The Beckmann Rearrangement of Alkyl Methyl Ketoximes

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The mechanism of the Beckmann rearrangement has been discussed by several authors with attention to the intermediate, the stereospecificity, and the kinetics. Kuhara and his co-workers established the kinetics of the rearrangement of benzophenone oxime acetate[1]. Pearson et al. studied the effect of substituents on the rate of substituted acetophenone oximes[2] and symmetrical dialkyl ketoximes in sulfuric acid.[3] Ogata and Okano measured the rate of cyclohexanone oxime in oleum.[4] For the reaction in sulfuric acid, it has been known that the rate-determining step involves the breaking of the nitrogen-oxygen bond. The actual migration may rapidly proceed after the fission (the iminonium ion mechanism) or simultaneously with the fission (the concerted mechanism). At first sight, the stereospecificity of the reaction would support the concerted mechanism, since the group trans to the nitrogen-oxygen bond migrates preferentially. However, one can assume the formation of an ion pair between the iminonium ion and the hydroxyl ion, followed by rapid migration; therefore, the iminonium ion mechanism does not conflict with the stereospecificity of the reaction. Pearson reported that the polar effect of the aryl group in aryl methyl ketoximes influenced the rate of the reaction. A good linearity was found between the rates and Hammett's sigma values corrected for the additional electrophilic resonance effect using Yukawa-Tsuno's equation.[5] The effect can be explained satisfactorily either by the concerted mechanism or the iminonium ion mechanism. The direct participation of the aryl group in the former or the polar assistance through the C=N bond to the breaking of the N–O bond in the latter fits the equation as well.

The rates of the rearrangement of the several

1) M. Kuhara, M. Matsumiya and N. Matsunami, *Memoirs Coll. Sci. Kyoto*, **1**, 105 (1916).
2) D. E. Pearson, J. E. Boxter and J. C. Martin, *J. Org. Chem.*, **17**, 1511 (1952): D. B. Pearson and J. D. Burton, ibid., **19**, 957 (1954).
3) P. T. Scott, D. E. Pearson and L. J. Bircher, ibid., **19**, 1815 (1954).
4) Y. Ogata and M. Okano, *J. Am. Chem. Soc.*, **77**, 4643 (1955).
5) Y. Tsuno, T. Ibata and Y. Yukawa, This Bulletin, **32**, 960 (1959).

alkyl methyl ketoximes were measured and the influence of the steric bulkiness of the migrating group were studied in this paper.

Experimental

Ketoximes.—The ketoximes used were prepared by the usual procedure from the corresponding ketones and were purified by recrystallization from petroleum ether or by distillation under reduced pressure.

n-Amyl methyl ketoxime	b. p. 107～107.5°C/21 mmHg
Cyclopentyl methyl ketoxime	b. p. 114～116°C/20 mmHg
2-Methylcyclopentyl methyl ketoxime	b. p. 120.5～121°C/20 mmHg
Cyclohexyl methyl ketoxime	m. p. 60°C
Cycloheptyl methyl ketoxime	m. p. 53～54°C b. p. 145°C/23 mmHg

Rearrangement Products.—After one milliliter of sulfuric acid had been added to 0.5 g. of ketoxime contained in a 30 ml. Erlenmeyer flask, the flask was held in the thermostat at 80°C for 10～15 hr. Ten milliliters of water was then added to the flask and the reaction mixture refluxed for 5～7 hr. to hydrolyze the acetamides produced. The solution was made strongly basic by adding a concentrated aqueous solution of potassium hydroxide, and the amine was extracted with 10 ml. of ether three times. After the removal of the solvent, it was derived to *N*-alkyl-*N'*-phenylurea by the reaction with phenyl isocyanate or to *N*-alkylbenzamide by Schotten-Baumann reaction. The melting points of these derivatives were not depressed by admixture with respective authentic samples prepared by the usual procedure.

N-*n*-Amyl-*N'*-phenylurea (from *n*-amyl methyl ketoxime), m. p. 237～238°C

N-Cyclopentyl-*N'*-phenylurea (from cyclopentyl ketoxime), m. p. 205°C

N-(2-Methylcyclopentyl)-benzamide (from 2-methylcyclopentyl methyl ketoxime), m. p. 116°C

N-Cyclohexyl-*N'*-phenylurea (from cyclohexylmethyl ketoxime), m. p. 182～182.5°C

N-Cycloheptyl-*N'*-phenylurea (from cycloheptyl methyl ketoxime), m. p. 182.5～183°C

Spectra of the 2,4-Dinitrophenylhydrazones in the Visible and Ultraviolet Region.—The absorption spectra of the 2,4-dinitrophenylhydrazones of alkyl methyl ketones in carbon tetrachloride were measured with a Hitachi photo-spectrometer. The spectra were essentially identical. The absorption curve in the case of *n*-amyl methyl ketone is shown in Fig. 1. The absorbance at 410 mμ was chosen for quantitative analysis. The correlation of the optical density with the concentration of the 2,3-dinitrophenylhydrazone of *n*-amyl methyl ketone is shown in Fig. 2.

Analysis of Ketoximes.—Pearson's method for the analysis of acetophenone oxime was modified as follows. A stock solution of ketoxime in 10% sulfuric acid was prepared. An aliquot of the solution was added from a burrett to each 100 ml. glass-stoppered flask with the flasks being weighed accurately before and after the addition. Twenty-five milliliters of 4% sulfuric acid and 0.300 g. of 2,4-dinitrophenylhydrazine were added to each flask. The flask was then sealed with a glass stopper and placed in a bath at 50°C for about 18 hr. After the flask had cooled, 25 ml. of carbon tetrachloride was added. The flask was then thoroughly shaken and allowed to stand for 18 hr. at room temperature. The carbon tetrachloride layer was transferred to a 100 ml. measuring flask using a separatory funnel fitted with a cotton filter. Another 5 ml. of carbon tetrachloride were added to wash the funnel and cotton filter and were combined with the filtrate. The combined solution was then diluted to 100 ml. with carbon tetrachloride. The optical density of this solution was determined at 410 mμ using a photo-spectrometer. A typical run is shown in Fig. 3.

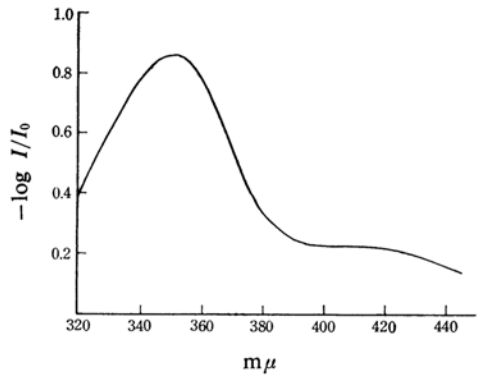

Fig. 1. The absorption curve of 2,4-dinitrophenylhydrazone of *n*-amyl methyl ketone.

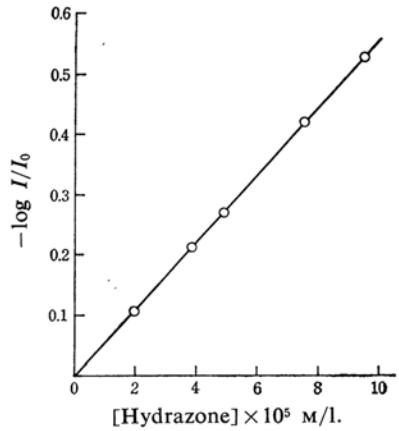

Fig. 2. Correlation of the optical density at 410 mμ to the concentration of 2,4-dinitrophenylhydrazone of *n*-amyl methyl ketone.

Rate Determination.—About 500 mg. of ketoxime was weighed accurately and then dissolved in 20 ml. of sulfuric acid which had been weighed exactly in a glass-stoppered flask. The flask was sealed and immersed in a thermostatted bath (49.70～49.95°C±0.01°C). At approximately equal time intervals, from zero time to a half-life, each 2 ml. portion of the solution was pipetted out and the

TABLA I.

Ketoxime	$k\times10^3$, min^{-1}	Taft's σ	Temp., °C
Acetone*	0.025	0.00	50.0
Diethyl ketone*	1.33	—	50.0
Diisopropyl ketone*	84.8	—	50.0
n-Amyl methyl ketone	1.07±0.06	−0.162	49.95±0.01
Cyclopentyl methyl ketone	2.32±0.04	−0.20	49.82±0.01
2-Methylcyclopentyl methyl ketone	3.55±0.13	—	49.70±0.01
Cyclohexyl methyl ketone	26.4 ±0.5	−0.15	49.70±0.01
Cycloheptyl methyl ketone	26.0 ±0.4	—	49.75±0.01
Acetophenone*	1.107	—	50.0

Taft's σ: R. W. Taft, Jr., *J. Am. Chem. Soc.*, **75**, 4231 (1953).
* Calculated from D. E. Pearson's data (Refs. 2 and 3).

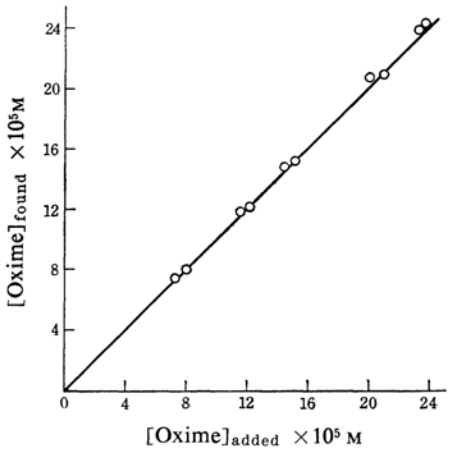

Fig. 3. Analysis of *n*-amyl methyl ketoxime.

quantity of unchanged keoxime was determined.

The rate is first order to ketoxime, the rate constant was calculated by the following equation.

$k=\ln(a/(a-x))\ (1/t)$

k: rate constant
t: time in minutes
a: concentration of initial ketoxime
x: concentration of reacted ketoxime at time t

The results are shown in Table I.

Results and Discussion

The first order rate-constants are given in Table I. The sequence of the rates was found to be: cycloheptyl≈cyclohexyl>2-methylcyclopentyl>cyclopentyl>*n*-amyl. As the steric bulkiness of the alkyl group in oximes is far greater than that of methyl, oximes have a methyl-syn configuration. It has been known that the group trans to the hydroxyl group in oxime migrates preferentially in sulfuric acid.*

Actually, the migration of the bulkier group was ascertained from the derivatives of the main products in the reaction, and the measured rates are those for the migration of alkyl groups.

The effect of the alkyl group upon the rates of reaction cannot be explained on the basis of the polar effect only, and there is no corre lation between the relative rates and Taft's sigma star values. The results can be elucidated only by the steric effect of the migrating group. The bulkiness of the *n*-amyl group would be smaller than that of cyclopentyl. Those of cycloheptyl and cyclohexyl would be the greatest, as these two groups have a non-planar ring.

If we consider the steric compression between the migrating alkyl group and the non-migrating methyl group, the sequence can be understood. When steric compression decreases in the transition state, the greater the steric compression in the initial state, the faster the reaction rate. The compression decreases during the reaction by means of: 1) the expansion of the angle between the migrating group and the non-migrating group, and 2) the increase of the length of the bond between the migrating group and the carbonyl carbon.

Our results can be explained by considering that the decrease of the steric compression might happen at the rate-determining step. On the basis of Pearson's data,[3] the ratios of k(diethyl ketone)/k(acetone) and k(diisopropyl ketone)/k(acetone) are 53 and 3400 respectively. The striking value in diisopropyl ketone may be also explained because the steric compression between two isopropyl groups is very much greater than that between two methyl groups or two ethyl groups. Pearson reported that the rate of *o*-methylacetophenone was much faster than that of acetophenone and explained the phenomenon as follows: The resonance interaction between phenyl group and the *d*-oximinoethyl group is diminished by the steric effect of the ortho substituent;

* This does not always hold in other media. (cf. S. Kim and Y. Yukawa, Unpublished.)

therefore, the ring system is geometrically more susceptible to participating with the nitrogen atom. Yukawa and Tsukamoto suggested the presence of the resonance inhibition due to the steric compression between the *o*-tolyl group and the methyl group of the oxime in its ultra-violet absorption spectra and also noticed the effect of the resonance inhibition in the aryl-carbonyl bond on the relative stability of *o*-substituted benzophenone oxime isomers.[6]

These suggestions agree with the above explanation of our results. The decrease in the steric compression seems to contribute to the rate. This implies that the migrating group participates in the cleavage of the N–O bond in the rate-determining step in sulfuric acid. The iminonium ion mechanism can not offer any explanation, but the concerted mechanism is supported. The carbon-14 kinetic isotope effect in a Beckmann rearrangement undertaken to confirm the mechanism will be reported in a succeeding paper.

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6) Y. Yukawa and A. Tsukamoto, Abstracts of 8th Annual Meeting, Chemical Society of Japan, 1955, p. 67.