Acid-Catalyzed Hydrolyses of 2-Alkoxytetrahydropyrans: Evidence for the Changeover from an A1 to an $A_{SE}2$ Mechanism

James L. Jensen* and William B. Wuhrman

Department of Chemistry, California State University, Long Beach, Long Beach, California 90840

Received May 5, 1983

Kinetics of the acid-catalyzed hydrolyses of 2-ethoxy-, 2-methoxy-, 2-(2-methoxyethoxy)-, 2-(2-chloroethoxy)-, 2-(propargyloxy)-, and 2-(2,2,2-trifluoroethoxy)tetrahydropyran have been studied in aqueous acidic solutions. The hydrolysis of 2-(2,2,2-trifluoroethoxy)tetrahydropyran occurs by an $A_{SE}2$ mechanism and exhibits the requisite general acid catalysis. While this mechanism cannot be strictly excluded for the hydrolysis of 2-ethoxytetrahydropyran, the lack of observation of general acid catalysis and the manner in which enthalpies and entropies of activation change as the 2-alkoxy group is changed strongly suggest an A1 mechanism. A rationale is presented for using entropies of activation as an indication of changeover from an A1 to an $A_{SE}2$ mechanism, based on the tetrahydropyran series (where such a changeover appears to occur) and on the benzaldehyde series (where hydrolyses occur by an $A_{SE}2$-like mechanism). It is observed that in order for a physical organic model to closely resemble the hydrolysis of a natural substrate at the active site of an enzyme (e.g., lysozyme), the leaving group must contain electronegative groups: aryloxy, 2,2,2-trifluoroethoxy, and 2-propargyloxy all seem adequate. This structural feature is much more important than inherent reactivity; thus 2-(2,2,2-trifluoroethoxy)tetrahydropyran is a better reaction model than methyl glucosides.

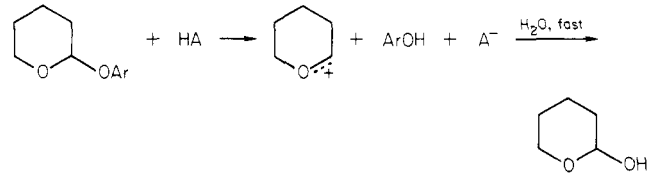
The hydrolyses of 2-substituted tetrahydropyrans have been investigated several times previously.[1,2] This is an important chemical system because it represents a close analogue of glycosides. Fife[1] has reported conclusive evidence showing that 2-(aryloxy)tetrahydropyrans hydrolyze by the $A_{SE}2$ mechanism (see Scheme I). These reactions are characterized by modest inverse kinetic solvent isotope effects ($k_{D_3O^+}/k_{H_3O^+}$ = 1–2), general acid catalysis, moderate Hammett ρ values (ρ = −0.9 for $k_{H_3O^+}$), and a hydrolysis process not catalyzed by acids when Ar contains strongly electron-withdrawing groups (Ar = *p*-nitrophenyl).

The relationship of the 2-aryloxy system to the 2-alkoxy system has not been addressed. The 2-alkoxy system has been investigated by Kankaanpera;[2] these hydrolyses are characterized by modest-to-large inverse kinetic solvent isotope effects ($k_{D_3O^+}/k_{H_3O^+}$ = 1.3–3) and a nonlinear Hammett correlation (general acid catalysis experiments have not been reported). Kankaanpera implied a change in mechanism[2b] from an A1 to an $A_{SE}2$ over the series R = CH_2CH_3, CH_3, $CH_2CH_2OCH_3$, CH_2CH_2Cl, CH_2CCl_3, CH_2CF_3 (see Scheme II).

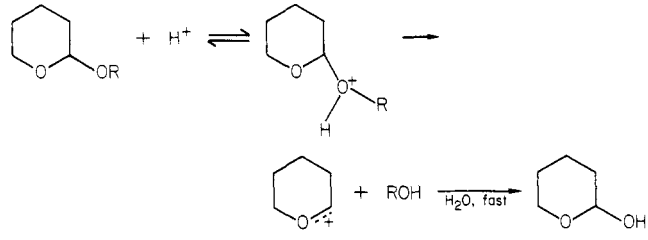
Since it has recently been demonstrated that the hydrolysis of various acetals of substituted benzaldehydes occur by an $A_{SE}2$-like mechanism[3] rather than by the previously believed A1 mechanism,[4] we thought it important to (1) establish the mechanistic changeover for the 2-alkoxy series, (2) relate the 2-alkoxy and the 2-aryloxy series, and (3) define the differences between the benzaldehyde acetal series and the tetrahydropyran series.

The work reported herein shows that, indeed, there is a mechanistic changeover for the series of 2-alkoxytetrahydropyrans; further, the changeover is different from that observed for the comparable series of benzaldehyde acetals. Finally, we conclude that the 2-aryloxy- or the 2-(trifluoroethoxy)tetrahydropyrans are better models for the natural glycosides than, say, are the methyl glucosides *if* the model is chosen to help define a hydrolysis catalyzed by a general acid (e.g., an amino acid in the active site of an enzyme).

Scheme I. $A_{SE}2$



Scheme II. A1

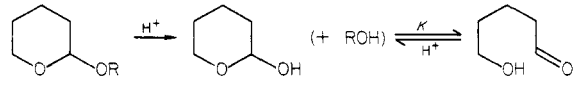


Experimental Section

Materials. The 2-alkoxytetrahydropyrans were synthesized as described by Kankaanpera;[2] the products were confirmed pure by ^1H NMR and gas chromatography.

Kinetic Method. Standard kinetic methodology was as described in previous studies.[3] Spectral experiments were performed with a Beckman Model 25, a Unicam SP 8-100, or a Durrum 132 stopped-flow spectrophotometer. A Beckman Model 4500 pH meter, equipped with a 5-mm Beckman combination electrode, was used for pH measurements. In the present study neither reactants nor products display an observable electronic absorption spectrum. We wish to maintain spectral concentrations to insure the irreversibility of the hydrolysis reaction; consequently, the product was converted to a chromophore-containing substance by using an excess of a trapping agent, thiosemicarbazide or semicarbazide. Provided the rate of the trapping reaction is an order of magnitude greater than the rate of the hydrolysis reaction, the appearance of the thiosemicarbazone or semicarbazone chromophore can be monitored as a measure of the rate of hydrolysis of the acetal. Since thiosemicarbazide is 1.8 pK units less basic than semicarbazide, it is useful to use thiosemicarbazide as the trapping agent below pH 3 and semicarbazide above pH 5 (where thiosemicarbazide slowly decomposes).

The Trapping Reaction. The product of the hydrolyzed pyran acetals is an aliphatic aldehyde, which exists in equilibrium with the cyclic hemiacetal in water.[5] Since aliphatic aldehydes



(1) (a) Fife, T. H.; Jao, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 4081. (b) Fife, T. H.; Brod, L. H. *Ibid.* **1970**, *92*, 1681.
(2) (a) Kankaanpera, A.; Miikki, K. *Suom. Kemistil. B* **1968**, *41*, 42. (b) Kankaanpera, A. *Ibid.* **1969**, *42*, 460.
(3) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergi, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* **1979**, *101*, 4672.
(4) (a) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581. (b) Fife, T. H. *Acc. Chem. Res.* **1972**, *5*, 264 and references therein.

0022-3263/83/1948-4686$01.50/0

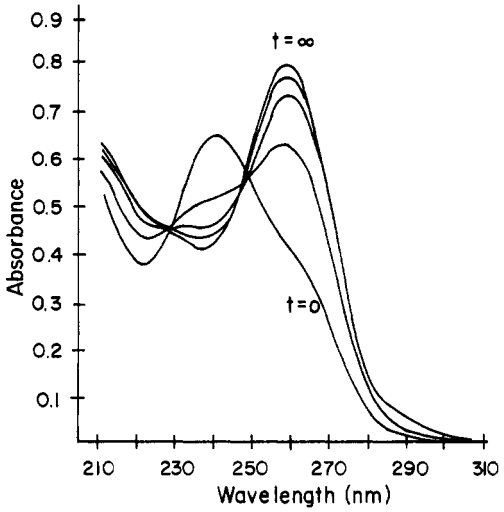


Figure 1. Repetitive scan of 10^{-2} M hydrolyzed acetal in aqueous solution 10^{-4} M in thiosemicarbazide, pH 2.

have a small molar extinction coefficient in the ultraviolet region (ϵ for butanal in water is 13 at λ_{max} = 283 nm),[6] it is difficult to monitor the hydrolysis of aliphatic acetals with the aldehyde chromophore. This problem is further compounded in the case of tetrahydropyran acetals by the equilibrium constant for the hemiacetal–aldehyde equilibrium ($K \sim 0.1$)[5] and the small concentrations used in this study ($\sim 10^{-4}$ M). Therefore, it was decided to use a trapping agent which would react rapidly with the free aldehyde produced by the hydrolysis reaction, irreversibly forming a condensation product with a sufficiently high molar absorptivity coefficient to enable the reaction to be monitored spectrophotometrically.[8d,e]

We chose an ammonia derivative as the trapping agent because these are classically used in making aldehyde derivatives and have large molar absorptivities in the ultraviolet. Since the reactions of semicarbazide and thiosemicarbazide with benzaldehyde have been extensively studied by Jencks and co-workers,[7,8a-c] they were chosen for use in this study. Employment of one or the other depended on the pH of the solution being investigated. Thiosemicarbazide (pK_a = 1.88)[7] was used in 0.01 N HCl, cyanoacetate, formate, and acetate buffers. Semicarbazide (pK_a = 3.65)[8] was used in the higher pH cacodylate buffer solutions.

Thiosemicarbazide (Aldrich) was purified by washing repeatedly with hot 95% ethanol (in which thiosemicarbazide is only slightly soluble) until no further discoloration of the ethanol was discernible. The white thiosemicarbazide crystals were then recrystallized from water, mp 184–185 °C (lit. 183–184 °C).[10] Semicarbazide was obtained in the form of the hydrochloride (Matheson, Coleman & Bell). The free base was formed in situ when needed by titrating with standard 1.00 N KOH.

The UV–visible spectrum of a solution containing a limiting amount of thiosemicarbazide ($\sim 10^{-4}$ M) reacting with hydrolyzed 2-ethoxytetrahydropyran ($\sim 10^{-2}$ M) was scanned repeatedly between 200 and 340 nm. The spectrum (Figure 1) showed the gradual disappearance of the thiosemicarbazide peak at 240 nm and the concurrent appearance of a peak at 261 nm corresponding to the thiosemicarbazone. The UV spectrum of butyraldehyde semicarbazone was determined by recording the spectrum of a 1.0×10^{-3} M semicarbazide solution containing 10^{-4} M butyraldehyde and using a 1.0×10^{-3} M semicarbazide solution as the reference. The resulting spectrum showed λ_{max} of the butyraldehyde semicarbazone to be 225 nm. The spectrum of the hydrolysis product semicarbazone (5-hydroxypentanal semicarbazone) was essentially identical with that of the butyraldehyde semicarbazone.

When the thiosemicarbazide was used as the trapping agent, the concentration necessary for rapid trapping reaction rates (0.02–0.03 M thiosemicarbazide) resulted in a high background absorbance at the absorption maximum of the thiosemicarbazone product. Therefore, the reactions had to be monitored in the 280–275-nm range, on the shoulder of the semicarbazide peak (see Figure 1). The background absorbance at this wavelength was usually ≤1 absorbance unit (although the instrument would function reliably were it 1.8 absorbance units). Since an absorbance change of about 0.5 absorbance units could usually be expected from thiosemicarbazone formation, this resulted in a final absorbance of about 1.5 (although reliable results could be obtained up to 2.3 absorbance units). The total absorption at $t = \infty$ is, of course, the limiting quantity and is limited by the stray light specifications of the monochromator: 2.3 absorbance units lies within those limits. Because the wavelength range of 280–275 nm lies on the side of the thiosemicarbazone peak (Figure 1), it was necessary to first show that Beer's Law violations would not be incurred. This was easily accomplished by placing a cuvette which contained the thiosemicarbazone product (a $t = \infty$ solution) in the spectrophotometer with air as the reference. After selecting the wavelength, the slit width was narrowed to the point where further narrowing did not change the observed absorbance of the solution. Further confirmation that Beer's Law was obeyed is the linearity of the first-order kinetic plots made from the absorbance data. (Semicarbazide, on the other hand, shows little absorbance at λ_{max} of the semicarbazone product at the concentrations used in this study, 0.01 M; therefore, reactions with semicarbazide as the trapping agent were followed at λ_{max} of the semicarbazone product.)

Sayer and Jencks[7] have shown that thiosemicarbazide formation exhibits pseudo-first-order kinetics when a large excess of thiosemicarbazide is used. In our case, the observed rate will be the rate of the 2-alkoxytetrahydropyran hydrolysis reaction, provided the trapping reaction is fast enough. Figures S1 and S2 (supplementary material) show the effect of the rate of the trapping reaction on the linearity of the first-order plots of the acetal hydrolysis reactions. In Figure S1, the rate of the trapping reaction is approximately twelve times faster than the hydrolysis reaction, and a perfectly linear plot over three half-lives of the hydrolysis reaction is observed. When the trapping reaction is only four times faster than the hydrolysis reaction, a linear first-order plot is also obtained; however, there is a brief induction period of about 0.5 half-lives before the plot becomes linear (Figure S2). Note that the calculated second-order hydrolysis rate constants from these two experiments are the same. In every instance where a hydrolysis rate constant was measured, it was verified that the trapping reaction was about an order of magnitude faster.

Results

All rate data were obtained spectrophotometrically to insure irreversibility of the hydrolysis of the 2-alkoxytetrahydropyrans; the observed rate constants were calculated in the traditional way from plots of log $(A_\infty - A)$ vs. time.[9,11] The pseudo-first-order rate constant, k_{obsd}, obtained from such a plot will be a product of the hydronium ion concentration and the second order rate constant k_{H^+} characteristic of each acetal:[1,2]

$$k_{obsd} = k_{H^+}[H_3O^+] \quad (1)$$

Table I lists the second-order hydrolysis rate constants for the 2-alkoxy tetrahydropyrans in HCl solutions at 25.0 °C calculated by dividing the observed first-order rate constants by the hydronium ion concentration (obtained from the measured pH), according to eq 1.

(5) Hurd, C. P.; Saunders, W. H. *J. Am. Chem. Soc.* **1952**, *74*, 5324.
(6) Grasselli, J. G., Ritchey, W. M., Eds. "Atlas of Spectral Data and Physical Constants of Organic Compounds", 2nd ed.; CRC Press: Cleveland, OH, 1975.
(7) Sayer, J. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6353.
(8) (a) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 4319. (b) Sayer, J. M.; Peskin, M.; Jencks, W. P. *Ibid.* **1973**, *95*, 4277. (c) Sayer, J. M.; Pinsky, B.; Schonbrum, A.; Jencks, W. P. *Ibid.* **1974**, *96*, 7998. (d) Evans, P. G.; Miller, G. R.; Kreevoy, M. M. *J. Phys. Chem.* **1965**, *69*, 4325–7. (e) Henaff, P. L. *C. R. Hebd. Seances Acad. Sci.* **1963**, *256*, 1752.
(9) Frost, A. A.; Pearson, R. G. "Kinetic and Mechanism", 2nd ed.; Wiley: New York, 1961; p 166.
(10) Weast, R. C., Ed. "Handbook of Chemistry and Physics", 59th ed.; CRC Press: Cleveland, OH 1979.
(11) Jensen, J. L.; Carré, D. J. *J. Org. Chem.* **1971**, *36*, 3180.

Table I. Second-Order Rate Constants for the Hydrolysis of 2-Alkoxytetrahydropyrans in μ = 0.5 M (KCl) Solutions[a]

R	k_{H^+}, M^{-1} s^{-1} [b] 25 °C	75 °C	pK_{ROH}[c]
CH_2CH_3	0.271	115	16.0
CH_3	0.226	87	15.5
$CH_2CH_2OCH_3$	0.304	120	14.8
CH_2CH_2Cl	0.392	117	14.3
$CH_2C{\equiv}CH$	0.372	97	13.5
CH_2CF_3	0.409	47	12.4
β =	−0.065 (0.85)	+0.083 (0.71)	

[a] [TSC] = 0.02–0.03 M, pH = 2.4–2.9. Values listed are means of ≥3 independent rate and pH measurements; % average deviation ≤6%. [b] Data at 25 °C calculated from eq 1 and the observed pH values of dilute HCl solutions; data at 75 °C calculated from eq 4 intercept by using pH values measured at 75 °C. [c] Reference 13. [d] ±0.03 in solutions described in *a*: in cyanoacetate and formate buffers of pH 2.8–3.8, k_{H^+} obtained from the intercept (i.e., k_{obsd} at [buffer] = 0) was 0.425 ± 0.02. Therefore,[20] eq 1 does not include a measurable k_0 term (as expected).[1]

General Acid Catalysis. For compounds exhibiting general acid catalysis, the observed rate constant will be a composite of all the rate constants of the acids present and their concentrations:

$$k_{obsd} = k_{H^+}[H^+] + \sum k_{HA}[HA] \quad (2)$$

If only one buffer acid is used, the only acidic species present in an aqueous solution will be H_3O^+ and HA, in which case eq 2 becomes

$$k_{obsd} = k_{H^+}[H^+] + k_{HA}[HA] \quad (3)$$

If the pH is maintained exactly constant over a series of buffer solutions in which [HA] is systematically varied, a plot of k_{obsd} vs. [HA] will yield a straight line of slope equal to k_{HA} and an intercept equal to $k_{H^+}[H^+]$. In practice, however, the pH often varies slightly in going from the most concentrated buffer solution (and therefore the least concentrated KCl solution) to the least concentrated buffer (and most concentrated KCl) solution. This phenomenon arises from a specific salt effect on pK_{HA} and is, of course, small; the variation in pH over a given series of buffers was ≤0.07 pH units. In order to take into account this salt effect and the resulting rate difference due to the slight variations in hydronium ion concentrations, plots of $k_{obsd}/[H^+]$ vs. $[HA]/[H^+]$ were made and yielded straight lines with slopes = k_{HA} and y intercepts of k_{H^+}, according to the following equation (obtained by dividing eq 3 through by $[H^+]$).[3]

$$k_{obsd}/[H^+] = k_{H^+} + k_{HA}[HA]/[H^+] \quad (4)$$

An additional advantage of this procedure is that all points for a given buffer acid lie on the same line *if* the only catalyzing species are H^+ and HA, as shown in Figure 2. For lines of such gentle slope, it is important to establish that what is actually being observed is general acid catalysis; the best method of demonstrating this can be seen in Figure 3, which illustrates the absence of significant acetic acid catalysis in the hydrolysis of 2-ethoxytetrahydropyran and the comparatively significant catalysis for the hydrolysis of 2-(2,2,2-trifluoroethoxy)tetrahydropyran.

While it was not feasible to measure k_{HA} values for all the 2-alkoxytetrahydropyrans, the following tabulation (Table II) shows the expected trend:[3] The substrate exhibiting the most catalysis is 2-(2,2,2-trifluoroethoxy)-tetrahydropyran, and the least catalysis is shown by 2-ethoxy- and 2-methoxytetrahydropyan. The other acetals exhibit an increasing importance of general acid catalysis as the alkoxy group becomes more electronegative—just as was observed more definitively for the analogous "mixed" acetals of benzaldehyde. Table II allows one to estimate quickly the k_{HA} values for these acetals, since we have measured k_{HOAc} = 7.18 × 10^{-5} M^{-1} s^{-1} for 2-(2,2,2-

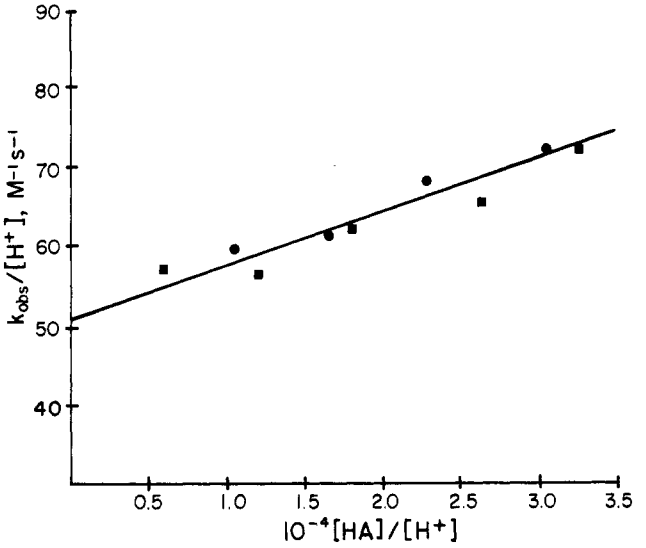


Figure 2. General acid catalysis plot for the hydrolysis of 2-(2,2,2-trifluoroethoxy)tetrahydropyran in 2:1 (●) and 1:1 (■) acetic acid/potassium acetate buffers at 75 °C: $k_{acetic\ acid}$ = 7.2 × 10^{-4} M^{-1} s^{-1}, k_{H^+} = 50 M^{-1} s^{-1}, μ = 0.5 (KCl).

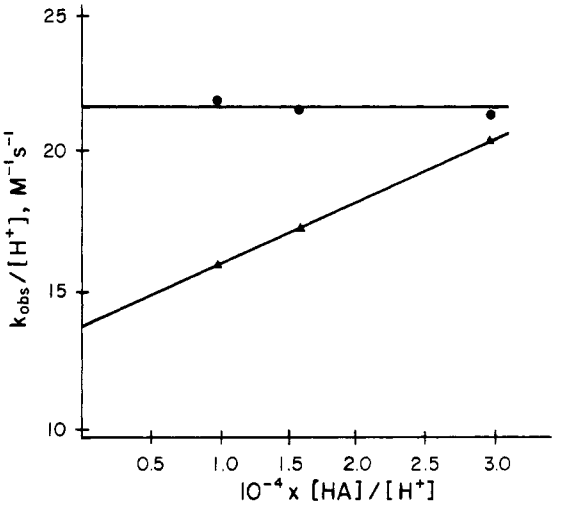


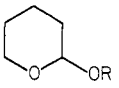
Figure 3. General acid catalysis plots for the hydrolyses of 2-(2,2,2-trifluoroethoxy)tetrahydropyran (▲) and 2-ethoxytetrahydropyran (●) in 2:1 acetic acid/potassium acetate buffers at 60 °C: $k_{acetic\ acid}$ = 2.3 × 10^{-4} M^{-1} s^{-1} and k_{H^+} = 13.6 M^{-1} s^{-1} for ▲, k_{H^+} = 21.6 M^{-1} s^{-1} for ●, μ = 0.5 (KCl).

Table II. Relative Amounts of General Acid Catalysis for 2-Alkoxytetrahydropyrans in 1:1 Acetic Acid Buffer Solutions[a]

2-alkoxy group	relative rate increase[b]
OCH_2CH_3	1.00
OCH_3	0.99
$OCH_2CH_2OCH_3$	1.05
OCH_2CH_2Cl	1.11
$OCH_2C{\equiv}CH$	1.09
OCH_2CF_3	1.38

[a] At 75 °C, μ = 0.5 (KCl). [b] ($k_{obsd}/[H^+]$ in 1.0 M buffer)/($k_{obsd}/[H^+]$ in 0.16 M buffer) relative to OCH_2CH_3 = 1.0.

Table III. Activation Parameters for the Hydrolysis of 2-Alkoxytetrahydropyrans[a]



R	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
CH_2CH_3	24.6[b]	21.1[b]
CH_3	23.7[c]	18.0[c]
$CH_2CH_2OCH_3$	24.1[c]	19.9[c]
CH_2CH_2Cl	23.1[c]	17.1[c]
$CH_2C{\equiv}CH$	21.6[c]	11.9[c]
CH_2CF_3	19.2[b]	4.0[b]

[a] Calculated at 25 °C from data in Table I. Statistical precision as limited by the k_{obsd} average deviation is ±0.7 kcal/mol and ±2 eu in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively. [b] Calculated from data at 40 and 60 °C in addition to Table I data: R = OCH_2CH_3, k_{H^+} = 1.85 and 21.6 M^{-1} s^{-1}, respectively, and the correlation coefficient for the Arrhenius plot is 0.9998; R = OCH_2CF_3, k_{H^+} = 1.77 and 13.6 M^{-1} s^{-1}, respectively, and the correlation coefficient is 0.9999. [c] Two temperature calculations and therefore tentative.

trifluoroethoxy)tetrahydropyran (Figure 2); for example, (7.18×10^{-5}) $(1.05/1.38) = 5.46 \times 10^{-5}$ M^{-1} $s^{-1} = k_{HOAc}$ for 2-(2-methoxyethoxy)tetrahydropyran. While the data are too limited to justify tabulation, it is interesting to note that such k_{HOAc} values, when taken together with $k_{H_3O^+}$ values, define two point α values. For the just-cited examples, α = 0.76 and 0.99, respectively, at 75 °C.

Our conclusion from Table II is that there is no significant general acid catalysis for the hydrolyses of 2-alkoxytetrahydropyrans when alkoxy = OCH_2CH_3, OCH_3, and $OCH_2CH_2OCH_3$; marginal catalysis is observed for alkoxy = OCH_2CH_2Cl and $OCH_2C{\equiv}CH$; the catalysis observed for alkoxy = OCH_2CF_3 is significant.

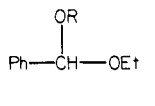
The discussion will focus on the 2-ethoxy- and the 2-(2,2,2-trifluoroethoxy)tetrahydropyran results, since these represent the two extremes of the continuous trend seen in Table II.

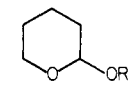
Activation Parameters. All values cited were calculated in the traditional manner at 25 °C.[9,11] The trends in enthalpies and entropies tabulated in Table III are clear. The discussion will focus on the data for 2-ethoxy- and 2-(2,2,2-trifluoroethoxy)tetrahydropyran because these examples represent the extremes of the trends observed; however, the 2-(propargyloxy)tetrahydropyran parameters, for example, are clearly intermediate.

While the second-order rate constants measured by Kankaanpera are only 45% of ours at 25 °C, the difference is very nearly constant (±3%) and therefore the trends are the same. Such differences are not unusual, as one of us (J.L.J.) has pointed out recently.[20] In the present instance, our k_{H^+} values would be 15–20% less if we had done the experiments in dilute HCl solutions and based the second-order rate constant on the titrated acid concentration.[21] Of course, there are differences in ionic strength and substrate concentration as well. At any rate, the activation parameters tabulated in Table III are within experimental error of literature values, except for 2-(2,2,2-trifluoroethoxy)tetrahydropyran, where our activation energy and entropy of activation are larger by 1.9 kcal/mol and 7.8 eu, respectively. This difference does not affect the qualitative trend observed.

Discussion

Structural Features Facilitating General Acid Catalysis. The data reported in Table I and Figures 2 and 3 taken with similarly measured data in formate buffers[12] give a value for the Brønsted α of 0.71 for the hydrolysis of 2-(2,2,2-trifluoroethoxy)tetrahydropyran at 25 °C. This is easily within experimental error of the Brønsted α of 0.70 measured for the hydrolysis of benzaldehyde *O*-ethyl *O*-2,2,2-trifluoroethyl acetal.[3] This is a significant observation, since it quantitates the relative importance of leaving-group ability vis-à-vis oxycarbocation stability in facilitating general acid catalysis.[4] Thus two acetals differing in reactivity by a factor of 10^3 and showing no or marginal general acid catalysis (R = Et below) can be changed structurally to show pronounced general acid catalysis simply by changing to R = CH_2CF_3.



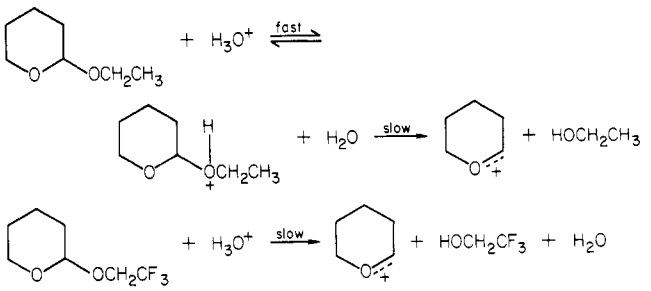


This is an intriguing example because one common way of measuring leaving-group ability is by the pK_a of the "generated" alcohol, ROH; the pK_a of trifluoroethanol[13] is 12.4 and that of the natural substrate[14c] of lysozyme is similar (the pK_a of glucose is about 12.3).[14] These results show explicitly that a substrate which is a reasonable model for disaccharides shows intermolecular general acid-catalyzed hydrolyses; further, the predominantly important structural feature required to produce this catalysis is a "lowered" pK_{ROH}. That is, the leaving group must contain electronegative groups to facilitate the coupling of proton transfer and C–O bond breaking. The mechanistic rationale for this is discussed subsequently.

Entropy of Activation as a Criteria of Mechanism. Schaleger and long[15] have demonstrated the danger of drawing mechanistic conclusions based on $\Delta S^{\ddagger}$ values. However, within a series of compounds that are closely related in structure and which undergo the same reaction, changes in the entropy of activation can have mechanistic significance, especially when supported by other mechanistic criteria.

In the proton-catalyzed hydrolyses of 2-alkoxy tetrahydropyrans, a large difference in the entropy of activation (17 eu) between 2-ethoxytetrahydropyran and 2-(2,2,2-trifluoroethoxy)tetrahydropyran is found (Table III). The direction of this entropy of activation difference resulted in a more positive $\Delta S^{\ddagger}$ for 2-ethoxytetrahydropyran relative to the trifluoro acetal. Moreover, rate-determining proton transfer was demonstrated for 2-(2,2,2-trifluoroethoxy)-tetrahydropyran and not for the ethyl acetal. All these factors indicate a difference in the mechanisms and activated complexes of these two acetals, and can be ration-

Scheme III

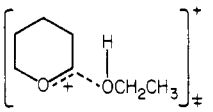


(12) $k_{formic\ acid}$ at 25 °C = 5×10^{-5} M^{-1} s^{-1}; k_{H^+} at 25 °C = 0.41 M^{-1} s^{-1} (Table I); $k_{acetic\ acid}$ at 25 °C was interpolated from the 60 and 75 °C data in Figures 2 and 3; the three point Brønsted α = 0.71, correlation coefficient = 0.9999.

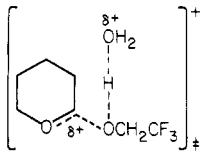
(13) Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.
(14) (a) Los, J. M.; Simpson, L. B., *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 267. (b) Christensen, J. J.; Rytting, J. H.; Izatt, R. M. *J. Chem. Soc. B* **1970**, 1646. (c) Nielsen, H., Ph.D. Thesis, Technical University of Denmark, Copenhagen, 1981.
(15) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1965**, *1*, 24.

alized assuming the mechanisms in Scheme III.

On the basis of these mechanisms, the transition states for the two acetals would be quite different. For the ethyl compound, the rate-determining step involves C–O bond cleavage which is partially complete in the transition state:



The rate-determining step for the trifluoro acetal, however, is a bimolecular proton-transfer step, with a transition state in which the proton is approximately seven-tenths transferred (α = 0.71):



In both of these mechanisms, similar transformations take place (desolvation of a proton, C–O bond cleavage, and the subsequent rearrangements involved in oxycarbocation formation). However, two factors are different between the two mechanisms: the extent of protonation in the transition state, and the inclusion of a water molecule in the transition state of the trifluoro acetal. Whether these two factors can account qualitatively for the difference in activation energy of the two acetals will be discussed in the following paragraphs.

Transfer of a proton from a highly solvated hydronium ion to a less solvated base (desolvation) results in a positive entropy change. For example, in the proton transfer equilibrium between H_3O^+ and trimethylamine Whalley[16] found $\Delta S°$ to be about 15 eu.

$$(CH_3)_3N + H_3O^+ \rightleftharpoons (CH_3)_3NH^+ + H_2O$$

Therefore, relative to a transition state in which the proton is only partially transferred, the entropy of a transition state in which the proton is completely transferred (as in the case of the ethyl acetal) will be greater.

In addition, in the transition state of the trifluoro acetal, a molecule of acid (H_3O^+) has been frozen out of the solvent, resulting in a negative change in entropy due to the loss of translational and rotational degrees of freedom. For example, in the hydration of ketones and aldehydes

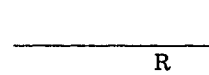
$$R_2C{=}O + H_2O \rightleftharpoons R_2C(OH)_2$$

Bell and McDougall[17] found large $\Delta S°$ values ranging from −7 eu for monochloroacetone, to −31 for formaldehyde with the majority of the compounds studied having $\Delta S°$ values of about −14 to −16 eu.

Furthermore, on the basis of these mechanisms, a prediction can be made that for rate-determining proton transfer, the entropy of activation will depend on the nature of the catalyzing acid. For example, if the catalyzing acid is a neutral acid, charge development in the transition state (brought about by ionization of the neutral catalyst) will result in a more negative activation energy than for the case where a charged catalyst (such as the hydronium ion) is involved. This prediction is borne out experimentally. $\Delta S^‡$ for the acetic acid catalyzed hydrolysis of 2-(2,2,2-trifluoroethoxy)tetrahydropyran is found to be 26 eu more negative than the hydronium ion catalyzed reaction. The actual value of $\Delta S^‡$ for HA = HOAc (−22 eu) is less well defined due to the fact that it is based on a two point Arrhenius plot of the k_{HOAc} values determined at 60 and 75 °C. However, qualitatively it is in agreement with the expected result.

(16) Whalley, E. *Trans. Faraday Soc.* **1959**, *55*, 803.
(17) Bell, R. P.; McDougall, A. D. *Trans. Faraday Soc.* **1960**, *56*, 1280.

Table IV. Activation Parameters for the Hydrolyses of Benzaldehyde Acetals in Dilute HCl Solution[a]



R	$\Delta H^‡$, kcal/mol	$\Delta S^‡$, eu
CH_2CH_3	11.3	−10.3
CH_2CF_3	13.7	−7.5

[a] μ = 0.5 (KCl); calculated from k_{obsd} data at 25, 30, 35, and 40 °C obtained by using a Durrum stopped-flow spectrophotometer; reaction monitored at 248 nm; [HCl] = 10^{-1} and 10^{-2} for R = CH_2CF_3 and CH_2CH_3, respectively.

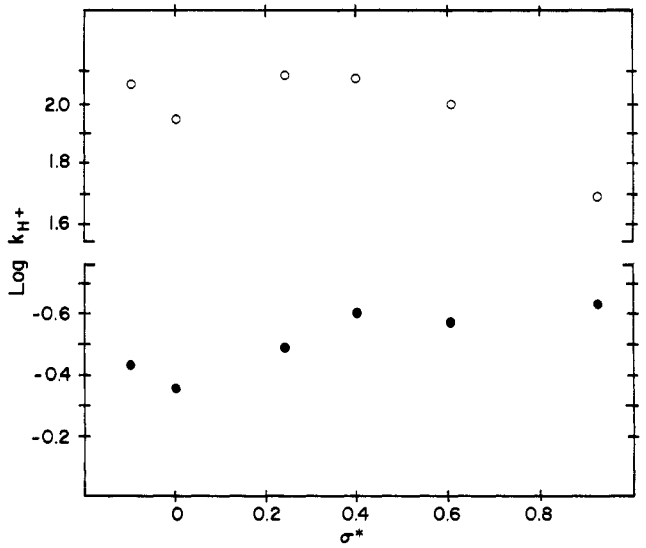


Figure 4. Plots of log k_{H^+} vs. σ^* for the hydrolyses of 2-alkoxytetrahydropyrans at 25 (bottom) and at 75 °C (top), μ = 0.5 (KCl).

Since the entropy of activation proved so helpful in the 2-alkoxytetrahydropyran series, we measured the activation parameters for the analogous mixed acetals of benzaldehyde under the same conditions; the results are reported in Table IV. According to the above arguments, the mechanisms proposed for both of these benzaldehyde acetals should give similar $\Delta S^‡$ values (since the mechanism is $A_{SE}2$ or $A_{SE}2$-like);[3] the values of −10.3 and −7.5 eu measured for benzaldehyde *O,O*-diethyl acetal and benzaldehyde *O*-ethyl *O*-2,2,2-trifluoroethyl acetal, respectively, are within a reasonable experimental error of each other. The fact that both of these values are quite different (~15 eu) from $\Delta S^‡$ observed for the 2-(2,2,2-trifluoroethoxy)-tetrahydropyran hydrolysis underscores the warning of Schaleger and Long[15] regarding excessive reliance on entropies of activation as a criterion of mechanism; however, the $\Delta S^‡$ trends observed over the two series reported in Tables III and IV are consistent within each series (but not between the series).

Substituent Effects. The use of substituent effects as a criterion of mechanism has been of tremendous value to the development of physical organic chemistry as a distinct field of study;[18] however, it bears reiterating that

(18) (a) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975. (b) Chapman, N. B., Shorter, J., Ed. "Correlation Analysis in Chemistry"; Plenum Press: New York, 1978. (c) Hansch, C.; Leo, A. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979.

any series of compounds with different activation energies (and different $\Delta H^{\ddagger}$) will give rise to a LFER which is temperature dependent. Figure 4 illustrates this nicely; in the 2-alkoxytetrahydropyran series, 2-(2,2,2-trifluoroethoxy)tetrahydropyran has the lowest $\Delta H^{\ddagger}$ (by 5 kcal mol^{-1}) and thus as the temperature is increased, the entire nature of the $\sigma^*\rho^*$ plot changes. Indeed, it appears that if the temperature could be raised sufficiently high, the hydrolysis mechanism would be Scheme II (A1) for all the acetals. This observation is independent of what function one uses to scale the substituent effect; thus if pK_{ROH} is used rather than σ^* in Figure 4, the β values generated are −0.065 and +0.083 at 25 and 75 °C, respectively.

The important conclusion to be reached for the 2-alkoxytetrahydropyrans is that the substituent effect is fortuitously near zero at 25 °C because of the change in mechanism. It appears that the $A_{SE}2$ mechanism has a very slightly positive ρ^* (negative β), while the A1 mechanism has a slightly negative ρ^* (positive β). These observations are further support for the mechanisms given in Scheme III.

The Reaction Mechanism. Our data, in its entirety, are most supportive of an A1 hydrolysis mechanism for 2-ethoxytetrahydropyran, an $A_{SE}2$ hydrolysis mechanism for 2-(2,2,2-trifluoroethoxy)tetrahydropyran (and benzaldehyde *O*-ethyl *O*-2,2,2-trifluoroethyl acetal), and a modified $A_{SE}2$ mechanism for the hydrolysis of benzaldehyde diethyl acetal. Since unstrained hemicyclic acetals hydrolyze by an A1 mechanism when the leaving group is poor (e.g., ethanol), it is not surprising that a recent report[19] could find no difference in the mechanisms of hydrolysis of an unstrained bicyclic acetal and one which was constrained so as to disfavor an $A_{SE}2$ mechanism. On the basis of our results, it would be necessary to fluorinate the leaving group in order to make the mechanism become $A_{SE}2$ for these types of acetals.

Acknowledgment. Support from the National Science Foundation (CHE7907588 and PRM7919451) is gratefully acknowledged. The kind hospitality of the Chemistry Department at the University of California, Irvine, was much appreciated during a 1981–82 sabbatical leave (J. L.J.) from CSULB.

Registry No. 2-Ethoxytetrahydropyran, 4819-83-4; 2-methoxytetrahydropyran, 6581-66-4; 2-(2-methoxyethoxy)tetrahydropyran, 4819-82-3; 2-(2-chloroethoxy)tetrahydropyran, 5631-96-9; 2-(2-propynyloxy)tetrahydropyran, 6089-04-9; 2-(2,2,2-trifluoroethoxy)tetrahydropyran, 16408-83-6; acetic acid, 64-19-7; potassium acetate, 127-08-2.

Supplementary Material Available: Figures S1 and S2, kinetic plots of experimental data (2 pages). Ordering information is given on any current masthead page.

(19) Wann, S. R.; Kreevoy, M. M. *J. Org. Chem.* **1981**, *46*, 419.
(20) Jensen, J. L.; Carr, M. D.; Yamaguchi, K. S. *Int. J. Chem. Kinet.* **1983**, *15*, 235–248.
(21) The pH of a 10^{-2} N HCl solution, μ = 0.5 (KCl), is 2.07 not 2.00; similarly, the pH of a 10^{-1} N HCl solution, μ = 0.1, is 1.10 not 1.00.[22]
(22) (a) Weast, R. C., Ed. "Handbook of Chemistry and Physics," The Chemical Rubber Co., Cleveland, Ohio, 1969, p. D102-3. (b) Long, C. Ed. "Biochemists Handbook," D. van Nostrand Co., Inc., New York, N. Y., 1968, p 30. (c) J.L.J., unpublished work (cf ref 3 and 20).

Reactions of Diphenylcyclopropenone and Tetracyclones with Potassium Superoxide

Douglas C. Neckers* and Gerhard Hauck

Department of Chemistry, Bowling Green State University, Bowling Green, Ohio 43403

Received January 10, 1983

Reactions of diphenylcyclopropenone and various tetracyclones with potassium superoxide are reported.

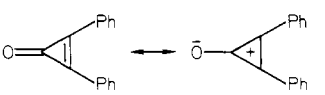
Introduction

The use of potassium superoxide as a versatile synthetic reagent has increased rapidly since the discovery[1] that it is solubilized in nonpolar solvents by crown ethers. Studies of superoxide radical anion prepared this way have led to the conclusion that $O_2^{-\cdot}$ reacts more as a nucleophile than as an oxidizing agent.[2] With carbonyl compounds, the predominant pathway is that of addition/elimination.[3]

The reactions of the annelones diphenylcyclopropenone (1) and tetracyclone (2) with potassium superoxide solubilized with crown ether were of interest to us in the context of a search for competitive chemical traps for superoxide/singlet oxygen.[4] Though there are reliable tests both for singlet oxygen and for superoxide radical anion, tests for $O_2^{-\cdot}$ in the presence of singlet oxygen and vice versa with organic trapping reagents are less well defined. At the outset, we point out that both annelones fail as competitive test systems for O_2^1 $O_2^{-\cdot}$ for reasons that shall become apparent.

We report herein reactions of diphenylcyclopropenone and various tetracyclones (tetraphenylcyclopentadienones) with potassium superoxide.

Reactions of Diphenylcyclopropenone with KO_2. Diphenylcyclopropenone (1) reacts with nucleophiles as a consequence of the large contribution of mesomeric structures **3**. A recent paper[5] suggested the ($_\pi2_s$ + $_\pi2_s$)



1 3

addition of singlet oxygen (generated from the thermal decomposition of K_3CrO_8) to **1** and prompted us to in-

(1) Valentine, J. S.; Curtis, A. B. *J. Am. Chem. Soc.* **1975**, *97*, 224.
(2) San Filippo, J.; Chern, C.; Valentine, J. S. *J. Org. Chem.* **1975**, *40*, 1678.
(3) Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393.
(4) Hauck, G.; Neckers, D. C., unpublished.
(5) Gurumurthy, R.; Narasimhan, K. *Ind. J. Chem.* **1979**, *18B*, 4.

0022-3263/83/1948-4691$01.50/0