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Mechanisms of acid catalyzed E/Z isomerization of methyl O-methylbenzohydroximate

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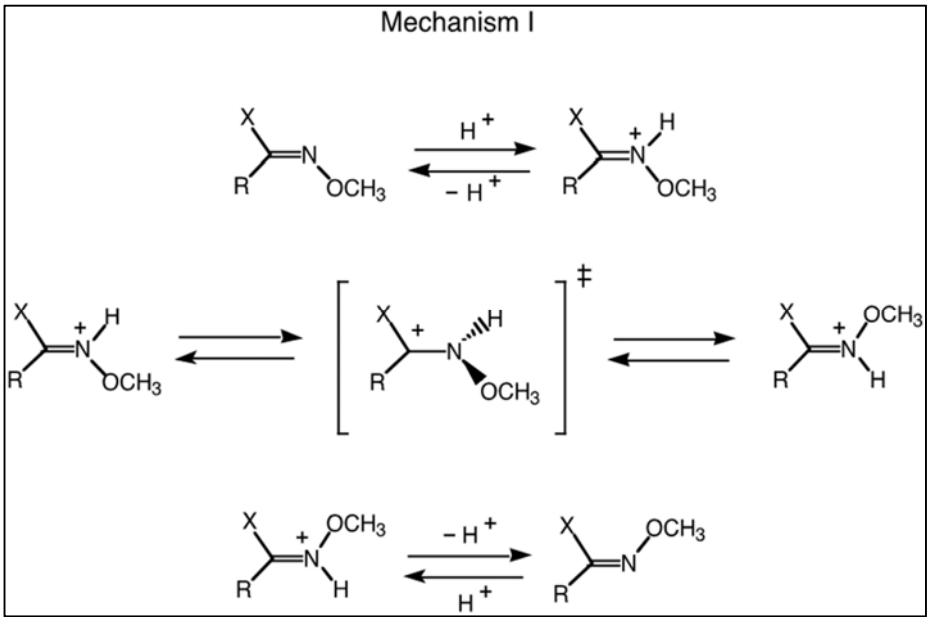
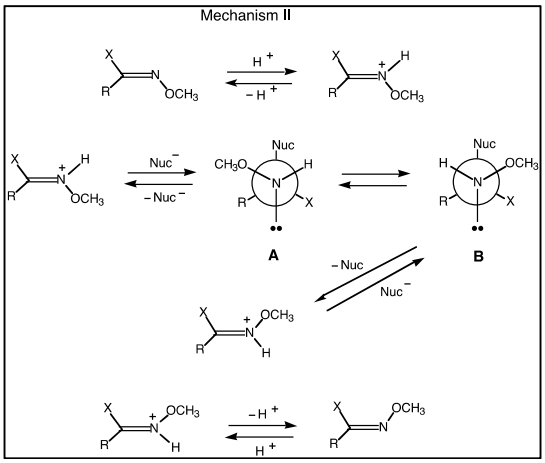
Abstract
An investigation into the acid-catalyzed E/Z isomerization of methyl O-methylbenzohydroximate in acetonitrile has been carried out. The data allows one to calculate the pK_b of methyl O-methylbenzohydroximate. The barrier to rotation of the iminium ion obtained at high concentrations of triflic acid is 22 kcal/mole at 25 °C. The isomerization in hydrochloric acid was determined to take place by nucleophilic catalysis. The pK_a of dibromoacetic acid was determined to be 13.58. A similar study was carried out on methyl O-methylbenzothiohydroximate. The barrier to rotation of the immium ion is 25 kcal/mol and the pK_b of the thiohydroximate is 23.7.

Keywords: Isomerization, O-methylbenzohydroximate, acid-catalyzed, triflic acid

1. Introduction
Most imines are capable of undergoing uncatalyzed [1-3] Z/E isomerization as well as acid catalyzed [4-18] isomerization. Base catalyzed isomerization is known [19, 20] but is much less common. The uncatalyzed isomerization of imines has been studied extensively [1-3] and in most instances proceeds by an inversion mechanism. We have investigated the acid catalyzed isomerization of O-methylhydroximoyl chlorides (1Za and 1Ea) and methyl O-methylbenzohydroximates (1Zb and 1Eb) [15-17]. Unlike many other imines, they are particularly resistant to thermal isomerization. In simple imines there are only two reasonable pathways for acid catalyzed Z/E isomerization of imines. One of these mechanisms involves rotation around the carbon-nitrogen double bond of the N-protonated imine (Iminium Ion Rotation, Mechanism I). In the second mechanism, the iminium ion

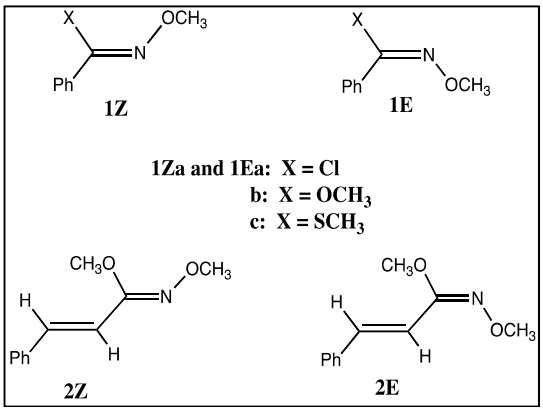


undergoes nucleophilic attack by the acid counter ion at the carbon atom of the carbon-nitrogen double bond to give a tetrahedral intermediate. The tetrahedral intermediate A produced from such an attack undergoes stereomutation by rotation around the



carbon-nitrogen single bond, proton exchange on the nitrogen atom, and nitrogen inversion. This would give tetrahedral intermediate B that is capable of losing the nucleophile to give the an iminium ion of the opposite configuration. Loss of a proton from the iminium ion gives the imine.

In our initial work [15] we demonstrated that the E to Z isomerization of benzohydroximoyl chloride (1Ea to 1Za) in HCl dioxane solution takes place by nucleophilic catalysis. This was demonstrated by the fact that the rate constant for incorporation of $^{36}Cl^-$ was one half the magnitude of the rate constant for isomerization of this compound.



In more recent work [17] we studied the rates of isomerization of methyl O-methylcinnamohydroximate (2Z and 2E) and methyl benzohydroximate (1Zb and 1Eb) in dioxane using three acids whose acid strengths are triflic acid > HCl > HBF_4. The rates of isomerization of 2E followed the order of acidity of the acids that we used for this study. We interpreted this observation to mean that the isomerization of 2E was taking place by iminium ion rotation.

The rate constants for isomerization of methyl O-methylbenzohydroximate (1Eb) did not follow the order of the acidity of the three acids studied. Instead the rate constants for isomerization were in the order HCl > triflic acid > HBF_4. This suggested that the pathway for isomerization of 1Eb in HCl is nucleophilic catalysis (Mechanism II). It was not possible to rule out some nucleophilic catalysis in the case of 2E and some iminium ion rotation for the isomerization of 1Eb in HCl.

Our previous work was carried out in dioxane a solvent that has been classified by the EPA as a probable human carcinogen. In addition not much is know about the acidities of organic acids in dioxane. For the work described here, we have chosen acetonitrile as the solvent, since it is a widely used solvent, and in addition, considerable data exists on the acidities of organic acids in this solvent [21].

2. Results and Discussion

This study was carried out on the E/Z isomerization of methyl O-methylbenzohydoximate (1Eb and 1Zb) and methyl O-methylthiobenzohydroximate (1Ec and 1Zc). The isomerization of 1Eb gives an equilibrium mixture of the Z and E isomers and followed reversible first order kinetics. At low concentrations of acid the rate of isomerization in triflic acid increases with increasing triflic acid concentration (Table 1). At higher concentration of acid the rate levels off and eventually reaches a constant value. The equilibrium constant (K = [Z]/[E]) for the isomerization increases with increasing triflic acid concentration until it too reaches a point where it levels off at higher concentrations of triflic acid. At low concentrations, [triflic acid]/[hydroximate] = 0.056, the equilibrium constant (K [Z]/[E]) is about 0.34. At higher concentrations of triflic acid, [triflic acid]/[hydroximate] = 60.1, the equilbrium constant is about 2.2.

The isomerization was measured in a total of seven acids that have weakly nucleophilic counter ions: triflic acid, fluorosulfonic acid, p-toluenesulfonic acid, trichloracetic acid, dichloroacetic acid, chloroacetic acid, and trifluoroacetic acid. Measurements were also carried out with hydrochloric acid. All of the measurements were carried out with the same concentration of acid and the acid concentration was higher than the hydroximate, [acid]/[hydroximate] = 60.1. A plot of the pK_a of the acid vs the log $k_{(\text{rate of E to Z isomerization})}$ is shown in Figure 1. It is clear from this figure that the imine is completely protonated with the two strongest acids used in this work (triflic acid and fluorosufonic acid). It is also clear that the rate of isomerization in HCl is proceeding by nucleophilic catalysis since the rate is much faster than a comparable acid with a weakly nucleophilic counter ion (p-toluenesulfonic acid). Using the extent that the HCl catalyzed reaction is off the line it is possible to calculate the percentage of nuclephilic catalysis for the HCl catalyzed reaction of the hydroximate:

Equation for the line from chlororacetic acid to p-toluenesulfonic acid in Figure 1:

$\log k_{obs\ (imin.\ rot.)} = -0.435\ pKa\ (acid) - 0.469$

$\log k_{obs\ (imin.\ rot.)} = -4.99$

$k_{obs\ (imin.\ rot.)} = 1.02 \times 10^{-5}\ s^{-1}$

$$\% \text{ iminium ion rotation} = \frac{k_{obs\ (imin.\ rot.)}}{k_{f\ (HCl)}} \times 100$$

$$\% \text{ iminium ion rotation} = \frac{1.02 \times 10^{-5}\ s^{-1}}{2.51 \times 10^{-3}\ s^{-1}} \times 100$$

% iminium ion rotation = 0.41%

% nucleophilic catalysis = 99.59%

From the plot in Figure 1 the K_a of the conjuguate acid of the imine can be calculated (see Appendix):

$$K_a = \frac{k_{rotation}}{k_{f(obs)}}\sqrt{K_{a(AH)}[AH]}$$

$$K_a = 3.2x10^5(ave)$$

$$pK_a = 4.5(ave)$$

Since the autoprotolysis constant for aceonitrile is known[22] it is possible to calculate the pK_b of the imine:

$$K_{autoprotolysis} = 3x10^{-27}$$

$$pK_{autoprotolysis} = 26.5$$

$$pK_a + pK_b = 26.5$$

$$pK_b = 22.0$$

The rate constants for isomerization of the hydroximate at high concentrations of triflic acid were measured at five different temperatures ($\Delta H^{\ddagger}$ = 21 kcal/mole; $\Delta S^{\ddagger}$ = -3.0 eu; Table 3). The free energy of activation energy, $\Delta G^{\ddagger}$ = 22 kcal/mol at 25 °C, corresponds to the rotational barrier around the carbon-nitrogen double bond of the iminium ion.

We have measured the rate of isomerization in dibromoacetic acid, an acid whose pKa has not been reported in the literature in acetonitrile. The rate constant for this isomerization is 2.82 x 10^{-6} s^{-1}. Using the graph in Figure 1 we estimate that the pk_a of this acid to be 11.68:

Determination of the pKa of dibromoacetic acid:

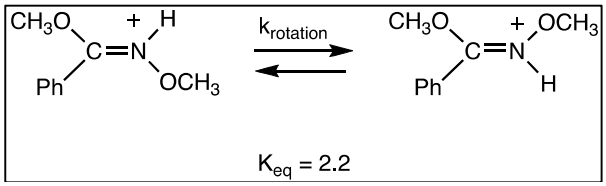
$\log k_{obs} = (-0.435\ pK_a) - 0.469$

$k_{obs} = 2.82 \times 10^{-6}\ s^{-1}$ for dibromoacetic acid

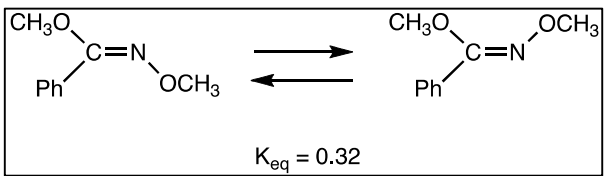
$pK_a = 11.68$

An explanation for the change in equilibrium constant with increasing triflic acid concentration is shown below. At high triflic acid concentration the equilibrium is between the Z and E isomers of the iminium ion (K = 2.2). At lower triflic acid concentrations the equilibrium is between the Z and E isomers of the imines (K = 0. 32).

At high triflic acid concentration:



At low triflic acid concentration:



Similar work was carried out on the E/Z isomerization of methyl O-methylthiobenzohydroximate (1Ec and 1Zc). The rate constant for the isomerization of the hydroximate 1Eb in 0.0173M trichloroacetic acid is 9.24 x 10^{-6} s^{-1} at 25 °C. This rate constant is about 4.2 time larger than the rate constant for isomerization of 1Ec (k = 2.22 x 10^{-6} s^{-1}) which was run at 10 times higher acid concentration (0.154 M) and about 30 degrees higher temperature. From the rates of isomerization the pk_b of 1Ec was calculated to be 23.7. This corresponds to a base strength that is about 50 times weaker than the hydroximate 1Eb. The rate constants for isomerization of 1Ec at high concentrations of triflic acid were measured at three different temperatures ($\Delta H^{\ddagger}$ = 25.8 kcal/mole; $\Delta S^{\ddagger}$ = 3.74 eu; Table 4). The free energy of activation energy, $\Delta G^{\ddagger}$ = 25 kcal/mol at 25 °C, corresponds to the rotational barrier around the carbon-nitrogen double bond of the iminium ion. The slower rate of isomerization of the thiohydroximate 1Ec as compared to the hydroximate 1Eb with trichloroacetic acid is attributed to a higher barrier of rotation about the carbon-nitrogen double bond of the iminium ion and to the fact that 1Ec is a much weaker base than 1Eb.

In conclusion, the measurement of E/Z isomerization rate constants for methyl O-methylbenzohydroximate (1Eb and 1Zb) with a variety of acids with weakly nucleophilic counterions has given a plot from which we can calculate the pk_b of the hydroximate. The isomerization rate with hydrochloric acid is off the line which is attributed to nucleophilic catalysis by chloride ion. The extent of the catalysis by chloride ion has been calculated. We have also determined the pKa of dibromoacetic acid by measuring its rate of isomerization of 1Eb. The E/Z isomerization of methyl O-methylthiobenzohydroximate (1Ec and 1Zc) was also studied.

3. Experimental

3.1 General Methods

The procedures for the preparation of 1Eb, 1Zb, 1EC and 1Zc have been reported previously. The acetonitrile used in these experiments was anhydrous and was purchased from Aldrich Chemical Company.

3.2 Kinetic Method

A stock solution of 1Eb was prepared in a 50 mL volumentric flask. A 25 mL volumetric flask and five marked graduated test tubes were placed in a dry box. The acid was weighed into a 25 mL volumetric flask in the dry box and filled to the mark with acetonitrile. About 8 mL of this solution was poured into 2 or 3 graduated test tubes. About 8 mL of acetonitrile was added to the marked tubes. The tubes were capped and and removed from the dry box. To another 25 mL volumetric flask, which had been purged with nitrogen, was pipeted 1 or 2 mL of the stock solution of 1Eb. About 18 mL of acetonitrile was added to the flask. The 25 mL volumetric flask containing 1Eb, a tube containing the acid solution, and a tube containing acetonitrile were placed into a water bath for at least 30 minutes. When the solutions were thermally equilibrated, 5 mL of the acid solution was pipetted into the 25 mL flask containing 1Eb. The timer was started and the flask was filled to the mark with acetonitrile and shaken quickly. Aliquots (about 1 mL) were removed at regular intervals, and were quenched with ice cold sodium hydroxide (3-4 drops of 0.6M) and brought to pH > 8. Samples (20 μL) were injected into an HPLC fitted with a Burdick and Jackson OD5 octadecyl column connected to a Varian UV/VIS detector set at 254 nm. Before the samples were injected into

the HPLC column the pH of the solution was brought to pH 4-7 by adding potassium dihydrogen phosphate (3-4 drops of 0.6 M). Retention times and a normalization factor for peak areas were determined by analysis of samples containing known amounts of 1Eb and 1Zb. Anhydrous p-toluenesulfonic acid was prepared according to a procedure described by Fujinaga and Sakamoto [24]. Rate constants were calculated using a linear regression program. Errors were calculated at the 95% confidence level.

4. Acknowledgements

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