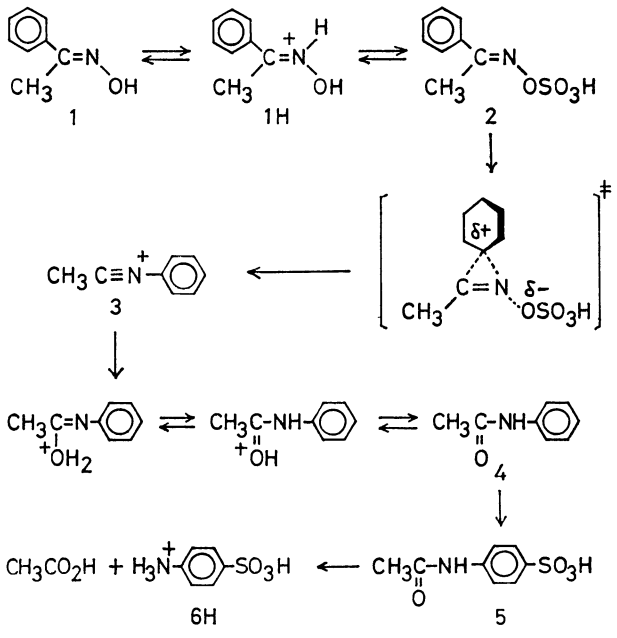
Results and Discussion

NMR Study. When a solution of acetophenone oxime (**1**) in 99.0% sulfuric acid (210 mg in 6 ml) was placed in a NMR probe preheated at 60 °C, the first change observed was the appearance of a new methyl signal at 3.17 ppm from tetramethylsilane as an external standard, together with that of the oxime at 2.88 ppm (Figs. 1a and b). The signal at 3.17 ppm was neither one of the methyl signals of acetanilide (**4**) nor that of acetophenone (**7**); the spectrum of **4** taken for comparison showed the methyl signals at 2.70 and 2.38 ppm in the same solvent (Fig. 1i). As the reaction proceeded, the signals of the rearranged product **4** appeared as expected but decreased again (Figs. 1c, d, and e). The new signals taking the place of those of **4** had an aromatic AA'BB' pattern (Fig. 1f), which was identified as that of 4-acetylaminobenzenesulfonic acid (**5**) by comparison with the spectrum of the authentic sample (Fig. 1j). It was not the final product, however, slow hydrolysis of **5** to acetic acid and 4-aminobenzenesulfonic acid (**6**)



Scheme 1.

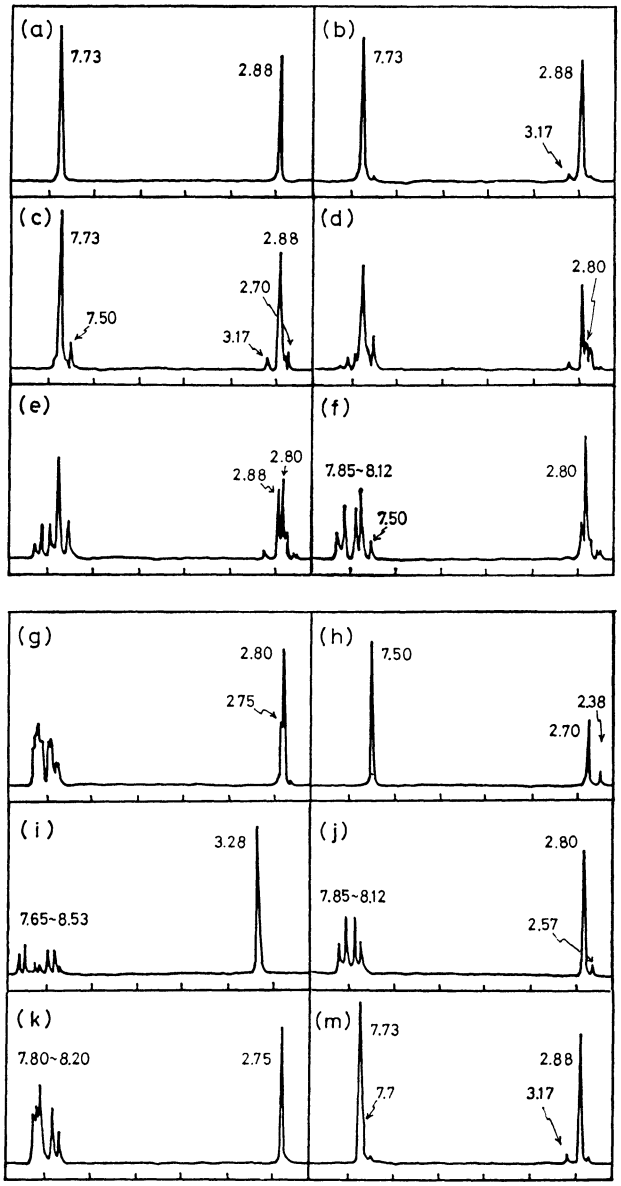


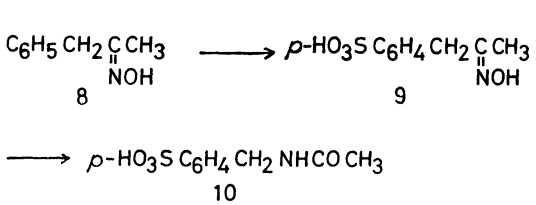
Fig. 1. NMR spectra of the reaction of acetophenone oxime (**1**) in 99.0% sulfuric acid at 60 °C and of reference compounds. (a) Acetophenone oxime (**1**); (b) after 2 min; (c) at 20% reaction; (d) at 40% reaction; (e) at 60% reaction; (f) at 80% reaction; (g) at "infinity"; (h) acetanilide (**4**); (i) acetophenone (**7**); (j) 4-acetylaminobenzenesulfonic acid (**5**); (k) 4-aminobenzenesulfonic acid (**6**) and acetic acid; (m) acetophenone oxime hydrogensulfate (**2**). ppm values from external tetramethylsilane are cited.

being observed later (Figs. 1g and k). The observations lead to a mechanistic scheme (Scheme 1) similar to that of Gregory *et al.*[5]

The structure of the species showing a methyl resonance at 3.17 ppm should be clarified. Gregory *et al.* also detected intermediates spectroscopically in the rearrangement of the oximes of 2-bromo-, 2-iodo-, 2-methyl-, and 2,4,6-trimethylbenzophenone, and 5,6,7,8,-9,10-hexahydrobenzocyclooctene-5-one. From kinetic and spectroscopic evidences, they concluded that the structure of the intermediates should be *N*-arylnitrilium ions. The chemical shifts of the α-methyl groups of these ions were reported to be 3.65—3.85 ppm, which are distinct from 3.17 ppm we observed. The difference of 0.5—0.7 ppm is too large to be attributed to the substituent effect. The species which shows methyl resonance at 3.17 ppm thus would not be *N*-phenylnitrilium ion (**3**). For the sake of comparison, acetophenone oxime hydrogensulfate (**2**) was prepared[9] and dissolved in concd sulfuric acid. The spectrum obtained was similar to that of the reaction solution at an early stage (Fig. 1m); a small methyl signal at 3.17 and a large one at 2.88 ppm, indicating that most of **2** was hydrolyzed to the original oxime in the solution. The intensity ratio of the two peaks remained constant at *ca.* 1 : 10 until 60% of the reaction was completed, after which the peak at 3.17 ppm was too small to be measured accurately. Kinetic treatment of NMR intensities of these methyl signals gave a linear plot with $k=(2.0\pm 0.1)\times 10^{-4}\ s^{-1}$ when the compound showing an absorption at 3.17 ppm was regarded as a species before the rearrangement step. The rate constant agrees fairly well with the value obtained by the gravimetric method, $k=(1.90\pm 0.01)\times 10^{-4}\ s^{-1}$, under the same conditions (*vide infra*). These results indicate that the observed species is acetophenone oxime hydrogensulfate (**2**), which has been postulated to be the reactive species of the rearrangement in concd sulfuric acid.[5]

Throughout the reaction, no signal due to acetophenone (**7**) was detected at all. Furthermore, the reaction solution after 40 h at 60 °C was negative to the 2,4-dinitrophenylhydrazine test. As acetophenone was confirmed to be stable under the reaction conditions, the results prove that acetophenone oxime is not hydrolyzed in 99% sulfuric acid. It is in line with the observations by Gregory *et al.*, who studied the kinetics of the hydrolysis of acetophenone oxime in sulfuric acid of concentration less than 70%.[5,10] Glover and Raaen gave no experimental detail; they might have mistaken the hydrolysis during isolation for that during reaction.[7]

A similar experiment on *anti*-1-phenyl-2-propanone oxime (**8**) at 50 °C showed that the first stage of the reaction in 99.0% sulfuric acid is rapid sulfonation of the benzene ring mainly at the para-position to give 4-(2-hydroxyiminopropyl)benzenesulfonic acid (**9**). The sulfonated benzyl group in **9** rearranges very slowly to 4-(acetylaminomethyl)benzenesulfonic acid (**10**) in the next stage (Scheme 2). Other minor peaks were observed at each stage of the reaction, most of which may be attributed to the presence of isomers other than the para sulfonated ones. Since **9** gave no precipitate of the 2,4-dinitrophenylhydrazone, the gravimetric method followed sulfonation and not rearrangement. Kinetic isotope effect study has no meaning in this case.[6,7]

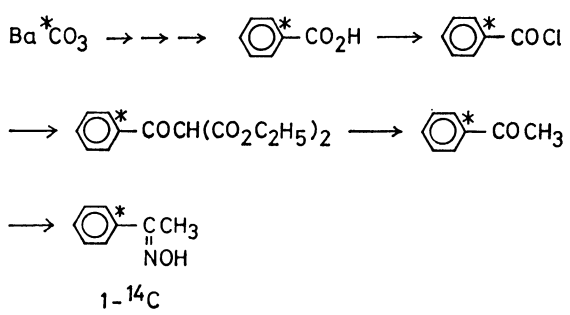


Scheme 2.

Differences in the observations by Gregory *et al.*[5] and by us are interesting; they detected *N*-arylnitrilium ions by UV and NMR and we observed the oxime hydrogensulfate by NMR. However, the two observations do not seem to be in conflict with each other. They recognized that ortho substituents were necessary for the detection of *N*-arylnitrilium ions. On the contrary, oxime hydrogensulfates should have no characteristic absorptions differing from those of oximes in the UV region. We have obtained information that the esterification equilibrium of oximes with sulfuric acid seems to be very sensitive to the concentration of sulfuric acid and the structure of the oximes. NMR spectroscopy is known to be less effective for detecting a small quantity of species present in solution.

Isotope Effect Study. Since the absence of hydrolysis of acetophenone oxime (**1**) under the reaction conditions was established, carbon-14 isotope effects were reexamined. In a previous work, the radioactivity was measured by G. M. counting of barium carbonate disks prepared by wet oxidation of the 2,4-dinitrophenylhydrazone (**11**) derived from the unreacted acetophenone oxime.[6] This is a well-established but old-fashioned method and said to be "the least sensitive and the least precise" one.[11a] In the present reinvestigation, the carbon dioxide gas prepared by wet oxidation of **11** was assayed for radioactivity by the ionization-chamber counting method. The ionization current was measured with a vibrating-reed electrometer by the rate-of-charge method.[11b] By use of this method, the accuracy of the measured radioactivity was much improved.

Acetophenone-*phenyl*-1-^{14}C (**7**-^{14}C) was prepared from benzoyl-*phenyl*-1-^{14}C chloride.[12] Benzoic-*phenyl*-1-^{14}C acid was prepared by the multi-step synthesis from barium carbonate-^{14}C.[13] The overall yield of acetophenone-*phenyl*-1-^{14}C oxime (**1**-^{14}C) from barium carbonate-^{14}C was *ca.* 4.5% (Scheme 3).



Scheme 3.

In order to measure the rates of rearrangement by the gravimetric method, quantitative isolation of the unreacted **1** as **11** was confirmed under the conditions similar to those applied in the reaction. Yield of **11** were 100.5±0.5% for 40—120 mg of **1**.

The rearrangement of **1** in 99.0% sulfuric acid at 0.25 M concentration was followed at 40 and 60 °C. Aliquots of the reaction solution were pipetted out at appropriate time intervals and poured into 0.4% solutions of 2,4-dinitrophenylhydrazine in 2 M hydrochloric acid. First-order rate plots by the gravimetric method using **11** gave straight lines throughout 85% reaction with correlation coefficients greater than 0.9996. The rate constants obtained were $(1.47\pm0.03)\times10^{-5}$ s^{-1} at 40.00±0.01 °C (average of three runs) and $(1.90\pm0.01)\times10^{-4}$ s^{-1} at 60.00±0.01 °C (average of four runs).

The reaction of the labeled compound (**1**-^{14}C) was carried out in the same way. The rate constants were $(1.42\pm0.01)\times10^{-5}$ s^{-1} and $(1.85\pm0.02)\times10^{-4}$ s^{-1} at 40 and 60 °C, respectively. The radioactivity of the purified samples of **11**-^{14}C was assayed with a Nuclear-Chicago Model 6000 Dynacon electrometer system by the rate-of-charge method using a Model T4 interval timer. Oxidation of the samples to carbon dioxide was performed with a Model GW-1 glassware system by the modified Van Slyke-Folch wet combustion method.[14]

Table 1. Reaction percentage and specific radioactivities in the rearrangement of **1**-^{14}C at 40.00±0.01 °C

No.	*t*/min	x[a]/%	n[b]	A_x[c]/mCi mol^{-1}
1	0	0	5	1.397
2	240	18.2	2	1.405
3	420	30.4	2	1.410
4	600	40.7	2	1.414
5	780	49.3	2	1.418
6	1020	58.6	2	1.430
7	1320	67.7	2	1.436
8	1740	77.0	2	1.450

a) Fraction of reaction. b) Number of measurements. c) Specific radioactivity.

Table 2. Reaction percentage and specific radioactivities in the rearrangement of **1**-^{14}C at 60.00±0.01 °C

No.	*t*/min	x[a]/%	n[b]	A_x[c]/mCi mol^{-1}
1	0	0	8	1.300
2	21	18.7	3	1.310
3	31	27.8	3	1.307
4	44	38.2	2	1.307
5	60	48.7	2	1.311
6	78	58.5	3	1.311
7	103	68.3	3	1.332
8	141.5	78.6	2	1.326

a) Fraction of reaction. b) Number of measurements. c) Specific radioactivity.

The results obtained are given in Tables 1 and 2. The specific radioactivities cited are the mean values of two to eight measurements of oxidation analysis for each sample with standard deviations within 0.5%.[15] Kinetic isotope effects were calculated by the linear regression method by means of

$$\log A_x = \log A_0 - [1-(k^{14}/k^{12})]\log(1-x), \quad (1)$$

where x is the fraction of reaction and A_0 and A_x are the specific activities of **11**-^{14}C at $x=0$ and $x=x$, respectively. The calculated isotope effects are given by

$$k^{12}/k^{14} = 1.026 \pm 0.001 \ (40\,^{\circ}C)$$

and

Table 3. Reaction percentage and specific radioactivities in the rearrangement of 1-^{14}C at 59.99±0.01 °C

No.	t/min	x[a]/%	n[b]	A_x[c]/mCi mol^{-1}
1	0	0	1	1.582
2	29	28.5	1	1.594
3	55	48.1	1	1.595
4	80	62.2	1	1.635
5	105	71.8	1	1.655
6	130.5	79.3	1	1.631
7	160	85.4	1	1.647

a) Fraction of reaction. b) Number of measurements. c) Specific radioactivity.

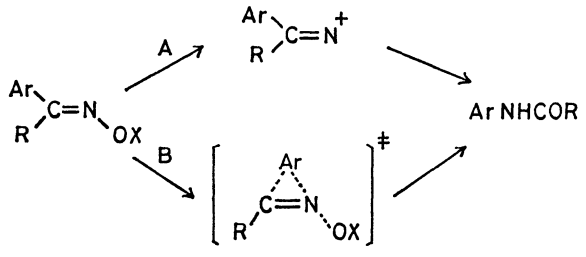
$$k^{12}/k^{14} = 1.014 \pm 0.003 \quad (60\,°C).$$

In order to make the results more reliable, another series of experiment at 60 °C was carried out using another lot of materials. The results are given in Table 3. The calculated isotope effect is given by

$$k^{12}/k^{14} = 1.023 \pm 0.006 \quad (60\,°C).$$

Calculation using the data reported by Glover and Raaen[7] by means of Eq. 1 gave the phenyl-1-^{14}C isotope effect of 1.028±0.006 at 62±1 °C, although the data are scanty. From the results of the present reinvestigation and of Glover and Raaen, all the data reported earlier[6] should have been accompanied by large errors inherent to old techniques and should be retracted.

Carbon-14 kinetic isotope effects of 1.4—2.6% are too large to be classified as secondary effects,[17] and should reflect some change in the bonding of the phenyl-1 carbon in the rate-determining transition state of the rearrangement. As has been verified from the tracer study using ^{18}O that the loss of the oxygen function from an oxime occurs in an irreversible step,[5] the present results of kinetic isotope effects are inconsistent with the stepwise mechanism (path A), giving an evidence for the concerted nature (path B) of the rearrangement (Scheme 4).



Scheme 4.

The large positive values of the resonance parameter, r, in the LArSR (linear aromatic substituent-reactivity) relationship (Eq. 2) of the Beckmann rearrangement (r=0.60—0.63) also indicate the additional conjugation effect to the reaction center in the transition state.[4,18-20]

$$\log k/k_0 = \rho(\sigma^\circ + r\Delta\bar{\sigma}_R^+) \qquad (2)$$

Thus, the mechanism (Scheme 1) has been further ensured.

The fact that the carbon-14 kinetic isotope effect at the phenyl-1 position is normal (positive) should be discussed. Decrease in force constant in the transition state leads in the direction of a normal isotope effect, an increased one in the direction of an inverse effect.[21,22] Bond formation between the phenyl-1 carbon and the nitrogen may cause an increase in bonding of the carbon. Nevertheless, actual observation of the normal effects at the phenyl-1 carbon can be attributed to a great extent to a decrease in bonding as a result of insulation of the carbon from the aromatic conjugation present at the initial state. Inverse carbon isotope effects caused by the appearance of additional bonding of conjugation have been reported in some cases.[23] Weakening of the bond between the phenyl-1 and carbonyl carbons might make some contribution to the phenomenon. Similar phenomena were observed in some other 1,2-nucleophilic rearrangements as well as in solvolysis with neighboring phenyl participation.[20,24,25] The normal temperature dependence, a larger isotope effect at a lower temperature, though not obvious because of an experimental error, is also considered to be an indication of a decrease in bonding at the transition state. In the case of bond rupture the temperature-dependent factor of the kinetic isotope effect is considered to increase from the higher temperature limit of unity with lowering in temperature.[25,26]

No reexamination was carried out on the kinetic isotope effect at the carbonyl carbon of acetophenone oxime.[6] However, treatment of the data of Glover and Raaen with use of Eq. 1 gave a normal isotope effect at this carbon, k^{12}/k^{14}=1.028±0.004, at 62 °C.[7] This indicates that bonding of this carbon also changes at the transition state of the rearrangement.[25] On the other hand, calculation of the isotope effects using the data of Glover and Raaen on the reaction of *anti*-1-phenyl-2-propanone oxime (**8**) shows that no effects are observed at both the methylene (k^{12}/k^{14}=1.002±0.002) and carbonyl (k^{12}/k^{14}=1.004±0.004) carbons. This is quite natural since the reaction that followed was actually the sulfonation of the benzene ring, and no bonding change at these two carbons is expected for the reaction.

Experimental

Materials. Acetophenone oxime hydrogensulfate (**2**) was prepared according to the procedure of Pearson and Ball[9] and dried over phosphorus pentaoxide in a vacuum at a low temperature. 4-Acetylaminobenzenesulfonic acid (**5**) was dried for many days in a vacuum at 100 °C before the NMR measurement.[27] *Anti*-1-phenyl-2-propanone oxime (**8**) was prepared according to the procedure of Kotera *et al.*:[28] mp 69.5—70.5 °C. All the compounds except **2** were subjected to elemental analysis, giving satisfactory results. Commercial sulfuric acid (99.0%, Wako guaranteed reagent) was used without further purification.

NMR Monitoring of the Reactions. NMR spectra were recorded on a Varian A-60 spectrometer at 60 MHz with tetramethylsilane as an external standard. All the samples were measured in concentrations of 3—5 (w/v)%. Operating temperature was calibrated using ethylene glycol signals. The NMR data are summarized in Table 4.

Table 4. Proton NMR spectroscopic data in concd sulfuric acid

Species	Chemical shifts and assignment[a)]
Acetophenone oxime (**1**)	2.88 (3H, s, CH_3), 7.73 (5H, s, aromatic)
Acetophenone oxime hydrogensulfate (**2**)	3.17 (3H, s, CH_3), 7.7 (5H, s, aromatic)
Acetanilide (**4**)	2.38 and 2.70 (3H, CH_3), 7.50 (5H, s, aromatic)
4-Acetylaminobenzenesulfonic acid (**5**)	2.57 and 2.80 (3H, CH_3), 7.85 and 8.12 (4H, J=7 Hz, aromatic AA'BB')
4-Aminobenzenesulfonic acid (**6**)	7.80 and 8.20 (4H, J=9 Hz, aromatic AA'BB')
Acetic acid	2.75 (CH_3)
Acetophenone (**7**)	3.28 (3H, s, CH_3), 7.65—8.53 (5H, m, aromatic)
1-Phenyl-2-propanone oxime (**8**)	2.50 (3H, s, CH_3), 4.02 (2H, s, CH_2), 7.25—7.45 (5H, m, aromatic)
4-(2-Hydroxyiminopropyl)benzenesulfonic acid (**9**)	2.50 (3H, s, CH_3), 4.15 (2H, s, CH_2), 7.58 and 8.04 (4H, J=8 Hz, aromatic AA'BB')
4-(*N*-Acetylaminomethyl)benzenesulfonic acid (**10**)	2.57 (3H, s, CH_3), 4.80 (2H, d, J=5.5 Hz, CH_2), 7.61 and 8.01 (4H, J=8 Hz, aromatic AA'BB'), 8.90 (1H, broad t, J=5.5 Hz, NH)

a) ppm from external tetramethylsilane.

*Preparation of Acetophenone-*phenyl-*1-*^{14}C *Oxime (1-*^{14}C*).* Benzoic-*phenyl*-1-^{14}*C* acid (4.45 g, 13.6 mCi/mol) was prepared from 7 mCi of barium carbonate-^{14}*C* by the multistep syntheses,[13] radiochemical yield being 7.1%. After dilution with nine times an unlabeled benzoic acid, 15 g of the acid (1.36 mCi/mol) was dissolved in 60 ml of dry ether. After addition of 23 g of thionyl chloride, the mixture was refluxed for 1 h. Benzoyl-*phenyl*-1-^{14}*C* chloride (16.5 g) was isolated by distillation: bp 97—98 °C/30 Torr.

Magnesium ethoxide was prepared from 2.7 g of a magnesium ribbon, 2.5 ml of anhydrous ethanol, and a few drops of carbon tetrachloride in 40 ml of dry ether. Diethyl malonate (17.1 g) in 10 ml each of anhydrous ethanol and ether was added to the above mixture and refluxed until all the magnesium was consumed. The benzoyl-*phenyl*-1-^{14}*C* chloride obtained above was added to this mixture with a small amount of ether and refluxed for 30 min. The reaction mixture was cooled and acidified with 20% sulfuric acid. The ether layer and the ether extract were combined and washed with water, and the solvent was distilled. To the residue was added a mixture of 30 ml of acetic acid, 3.8 ml of concd sulfuric acid, and 30 ml of water, and the mixture was refluxed for several hours until decarboxylation was complete. The reaction mixture was cooled in an ice-bath, made alkaline with 20% sodium hydroxide solution, and extracted with several portions of ether. The ether layer was washed with water and dried with anhydrous sodium sulfate, the solvent being removed. Acetophenone-*phenyl*-1-^{14}*C* (**7**-^{14}*C*: 11.0 g) was obtained by distillation: bp 100.0—101.5 °C/27—28 Torr.

7-^{14}*C* (11.0 g) was treated with 29.7 g of hydroxylamine hydrochloride and 55 g of potassium carbonate in a mixture of 100 ml of water and 500 ml of ethanol in the usual way. Acetophenone-*phenyl*-1-^{14}*C* oxime (**1**-^{14}*C*) obtained (10.8 g) was recrystallized from petroleum ether seven times, when the sample showed a constant radioactivity (1.300±0.003 mCi/mol): mp 60 °C.

Quantitative Isolation of Acetophenone Oxime (1) as the 2,4-Dinitrophenylhydrazone Derivative (11). Forty to 120 mg of **1** was taken in a 150-ml Erlenmeyer flask equipped with a ground glass stopper. Sixty ml of 0.4% 2,4-dinitrophenylhydrazine solution in 2 M hydrochloric acid was added and the resulting solution was kept at 50 °C for 24 h. After addition of 10 ml of distilled water, precipitates of **11** were filtered while warm with a glass filtering crucible, washed thoroughly with warm 2 M hydrochloric acid and then with warm distilled water. The crucible was dried in an oven at 85 °C for 24 h, cooled in a desiccator, and weighed. For repeated measurements, yields of **11** were 100.5±0.5% of the theoretical values.

Gravimetric Rate Measurement. Concd sulfuric acid (*ca.* 30 ml) was added to a weighed sample of **1** (*ca.* 1 g) and weighed. After being thoroughly shaken, the mixture was transferred to a reaction flask which had been heated in a thermostated bath. Aliquots of the solution were pipetted out at appropriate time intervals and poured rapidly into 0.4% solutions of 2,4-dinitrophenylhydrazine in 2 M hydrochloric acid. The quantities of the solutions pipetted out were determined by weighing the flasks before and after the addition. Precipitates of **11** were treated as mentioned above. The fractions of reaction were thus calculated from the observed and theoretical weights of **11**.

Radioactivity Measurement. Samples of the purified **11**-^{14}*C* (7—10 mg) were oxidized to carbon dioxide by the modified Van Slyke-Folch wet combustion method with a Nuclear-Chicago Model GW-1 glassware system. The radioactivities of the carbon dioxide gases collected in an ionization chamber were measured with a Nuclear-Chicago Model 6000 Dynacon electrometer system by the rate-of-charge method using a Model T4 interval timer. The samples were assayed after recrystallization three or four times from ethyl acetate–chloroform (2: 1). For the samples obtained at several stages of the reaction, it was confirmed that further recrystallization does not change the radioactivities beyond experimental errors (±0.5%).

References

1) P. A. S. Smith in "Molecular Rearrangements," ed by P. de Mayo, Interscience, London (1963), Part I, p. 483.
2) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 1 (1960).
3) A. W. Chapman and F. A. Findler, *J. Chem. Soc.* **1936**, 448.
4) R. Huisgen, J. Witte, H. Walz, and W. Jira, *Justus Liebigs Ann. Chem.*, **604**, 191 (1957).
5) B. J. Gregory, R. B. Moodie, and K. Schofield, *J. Chem. Soc., B*, **1970**, 338.
6) Y. Yukawa and M. Kawakami, *Chem. Ind. (London)*, **1961**, 1401.
7) I. T. Glover and V. F. Raaen, *J. Org. Chem.*, **31**, 1987

(1966).

8) Part of this work appeared in communication form: Y. Yukawa and T. Ando, *J. Chem. Soc., D.*, **1971**, 1601.

9) D. E. Pearson and F. Ball, *J. Org. Chem.*, **14**, 118 (1949).

10) B. J. Gregory and R. B. Moodie, *J. Chem. Soc., B*, **1970**, 862.

11) a) V. F. Raaen, G. A. Ropp, and H. P. Raaen, "Carbon-14," McGraw-Hill, New York (1968), p. 208; b) *ibid.*, pp. 235—240.

12) H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

13) a) A. Murray, III and D. L. Williams, "Organic Syntheses with Isotopes," Interscience, New York (1958), p. 34; b) *ibid.*, p. 102; c) M. Fields, M. A. Leaffer, S. Rothchild, and J. Rohan, *J. Am. Chem. Soc.*, **74**, 5498 (1952); d) G. A. Ropp, *ibid.*, **72**, 2299 (1950).

14) D. D. Van Slyke, J. Plazin, and J. R. Weisiger, *J. Biol. Chem.*, **191**, 299 (1951).

15) Measurements of the radioactivities were performed in 1965 and 1966. At present we can measure the activities as accurately as with standard deviations of 0.1—0.3% by use of the dry combustion method and with a new electrometer system. Thus, the accuracy of the kinetic isotope effect has been improved.[16] The level of inaccuracy in the present investigation does not affect the conclusion of this paper.

16) For example, see a) T. Ando, H. Yamataka, J. Kuramochi, J. Yamawaki, and Y. Yukawa, *Tetrahedron Lett.*, **1976**, 1879; b) H. Yamataka and T. Ando, *ibid.*, **1975**, 1059.

17) V. F. Raaen, A. K. Tsiomis, and C. J. Collins, *J. Am. Chem. Soc.*, **82**, 5502 (1960); M. Saunders, L. Telkowski, and M. R. Kates, *ibid.*, **99**, 8070 (1977).

18) Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc. Jpn.*, **39**, 2274 (1966).

19) P. J. McNulty and D. E. Pearson, *J. Am. Chem. Soc.*, **81**, 612 (1959).

20) T. Imamoto, S.-G. Kim, Y. Tsuno, and Y. Yukawa, *Bull. Chem. Soc. Jpn.*, **44**, 2776 (1971).

21) G. A. Ropp, V. F. Raaen, and A. J. Weinberger, *J. Am. Chem. Soc.*, **75**, 3694 (1953).

22) C. L. Wilkins and T. W. Regulski, *J. Am. Chem. Soc.*, **94**, 6016 (1972); S. -H. Dai and W. R. Dolbier, Jr., *ibid.*, **94**, 3946 (1972).

23) a) Y. Yukawa, T. Ando, and T. Otsubo, *Bull. Chem. Soc. Jpn.*, **45**, 2645 (1972); b) A. J. Kresge, N. N. Lichtin, K. N. Rao, and R. E. Weston, Jr., *J. Am. Chem. Soc.*, **87**, 437 (1965).

24) a) Y. Yukawa and T. Ando, *Mem. Inst. Sci. Ind. Res., Osaka Univ.*, **34**, 39 (1977); b) Y. Yukawa, T. Ando, K. Token, M. Kawada, and S.-G. Kim, *Tetrahedron Lett.*, **1969**, 2367; **1971**, 847; c) Y. Yukawa, S.-G. Kim, and H. Yamataka, *ibid.*, **1973**, 373; d) B. W. Palmer and A. Fry, *J. Am. Chem. Soc.*, **92**, 2580 (1970).

25) A. Fry in "Isotope Effects in Chemical Reactions," ed by C. J. Collins and N. S. Bowman, Van Nostrand Reinhold, New York (1970), Chap. 6.

26) J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).

27) E. Sakellarios, *Ber.*, **58**, 2286 (1925).

28) K. Kotera, T. Okada, and S. Miyazaki, *Tetrahedron*, **24**, 5677 (1968).