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KINETICS OF UNCATALYZED ISOMERIZATION OF ALIPHATIC KETOXIMES

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Abstract: Three acyclic, aliphatic ketoximes studied show similar rates of isomerization at room temperature. From the rates of isomerization of one oxime at four temperatures, the thermodynamic activation parameters are calculated and a bimolecular transition state is postulated to account for the large negative entropy of activation.

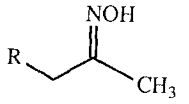
Oximes as synthetic intermediates have been important to organic chemistry for the past 100 years, since the discovery of the Beckmann rearrangement in 1886.[1] Much of the recent progress in Beckmann rearrangement chemistry involves conversion of aliphatic ketoximes into species other than amides.[2] Thus imidoyl iodides,[3] sulfides and selenides,[4] may be made in one step from oxime derivatives. Oxime mesylates may also be used in the preparation of a variety of secondary amines.[4] Moreover, oximes may be used as precursors to nitrilium ions used as cyclization initiators.[5] All of these transformations are stereospecific, and efficient utilization of starting materials therefore dictates employment of pure oxime stereoisomers.

Ten years ago, in an extension of earlier work by Hauser,[6] two laboratories reported independently on the regiospecificity of oxime deprotonations and alkylations.[7] Thus, certain Z-oxime isomers are available, but no comparable method exists for the stereoselective preparation of *E* isomers. Two alternatives remain: use of a mixture of isomers or chromatographic separation. If one is going to separate oxime stereoisomers, it would be useful to have some knowledge of the rates of isomerization. Although some kinetic data are available, we have observed qualitatively that the rates of isomerization are different for aliphatic and aromatic ketoximes and for aldoximes.

In 1949, LeFevre and Northcott used dilatometric techniques to measure the rate of the uncatalyzed isomerization of piperonal oxime in several solvents. For example, they found the *Z* isomer to have a $t_{1/2}$ of 3.6 hours in benzene at 25°.[8] In 1979, Holloway and Vuik used NMR techniques[9] to measure the kinetics of acetaldoxime isomerization.[10] From their data, the uncatalyzed $t_{1/2}$ in D_2O can be calculated to be 9.6 hours. In 1962, Vassian and Murmann measured rates of isomerization of phenyl 2-pyridyl ketoxime by observing the iron(II) complex of the *Z*-isomer spectroscopically.[11] They reported a $t_{1/2}$ of 2.5 minutes in the molten state (175°); in cyclohexanol solution at 144° they reported a $t_{1/2}$ of 34 minutes for the Z-isomer and 67 minutes for the *E*. Kinetic data for the uncatalyzed isomerization of aliphatic ketoximes have not been reported to date.

Because of our interest in the use of aliphatic oximes as cationic cyclization initiators and because of the importance of these compounds in the processes outlined above, we undertook a study of the kinetics of uncatalyzed aliphatic ketoxime isomerization, and report the results herein.

Using the NMR techniques developed first by Lustig[9a] and later by Karabatsos,[9b] we recorded the rates of isomerization of oximes **1a-c** and acetaldoxime. The oximes were chosen because of their availability and because of the freedom of spectral clutter in the region of the α-methyl signals. The data are summarized in **Table 1.**



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(a) R = $CH_2{=}CHCH_2$
(b) R = $CH_2{=}C[Si(C_2H_5)_3]CH_2$
(c) R = $(CH_3)_2C{=}CHCH_2$

All of the isomerizations appear to follow first order kinetics. While the rates for **1a-c** were similar, the best data were obtained for the isomerization of oximes **1a** and **1b**, because of overlapping signals in the spectrum of **1c**. The data indicate that the $t_{1/2}$ of an oxime such as **1** may be expected to be on the order of 1 to 2 weeks in benzene at 25°. From the rates of isomerization of oxime *Z*-**1a** at four temperatures (entries 1, 3, 4, and 5),[12] the following activation parameters can be calculated: $\Delta G^{\neq} = 26.3$ kcal/mole, $\Delta H^{\neq} = 16.5$ kcal/mole, and $\Delta S^{\neq} =$ –32.7 eu. The large negative entropy of activation is noteworthy, but appears to be in line with other recently reported data. Specifically, $\Delta S^{\neq} = -41.4$ eu can be calculated (2 data points) from Holloway and Vuik's data[10] for the uncatalyzed isomerization of acetaldoxime in water.

To account for the large negative entropy of activation, we postulate that the substrate must first hydrogen bond with another molecule of oxime, and then rearrange. At first glance, it would appear that second order kinetics must be followed by this scheme. However, the hydrogen bond donor may be either isomer of the oxime (*E* or *Z*), the sum of whose concentrations is constant. As a consequence, the reaction is likely *pseudo*-first order. The data do not permit assignment of the rate determining step.

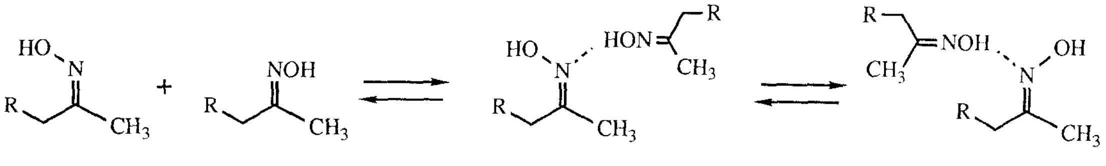

Table 1. Kinetic Data[a]

Entry	Oxime	Temp.(°C)	k($\text{x}10^3\text{hr}^{-1}$)[b]	r	$t_{1/2}$
1	**1a** *($Z \rightarrow E$)*	27	1.64±.04	.989	17.6 d
2	**1a** *($E \rightarrow Z$)*	27	(.703)	-	41.1 d
3	**1a** *($Z \rightarrow E$)*	40	4.74±.16	.984	6.09 d
4	**1a** *($Z \rightarrow E$)*	48	9.82±.21	.991	2.94 d
5	**1a** *($Z \rightarrow E$)*	67	46.2±4.7	.953	15.0 h
6	**1b** *($Z \rightarrow E$)*	25	3.65±.04	.997	7.91 d
7	**1b** *($E \rightarrow Z$)*	25	1.65±.06	.967	17.5 d
8	**1c** *($Z \rightarrow E$)*[c]	25	(14.6)	-	1.98 d
9	**1c** *($E \rightarrow Z$)*[c]	25	6.24±.20	.982	4.63 d
10	MeCH=NOH *($Z \rightarrow E$)*[d]	25	122	.974	5.69 h

[a] NMR's run in C_6D_6.
[b] Values in parenthesis are calculated from the reverse reaction and K.
[c] May be subject to larger error than other runs due to partial overlap of Z-methyl and vinyl methyl signals.
[d] Average of 3 runs.

The accuracy of the rate data can be seen by comparison of the rates for **1b**, which were available for both the *Z*→*E* and *E*→*Z* reactions. Calculation of the equilibrium constant from the two independently determined rates indicates a 69:31 *E*/*Z* ratio, in agreement with the 70:30 ratio determined by integration of the equilibrium mixture.

For comparison purposes, the rate of isomerization of acetaldoxime was measured in benzene solution. The rate constant observed is somewhat larger than that observed by Holloway and Vuik in water.[10] It corresponds more closely with the rate measured dilatometrically for piperonal oxime in benzene.[8] The $t_{1/2}$ of 5.7 hours at 25° is therefore probably what one should expect for any *Z*-aldoxime. Interestingly, the dilatometrically recorded data (2 data points) of LeFevre[8] yield an entropy of activation of -3.9 eu. We have no explanation for the discrepancy.

Experimental

NMR spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-600 FT-NMR. Isomerizations were monitored by integration of the α–methyls, as described by Lustig and Karabatsos.[9] Acetaldoxime and 6-methylhept-5-en-2-one were purchased from Aldrich. *Z*-**1a** and **1b** were prepared by alkylation of acetone oxime dianion.[7] *E*- and *Z*-**1b** were isolated by short column chromatography.[13]

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