# Acid-Catalyzed Hydrolysis of *cis*- and *trans*-1,2-Dimethoxyethene in Aqueous Solution

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Rates of hydrolysis of *cis*- and *trans*-1,2-dimethoxyethene were measured in concentrated aqueous perchloric acid solution, and extrapolation of these data to dilute acid gave the catalytic coefficients $k_{H^+} = 1.16 \times 10^{-4}$ M$^{-1}$ s$^{-1}$ for the cis isomer and $k_{H^+} = 3.98 \times 10^{-5}$ M$^{-1}$ s$^{-1}$ for the trans isomer. These results, plus solvent isotope effects measured in 0.5 M hydrochloric acid ($k_{H^+}/k_{D^+} = 2.29$ for the cis isomer and $k_{H^+}/k_{D^+} = 2.21$ for the trans isomer), indicate that these reactions occur by rate-determining protonation of the substrates on carbon. The reactivities of the two substrates are discussed.

It is well known that alkoxy substituents have a strong accelerating effect on the reactions of carbon–carbon double bonds with electrophiles. Methyl vinyl ether, **1**,[1] for example is more reactive to carbon protonation than ethylene, **2**,[2] by 15 orders of magnitude. Further alkoxy substitution on the second olefinic carbon atom, on the other hand, produces a decrease rather than a further increase in reactivity. We have demonstrated this recently in the case of dihydro-1,4-dioxin, **3**,[3] and tetramethoxyethene, **4**,[4] by measuring rates of acid-catalyzed hydrolysis of these substances. We now extend that work to the cis and trans isomers of 1,2-dimethoxyethene, **5** and **6**.

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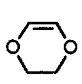

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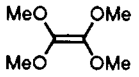

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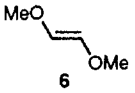

**6**

The present system is of further interest because the equilibrium constant for interconversion of these cis and trans isomers has been measured,[5] and we can combine that information with our results to evaluate the transition-state cis–trans free energy difference for the carbon protonation reaction.

## Experimental Section

**Materials.** *cis*- and *trans*-1,2-dimethoxyethene were prepared by pyrolysis of 1,1,2-trimethoxyethene (Aldrich Chemical Co.).[6] This gave a mixture of the two isomers in the ratio 4:1 (cis:trans), which was separated into the pure components by gas chromatography. Stereochemical assignments were made by comparing infrared and $^1$H NMR spectral parameters with published values.[5-7] All other materials were best available commercial grades. Solutions were prepared using deionized $H_2O$, purified further by distillation, or $D_2O$ (Merck, Sharp, & Dohme, 99.8 atom % D) as received.

**Table I. Rate Data for the Hydrolysis of *cis*- and *trans*-1,2-Dimethoxyethene in Aqueous Perchloric Acid Solutions at 25 °C**

| wt % $HClO_4$ | $k_{obs}$, $10^{-2}$ s$^{-1}$ |
|---|---|
| | *cis*-1,2-Dimethoxyethene |
| 10.8 | 0.0368, 0.0359 |
| 20.5 | 0.178, 0.168, 0.181, 0.180 |
| 25.8 | 0.391, 0.409, 0.426, 0.417, 0.450, 0.425 |
| 30.6 | 0.976, 1.01, 0.952, 0.984, 0.946, 0.978, 1.10, 1.06 |
| 33.7 | 1.63, 1.69, 1.71, 1.79, 1.68, 1.75, 1.71, 1.78 |
| 36.6 | 2.92, 3.04, 2.83, 2.93, 2.84, 2.94, 2.87, 2.98 |
| 39.6 | 5.29, 5.41, 5.84, 6.00, 5.69, 5.89, 5.79, 6.02, 5.61, 5.95 |
| 43.5 | 10.9, 11.3, 10.9, 11.7, 11.6, 11.0, 12.1 |
| | *trans*-1,2-Dimethoxyethene |
| 20.5 | 0.0474, 0.0471, 0.0486, 0.0459 |
| 25.8 | 0.114, 0.110, 0.108, 0.109, 0.106 |
| 30.6 | 0.289, 0.242, 0.244, 0.238 |
| 33.7 | 0.414, 0.425, 0.391, 0.396 |
| 36.6 | 0.692, 0.673, 0.738, 0.730 |
| 39.6 | 1.38, 1.30, 1.29 |
| 43.5 | 3.21, 3.19, 3.15, 3.04, 3.13, 3.07 |
| 46.6 | 6.72, 6.69, 6.80, 6.82, 6.57, 7.09, 6.97, 6.92, 6.96 |

**Kinetics.** Rates of hydrolysis of *cis*- and *trans*-1,2-dimethoxyethene were measured spectroscopically by monitoring the decrease in substrate absorbance at λ = 210 nm. Measurements were made with Cary Model 2200 and 118 spectrophotometers whose cell compartments were thermostatted at 25.0 ± 0.1 °C. Reactions were initiated by addding 5 μL of substrate in acetonitrile solution to a cuvette containing 3.0 mL of aqueous acid which had been allowed to come to temperature equilibrium with the spectrometer cell compartment. Substrate concentrations in these reaction mixtures were ca. $1 \times 10^{-3}$ M. The kinetic data obtained followed the first-order rate law accurately, and observed first-order rate constants were evaluated either as slopes of appropriate linear expressions or by least-squares fitting to an exponential function.

## Results

Rates of hydrolysis of *cis*- and *trans*-1,2-dimethoxyethene were measured in aqueous perchloric acid solutions over the concentration range 10–45 wt% acid. The results obtained are summarized in Table I.

Observed first-order rate constants increased with increasing acidity of the reaction medium, but the rate of increase was much steeper than in direct proportion to acid molarity. Such behavior is common for acid-catalyzed reactions in concentrated acid solutions, and acidity functions are generally used to correlate the data; the $X_o$ function[8] appears to be the best scale currently available for this purpose.[9]

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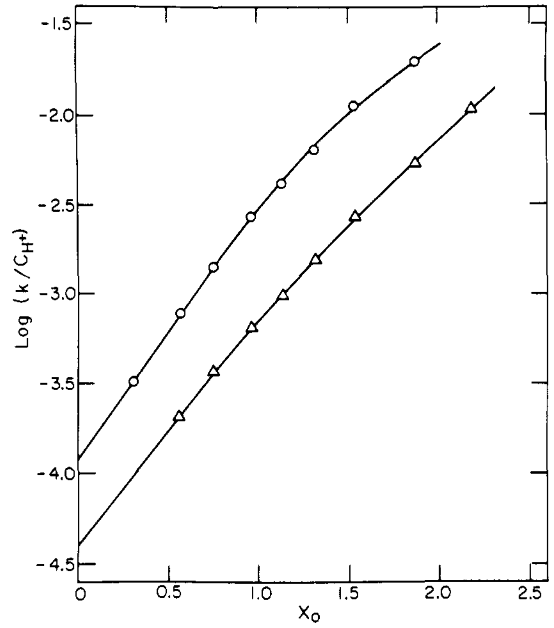
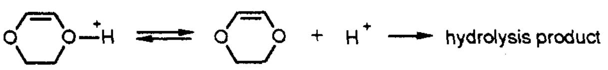


**Figure 1.** Relationship between rates of hydrolysis of 1,2-dimethoxyethenes in aqueous perchloric acid solutions and the $X_o$ acidity function; (○) *cis*-1,2-dimethoxyethene, (△) *trans*-1,2-dimethoxyethene.

Correlations using this acidity function are usually made by fitting the data to an expression which has the form of eq 1, in which $k_{H^+}$ is the bimolecular catalytic coefficient that applies in dilute solution where $X_o = 0$ and $m^*$ is a slope parameter. This treatment implies that log $(k_{obs}/C_{H^+})$ is a linear function of $X_o$, but Figure 1 shows that this was not the case for either of the substrates examined here: although the relationship is reasonably linear at low acidities, curvature develops in the more concentrated acids. Such behavior has been observed before in the hydrolysis of dihydro-1,4-dioxin,[3] and it has been reasonably attributed to partial conversion of the substrate into a less reactive form through rapid equilibrium protonation on oxygen (eq 2).

$$\log (k_{obs}/C_{H^+}) = \log k_{H^+} + m^*X_o \qquad (1)$$



(2)

This situation can be handled by using a modified form of eq 1, shown as eq 3, in which the additional parameters $K_{SH^+}$ and $m$ are the acidity constant of the oxygen protonated substrate and the slope governing this equilibrium protonation, respectively. Least-squares fitting of the data to this expression gave, for *cis*-1,2-dimethoxyethene $k_{H^+} = (1.16 \pm 0.07) \times 10^{-4}$ M$^{-1}$ s$^{-1}$, p$K_{SH^+} = -2.07 \pm 0.20$, $m^* = 1.51 \pm 0.06$, and $m = 0.95 \pm 0.05$; and for *trans*-1,2-dimethoxyethene $k_{H^+} = (3.98 \pm 0.05) \times 10^{-5}$ M$^{-1}$ s$^{-1}$, p$K_{SH^+} = -1.46 \pm 0.29$, $m^* = 1.41 \pm 0.15$, and $m = 0.56 \pm 0.05$. These acidity constants are reasonable values for oxygen-protonated aliphatic ethers; for example, p$K_a = -2.48$ has been reported for the conjugate acid of dimethyl ether and p$K_a = -2.39$ for that of diethyl ether.[10] The presently determined values are also consistent with p$K_{SH^+} = -2.51 \pm 0.45$ for the conjugate acid of dihydro-1,4-dioxin.[3]

$$\log (k_{H^+}/CH^+) = \log k_{H^+} + m^*X_o + \log\left(\frac{K_{SH^+}}{K_{SH^+} + C_{H^+}10^{mX_o}}\right) \qquad (3)$$

**Table II. Rate Data for the Hydrolysis of *cis*- and *trans*-1,2-Dimethoxyethene Catalyzed by Hydrochloric Acid in $H_2O$ and $D_2O$ Solutions at 25 °C**

| acid | [acid], M | $k_{obs}$, $10^{-5}$ s$^{-1}$ |
|---|---|---|
| | *cis*-1,2-Dimethoxyethene | |
| HCl | 0.492 | 5.78, 5.74 |
| DCl | 0.494 | 2.49, 2.54 |
| | *trans*-1,2-Dimethoxyethene | |
| HCl | 0.492 | 2.39, 2.41 |
| DCl | 0.494 | 1.10, 1.07 |

Rates of hydrolysis of *cis*- and *trans*-1,2-dimethoxyethene were also measured in 0.5 M hydrochloric acid solutions in $H_2O$ and in $D_2O$. These data, summarized in Table II, provide the hydronium ion isotope effects, $k_{H^+}/k_{D^+} = 2.29 \pm 0.02$ for the cis isomer and $k_{H^+}/k_{D^+} = 2.21 \pm 0.03$ for the trans isomer. These isotope effects suggest that the carbon protonation step in the hydrolysis of these substrates (eq 4) is rate-determining and nonreversible, for, if it were reversible and some subsequent step were rate-determining, the isotope effect would be inverse: $k_{H^+}/k_{D^+} < 1$.[11]

$$\text{MeOCH=CHOMe} + \text{H}^+ \rightarrow \text{MeOCH}_2\text{CHOMe}^+ \qquad (4)$$

This mechanistic assignment is supported by the fact that different rate constants were obtained for hydrolysis of the cis and trans isomers and that each reaction obeyed the first-order rate law accurately. These observations indicate that no interconversion of the isomers took place during the course of these reactions. Reversible carbon protonation would have effected interconversion and, in the limit of rapid and reversible protonation followed by some much slower subsequent rate-determining step, would have led to a common rate constant for the two isomers. Reversible carbon protonation occurring at a rate comparable to some subsequent step, on the other hand, would have produced deviations from first-order kinetics; this was not observed. The mechanistic assignment of rate-determining carbon protonation therefore seems secure.

## Discussion

**Reactivity.** The hydronium ion catalytic coefficients determined here for *cis*-1,2-dimethoxyethene, $k_{H^+} = 1.16 \times 10^{-4}$ M$^{-1}$ s$^{-1}$, and *trans*-1,2-dimethoxyethene, $k_{H^+} = 3.98 \times 10^{-5}$ M$^{-1}$ s$^{-1}$, are both considerably less than that reported for the corresponding monomethoxy substrate, methyl vinyl ether (1), $k_{H^+} = 7.6 \times 10^{-1}$ s$^{-1}$.[1] This is consistent with the fact that the second methoxy group in 1,2-dimethoxyethene cannot exert an accelerative effect by interacting conjugatively with the positive charge being generated on the substrate in the transition state of the rate-determining step of this reaction (eq 4); this second methoxy group can, however, retard the reaction rate by lowering the energy of the initial state through the well-known carbon–carbon double bond stabilizing effect of alkoxy groups.[12]

It is of interest to make a quantitative comparison of this stabilizing effect with the rate retardations observed here. The presently determined rate constants, when compared to that for methyl vinyl ether taking into ac-

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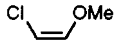
count the fact that 1,2-dimethoxyethene has two equivalent reaction sites, give free energy of activation differences of $\delta\Delta G^{\ddagger} = 5.6 \pm 0.1$ kcal mol$^{-1}$ for the cis isomer and $\delta\Delta G^{\ddagger} = 6.2 \pm 0.1$ kcal mol$^{-1}$ for the trans isomer. Each one of these is significantly greater than the double bond stabilizing effect of methoxy, $D = 5.2$ kcal mol$^{-1}$.[12] Such differences have been noted before, for dihydro-1,2-dioxin[3] and tetramethoxyethene;[4] it is likely that they are the result of an additional, transition-state destabilizing interaction produced by the electron-withdrawing polar effect of the methoxy group: this interacts unfavorably with the positive charge being generated on the substrate in these reactions.

**Cis–Trans Effects.** The presently determined hydronium ion catalytic coefficients make *cis*-1,2-dimethoxyethene 2.9 times more reactive than its trans isomer. This difference is in the same direction as the difference in thermodynamic stability of the two substrates: equilibration experiments provide the equilibrium constant $K = 7.0$ for the trans-to-cis isomerization of the neat liquid olefins at 25 °C.[5] This equilibrium constant corresponds to the free energy difference $G_t - G_c = 1.15$ kcal mol$^{-1}$, which, when combined with the rate ratio $k_c/k_t = 2.9$, gives $G_t^{\ddagger} - G_c^{\ddagger} = 1.78$ kcal mol$^{-1}$ for the difference in free energy between the cis and trans transition states.

It is not clear why *cis*-1,2-dimethoxyethene is more stable than its trans isomer, but the difference in stability of the transition states for the carbon protonation reactions would seem to have a straightforward explanation. The positive charge being generated on the substrates in this transition state will be delocalized onto a methoxy group oxygen atom and so will be displaced to one side of the (now partial) carbon–carbon double bond. The oxygen atom of the other methoxy group, being the negative end of a carbon–oxygen bond dipole, will then be able to interact more favorably with this positive charge when it is on the same side of the (partial) olefinic bond than when it is on the opposite side.

A similar reactivity difference has been found for *cis*- and *trans*-2-chloro-1-methoxyethene, **7** and **8**. The cis isomer here is 4 times more reactive to acid-catalyzed alcoholysis in ethanol solution than is the trans isomer.[13] The cis olefin is also the more stable isomer in this system.[14]



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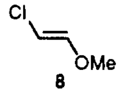

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# Formation and Crystal Structure of 1-[*N*-Methylpyridoxylidenium]-2-[2′-*N*-methylpyridinium]hydrazine Diperchlorate and Its Red Tautomer[†]

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The isolation, characterization, and single-crystal structures of 1-[*N*-methylpyridoxylidenium]-2-[2′-*N*-methylpyridinium]hydrazine diperchlorate (**9**) (yellow, mp 258–259 °C) and of its red tautomer (**10**) (mp 215 °C) are herein described. Compound **9** was obtained from the reaction of an isomeric mixture of the respective monoiodides **5** and **6**, with 5% $HClO_4$; **5** and **6**, in turn, were formed in minor quantities in the reaction of 1-[pyridoxylidene]-2-[2′-pyridyl]hydrazine with a 4-fold excess of methyl iodide in boiling ethanol (48 h). The red isomer **10** was derived from **9** during its recrystallization. Whereas the crystals of the parent monomethylated diquaternary salt, 1-[*N*-methylpyridoxylidenium]-2-[2′-pyridyl]hydrazine diperchlorate (**2b**), are aligned in dimers through single $(O^2)\text{-}H\cdots N^{4'}$ contacts, those of **9** and **10** are monomeric. Their formation is rationalized in terms of cooperative hydrogen bonding.

## Introduction

1-[Pyridoxylidene]-2-[2′-pyridyl]hydrazine (**1**) is a representative of a new generation of lipophilic chelators based on pyridoxal, which manifest high affinity for iron, oral activity, therapeutic safety, and high efficiency in removal of toxic accumulation of iron in transfusional iron overload.[1-3] Of the six distinctly different heteroatoms in **1**,

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[†] Dedicated to the memory of Professor David Ginsburg (deceased March 9, 1988).

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