The Acid-Catalyzed Isomerization of Cyclohexyl Phenyl Ketoxime in Liquid Sulfur Dioxide[1]

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It has been previously demonstrated that the Beckmann rearrangement of a geometrical isomer of a ketoxime in liquid sulfur dioxide at -70°C results in the trans-migrated products exclusively[2]. Although the slow syn-anti isomerization of the ketoxime in liquid sulfur dioxide has also been observed in the same medium, the rate of the Beckmann rearrangement has been too fast to be competitive against the rate of the isomerization[2]. According to Tokura and Shiina[3], the sulfur dioxide-catalyzed isomerization is accelerated by light and retarded by hydroquinone, and the rate is of the first order with respect to the concentration of the oxime.

Since the isomerization of the oxime may also be undertaken by an acid and since such an acid may often be present in the medium by the decomposition of the Lewis acid (the reagent of the Beckmann rearrngement) with a trace of water in liquid sulfur dioxide, the acid-catalyzed isomerization of β-cyclohexyl phenyl ketoxime has been carried out in order to obtain further information about the competition of the isomerization versus the Beckmann rearrangement. Such hydrohalogenic acids as hydrochloric acid, hydrobromic acid and hydroiodic acid have been used as the catalyst.

The acid-catalyzed isomerization experiment has been preceded by an NMR spectrometry to confirm the intrinsic structures of the respective geometrical isomers, the α- and the β-ketoxime, since the previous establishment of the structures of the ketoximes has only been proved by the results of the Beckmann rearrangement[2]. The experience of Lustig[4] has also prompted the present writers to this procedure.

Experimental

Materials. — β-Cyclohexyl phenyl ketoxime was prepared and separated as described in a preceding paper[2]. Commercial sulfur dioxide was dehydrated with phosphorus pentoxide and distilled. The hydrogen halogenide (Cl, Br or I) solution of liquid sulfur dioxide was prepared by passing a dry hydrogen halide gas into liquid sulfur dioxide cooled to -70°C. From the increase in the weight and by volumetric analysis, the strength of the acid was determined. An acid solution of liquid sulfur dioxide of a definite concentration was prepared by adding liquid sulfur dioxide to this parent mixture. The DCl solution of liquid sulfur dioxide was prepared by the following reaction in liquid sulfur dioxide:

$$SOCl_2 + D_2O \rightarrow 2DCl + SO_2$$

Method of Analysis. — The analysis of the α-oxime produced and of the unchanged β-oxime was made by infrared spectroscopy using a Perkin-Elmar model 21 doule-beam spectrophotometer[3]. The specimen in carbon disulfide was analyzed at the absorption maxima, with 762 and 957 cm^{-1} as key bands. The contents of the oximes were calculated by the following equations:

$$E_{\mathrm{m}}^{762} = C_\alpha E_\alpha^{762} + C_\beta E_\beta^{762} \tag{1}$$

$$E_{\mathrm{m}}^{957} = C_\alpha E_\alpha^{957} + C_\beta E_\beta^{957} \tag{2}$$

where E_α^{762}, E_β^{762}, E_α^{957} and E_β^{957} are the molar absorption coefficients of α- and β-oxime at 762 and 957 cm^{-1} respectively, E_{m}^{762} and E_{m}^{957} are those of the sample for analysis, and C_α and C_β are the content of the α- and β-oximes in the sample.

TABLE I. A TYPICAL KINETIC RUN

Oxime, 0.05 M/l.; HCl, 0.15 M/l., at 0°C

t, min.	E_{m}^{762}	E_{m}^{957}	Conversion α-oxime, %	$a/(a-x)$	$\ln a/(a-x)$	$k\times10^5$ sec^{-1}
45	49.8	76.9	3.56	1.0367	0.0363	1.343
90	50.1	75.6	7.12	1.0767	0.0739	1.369
135	50.6	74.0	11.63	1.1316	0.1237	1.526
180	50.5	73.6	12.37	1.1412	0.1321	1.223
						Mean 1.36

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[1] The Beckmann Rearrangement in Liquid Sulfur Dioxide. Part XI.

[2] R. Tada, Y. Masubuchi and N. Tokura, This Bulletin 34, 209 (1961).

[3] N. Tokura and K. Shiina, ibid.. 35, 1779 (1962).

[4] E. Lustig, *J. Phys. Chem*, 65, 491 (1961).

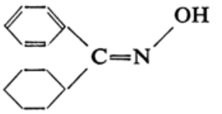
Beer's law was obeyed throughout this experiment, and the range of experimental error was within three percent.

Kinetic Procedure. — The β-oxime was dissolved into a sulfur dioxide solution of an acid at −70°C to make a 50 ml. solution of the reaction mixture. The mixture was then placed in a thermostat. A 10 ml. aliquot was taken off after a definite time interval, and the mixture was mixed with ice water, neutralyzed with ammonia water, and filtered. The precipitate was well rinsed with water, dried in vacuo, and analyzed for the oxime content. A typical run is listed in Table I. No symptom of the Beckmann rearrangement was observed during the course of the isomerization experiment.

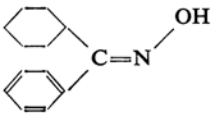
NMR Spectrometer.—A Varian Associates' type V-4300B (60 Mc.) was used.

Results and Discussion

NMR Spectrometry of the Geometrical Isomers.—The geometrical structures of the cyclohexyl phenyl ketoximes were assigned as below in a previous paper[2], the hydroxyl group in the α-oxime being syn-positioned to the phenyl groups. If the Beckmann rearrangement in liquid sulfur dioxide should take place in the migration of the group trans to the hydroxyl group, such a conclusion must be accepted. Moreover, no contamination by another acidamide which might be derivable by a competitive isomerization of the ketoxime was observed.



α-Oxime



β-Oxime

However, Lustig[4] has recently disclosed that the assignments of the isomeric ketoximes by the Beckmann rearrangement are not always safe since the oximes considered as single materials were often found by the NMR spectrometry to be contaminated by another isomers. Since no contamination of acidamides other than the authentic trans-migrated product was seen after the rearrangement in liquid sulfur dioxide, and since the oximes afforded only the corresponding acidamides, which were proved to be the proper (trans-migrated) ones[2], further examination into the purity of the respective oximes may not be needed.

An NMR study of the α- and β-oximes was undertaken in order to confirm the previous assignments for the geometrical structures of the respective oximes; the results are listed in Table II.

As is seen in Table II, the Tau values assigned for the cyclohexyl and phenyl groups coincide well with the literature values[5] of cyclohexane and benzene, 8.564 and 2.734 respectively.

TABLE II. NMR CHEMICAL SHIFT OF α- AND β-KETOXIMES

in CCl_4 in Tau value (T.M.S. as reference)

Assigned	Oxime	
	α	β
Cyclohexyl	8.76 8.27	8.76 8.27
Phenyl	2.91	2.90
=N-O-H	1.04	1.37
in Dioxane in c. p. s.		
Cyclohexyl	−2.28 −2.21 −1.81	−2.26 −2.21 −1.91
Phenyl	+3.72	+3.70
=N-O-H	+5.48	+5.95

The NMR spectrum of the hydroxyl proton of the α-oxime always shifts to a lower field than that of the β-oxime. This may be interpreted as being caused by the interaction of the hydroxyl proton with the benzene ring. In addition, no anisotropic effect may be anticipated from the Fischer-Hilschfelder model of the oxime. Moreover, our calculation, by the method of Johnson and Bovey[6], of the difference in the shifts between the two ketoximes on the hydroxyl proton, the results of which will be published elswhere in the near future, supports the above explanation.

Effect of Temperature.—The reaction rate of the acid-catalyzed isomerization was a faster reaction than the isomerization by sulfur dioxide itself. The concentrations of the β-oxime and of hydrochloric acid were 0.05 M/l.

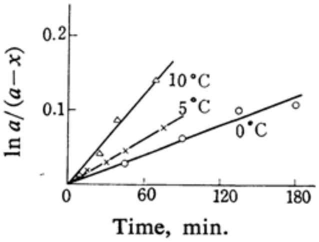


Fig. 1

TABLE III. RATE CONSTANT k, FOR $R=k[\text{oxime}]$

Temp., °C	$k \times 10^5$ sec^{-1}
0	1.36
5	1.87
10	3.44

The Arrhenius parameters

Activation energy, $E_a=13.1$ kcal./mol.

Frequency factor, $A=3.5\times10^5$ sec^{-1}

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[5] G. van Dyke Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

[6] C. E. Johnston, Jr. and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

and 0.15 M/l. respectively. The order of the reaction is of the first order with respect to the concentration of the oxime, as may be seen in the $\ln a/(a-x)$ vs. time plots at 0, 5 and 10°C in Fig. 1. The rate constant k and the Arrhenius parameters calculated are listed in Table III.

Effect of Light. — The isomerization of the ketoxime in liquid sulfur dioxide has been reported to be effected by diffused daylight in the room[2]. In the acid-catalyzed isomerization, the reaction in diffused daylight was compared with the reaction in the dark. (Table IV)

TABLE IV. EFFECT OE DIFFUSED DAYLIGHT ON ACID-CATALYZED ISOMERIZATION

[oxime] = 0.05 M/l. ; [HCl] = 0.15 M/l. Temp. 10°C

$$k(\text{dark}) = 3.20\times10^{-5}\ \text{sec}^{-1}$$
$$k = 3.44\times10^{-5}\ \text{sec}^{-1}$$

where, k (dark) and k are the constants in the dark and in diffused room daylight respectively.

The reaction was slightly accelerated by daylight, but the effect was not significant.

Effect of Salts and Deuteriochloric Acid. — Tetraethylammonium halides, $(C_2H_5)_4NX$, X= Cl, Br or I, were used as the salts. The salt, 0.005 M/l., was added to the reaction mixture. Table V lists the results. The results of Table V agree with the general trend of ionic catalysis. The depression of the rate by the addition of the chloride may be explained by a mass law effect, while the increase of the rate by the bromide and iodide may be due to the ionic strength effect[7].

TABLE V. THE EFFECT OF SALT ON THE HCl-CATALYZED ISOMERIZATION

[oxime] = 0.05 M/l., [HCl] = 0.15 M/l. Temp. 0°C

Salt, $(C_2H_5)_4NX$ salt	$k\times10^5$ sec^{-1}
None	1.36
X=Cl	1.07
Br	1.95
I	2.04

The isomerization experiment using DCl as the catalyst resulted in the isotope effect;

$$k_{HCl}/k_{DCl} = 1.21 \text{ (at 30°C)}$$

Both the salt and isotope effect suggest the importance of the dissociation equilibrium of the acid catalyst in liquid sulfur dioxide.

Acid-Catalyzed Reaction with Hydrogen Bromide or Hydrogen Iodide. — Neither hydrogen bromide nor hydrogen iodide has had any reproducible effect on the isomerization. In both cases the color of the reaction mixture gradually changed to a yellowish red, suggesting the slow decomposition of the reagent in liquid sulfur dioxide. The gradual decomposition of hydrogen iodide to iodine in liquid sulfur dioxide has already been noticed by Steele and Bagster[8]. Moreover, the result may have been complicated also by an accompanying Beckmann rearrangement if the bromine or iodine produced was present[9].

The Effect of the Concentration of Hydrogen Chloride.—No symptom of the Beckmann rearrangement was observed by hydrogen chloride in liquid sulfur dioxide. The reason for this has been discussed in a preceding paper[10]. The isomerization reaction was carried out at various concentrations of [HCl], 0.05, 0.15 and 0.27 M/l., with [oxime], 0.05 M/l. at 0°C.

From the log-log plot of the initial rate, ***R***, and the concentration of hydrogen chloride, [HCl], the order of the [HCl] is obtained as 1.43 (approximately 1.5) (Fig. 2). Because the linear plot of $\log R$ vs. $\log[\text{HCl}]$ does not pass through the origin and because the simultaneous catalysis by sulfur dioxide itself must be considered, the overall rate expression may be as follows:

$$R = A + k_{HCl}[\text{oxime}]\cdot[\text{HCl}]^{1.5} \qquad (3)$$

where k_{HCl} is the rate constant catalyzed by hydrogen chloride and A is the rate when [HCl] = 0, i. e., the rate of the isomerization by liquid sulfur dioxide itself, as has been reported in a previous paper[2]. Judging from previous results[2].

$$A = k_{SO_2}[\text{oxime}] \qquad (4)$$

Therefore,

$$R = k_{SO_2}[\text{oxime}] + k_{HCl}[\text{oxime}]\cdot[\text{HCl}]^{1.5} \qquad (5)$$

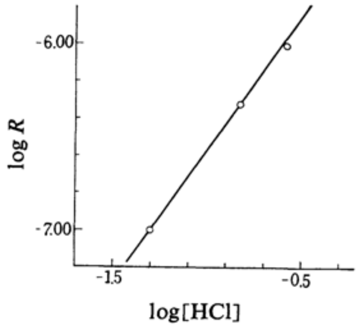

Fig. 2. Plot of $\log R$ vs. $\log[\text{HCl}]$.

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[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, New York (1953), p. 362.

[8] B. D. Steele and L. S. Bagster, *J. Chem. Soc.*, **97**, 2607 (1910).

[9] N. Tokura, R. Asami and R. Tada, *J. Am. Chem. Soc.*, **79**, 3135 (1957).

[10] N. Tokura, R. Tada and K. Yokoyama, This Bulletin, **34**, 1812 (1961).

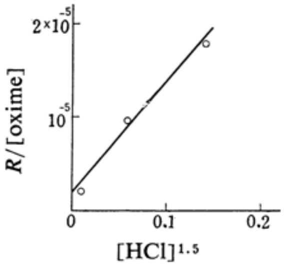


Fig. 3

Eq. 5 is transformed to 6 by dividing it with [oxime]:

$$R/[\text{oxime}]=k_{SO_2}+k_{HCl}[\text{HCl}]^{1.5} \qquad (6)$$

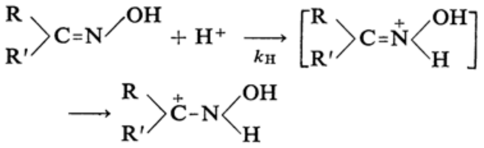
From the linear plot of $R/[\text{oxime}]$ vs. $[\text{HCl}]^{1.5}$, as shown in Fig. 3, k_{SO_2} and k_{HCl} are obtained from the intercept and the slope of the plot as:

$$k_{SO_2}=0.23\times10^{-5}\ \text{sec}^{-1}$$
$$k_{HCl}=1.04\times10^{-4}\ \text{l}^{1.5}\ \text{mol}^{-1.5}\ \text{sec}^{-1}$$

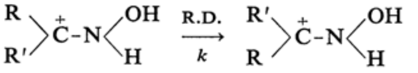
The value of k_{SO_2} agrees well with the rate constant of the liquid sulfur dioxide-catalyzed isomerization (0.65×10^{-5})[2] in its order, when the accuracy of the treatment is considered. Although the rate as catalyzed by hydrogen chloride is over three times as fast as the rate by sulfur dioxide, yet the order of both rates is of $10^{-4}-10^{-5}$. When the β-oxime, $[\text{oxime}]=5.0\times10^{-2}$ M/l., was subject to the Beckmann rearrangement in liquid sulfur dioxide with thionyl chloride, $[SOCl_2]=5.0\times10^{-2}$ M/l., the reaction was completed within 5 and 3 min. at 0 and -75°C respectively, the rate being so fast that no accurate kinetic measurement was possible[2].

A discussion should be added on the reason of the order of hydrogen chloride, 1.5, in rate expression 5. For the mechanism of the acid-catalyzed isomerization, the following scheme may be considered:

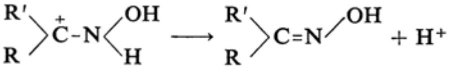
$$\text{HCl} \underset{K_{HCl}}{\rightleftharpoons} \text{H}^+ + \text{Cl}^- \qquad (7)$$



$$\text{RR}'\text{C=N-OH} + \text{H}^+ \xrightarrow[k_H]{} [\text{RR}'\text{C=}\overset{+}{\text{N}}\text{(OH)H}] \longrightarrow \text{RR}'\overset{+}{\text{C}}\text{-N(OH)H} \qquad (8)$$

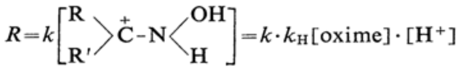


$$\text{RR}'\overset{+}{\text{C}}\text{-N(OH)H} \xrightarrow[k]{\text{R.D.}} \text{R}'\text{R}\overset{+}{\text{C}}\text{-N(OH)H} \qquad (9)$$



$$\text{R}'\text{R}\overset{+}{\text{C}}\text{-N(OH)H} \longrightarrow \text{R}'\text{RC=N-OH} + \text{H}^+ \qquad (10)$$

If Eq. 9 is selected as the rate-determining step, the rate expression is found to be:



$$R=k[\text{RR}'\overset{+}{\text{C}}\text{-N(OH)H}]=k\cdot k_H[\text{oxime}]\cdot[\text{H}^+]$$
$$=k\cdot k_H\cdot K_{HCl}{}^{0.5}[\text{oxime}]\cdot[\text{HCl}]^{0.5}$$
$$=k'[\text{oxime}][\text{HCl}]^{0.5} \qquad (11)$$

when the value of K_{HCl} is very small. Thus, in the above scheme the order of hydrogen should be 0.5, whereas in reality the order is 1.5 in this experiment.

In such a non-aqueous solvent as sulfur dioxide, the association of ion pairs is a phenomenon of considerable importance. If the three associated molar hydrochloric acids could give one set of cations and anions, and if the cation could behave as the catalyst for the oxime isomerization, the order for hydrogen chloride, 1.5 may be derived; however, the kinetics can give no detailed information on the nature of the active species for the isomerization. The following dissociation equilibria may be considered as examples:

$$3\,\text{HCl} \rightleftharpoons \text{H}^+ + (\text{HCl})_2\cdot\text{Cl}^-$$
$$3\,\text{HCl} \rightleftharpoons \text{HCl}\cdot\text{H}^+ + \text{Cl}\cdot\text{HCl}^-$$

In conclusion, sulfur dioxide-catalyzed or acid catalyzed-isomerization is not competitive against the Beckmann rearrangement of the oxime in liquid sulfur dioxide.

Summary

1. The hydrochloric acid-catalyzed isomerization of β-cyclohexyl phenyl ketoxime has been carried out in liquid sulfur dioxide. The effects of temperature, light, deuterium chloride and the concentrations of hydrogen chloride have been examined.

2. The overall rate may be expressed as;

$$R=k_{SO_2}[\text{oxime}]+k_{HCl}[\text{oxime}]\cdot[\text{HCl}]^{1.5}$$

and the k_{SO_2} and the k_{HCl} have been estimated. The reason for the order of hydrogen chloride, 1.5 has also been discussed.

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