Hydrolysis of α-Acetoxystyrenes. Kinetics and Investigations of ^{18}O Exchange

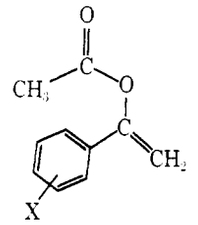
Michael Novak[1] and Gordon Marc Loudon*

The Spencer T. Olin Laboratory, Department of Chemistry, Cornell University, Ithaca, New York 14853

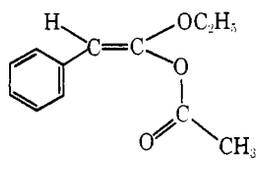
Received December 21, 1976

The alkaline hydrolyses of α-acetoxystyrenes **1a–f** and 1-acetoxy-1-ethoxy-2-phenylethylene (**2**) have been shown to proceed by the same mechanism which has been demonstrated for the hydrolysis of alkyl and aryl acetates. Among the pieces of experimental evidence leading to this conclusion are the inverse solvent deuterium isotope effects (0.74 + 0.07 for **1c**, 0.80 ± 0.09 for **2**), the kinetics of hydrolysis, which are first order in hydroxide ion, and the absence of general base catalysis of hydrolysis. In mildly acidic solution, however, the hydrolysis of **2** proceeds exclusively by a mechanism involving a rate-determining proton transfer to the leaving group double bond, a mechanism which was previously demonstrated for α-acetoxystyrenes in strongly acidic solution. Carbonyl labeled α-acetoxystyrene-^{18}O was synthesized, and ^{18}O exchange from the carbonyl position during alkaline hydrolysis was investigated; no ^{18}O exchange was observed. This behavior is similar to that observed for aryl esters, and contrasts with that observed for hydrolysis of esters with less acidic leaving groups. These observations support our contention that acetophenone enols are about as acidic as phenols, a conclusion which, along with the fraction enol in acetophenone, leads to a carbon pK_a for acetophenone of 15.8 ± 1.0.

Recently, we reported[2] that results from a kinetic investigation of the aminolysis of the α-acetoxystyrenes **1a–f** indicate that these compounds aminolyze by a mechanism identical



1a, X = *p*-OCH_3 **d**, X = *p*-Cl
b, X = *p*-CH_3 **e**, X = *m*-Cl
c, X = H **f**, X = *p*-NO_2



2

with that observed for aminolysis of aryl acetates.[3,4] In addition, our results indicated that acetophenone enols are about as acidic as phenol, with an estimated pK_a for acetophenone enol itself of 11.0 ± 1.0.[2,5] If phenols and enols are indeed as similar in their acid–base behavior as our previous studies suggest, then the hydrolysis of enol acetates should resemble hydrolysis of aryl acetates in any mechanism in which leaving group basicity and rate of reaction are correlated, in the absence of a strongly overriding steric effect.

We have completed a study of the alkaline hydrolysis of compounds **1a–f** and **2**. Correlations of kinetic data, solvent deuterium isotope effects, and ^{18}O exchange data (for **1c**) have been gathered, and these results, which we now report, suggest that α-acetoxystyrenes and aryl acetates hydrolyze in base by the same mechanism. Furthermore, the hydrolysis of **2** in acid proceeds by a mechanism, previously observed for α-acetoxystyrenes,[6] which involves a rate-determining protonation of the carbon–carbon double bond.

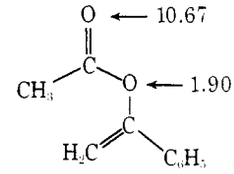
Experimental Section

Materials. Deuterium oxide (99.8%) was obtained from the Stuart Oxygen Co., and was flushed with argon before use. Solutions of 20% DCl in D_2O (Ventron) and 40% KOD in D_2O (Aldrich) were used to prepare standardized 1.0 M DCl and KOD solutions.

All water used in the experiments was deionized, double distilled, flushed with argon, and stored under argon in glass containers. Absolute ethanol and reagent grade KCl were used without further purification. Phenyl acetate was obtained commercially (Aldrich).

Acetic acid-^{18}O was prepared from acetyl chloride and 22.5 atom % ^{18}O enriched water (Yeda Research and Development Co.). A slight excess of the acetyl chloride was slowly added to the isotopically enriched water, which was stirred at 0 °C under argon. After addition, the solution was refluxed to help remove dissolved HCl. The extent of the reaction was monitored by the position of the hydroxyl proton resonance of acetic acid in the NMR, and more acetyl chloride was added if necessary. The acetic acid-^{18}O was distilled under argon when the reaction was complete.

Isopropenyl acetate-^{18}O was prepared by a modification of a procedure due to Hennion and Nieuwland.[7] Methylacetylene was condensed into a 40-mL, thick-walled hydrolysis tube to an approximate volume of 30 mL. Then 0.5 mL of boron trifluoride etherate, 0.5 g of HgO, and 4.0 g of acetic acid-^{18}O were added, the tube was sealed under vacuum, and the mixture was incubated at 30 °C for 10 h. After incubation was complete, the tube was cooled in liquid N_2 and opened. The contents were dissolved in 100 mL of ether and the methylacetylene was allowed to evaporate. The ethereal solution was then washed twice with 50 mL of 5% $NaHCO_3$ and once with 50 mL of distilled water. The ethereal solution was then rapidly dried over $MgSO_4$. The solution was not allowed to remain in contact with $MgSO_4$ for more than 2 min since it has been reported that carbonyl-^{18}O-enriched esters lose their isotopic oxygen in the presence of this salt.[8d] The ether was then removed under argon, and the remaining volatiles were collected in a cold trap under vacuum. The isopropenyl acetate-^{18}O was then distilled from the volatiles. The yield of the ester never exceeded 20% in any specific preparation. The α-acetoxystyrene-^{18}O was then prepared from the isopropenyl acetate-^{18}O by the method previously described for normal α-acetoxystyrene.[2] The analysis of these materials for isotopic content is described below, and indicates the following isotopic distribution for α-acetoxystyrene (numbers are atom % excess ^{18}O):



1-Acetoxy-1-ethoxy-2-phenylethylene was prepared by acetoxymercuration of 1-ethoxy-2-phenylacetylene, the synthesis of which has been previously described.[9] Approximately 2.9 g (20 mmol) of 1-ethoxy-2-phenylacetylene and 0.10 g of $Hg(OAc)_2$ were dissolved in 20 mL of methylene chloride and stirred at 0 °C as a solution of 1.00 g (16.7 mmol) of acetic acid in 30 mL of methylene chloride was added dropwise. The mixture was allowed to reach room temperature and was then stirred for 23 h. The mixture was then partitioned between 100 mL of water and 150 mL of ether, and the ether layer was washed a second time with water. Drying and concentration of the ether solution left a yellow oil which was distilled to give starting material and the desired compound (78% yield based on unrecovered starting

material): bp 76–78 °C (0.01 Torr); NMR ($CDCD_3$, downfield from internal Me_4Si) δ 1.32 (t, 3 H), 2.17 (s, 3 H), 3.95 (q, 2 H), 5.32 (s, 1 H), 7.0–7.6 (m, 5 H); IR (liquid film) 3050, 2970, 1780, 1680, 1205, 755, 695 cm^{-1}; mass spectrum (electron impact, 70 eV) *m/e* 206, 164, 91, 77, 43, 29.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.64; H, 6.80.

All spectral and physical evidence (including reaction kinetics) indicated that this material is one geometrical isomer, although there is no conclusive evidence available which would indicate which isomer is in hand. The usual trans mode of addition in acetoxymercuration suggests that the compound is the *Z* isomer shown in structure **2**. Product studies from the kinetics and a nuclear Overhauser experiment (NOE)[10] established without doubt that the vinyl proton and the phenyl group are bonded to the same carbon; however, the NOE experiment was inconclusive in identifying the geometrical isomer present.

Products of Hydrolysis. The products of basic hydrolysis of a acetoxystyrene, **1c**, were shown to be acetophenone and presumably acetic acid. The former product could be isolated from hyrolysis reaction mixtures in nearly quantitative yield by extraction with ether and comparison with authentic material. Likewise, UV spectra of hydrolysis mixtures at the completion of reaction were identical with those of acetophenone. Acetic acid was not specifically identified, although in *n*-butylaminolysis reactions of α-acetoxystyrene, *N*-*n*-butylacetamide and acetophenone were isolated.[2,5]

The products of acidic and basic hydrolysis of **2** were ethyl phenylacetate, isolated by ether extraction and identified by comparison with authentic material, and presumably acetic acid, which was not specifically identified. Aminolysis of **2** with glycinamide, however, yielded *N*-acetylglycinamide and ethyl phenylacetate.

Kinetic Methods. The solvent system employed in the kinetic studies was 5 vol % ethanol–water, ionic strength μ = 0.5 M (KCl), at 29.9 ± 0.1 °C. In deuterated solvent it was established that the pH meter reading was related to pD by

$$\text{pD} = \text{meter reading} + 0.30 \quad (1)$$

A value for the pK_a of D_2O in this solvent system was established as 14.50 ± 0.02 at 30 °C. The pseudo-first-order reactions of **2** were followed by the disappearance of the 272-nm UV absorption of this compound. The reactions of **1c** were observed by the appearance of the 279-nm absorption of acetophenone. The alkaline hydrolysis of phenyl acetate in nondeuterated solutions was also followed spectrophotometrically. Wavelengths and concentrations used for these experiments are from Jencks and Carriuolo.[3a] Preparation of solutions for kinetics and calculations of the rate constants have been previously described for the rate constants determined under pseudo-first-order conditions.[2]

The alkaline hydrolysis of α-acetoxystyrene under second-order conditions, $[OH^-] = [\mathbf{1c}]$, was followed to verify that we could reproduce the rate constant observed under first-order conditions, and to provide a method for following the progress of the hydrolysis reaction during the ^{18}O exchange experiments which were themselves performed under second-order conditions. Kinetic solutions were prepared in a manner identical with that used in the first-order cases, and solutions of KOH and **1c** were made so that injection of 25 μL of an ethanolic solution of **1c** into 3 mL of the KOH solution would give an initial concentration of each reagent equal to 1.08×10^{-3} M. The progress of the reaction was followed at 29.9 ± 0.1 °C by the change in UV absorbance at 302 nm. The respective extinction coefficients for acetophenone (=S) and **1c**, ϵ_S and ϵ_α, could be determined from A_∞, A_0, and the initial concentration of **1c** by

$$\epsilon_S = A_\infty/(1.08 \times 10^{-3}) \quad (2)$$

$$\epsilon_\alpha = A_0/(1.08 \times 10^{-3}) \quad (3)$$

The concentration of the starting material as a function of time could then be calculated by

$$[\mathbf{1c}]_t = 0.00108 \text{ M} - \frac{A_t - A_0}{\epsilon_S - \epsilon_\alpha} \quad (4)$$

Plots of $1/[\mathbf{1c}]$ vs. time were linear to at least 70% completion, and rate constants determined from the slopes of these plots for both the ^{18}O-enriched and normal ester were in excellent agreement with the value of 63 ± 2 M^{-1} min^{-1} which was previously determined under first-order conditions.

General Methods and Sample Handling in ^{18}O Experiments. The synthesis of the ^{18}O-enriched α-acetoxystyrene has been described above. During all experiments concerning this ester, great care was taken to avoid contact of the ester with atmospheric moisture in order to avoid possible exchange reactions. When possible, the ester was protected with a blanket of argon, and stored in a desiccator. Contact with drying agents such as $MgSO_4$ was kept to a minimum because of the reported exchange of the carbonyl oxygen of esters in the presence of such drying agents.[8d]

Methylene chloride and pentane used in the experiments with the ^{18}O-enriched ester were distilled prior to use. The pentane was distilled under argon from CaH_2 since it was the solvent used in the analysis of the ester by gas chromatography–mass spectroscopy.

Mercuric chloride, used in the pyrolysis of ester samples of CO_2, was sublimed under a dry vacuum and stored in a desiccator. The amine 7,8-benzoquinoline, which was used as an HCl trap in the pyrolysis experiments, was recrystallized to a constant melting point from ethanol, thoroughly dried under vacuum, and stored in a desiccator. Water used in the experiments was deionized, and distilled under argon. After distillation, it was flushed with argon and stored in an all-glass bottle under an argon blanket until used. The Finnigan 3300 mass spectrometer was used for all ^{18}O analyses.

Methods of ^{18}O Analysis. The ^{18}O-enriched samples of α-acetoxystyrene were analyzed for ^{18}O content by mass spectrometric analysis of samples of the intact compound. Samples were prepared for analysis by dissolving 1 μL of the ester in 1 mL of dry pentane. Two GLC columns were used for gas chromatographic separation of the ester from solvent on the mass spectrometer: a 6 ft × 0.125 in. 5% DEGS column used at 130 °C, and a 6 ft × 0.125 in. 3% OV 101 column used at 90–100 °C. Both columns gave comparable results.

The ^{18}O content of the **1c** was determined by monitoring the relative abundance of ^{18}O- and ^{16}O-containing fragments of this compound. Three sets of ions with the following *m/e* ratios were monitored: 43 and 45; 120 and 122; 162 and 164. The ions with *m/e* of 43 and 45 contained oxygen from only the carbonyl position (see below), the ions with *m/e* of 120 and 122 contained oxygen from the acetophenone enol portion of the molecule, and the ions of *m/e* 162 and 164 are the molecular ions for molecules of **1c** containing no ^{18}O atoms and one ^{18}O atom, respectively. Depending on the conditions, either the peak at *m/e* 43 or 120 was the base peak. The molecular ion peak was about 12% as large as the base peak.

The abundance data for these peaks were collected from intact **1c** by one of two methods. Method A involved taking the average value of the ratio $(p + 2)/p$ for the three sets of ions from a total of four to six mass spectral scans in the region near the peak of the reconstructed gas chromatogram of this compound. Method B involved the use of a program which summed the relative abundances of the six peaks for all the mass spectral scans within the gas chromatographic peak of the ester. Three injections of each sample were made to establish an average value and a standard deviation for the ratios $(p + 2)/p$. In method A, the normal procedure of substracting a background spectrum from the spectrum of **1c** was employed. It was shown that for method B, substracting a background collected by summing over an equal number of scans containing no solvents or other compounds resulted in no appreciable change of the $(p + 2)/p$ ratios. This background substraction method was therefore, not used.

In both cases, the excess fraction of ^{18}O in the enriched compound was obtained by correcting for the normal isotope level of ^{18}O and other isotopes by the use of abundance data collected in an identical manner for a sample of the unlabeled compound. The excess fraction of ^{18}O, calculated from a given set of peaks $(p + 2)$ and p, X_p, could be determined for each of the three sets of peaks from

$$X_p = \left(\frac{(p+2)}{p} \Big/ \left(1 + \frac{(p+2)}{p}\right)\right)_e - \left(\frac{(p+2)}{p} \Big/ \left(1 + \frac{(p+2)}{p}\right)\right)_u \quad (5)$$

where $(p + 2)/p$ is the average ratio of the abundance of the ^{18}O-containing ion to the abundance of the unlabeled ion as determined by one of the two methods previously described. The subscripts e and u refer to the enriched and unenriched samples, respectively. Table I gives the values of X_p for the ^{18}O-enriched α-acetoxystyrene as determined by the two methods.

If the peaks at *m/e* 43 and 45 contain only oxygen from the carbonyl position, and the peaks at *m/e* 120 and 122 contain only oxygen from the enol position of the molecule, then X_{162}, the observed excess fraction of ^{18}O for the molecular ion, is given by

$$X_{162} = X_{43} + X_{120} - 2X_{43}X_{120} \quad (6)$$

This is due to the fact that X_{43} and X_{120} do not represent mutually exclusive events, and X_{162} is the excess fraction of molecules containing one and only one ^{18}O atom. Contributions from a peak at *m/e* 166, which is too small to measure, would need to be included to represent the excess fraction of molecules containing either one or two ^{18}O atoms.

Table I. Excess Fractions of ^{18}O, X_p, as Determined for p = 43, 120, and 162 for α-Acetoxystyrene by Methods A and B

	X_p[a]	
	Method A	Method B
X_{43}	0.1068 ± 0.0031	0.1066 ± 0.0011
X_{120}	0.0195 ± 0.0005	0.0186 ± 0.0002
X_{162}	0.1214 ± 0.0042	0.1214 ± 0.0008

[a] X_p is defined by eq 5. The values are given with their standard deviations.

The calculated value of X_{162} given by the results of X_{43} and X_{120} for the two methods is 0.1221 ± 0.0038 from method A, and 0.1212 ± 0.0014 from the results of method B. In both cases, the agreement between observed and calculated values of X_{162} is excellent. The results are consistent with the idea that the peaks of *m/e* 43 and 120 arise from portions of the molecule which contain the two different oxygens.

Inspection of Table I also shows that the standard deviations of the excess fractions as determined by method B are less than those determined by method A. This was a general phenomenon also observed during analysis of the samples of **1c** recovered from partial hydrolysis experiments, and probably reflects the very much larger sample size used in the determination of the excess fractions by method B.

A sample of this ester was also analyzed for ^{18}O content by conversion to CO_2 by the method of Rittenburg and Ponticorvo.[11] The ester (5 μL) and 0.5 g of mercuric chloride were sealed in a 12-cm pyrolysis tube, with a break-seal at the closed end, under a vacuum of approximately 5×10^{-4} Torr. The tube was immersed in a 2-propanol–dry ice bath to prevent loss of the α-acetoxystyrene during the evacuation and sealing process. This tube was then heated at 400 °C in a glass pyrolysis oven for 4.5 h to convert the ester to CO_2. The tube was then placed in a larger glass tube (about 30 cm long) with a standard taper joint which would allow easy connection to a vacuum line. Since HCl is a by-product of the pyrolysis, 0.25 g of 7,8-benzoquinoline was used as an HCl trap. The amine had been applied to the inner walls of the large tube before the pyrolysis tube was inserted by melting the amine in the tube with a heat gun. A stainless steel weight was also included to provide a means to break the break-seal of the pyrolysis tube. The contents of the large tube were evacuated to a vacuum of 10^{-4} Torr. The tube was immersed in a 2-propanol–dry ice bath during this time to prevent sublimation of the benzoquinoline. After approximately 0.5 h of evacuation, the tube was isolated from the vacuum line, the break-seal of the pyrolysis tube was broken, and the HCl was allowed to react with the benzoquinoline for about 5 min. The tube was then immersed in a liquid nitrogen bath, and was again subjected to evacuation at about 10^{-4} Torr to remove noncondensable gases. After about 10 min, the vacuum line was isolated from the pump and the liquid nitrogen cold traps, the liquid nitrogen bath was removed from the tube and replaced by a 2-propanol–dry ice bath, and the CO_2 was allowed to sublime into a 2 × 7 cm tube, with an adjustable high vacuum Teflon valve, that was cooled in a liquid nitrogen bath. The valve was then closed, and the contents of the tube were analyzed by mass spectrometry. The ratio of the abundance of the *m/e* 46 peak to the *m/e* 44 peak could be converted into the excess fraction of ^{18}O, X_{CO_2}, by use of

$$X_{CO_2} = \frac{(r) + \frac{1}{2}(r)^2}{2 + 2(r) + \frac{1}{2}(r)^2} - Q \qquad (7)$$

where Q is the fraction of ^{18}O in a sample of unenriched **1c** and r is equal to the ratio of the abundance of the peak at *m/e* 46 to the abundance of the peak at *m/e* 44. The equations used by others[8,12] are approximations to this equation in which the terms in $(r)^2$ are ignored. This approximation is only valid in the limit of low levels of ^{18}O and amounts to an error of several percent in the case of a compound with the amount of label used in this study. The value of Q was determined to be 0.0021 ± 0.0001 from the pyrolysis of a sample of the unenriched ester. This is in excellent agreement with the accepted value of 0.00204.[8c]

Analysis of the excess fraction of ^{18}O in the α-acetoxystyrene by this method gave a value of X_{CO_2} of 0.0637 ± 0.0009. This is in excellent agreement with the value of $(X_{43} + X_{120})/2$ of 0.0626 ± 0.0007 as determined by the analysis of the intact ester via method B. This is further evidence that the original assumptions concerning the origin of the oxygen atoms in the *m/e* 43 and 120 fragments are valid.

In the analysis of the ^{18}O exchange experiments, it was therefore assumed that X_{43} represented the excess fraction of ^{18}O in the carbonyl position, and that X_{120} represented the excess fraction of ^{18}O in the enol position of the compound **1c**.

The CO_2 method of ^{18}O determination was not used in the analysis of the samples subjected to partial hydrolysis because we had considerable difficulty in obtaining reproducible results by that method. The source of this problem could not be determined. Further disadvantages of this method compared to direct analysis of **1c** were the necessity for larger sample sizes (5 μL, compared to 1 μL for direct analysis), and the inability to monitor the ^{18}O content of the carbonyl and enol positions independently.

^{18}O Exchange Experiments. The concentrations of the ^{18}O-enriched α-acetoxystyrene and KOH used in the exchange experiment were identical with those used in the second-order hydrolysis experiments described above. Before each exchange experiment, the ester was preparatively gas chromatographed at 140 °C on an 8 ft × 0.25 in. 10% SE-30 column to ensure purity.

A volume of 500 or 1000 mL of the KOH solution (1.09×10^{-3} M KOH) was stirred under argon in a three-necked, 2-L, round-bottomed flask immersed in a water bath at 30.0 ± 0.5 °C. When the KOH solution has reached the temperature of the bath (30–40 min), a quantity of a freshly prepared 0.1309 M solution of the ^{18}O-enriched α-acetoxystyrene in ethanol was added so that the concentration of the α-acetoxystyrene was equal to that of KOH. The progress of the reaction was followed by monitoring the change in absorbance at 302 nm of 3 mL of the hydrolysis reaction mixture. Aliquots, which were adjusted in size in order to contain about 10–15 mg of the unreacted **1c**, were withdrawn at intervals and quickly neutralized with 0.1 M HCl. The pH of the aliquots after neutralization was between 6.5 and 7.0. These solutions were then extracted five times with 0.25 volumes of methylene chloride after 10 g of NaCl per 100 mL of aqueous solution was added to aid in the extraction. The methylene chloride extracts were combined and quickly dried with $MgSO_4$ on a fritted filter. Contact with $MgSO_4$ was kept to less than 1 min to avoid loss of the carbonyl enrichment. The methylene chloride solutions were then distilled through a 12-in. Hempel column until no further material would distill at a pot temperature of 55 °C. The remaining material was transferred to a 25-mL pear-shaped flask, and the methylene chloride which remained was removed under a dry vacuum on a rotary evaporator. Argon was bled into the system upon completion of the evaporation to protect the samples from atmospheric moisture. The α-acetoxystyrene was then separated from the hydrolysis product, acetophenone, by preparative gas chromatography on an 8 ft × 0.25 in. SE-30 comumn at 140 °C. Control experiments with unlabeled **1c** showed that approximately 90% recovery of the ester could be achieved by this method. The purified samples of the ester were stored in sealed glass ampules until ^{18}O analysis could be performed by the methods described above. A control experiment in which the recovery procedure was followed for an ^{18}O-enriched sample of the α-acetoxystyrene dissolved in the 5% ethanol solvent system containing no KOH showed that no diminution in the excess fraction of ^{18}O had occurred.

The data from the exchange experiments were evaluated according to the methods of Bender[8a] and Shain and Kirsch[8c] by plotting log $(100X_{43}/X_{0,43})$ vs. log $(100\ E/E_0)$, where $X_{0,43}$ is the initial value of X_{43} before hydrolysis, and E/E_0 is the fraction unreacted ester as *observed* from a plot of absorbance at 302 nm vs. time. The experiment was repeated three times to establish the reproducibility of the results.

Results and Discussion

Products of Hydrolysis. The products of alkaline hydrolysis of **1** were identified as acetophenone and (presumably) acetic acid. The hydrolysis of **2** under both acidic and alkaline conditions was found to yield ethyl phenylacetate and acetic acid.

Kinetics of Alkaline Hydrolysis of 1a–f and 2. The hydrolytic pseudo-first-order rate constants, k_{obsd}, in alkaline solution [5 vol % ethanol, μ = 0.5 M (KCl), 29.9 °C] for compounds **1a–f** and **2** were determined to have a first-order dependence on $[OH^-]$:

$$k_{obsd} = k_2[OH^-] \qquad (8)$$

Values of k_2 for **1a–f** and **2** are given in Table II. A correlation of log k_2 for **1a–f** against σ for the substituent on the leaving group is excellent and has a slope, ρ, equal to 0.47 ± 0.03. For

Table II. Rate Constants for Alkaline Hydrolysis of 1a–f and 2

Compd	k_2,[a] M^{-1} min^{-1}	Compd	k_2,[a] M^{-1} min^{-1}
1a	54 ± 1	1e	102 ± 3
1b	55 ± 1	1f	158 ± 4
1c	63 ± 2	2	410 ± 30
1c (D_2O)[b]	85 ± 6	2 (D_2O)[b]	510 ± 20
1d	94 ± 3		

[a] Second-order rate constants for hydrolysis by OH^- at 29.9 °C, reported with their standard deviations (eq 8). The range of hydroxide ion concentration used to establish the second-order rate law was 0.008–0.08 M. [b] The solvent system is identical with that used in the other hydrolysis experiments, except that C_2H_5OH, H_2O, and KOH are replaced by C_2H_5OD, D_2O, and KOD, respectively.

Table III. Rate Constants for the Acid Hydolysis of 1-Acetoxy-1-ethoxy-2-phenylethylene (2) in HCl, DCl, and Formic Acid Buffers[a]

Catalyzing species HA	k_{HA}, M^{-1} min^{-1}	k_{DA}, M^{-1} min^{-1}
H_3O^+(D_3O^+)	7.19 ± 0.07[b]	2.30 ± 0.05[c]
Formic acid[e]	0.0564 ± 0.0002[d]	

[a] Rate constants reported with their standard deviations. [b] Determined in HCl solutions from pH ca. 1.00 to 2.70 and from the intercepts of formic acid buffer plots, pH 2.56 to 3.12. [c] Determined in two DCl solutions, pD 1.51 and 2.24, made from standardized ca. 1.0 M DCl. [d] Determined from the intercept of a plot of buffer slopes vs. fraction of formate. This plot gave no evidence for a term in formate ion. [e] $pK_a = 3.50 \pm 0.02$ under the conditions of our experiment.

Table IV. Results of ^{18}O Exchange Experiments for the Partial Hydrolysis of ^{18}O-Enriched α-Acetoxystyrene[a]

Expt no.	E/E_0[b]	X_{43}[c]
1	1.00	0.1086 ± 0.0045
	0.73 ± 0.02	0.1092 ± 0.0018
	0.54 ± 0.01	0.1081 ± 0.0016
	0.38 ± 0.01	0.1069 ± 0.0021
	0.23 ± 0.01	0.1089 ± 0.0069
2	1.00	0.1028 ± 0.0027
	0.70 ± 0.02	0.1042 ± 0.0022
	0.37 ± 0.01	0.1024 ± 0.0023
	0.19 ± 0.01	0.1043 ± 0.0025
3	1.00	0.1083 ± 0.0004
	10.71 ± 0.02	0.1083 ± 0.0004
	0.37 ± 0.01	0.1084 ± 0.0011
	0.28 ± 0.01	0.1089 ± 0.0004

[a] Conditions: 5% ethanol–water, μ = 0.5 M (KCl), [ester] = $[OH^-] = 1.08 \pm 0.01 \times 10^{-3}$ M, 30.0 ± 0.5 °C. [b] Fraction ester unreacted as observed from a plot of absorbance vs. time of an aliquot of the reaction mixture at 302 nm. [c] Excess ^{18}O fraction in carbonyl as determined in the Experimental Section. Experiments 1 and 2 were determined by method A and experiment 3 by method B. Errors are standard deviations.

comparison purposes, the value of k_2 for phenyl acetate, determined in the same solvent system, was found to be 138 ± 3 M^{-1} min^{-1}.

Solvent Deuterium Isotope Effects. Buffer Catalysis. It was previously shown[2] that the amine-containing terms in the rate law for aminolysis of **1a–f** corresponded to true aminolysis rather than amine-catalzyed hydrolysis; thus, the hydrolysis of **1a–f** in alkaline solution does not show detectable buffer catalysis with the amine buffers examined. A comparison of the hydrolytic rate constants of **1c** in deuterated and nondeuterated solvent (Table II) yields the solvent isotope effect, $k_{2,OH}/k_{2,OD}$, equal to 0.74 ± 0.07, which is identical with that observed during alkaline hydrolysis of phenyl acetate under similar conditions.[3a] The relative rate constants for hydrolysis of **2** in OH^- and OD^- (Table II) yield a solvent isotope effect for the hydrolysis of this compound equal to 0.80 ± 0.09, similar to that observed for the hydrolysis of **1c** as well as that observed for other esters.[3a,13]

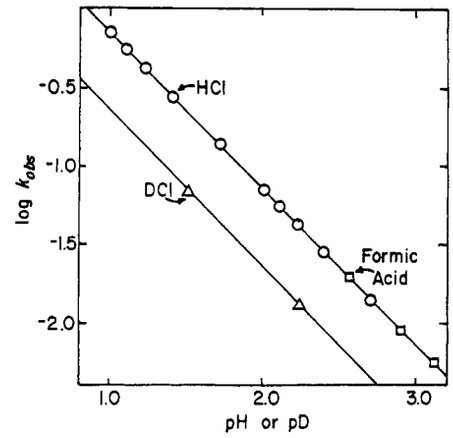


Figure 1. The dependence of the observed, pseudo-first-order rate constant for the hydrolysis of **2** on pH and pD in the acidic pH region. The circles are directly measured, and the squares are extrapolated to zero buffer concentration in the plots shown in Figure 2.

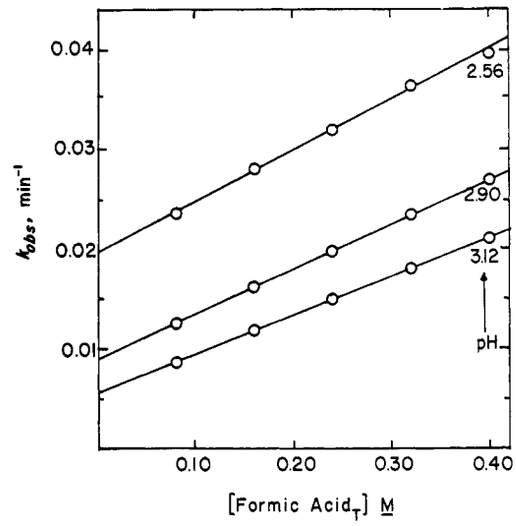


Figure 2. The dependence of the observed, pseudo-first-order rate constant for the hydrolysis of **2** on total buffer concentration.

However, in mildly acid solution the hydrolysis of **2** does not appear to conform to the normal behavior observed for alkyl and aryl esters.[14,15] Table III summarizes the rate constants for hydrolysis of **2** in HCl and DCl solutions and in formate buffers. Figure 1 shows the pH (and pD) rate profile for acid-catalyzed hydrolysis of **2**, and Figure 2 shows the dependence of the rate constant for hydrolysis on the concentration of formic acid in formate buffers. The solvent deuterium isotope effect for hydrolysis, $k_{H_3O^+}/k_{D_3O^+}$, 3.1 ± 0.1, and general acid catalysis of hydrolysis by the acidic components of formate buffers is observed.

^{18}O Exchange Experiments. α-Acetoxystyrene, ^{18}O enriched largely in the carbonyl oxygen, was synthesized by an acid-catalyzed acetate exchange between acetophenone and isopropenyl acetate-^{18}O, as described in the Experimental

Table V. ^{18}O Exchange Data for the Alkaline Hydrolysis of Various Esters

Ester	pK_a of the alcohol	Conditions	k_2/k_{ex}	Ref
tert-Butyl benzoate	17.3[a]	62.5 °C, 33% dioxane–water	7.6	8a
Isopropyl benzoate	16.6[a]	25.1 °C, 33% dioxane–water	3.7	8a
Ethyl benzoate	16.0[b]	25.1 °C, water	4.8	8a
Ethyl benzoate	16.0[b]	25.1 °C, water, μ = 0.003 M	12.6	8c
Methyl benzoate	15.5[b]	25 °C, water, μ = 0.003 M	27.7	8c
Methyl benzoate	15.5[b]	25 °C, 33% dioxane–water, μ = 0.01 M	89	8c
Methyl formate	15.5[b]	25 °C, water, μ = 0.1 M	18.3	8d
p-Chlorobenzyl benzoate	*c*	25 °C, 66.7% dioxane–water	>100	8e
p-Chlorobenzyl benzoate	*c*	25 °C, 50% dioxane–water	60	8e
p-Methoxybenzyl benzoate	*c*	25 °C, 66.7% dioxane–water	>100	8e
Phenyl benzoate	10.0[d]	50% dioxane–water	>100	8f
α-Acetoxystyrene	11.0[e]	5 vol % ethanol–water, μ = 0.5 M	>100	This work

[a] These values estimated from a correlation of pK_a vs. σ^* (ρ = −1.42) for a series of substituted methanols from ref 17, and σ^* values from ref 18. [b] Source: ref 17. [c] The pK_a of benzyl alcohol in water can be estimated to be 15.0 based on a correlation of pK_a values of substituted methyl alcohols vs. σ^* from ref 17 and a value of σ^* for C_6H_5 of 0.60 from ref 18. The *p*-chloro and *p*-methoxy substituted alcohols would be expected to have slightly lower and slightly higher pK_a values, respectively. [d] Source: ref 4a. [e] Source: ref 2 and 5.

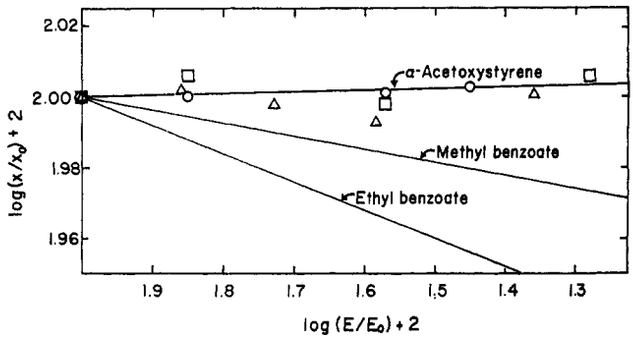


Figure 3. A plot of the logarithm of the percent ^{18}O exchange vs. logarithm of the percent observed reaction for the hydrolysis of **1c** with an ^{18}O-enriched carbonyl group. The different symbols represent different experiments (see text). The similar plots (from ref 8c) for methyl and ethyl benzoate, k_{obsd}/k_{ex} = 27.7 and 12.6, respectively, are presented for comparison purposes.

Section. The labeled isopropenyl acetate was in turn prepared from the addition of acetic acid-^{18}O to methylacetylene. Table IV gives the results of three experiments in which the ^{18}O content of the labeled α-acetoxystyrene was monitored as a function of the extent of alkaline hydrolysis by mass spectral analysis of unreacted compound recovered at appropriate times during alkaline hydrolysis under conditions in which [OH^-] = [**1c**]. The results indicate that X_{43}, the excess fraction of ^{18}O in the carbonyl position of **1c**, does not decrease as the hydrolysis proceeds. This fact indicates that there is no ^{18}O exchange with solvent during the hydrolysis. The results were fit by means of a weighted linear least-squares calculation to

$$\log (100X/X_0) = (k_{ex}/k_2) \log (100E/E_0) + 2.0 - 2.0(k_{ex}/k_2) \quad (9)$$

in which E/E_0 is the ratio of unreacted α-acetoxystyrene at time t to the initial concentration of this compound, X/X_0 is the ratio of the excess fraction ^{18}O in the carbonyl position of **1c** at time t to the initial excess fraction, k_2 is the rate constant for alkaline hydrolysis (eq 8), and k_{ex} is the rate constant for ^{18}O exchange. This equation, or one similar to it, has been used previously to calculate the ratio k_2/k_{ex} from ^{18}O exchange data.[8a,c]

The correlation line which resulted from the calculation had a negative slope (−0.0048 ± 0.0021), a fact which indicates that the ^{18}O content of the carbonyl position of labeled **1c** increases as the hydrolysis proceeds. This kind of phenomenon has been observed previously in the concurrent ^{18}O exchange and alkaline hydrolysis of esters which very large k_2/k_{ex} ratios, and has been attributed to the kinetic isotope effect, k_{16O}/k_{18O}, for the hydrolysis reaction.[8c]

Figure 3 is a plot of log ($100X/X_0$) vs. log ($100E/E_0$) for the data derived for hydrolysis of **1c**. The correlation lines for the ^{18}O exchange data in alkaline solution determined for ethyl and methyl benzoate in water[8c] are included for comparison purposes. The values of k_2/k_{ex} for the two latter esters at 25 °C are 12.6 and 27.7, respectively.[8c] The behavior of α-acetoxystyrene much more closely resembles that of phenyl benzoate, which also shows no ^{18}O exchange upon alkaline hydrolysis.[8f] A lower limit for k_2/k_{ex} for **1c** of approximately 10^2 can be estimated from the limits of detection of very small changes in ^{18}O levels and the carbonyl oxygen isotope effect, which can lead to an overall increase in the excess fraction of ^{18}O as a function of the extent of reaction if k_2/k_{ex} is very large.[8c]

The fact that no ^{18}O exchange could be detected during the partial hydrolysis of carbonyl-^{18}O enriched **1c** is further evidence that acetophenone enols are quite acidic. Ester of weakly acidic alcohols such as methyl and ethyl benzoate[8a,c] or methyl formate[8d] show considerable ^{18}O exchange, as Table V indicates. This table shows that the ratio of hydrolysis to exchange, k_2/k_{ex}, generally increases as the pK_a of the alcohol corresponding to the leaving group decreases. The results for *p*-chlorobenzyl and *p*-methoxybenzyl benzoates[8e] appear to be anomalous, but may be due to the large fraction of dioxane cosolvent used in these experiments.[8c] It has been shown that the ratio k_2/k_{ex} increases as the fraction of dioxane in the solvent is increased. The behavior of α-acetoxystyrene resembles that of phenyl benzoate with regard to a lack of observed ^{18}O exchange during alkaline hydrolysis.

The acid-catalyzed hydrolyses of compounds **1a–f** and **2** do not correspond in their mechanistic behavior to that observed for the corresponding hydrolyses of alkyl and aryl esters. Solvent deuterium isotope effects, $k_{H_3O^+}/k_{D_3O^+}$, for the hydrolysis of esters by the $A_{AC}2$ mechanism are inverse,[19a] and no general acid catalysis of hydrolysis in aqueous solution is observed.[19b] These and other pieces of evidence[8a,d,15,20] indicate that the acid-catalyzed hydrolysis of esters by the $A_{AC}2$ mechanism proceeds by a rate-limiting attack of water on a protonated ester which is formed in a rapid preequilibrium.

The hydrolysis of α-acetoxystyrenes in strongly acidic media ($H_0 < -1.0$) has been shown to proceed by a different mechanism, however.[6] A primary solvent deuterium isotope

effect of 3.1 for the hydrolysis of **1a** in strongly acidic media indicates that the rate-limiting step of the hydrolysis of this ester under these conditions is proton transfer from solvent to the double bond to form a carbonium ion which is subsequently rapidly attacked by water. Under mildly acidic conditions the α-acetoxystyrenes apparently hydrolyze via the normal $A_{AC}2$ mechanism of acid-catalyzed ester hydrolysis.[6] However, our studies with the acylenol **2** indicate that this compound hydrolyzes via rate-determining proton transfer to the double bond even in the mildly acidic pH region. The solvent deuterium isotope effect, 3.1 ± 0.1, for the hydrolysis of **2**, determined in the acidic pH region is similar to solvent deuterium isotope effects of 2.5–3.0 observed for the hydrolysis of ketene acetals[21] and vinyl ethers,[22] both of which hydrolyze by rate-determining protonation of the double bond. This isotope effect is also identical with that observed for hydrolysis of **1a** (see above) in the strong acid region of acidity.

Acknowledgment. This work was supported by a grant from the National Institute of General Medical Sciences. Michael Novak acknowledges support by a National Institutes of Health Training Grant.

Registry No.—**1a**, 22390-98-3; **1b**, 22390-99-4; **1c**, 2206-94-2; **1d**, 22479-32-9; **1e**, 22391-00-0; **1f**, 22391-01-1; **2**, 62415-90-1; acetyl chloride, 75-36-5; $H_2{}^{18}O$, 14314-42-2; isopropenyl acetate-^{18}O, 62415-91-2; acetic acid-^{18}O, 60321-43-9; methylacetylene, 74-99-7; 1-ethoxy-2-phenylacetylene, 32569-84-9; $Hg(OAc)_2$, 1600-27-7; α-acetoxystyrene-^{18}O, 62415-92-3.

References and Notes

(1) NSF Predoctoral Fellow, 1972–1975.
(2) M. Novak and G. M. Loudon, *J. Am. Chem. Soc.*, **98**, 3591 (1976).
(3) (a) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 675 (1960); (b) T. C. Bruice and M. F. Mayahi, *ibid.*, **82**, 3067 (1960); (c) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, **89**, 2106 (1967); (d) L. doAmaral, K. Koehler, P. Bartenbach, T. Pletcher, and E. H. Cordes, *ibid.*, **89**, 3537 (1967); (e) G. M. Blackburn and W. P. Jencks, *ibid.*, **90**, 2638 (1968); (f) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968); (g) A. C. Satterthwait and W. P. Jencks, *ibid.*, **96**, 7018 (1974).
(4) (a) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, **86**, 837 (1964); (b) J. T. Ryan and A. A. Humffray, *J. Chem. Soc. B*, 842 (1968); (c) B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2982, 2985 (1969).
(5) M. Novak and G. M. Loudon, *J. Org. Chem.*, preceding paper in this issue.
(6) D. S. Noyce and R. M. Pollack, *J. Am. Chem. Soc.*, **91**, 119 (1969).
(7) G. F. Hennion and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 1802 (1934).
(8) (a) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951); (b) M. L. Bender, R. D. Ginger, and J. P. Unik, *ibid.*, **80**, 1044 (1958); (c) S. A. Shain and J. F. Kirsch, *ibid.*, **90**, 5848 (1968); (d) C. B. Sawyer and J. F. Kirsch, *ibid.*, **95**, 7375 (1973); (e) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *ibid.*, **83**, 4193 (1961); (f) C. A. Bunton and D. A. Spatcher, *J. Chem. Soc.*, 1079 (1956).
(9) R. Tanaka and S. I. Miller, *Tetrahedron Lett.*, 1753 (1971).
(10) W. von Philipsborn, *Angew. Chem., Int. Ed. Engl.*, **10**, 472 (1971).
(11) D. Rittenburg and L. Ponticorvo, *Int. J. Appl. Radiat. Isot.*, **1**, 208 (1956).
(12) M. L. Bender and H. d'A. Heck, *J. Am. Chem. Soc.*, **89**, 1211 (1967).
(13) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955).
(14) (a) A. J. Kirby in "Comprehensive Chemical Kinetics", Vol. 10, G. H. Bamford and C. F. H. Tipper, Ed., American Elsevier, New York, N.Y., 1972, p 57; (b) K. Yates, *Acc. Chem. Res.*, **4**, 136 (1971).
(15) K. Yates and R. A. McClelland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).
(16) C. A. Bunto and T. Hadwick, *J. Chem. Soc.*, 3034 (1957); 943 (1961); 3248 (1958).
(17) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).
(18) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **75**, 4231 (1953).
(19) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) M. L. Bender, "Mechanisms of Homogeneous Catalysis, from Protons to Proteins", Wiley, New York, N.Y., 1971, pp 37–71.
(20) (a) C. A. Lane, *J. Am. Chem. Soc.*, **86**, 2521 (1964); (b) C. A. Lane, M. F. Cheung, and G. F. Dorsey, *ibid.*, **90**, 6492 (1968).
(21) (a) R. Herschfield, M. J. Yeager, and G. L. Schmir, *J. Org. Chem.*, **40**, 2940 (1975); (b) V. Gold and D. C. A. Waterman, *J. Chem. Soc.*, 839, 849 (1968).
(22) (a) G. M. Loudon, C. K. Smith, and S. E. Zimmerman, *J. Am. Chem. Soc.*, **96**, 465 (1974); (b) A. J. Kresge and H. J. Chen, *J. Am. Chem. Soc.*, **94**, 2819 (1972), and references cited therein.

Notes

Quinoxaline Studies. 24.[1a] 3-(α-Cyano)benzyl-2(1*H*)-quinoxalinone *vs.* 2,3-Di(α-cyano)benzylquinoxaline. A Reinvestigation

Michaelee Moffitt[1b] and Harry P. Schultz*

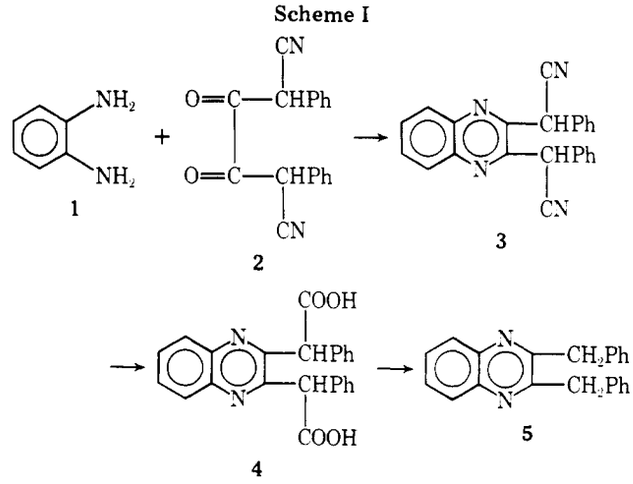
Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received December 10, 1976

Dutt and Sen[2] reported the preparation of quinoxalines of structure **3** by condensation of *o*-phenylenediamine (**1**) with the diketone **2** prepared by condensation of diethyl oxalate with 2 mol of benzyl cyanide. In an effort to repeat this work for the purpose of preparing **4** and **5** (Scheme I) we found that the starting carbonyl compound used by Dutt and Sen was actually the 1:1 condensation product **6**, and their final condensation product was 3-(α-cyanobenzyl)-2(1*H*)-quinoxalinone (**7**). Our experiments also indicated that **2** would not condense with **1** to give **3**, but fortuitously synthesis of type **5** compounds has been recently reported.[3]

Interestingly, Dutt and Sen[2] claimed to have prepared 1,4-dicyano-1,4-diphenyl-2,3-butanedione (**2**) by a variation of the method of Volhard,[4] wherein diethyl oxalate was condensed with 2 equiv of benzyl cyanide with sodium in ethanol.

Scheme I



But in contrast to Volhard's procedure, Dutt and Sen omitted the ethanol. Repetition of both procedures showed that Volhard prepared **2**, but that Dutt and Sen had prepared ethyl phenylcyanopyruvate (**6**). Formation of **6** in the absence of EtOH and an excess of benzyl cyanide is probably the consequence of precipitating the sodium salt of **6** formed by interaction of 1 equiv each of diethyl oxalate and benzyl cyanide,