MECHANISM OF THE "SPONTANEOUS" REACTION OF p-METHOXYSTYRENE OXIDE IN AQUEOUS SOLUTION

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Summary: An ^{1}H NMR study of the spontaneous reaction of p-methoxy-trans-β-deutereostyrene oxide and its cis-β-deutereo isomer has provided evidence that the trans-β-D and cis-β-D have equal migrating aptitudes in the aldehyde-forming reaction.

It was recently reported from this laboratory[1] that p-methoxystyrene oxide (**1b**) undergoes acid-catalyzed hydrolysis at low pH to yield p-methoxy-styrene glycol and a "spontaneous" or "k_O" reaction at pH > ca. 7.5 to yield mainly p-methoxyphenylacetaldehyde (~85%) and a lesser amount of glycol (~15%).
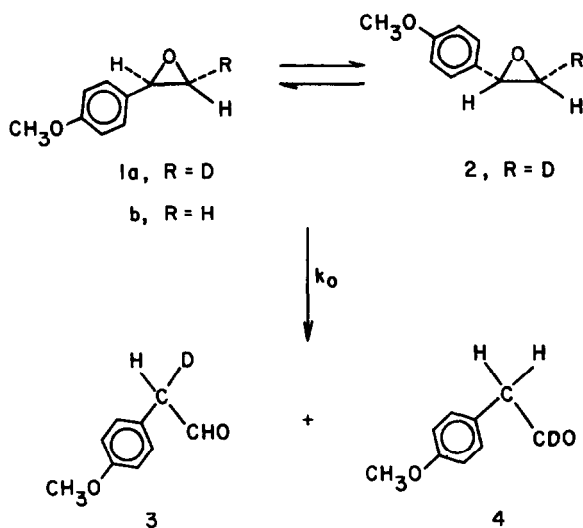
The k_O reaction of p-methoxy-trans-β-deutereostyrene oxide **1a** was also studied, and ^{1}H NMR analysis of the remaining epoxide after ca. one half-life for the k_O reaction showed that deuterium was significantly distributed in both the trans and cis positions. From the deuterium-scrambling information it was concluded that benzyl C-O bond cleavage in the k_O reaction of **1a** occurred to yield an intermediate with a sufficient lifetime such that the rate of rotation about the C(α)-C(β) bond and ring closure back to the cis-labeled isomer 2 exceeded the rates of other product-forming steps.

We also reported that ^{1}H NMR and mass spectral analyses of the

aldehyde product (**3** and **4**) from the k_O reaction of **1a** showed that the ratio of hydrogen migration to deuterium migration was ca. 3:1. Since this value for the ratio of hydrogen/deuterium migration is similar to reported kinetic isotope effects for 1,2-migration of deuterium, it was suggested that both of the methylene hydrogens of **1b** undergo migration "to similar extents."

In a later publication that appeared in this journal,[2] our suggestion that both hydrogens in the methylene position of **1b** undergo migrations to "similar extents" was challenged. It was stated that for our conclusion to be valid, the interconversion of deuterated epoxides **1a** and **2** would have to be fast relative to the rearrangement involving hydride/deuteride migration. This statement is not correct. For our conclusion to be valid, it is necessary only that the rate of rotation about the $C(\alpha)$-$C(\beta)$ bond of the intermediate be rapid relative to the rate of hydride/deuteride migration. It is not necessary that the rate of interconversion of deuterated epoxides **1a** and **2** exceeds that of hydride/deuteride migration.

We now wish to present new data to show that the interconversion of deuterated epoxides **1a** and **2** in the k_O reaction is only several times faster than the rate in which epoxide is converted to aldehyde and glycol, but that the two methylene hydrogens of **1b** do have, within experimental error, the same migratory aptitudes in the k_O reaction. This result is in contrast to the reported stereoselective migration of the trans C(1)-hydrogen in the boron trifluoride-catalyzed rearrangements of 1,2-epoxyoctane[3] and (R)-1,2-epoxy-2,3,4-trimethylbutane[4] in benzene.

The reaction of **1a**[5] to an equilibrium mixture of **1a** and **2** in 1:9 dioxane(d_8)-water (v/v)[6] at 21°C, pH 9.1, has been monitored by ^{1}H NMR spectroscopy (see Figure 1). A nonlinear, least squares fit of the percent of **2** in the mixture of **1a** and **2** to the first-order rate equation yielded a value of $2.4 \pm 0.1 \times 10^{-3}$ s^{-1} for the specific first-order rate constant for the approach of **1a** to an equilibrium mixture of **1a** and **2**, and an extrapolated ratio for **1a**:**2** of 1.04 ± 0.02 at infinite time. The rate of reaction of **1a**[5] to aldehyde and glycol was also determined spectrophotometrically in this same solvent system at 21°C, and a value of k_O was calculated to be 7.1×10^{-4} s^{-1}.[7] Under these conditions, therefore, the rate at which **1a** approaches an equilibrium mixture of **1a** and **2** exceeds the rate at which total epoxide is converted to aldehyde (**3** and **4**) by a factor of 3.4.

We have also analyzed the absorbances due to the aldehydic proton at δ 9.71 (d, J = 2.4 Hz) and methylene protons at δ 3.61 in the ^{1}H NMR spectrum of the reaction mixture as a function of reaction time. From the relative areas of these two resonances, the ratio of deuterium migration to hydrogen migration in the aldehyde-forming reaction was calculated at times 1m, 3m, 6m, 12m, and 25m to be 0.38, 0.38, 0.34, 0.34, and 0.35, respectively. Since the half-life for deuterium scrambling is 4.9m, then throughout the first 6m the
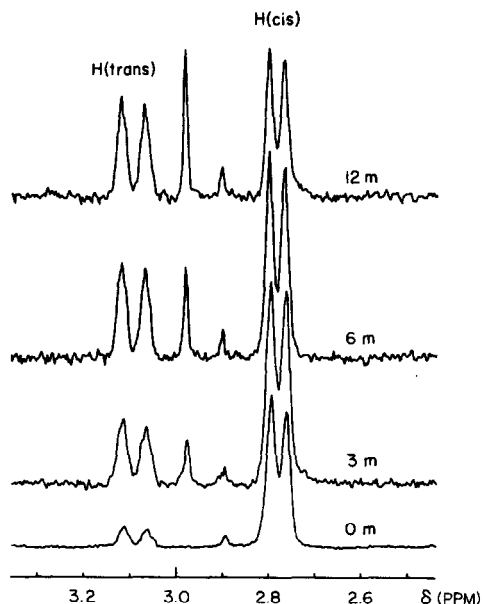
Figure 1. ^{1}H NMR absorptions due to the methylene hydrogens of **1a** and **2** as a function of time in the scrambling reaction of **1a** to a mixture of **1a** and **2**.

epoxide mixture was highly enriched in the trans-D isomer **1a**. Yet the ratio of hydrogen migration to deuterium migration remained relatively constant throughout ca. 5 half-lives for the deuterium scrambling reaction. It can therefore be concluded from these data that the migratory aptitude for the deuterium in the trans position of **1a** is essentially the same (within ca. 10%) as that for the deuterium in the cis position of **2**, and consequently, that the trans-H and cis-H of **1b** have migratory aptitudes that are the same within our experimental uncertainty.

Further evidence that the trans-D of **1a** and cis-D of **2** have equal or nearly equal rates of migration comes from the spectrophotometric determination of the rate constant (k_O) for conversion of **1a** to aldehyde (**3** and **4**) and glycol.[8a] Initially the reaction solution is highly enriched in the trans-D isomer **1a**, but as the hydrolysis reaction proceeds, the epoxide mixture contains increasingly greater amounts of the cis-D isomer **2**. If deuterium migration in the aldehyde-forming reaction of **1a** were kinetically favored over deuterium migration in the aldehyde forming reaction of **2**, then biphasic kinetics for the conversion of epoxide to aldehyde and glycol should result. However, the entire absorbance data throughout >10 half-lives for the reaction adhered strictly to first-order kinetics. For a given kinetic run, the value of k_O determined from absorbance data after one half-life for reaction of epoxide generally agreed with the value of k_O determined from absorbance data for the entire reaction to within 1%. Therefore, the spontaneous reaction rate of **1a** is equal or very nearly equal to that of **2**.[8b]

A number of kinetically indistinguishable mechanisms can account for the

observations. In our original publication, we discussed our results in terms of either a dipolar intermediate **5** or a carbocation **6** resulting from
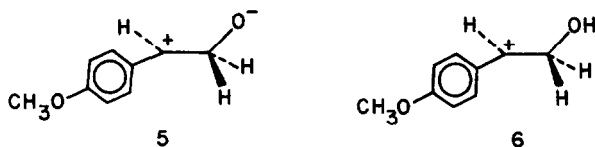
general acid-catalyzed opening of **1b** by H_2O. In either case, our data suggest that the trans hydrogen and cis hydrogen of **1b** become chemically equivalent in the intermediate. This chemical equivalency would result if rotation about the $C(\alpha)-C(\beta)$ bond <u>of the intermediate</u> were rapid relative to hydrogen migration. Recent data for the hydrolysis of precocene I oxide suggest that a dipolar species similar to **5** may be too unstable to be an intermediate for either diol or carbonyl-forming reactions of precocene I oxide in water solutions.[9]

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5. The sample of **1a** used for this study contained 13% of the cis-D isomer **2**.

6. The rate of reaction of **1a** to a mixture of **1a** and **2** was determined by adding <u>ca.</u> 5 mg of **1a** in 1.0 ml of dioxane(d_8) to 9.0 ml of rapidly stirred 0.1 M $NaClO_4$ solution containing 1×10^{-3} M CHES buffer, pH 9.1. At a given time, 5 ml of $CHCl_3$ was added and the mixture was rapidly mixed. After separation of the organic phase, the solvent was removed and the residue analyzed by ^{1}H NMR.

7. This specific first-order rate constant represents the rate of reaction of both **1a** and **2** to aldehyde and glycol, since they interconvert more rapidly then they form aldehyde and glycol products.

8. (a) The reaction of **1a** in 1:9 dioxane(d_8)- 0.1 M $NaClO_4$ solution, pH 9.1, was monitored at 232 nm in the thermostatted cell compartment (21.0 $\pm$ 0.1°C) of a Gilford Response spectrophotometer. (b) In order for the reaction of **1a** to an equilibrium mixture of **1a** and **2** to follow first-order kinetics, it is necessary that the spontaneous rate constant for **1a** be equal to that for **2**.

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