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Kinetic α Secondary Deuterium Isotope Effects for *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal Hydrolysis[1]

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Received July 3, 1978

Abstract: The rate of hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal at 25 °C in 20% dioxane–80% water is independent of pH over the range pH 6–12; $k_{obsd} = 1.9 \times 10^{-7}\ s^{-1}$. Under more acidic conditions, the rate increases linearly with the activity of the hydrated proton; $k_2 = 2.95 \times 10^{-2}\ M^{-1}\ s^{-1}$. The kinetic α secondary deuterium isotope effect for acid-catalyzed hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal, measured at 25 °C in 20% aqueous dioxane containing 0.05 M HCl, is $k_H/k_D = 1.038 \pm 0.008$, a value consistent with a transition state in which the C–S bond is stretched rather little. In contrast, the corresponding isotope effect for the pH-independent hydrolysis of this substrate, measured at 42.5 °C in 20% dioxane, is 1.13 ± 0.02, a value consistent with complete C–S bond cleavage in the transition state and rate-determining diffusion apart of the ion-pair formed as the initial intermediate, in accord with the suggestion of Jensen and Jencks.

The hydrolysis of *O*-alkyl *S*-phenyl benzaldehyde acetals occurs with acid catalysis[3,4] as does that for the structurally related 2-phenyl-1,3-oxathiolanes.[5,6] For the former compounds at least, acidic hydrolysis is known to involve initial C–S bond cleavage followed by C–O bond cleavage in a subsequent step.[3,4] Structure–reactivity correlations, the entropy of activation, and a solvent deuterium isotope effect are all consistent with an A-1 mechanism. In addition, the hydrolysis of *O*-methyl-*S*-2,4-dinitrophenylbenzaldehyde acetal occurs with a pH-independent reaction, thought to reflect an unimolecular decomposition of this substrate to form the thiophenoxide anion and the oxocarbonium ion.[3]

Both to better understand the mechanism of hydrolysis of *O*-alkyl *S*-phenyl acetals and its relationship to those determined in some detail for hydrolysis of simple acetals,[7] it is desirable to examine these reactions more thoroughly. Herein, we report kinetic α deuterium isotope effects for hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal, both for the acid-cat-

0002-7863/79/1501-1488$01.00/0

Table I. First-Order Rate Constants for Hydrolysis of *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal in 20% (v/v) Dioxane-Water at 25 °C[a]

buffer	pH	k_{obsd}, s^{-1}
0.4 M HCl	0.45	1.13×10^{-2}
0.2 M HCl	0.74	5.02×10^{-3}
0.1 M HCl	1.11	2.22×10^{-3}
0.05 M HCl	1.38	1.20×10^{-3}
0.01 M HCl	2.03	2.62×10^{-4}
chloroacetate	2.96	2.57×10^{-5}
formate	3.94	3.44×10^{-6}
acetate	5.07	4.15×10^{-7}
phosphate	6.47	1.77×10^{-7}
Tris	8.03	1.87×10^{-7}
carbonate	11.26	2.03×10^{-7}

[a] Potassium chloride was added to give a total ionic strength of 0.1 except for those solutions containing ≥0.1 M HCl.

alyzed and the pH-independent reaction. In the accompanying paper, Jensen and Jencks have examined this and related reactions in detail, focusing on structure-reactivity relationships. Two conclusions reached on the basis of their work, (1) that the pH-independent reaction involves rate-determining diffusion apart of the ion pair formed by unimolecular C-S bond cleavage and (2) that the acid-catalyzed reaction occurs with relatively little C-S bond cleavage, are supported by the isotope effects determined in this study.

Experimental Section

Materials. Reagent grade inorganic salts were used without further purification. Glass-distilled water was used throughout. Tetrahydrofuran and dioxane were distilled from lithium aluminum hydride prior to use. Nitrogen was purified according to the procedure of Fieser.[8] A solution of *n*-butyllithium in *n*-heptane was obtained from Matheson Coleman & Bell and deuterium oxide was obtained from Diaprep Inc.

The *O*-ethyl *S*-phenyl acetal of benzaldehyde was prepared according to the procedure of Jensen and Jencks[4] with some modifications. Eleven grams (0.1 mol) of benzenethiol and 10.6 g (0.1 mol) of benzaldehyde were dissolved in an ethanol solution containing 0.1 M HCl. An oil separated after a few hours. After two days 20 mL of 1 M NaOH was added to quench the reaction and the layers were separated after standing overnight. The oil was dissolved in 1:1 (v/v) dichloromethane-hexane, washed with saturated salt solution, and then dried over anhydrous sodium sulfate. Evaporation of the solvent on a rotary evaporator and vacuum distillation of the residue yielded 12.8 g (52%) of pure *O,S*-acetal that boiled at 105-108 °C (0.005 mm). The product yielded a single peak on gas-liquid chromatography. ^{1}H NMR spectra recorded on Varian A-60 and HR-220 spectrometers were consistent with the assigned structure and revealed no evidence for impurities.

The *O*-ethyl *S*-phenyl acetal of benzaldehyde-*1-d* was prepared from the corresponding protio compound by the following procedure. A solution of 4.11 g (17 mmol) of protio *O,S*-acetal in 30 mL of dry tetrahydrofuran was treated under nitrogen at −60 °C with 13.7 mL (19 mmol) of *n*-butyllithium in heptane. After the mixture had stood for 5 h, 2 mL (0.11 mol) of deuterium oxide (100% *d*) was added and the mixture warmed to room temperature. After filtration to remove the white precipitate formed, the solvent was removed on a rotary evaporator; the residue was dissolved with 1:1 (v/v) dichloromethane-hexane; the organic phase was washed three times with 20 mL of saturated salt solution and then dried over anhydrous sodium sulfate. Evaporation of solvent and vacuum distillation of the residue yielded 3.55 g (85%) of desired product, bp 110-112 °C (0.01 mm). The ^{1}H NMR singlet at 5.60 ppm observed for the protio compound and due to the proton at C-1 was absent in the product. Deuterium incorporation at C-1 was greater than 99.7% as judged from mass spectral comparison of relative abundances in peaks with *m/e* 136 and 135 (AEI-MS-9 spectrometer).

Kinetic Measurements. The rates of hydrolysis of the *O,S*-acetal were measured spectrophotometrically on a Zeiss PMQ II spectrophotometer by following the appearance of benzaldehyde at 252 nm. Usually reactions were conducted in stoppered quartz cells placed into a modified brass cell holder mounted in the standard cell compartment of the spectrophotometer and connected to a thermostated circulating water bath. For those kinetic runs conducted at 65.5 °C or higher, the reactions were conducted in ampules sealed with nylon bushings and immersed in a constant temperature bath. At appropriate intervals aliquots were removed and the absorbance was measured.

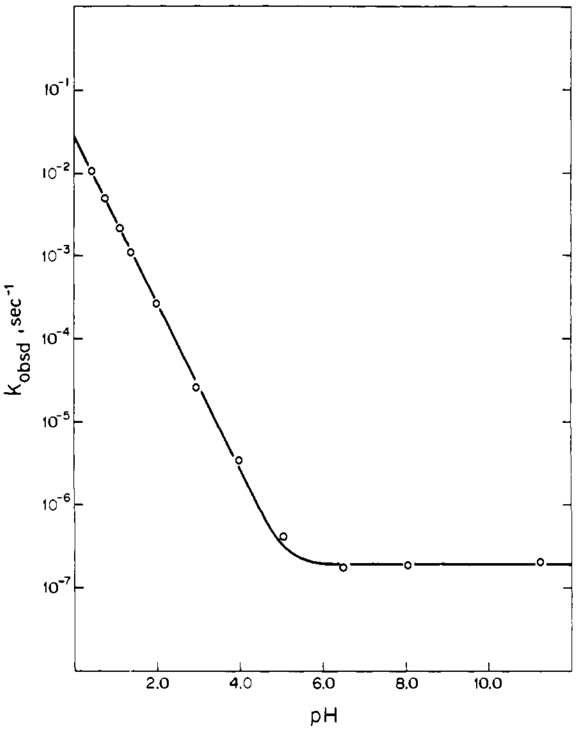

Figure 1. Logarithms of first-order rate constants for hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal in 20% aqueous dioxane at 25 °C plotted against pH.

Hydrolysis rates were measured in 20% aqueous dioxane and pH was maintained constant with the use of 0.05 M chloroacetate, formate, acetate, phosphate, Tris, and carbonate buffers, or dilute hydrochloric acid, as appropriate. When possible the ionic strength was adjusted to 0.1 with potassium chloride.

Acid-catalyzed reactions were followed to completion. Pseudo-first-order rate constants were determined from the slope of plots of $A_\infty - A_0$ vs. time which were linear through 2-4 half-lives. The pH-independent reactions were followed for 1.5-3 half-lives and absorbances at t_∞ were estimated using the Guggenheim equation and corrected to the best value utilizing a computer program, KINPROG, and a CDC 6600 computer facility. The same program was used for determination of k_{obsd} in those reactions involving determination of isotope effects, as previously described.[9]

Values of pH were recorded with a Radiometer PHM 4c pH meter equipped with a glass electrode.

Results

First-order rate constants for hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal in 20% aqueous dioxane at 25 °C were measured as a function of pH; results are collected in Table I and are presented graphically in Figure 1. From data in the region of the plot where rate constants are accurately first order in the hydrated proton, a second-order rate constant for the acid-catalyzed reaction was determined to be 2.95×10^{-2} M^{-1} s^{-1}. This value is close to that previously determined for acid-catalyzed hydrolysis of *O*-methyl *S*-phenyl benzaldehyde acetal, 1.92×10^{-2} M^{-1} s^{-1}, measured at 30 °C in the same solvent.[3] The first-order rate constant for the pH-independent reaction was determined to be 1.99×10^{-7} s^{-1}, corresponding to a half-life of 40 days. This value is, as expected, very much less than that previously determined for pH-independent hydrolysis of *O*-methyl *S*-2,4-dinitrophenyl benzaldehyde acetal, 1.0×10^{-2} s^{-1}.[3]

Table II. First-Order Rate Constants and Activation Parameters for the pH-Independent Hydrolysis of *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal in 20% (v/v) Dioxane-Water

temp, °C	k_{obsd}, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
25.0	1.89×10^{-7}	23.6	−9.9
65.5	3.02×10^{-5}		
75.5	8.86×10^{-5}		

Table III. Kinetic α Deuterium Isotope Effect for Acid-Catalyzed Hydrolysis of *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal in 20% Dioxane at 25 °C[a]

$k_H \times 10^3$, s^{-1}	$k_D \times 10^3$, s^{-1}	k_H/k_D
1.216	1.179	1.031
1.207	1.169	1.033
1.201	1.146	1.048
1.191	1.148	1.038
		mean = 1.038 (±0.008)

[a] Ionic strength 0.1 (potassium chloride) 0.05 M hydrochloric acid.

Table IV. Kinetic α Deuterium Isotope Effect for pH-Independent Hydrolysis of *O*-Ethyl *S*-Phenyl Benzaldehyde Acetal in 20% Dioxane-Water at 42.5 °C[a]

$k_H \times 10^6$, s^{-1}	$k_D \times 10^6$, s^{-1}	k_H/k_D
3.885	3.443	1.128
3.750	3.327	1.127

[a] 0.05 M phosphate buffer, pH 6.52. Ionic strength adjusted to 0.1 with potassium chloride.

First-order rate constants for the pH-independent hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal in 20% dioxane were also measured at 65.5 and 75.5 °C. The results together with derived activation parameters are collected in Table II. The entropy of activation of −9.9 eu is slightly more negative than that previously measured, −4.8 eu, for the acid-catalyzed hydrolysis of *O*-methyl *S*-phenyl benzaldehyde acetal.[3]

The kinetic α deuterium isotope effect for acid-catalyzed hydrolysis of the *O,S*-acetal was measured in the presence of 0.05 M HCl in 20% aqueous dioxane at 25 °C. These conditions yield reaction half-times which are convenient for the collection of 100–150 data points which are employed in the determination of each rate constant. The results are collected in Table III. Reproducibility of the first-order rate constants was acceptable; the slight trend toward lower values for later measurements may reflect a small decrease in temperature. Reproducibility of the secondary deuterium isotope effects was excellent and a value of k_H/k_D of 1.04 ± 0.01 may be accepted with confidence.

Kinetic α deuterium isotope effects were also measured for the pH-independent hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal. The reaction is too slow at 25 °C to permit an accurate determination at this temperature. Consequently, a measurement was made in duplicate at 42.5 °C, where the half-life for the reaction is a little more than 2 days. The data are collected in Table IV. These are not ideal conditions under which to determine a small isotope effect. Nonetheless, the values agree quite well. An independent determination made under the same conditions yielded a value of 1.11 and a final determination made at 65.5 °C yielded a value of 1.14. The accuracy of this isotope effect is not as good as that for the acid-catalyzed reaction but a value of 1.13 ± 0.02 is consistent with all the measurements.

Discussion

Previous work suggests that the acid-catalyzed and pH-independent hydrolysis of *O*-alkyl *S*-phenyl benzaldehyde acetals, like that for simple oxygen acetals,[7] occurs with unimolecular substrate decomposition to yield an oxocarbonium ion and either a benzenethiol or benzenethiolate anion.[3,4] This simple interpretation is consistent with the recent studies by Young and Jencks which suggest that oxocarbonium ions derived from benzaldehyde acetals may be sufficiently stable to be reaction intermediates.[10] Nonetheless, this interpretation must be accepted with some degree of caution and the possibility that some form of nucleophilic participation by solvent occurs in the transition state must be entertained. However, the earlier results,[3] those of Jensen and Jencks,[4] as well as those presented herein are all consistent with the interpretation that reaching the transition state for these hydrolytic reactions involves some degree of rehybridization at carbonyl carbon from sp^3 toward sp^2 geometry.

α secondary deuterium isotope effects may both (1) provide strong evidence in favor of rehybridization from tetrahedral to trigonal geometry in the transition state and (2) yield useful information concerning details of transition-state structure.[11,12] This follows from the consideration that such isotope effects are largely determined by changes in the C-L-X out of plane bending mode that accompanies such rehybridization.[12–14]

Characteristically, those reactions in which carbon moves from tetrahedral toward trigonal geometry in the transition state show values of k_H/k_D significantly greater than unity. In contrast, reactions involving nucleophilic participation in the transition state usually have corresponding values near unity.[11,12] The observed value for the acid-catalyzed hydrolysis of *O*-ethyl *S*-phenyl benzaldehyde acetal, 1.04 ± 0.01, is not sufficiently different from unity to distinguish between an A1 and A2 mechanism. That the former alternative is correct is strongly suggested by other lines of evidence[3,4] and we shall interpret the isotope effect on this basis. In contrast, the isotope effect observed for the pH-independent hydrolysis of this substrate, 1.13 ± 0.02, is clearly beyond the limits expected for a transition state in which bond breaking is balanced by bond making and requires that the transition state have carbonium-ion character. This interpretation is consistent with the value obtained for the entropy of activation for this reaction, −9.9 eu, although this value is more negative than is typical for simple unimolecular decomposition reactions.

Detailed interpretation of the observed kinetic α deuterium isotope effects requires that one have a reasonable estimate of the upper limit expected for complete rehybridization from tetrahedral to trigonal geometry, i.e., the equilibrium isotope effect for conversion of an *O*-alkyl *S*-phenyl benzaldehyde acetal to the oxocarbonium ion and benzenethiol or benzenethiolate. It would be exceptionally difficult to measure this value directly and no reliable detailed calculations for it are available. However, in a semiquantitative sense, one expects a sulfur leaving group to behave much like a chlorine leaving group and the limiting isotope effect for the latter type of reaction has been established with confidence: $k_H/k_D = 1.15$.[12] Consequently, we shall employ this value as a guide to the understanding of the observed isotope effects.

The small kinetic α deuterium isotope effect for the acid-catalyzed hydrolysis of the *O,S*-acetal suggests a transition state in which rather little C-S bond cleavage has occurred. Provided that bond order in the transition state is linearly related to the magnitude of the isotope effect, one may estimate that the bond order is $(0.15 - 0.04)/0.15 = 0.7$ in the transition state. This is probably an underestimate since there is reason to believe that the isotope effect may be largely realized with modest amounts of bond breakage.[15] The isotope effect for this reaction is similar to those observed for the hydrolysis of ortho esters and benzaldehyde acetals possessing strongly electrondonating substituents[9] but is significantly smaller than those observed for hydrolysis of ordinary benzaldehyde acetals,[9] the acid-catalyzed hydrolysis of purine nucleosides,[16] and the pH-independent decomposition of nicotinamide nucleosides.[17] On the basis of large isotope effects for the reverse reactions, the transition states for loss of cyanide from benzaldehyde cyanohydrins[18] and hydroxide ion and water from carbinolamines[19] also appear to occur quite early along the reaction coordinate. At any event, the isotope effect for the acid-catalyzed hydrolysis of the *O,S*-acetal is much less than the limiting value and clearly indicates only partial cleavage of the C-S bond in the transition state.

The situation is notably different for the pH-independent hydrolysis of the same substrate. In this case, the isotope effect is relatively large and requires either substantial or *complete* cleavage of the C-S bond in the transition state. The observed isotope effect is entirely consistent with the suggestion of Jensen and Jencks that the rate-determining step for this reaction is diffusion apart of the ion pair formed by unimolecular substrate decomposition with C-S bond cleavage.[4]

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Aliphatic Semidiones. 38. Conversion of Polymeric Peroxides and Hydroperoxides to 1,2- and 1,4-Semidiones in Basic Solution[1]

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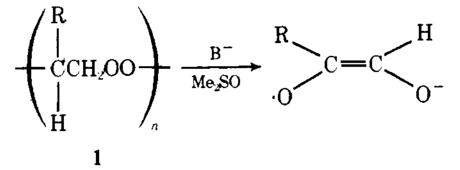
Received September 27, 1978

Abstract: Polymeric peroxides of substituted olefins or of cyclic 1,3-dienes are converted by potassium *tert*-butoxide in Me_2SO to 1,2-semidiones ($RC(O^-){=}C(O\cdot)H$) and 1,4-semidiones ($RC(O\cdot){=}CHCH{=}C(O^-)R$), respectively. The methylsulfinylmethide ion will convert $RC({=}O)C({=}O)X$, where X = H or CO_2^-, to the methylated semidione $RC(O\cdot){=}C(O^-)CH_3$. However, in a flow system semidiones with the structure $RC(O\cdot){=}C(O^-)X$, where X = H, OR, or CO_2^-, can be observed before the methylation occurs. Secondary hydroperoxides containing an α-methylene group are converted in basic Me_2SO to 1,2-semidiones.

Treatment of polymeric peroxides prepared from a polymerizable olefin or a cyclic 1,3-diene with potassium *tert*-butoxide in Me_2SO leads to the formation of the 1,2- and 1,4-semidiones, respectively (eq 1 and 2). The process involves



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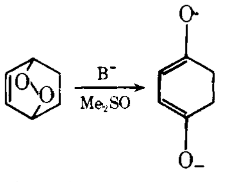

(2)

the known decomposition of a peroxide with α-hydrogen atoms by base (Scheme I)[2,3] followed by the recognized comproportionation reactions of α-hydroxy ketones (Scheme Ib).[4]

Scheme I