Structural Effects and Transition State Acidities in the Hydrolysis of 2-Aryloxytetrahydrofurans by Concerted Proton Transfer; Shortcuts to the Brønsted Coefficient

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Rates of hydrolysis of some substituted 2-aryloxytetrahydrofurans have been measured in dilute aqueous acids. Rate-limiting carbon–oxygen bond cleavage, concerted in some sense with proton transfer to the oxygen atom, is suggested for the mechanism of the reaction. Structural effects of the substituents on the phenoxy group reveal, from the Hammett reaction constant, that protonation is relatively more advanced than carbon–oxygen bond cleavage in the transition state. The substituent constant for *para*-substituents which tend to withdraw electrons by resonance is suggested to be a linear combination of σ and σ^- values, the combining factor being a Brønsted-like coefficient α. Transition state acidities were calculated using the rate constants for oxonium ion catalysed and uncatalysed reactions. Comparison of this acidity with that of the phenol corresponding to the leaving group in the reaction was suggested to give a Brønsted-like coefficient as well. Both treatments gave similar values for the α coefficient.

In the hydrolytic decomposition of acetals and orthoesters, three catalytically different reaction pathways have been reported. The hydrolysis may be oxonium ion-catalysed, general acid-catalysed, or uncatalysed.[1,2]

General acid catalysis has been observed in the hydrolysis of acetals with phenolic leaving groups.[3–9] There, the low basicity of the substrate oxygen atom makes protonation more difficult and the easy cleavage of the bond between that oxygen and the pro-acyl carbon atom facilitates the heterolysis step. Accordingly, the proposed mechanism for the general acid-catalysed hydrolysis of acetals is rate-limiting cleavage of carbon-oxygen bond concerted with proton transfer from the catalyst to the substrate.[1,2]

The water-induced or uncatalysed hydrolysis has been reported to take place in aqueous base solutions for acetals and orthoesters with phenolic leaving groups.[4,5,7,9–12] A spontaneous unimolecular mechanism, without a water molecule acting as a proton-transfer agent in the transition state, is suggested for this hydrolysis.[5,9–12]

Attempts have been made to explain the interdependence of the occurrence of different catalytic pathways. The observation of the uncatalysed hydrolysis is suggested to be related to the observation of general acid catalysis.[2,5,9]

The ratio of uncatalysed and oxonium-ion catalysed rate constants expresses transition-state acidity.[13,14] Comparison of this acidity with that of the phenol corresponding to the leaving group in the reaction has been suggested to give a Brønsted-like coefficient which may be used for transition state characterization.[9]

We here report kinetic data on the acid catalysed hydrolysis of 2-aryloxytetrahydrofurans. The uncatalysed pathway for these compounds has been reported earlier.[12] Short cuts to obtain the Brønsted coefficient α using these rate constants are presented.

Experimental

Materials.—The preparation of 2-aryloxytetrahydrofurans has been described earlier.[12]

Reaction Solutions.—The acid solutions were prepared by dilution of perchloric acid. The acid concentration of the reaction solutions (10^{-2}–10^{-3} mol dm^{-3}) was determined by titration with a standard sodium hydroxide solution.

Acetate buffer solution was prepared by dissolving a weighed amount of acetic acid in water. This solution was partially neutralized with standard sodium hydroxide solution. Dilutions of this solution were made with 0.100 mol dm^{-3} sodium chloride solution to maintain the constancy of ionic strength.

Kinetics.—The performance of kinetic measurements has been described earlier.[5]

Results and Discussion

The rates of hydrolysis of 2-aryloxytetrahydrofurans were measured in dilute perchloric acid solutions in ordinary and heavy water. The second-order rate coefficients for the oxonium ion-catalysed hydrolysis were obtained by dividing the observed first-order rate constants by the acid concentration. They remained constant indicating that the contribution of uncatalysed hydrolysis in the observed rate constant was negligible. The results are presented in Table 1.

To determine the occurrence of general acid catalysis, the rate of hydrolysis of 2-(3-chlorophenoxy)tetrahydrofuran was measured in acetic acid–sodium acetate buffer solutions with constant buffer ratio and ionic strength, but changing the total buffer concentration. Observed rate constants are presented in Table 2. General acid catalysis is indisputable in this case as shown by the non-zero slope of the rate constant *versus* acetic acid concentration plot. This indicates that the mechanism of the reaction involves the presence of the conjugate base of the catalyst in the transition state of the reaction. The proposed mechanism for the general acid-catalysed hydrolysis of acetals is proton transfer from the catalyst to the substrate concerted in some sense with the cleavage of the carbon–oxygen bond.[1,2]

The kinetic solvent deuterium isotope effect on the rate of hydrolysis of 2-aryloxytetrahydrofurans (Table 1) supports the concerted mechanism to be operative in the oxonium ion catalysed hydrolysis as well. Solvent deuterium isotope effects for the hydrolysis of acetals, which are believed to be hydrolysed by a simple A-1 mechanism, fall into the range $k(H_3O^+)/$

Table 1. Second-order rate coefficients for the oxonium ion catalysed hydrolysis of 2-aryloxytetrahydrofurans in perchloric acid solutions in ordinary and heavy water.

Substituent	T/°C	$k(H_3O^+)$ / $dm^3\ mol^{-1}\ s^{-1}$	$k(D_3O^+)$ / $dm^3\ mol^{-1}\ s^{-1}$	$k(H_3O^+)$ / $k(D_3O^+)$
H	25	4.95	8.44	0.58
4-Cl		2.96	4.70	0.63
3-Cl		2.16	4.24	0.51
4-$COCH_3$		1.32	2.46	0.54
3-Cl	15	0.908		
3-Cl	35	5.38		
3-Cl	45	11.78		

Table 2. First-order rate constants for the hydrolysis of 2-(3-chlorophenoxy)tetrahydrofuran in acetic acid–sodium acetate buffer solutions (buffer ratio = 1) at 65 °C. Ionic strength maintained at 0.100 mol dm^{-3} with sodium chloride.

c(HOAc) / mol dm^{-3}	$10^3\ k$(obs) / s^{-1}	$10^3\ k$(HOAC) / $dm^3\ mol^{-1}\ s^{-1}$
0.100	2.93	
0.075	2.65	
0.050	2.52	
0.025	2.44	
0	2.24 ± 0.09[a]	6.4 ± 1.3[b]

[a] Intercept of the linear least-squares fit. [b] Slope of the linear least-squares fit.

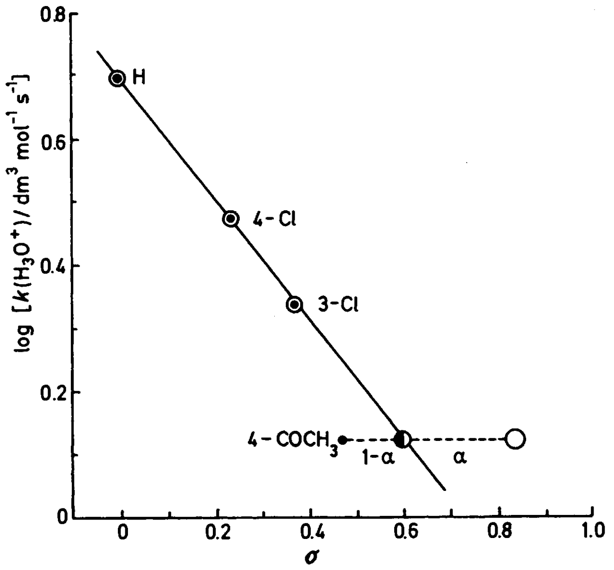

Figure. Structural effects on the rate of the oxonium ion catalysed hydrolysis of 2-aryloxytetrahydrofurans at 25 °C, presented as the Hammett relationship. Filled circles refer to σ, open circles to σ^- values, and half-filled to a linear combination of the two values combined with a Brønsted-like coefficient α.

($k(D_3O^+)$ 0.3–0.4.[1] The observed values, 0.5–0.6, are distinctly higher suggesting a shift toward uncatalysed hydrolysis which exhibits values near 1.6.[9,11]

The entropy of activation $\Delta S^\ddagger$ for the oxonium ion catalysed hydrolysis of 2-(3-chlorophenoxy)tetrahydrofuran can be calculated from the results in Table 1. The value of -27 ± 3 J K^{-1} mol^{-1} is more negative than could be expected for acetal hydrolysis by a unimolecular A-1 mechanism.

Structural effects of the substituents on the phenoxy group can be used to evaluate the relative importance of bond-making and -breaking processes in the concerted reaction mechanism.[15] The Hammett plot is presented in the Figure. A straight-line relationship with excellent correlation between the logarithm of the rate coefficients for oxonium-ion catalysed hydrolysis and substituent constant σ is obtained with unsubstituted and 4- and 3-chloro substituted compounds.[16] The slope of this line, the Hammett reaction constant, has a value of -0.965 ± 0.032. The relatively small value, compared with that observed for uncatalysed hydrolysis (2.4–3.2),[9–12] indicates that the opposite structural effects on protonation and carbon–oxygen bond cleavage partially cancel each other. The negative sign of the reaction constant is an indication of a development of positive charge on the atom adjacent to the aromatic ring on passing from the initial to the transition state. Protonation has taken place more than the cleavage of C–O bond has proceeded in the transition state.

The hydrolysis of the 4-acetyl-substituted compound, where resonance interaction between the reactive centre and the electron withdrawing substituent is possible, does not fit the Hammett plot using the substituent constant σ (0.47) or the σ^- value (0.84).[16] The resonance contribution in the transition state of the acid-catalysed hydrolysis of 2-aryloxytetrahydrofurans is larger than in benzoate anions, represented by the former substituent constants but smaller than in phenoxide anions represented by the latter. Protonation diminishes the electron-donating ability of the reactive centre. The decrease of the resonance interaction in the transition state of the concerted reaction from that for phenoxide ions, represented by σ^-, will be related to a Brønsted-like α coefficient describing the degree of protonation. The substituent constant for *para*-substituents which tend to withdraw electrons by resonance is suggested to be a linear combination of σ and σ^- values [equation (1)].

$$\sigma_{con} = \sigma^- + \alpha(\sigma - \sigma^-) \qquad (1)$$

The procedure is related to the more general treatment of through-resonating substituents by the Yukawa–Tsuno equation.[15,17] Estimation of σ_{con} for the 4-acetyl group in the oxonium-ion catalysed hydrolysis of 2-aryloxytetrahydrofurans from the linear plot in the Figure gives a value of σ_{con} of 0.60. Equation (1) then gives a Brønsted-like coefficient α of 0.65 for the hydrolysis of 2-(4-acetylphenoxy)tetrahydrofuran.

The rate constants for the uncatalysed hydrolysis of 2-aryloxytetrahydrofurans have been measured earlier.[12] Extrapolation of these to the same temperature with the oxonium ion catalytic coefficients makes possible the calculation of transition state acidities by a simple rate constant ratio [equation (2)].[13,14]

$$pK_a^\ddagger = \log [k(H_3O^+)/k(H_2O)] \qquad (2)$$

The $pK_a^\ddagger$ values are presented in Table 3. The range of these values for 2-aryloxytetrahydrofurans is similar to that for aryl methyl acetals of acetone and acetals of acetaldehyde.[9]

The transition state acidity approach has been used to obtain another Brønsted-like α coefficient.[9] The $pK_a^\ddagger$ value represents the difference in the Gibbs energy of activation between catalysed and uncatalysed reactions. The corresponding difference in the standard Gibbs energy for the products of the rate-limiting step, phenol and phenoxide ion, is represented by the acidity constant of the phenol forming the leaving group in the reaction, pK_a(PhOH). The Brønsted coefficient α measures the extent to which the stabilizing effect of the catalyst in the transition state resembles that in products. An expression for the coefficient α by the transition state acidity treatment is obtained [equation (3)]. The calculated α values for the

Table 3. Transition state acidities in the hydrolysis of 2-aryloxytetrahydrofurans at 25 °C.

Substituent	$10^6\,k(H_2O)/\,s^{-1}$	$pK_a^{\ddagger}$	$pK_a(PhOH)$	α[a]
H	0.076[b]	7.81	9.99[e]	0.78
4-Cl	0.29[b]	7.01	9.42[e]	0.74
3-Cl	0.59[b]	6.56	9.02[e]	0.73
4-COCH_3	7.87[c]	5.22	8.05[e]	0.65
4-COCH_3	6.13[d]	5.60	8.60[f]	0.65

[a] Brønsted-like coefficient of equation (3). [b] Estimated using the values of ref. 12 and assuming temperature independence of the structural effects. [c] Extrapolated from the measurements at temperatures 55–85 °C of ref. 12 by the Arrhenius equation. [d] In heavy water, extrapolated from the values of ref. 18. [e] Taken from ref. 21. [f] Estimated by the linear relation between ΔpK_a and pK_a^H in ref. 19.

$$\alpha = pK_a^{\ddagger}/pK_a(PhOH) \qquad (3)$$

hydrolysis of 2-phenoxytetrahydrofurans are presented in Table 3. Comparison with the value obtained by the best-fit method for the 4-acetyl-substituted compound in the Hammett plot for the oxonium-ion catalysed hydrolysis shows a remarkable accord in the results of two totally different treatments.

Comparison of the results for the hydrolysis of 2-(4-acetylphenoxy)tetrahydrofuran in ordinary and heavy water (Table 3) shows that the Brønsted-like α coefficient is independent of the isotopic composition of the solvent water. This allows the derivation of an expression for the solvent deuterium isotope effect on the transition-state acidity [equation (4) where $\Delta pK_a = \log(K_a^H/K_a^D)$].

$$\Delta pK_a^{\ddagger} = \alpha\,\Delta pK_a(PhOH) \qquad (4)$$

Substitution of the transition-state acidities by corresponding rate-coefficient ratios leads to an equation describing the relationship between the kinetic solvent deuterium isotope effects and the equilibrium isotope effect of the phenol corresponding to the leaving group in the reaction [equation (5)]. Estimation of the α coefficient by this equation gives, of

$$\log\frac{k(H_2O)}{k(D_2O)} - \log\frac{k(H_3O^+)}{k(D_3O^+)} = \alpha\log\frac{K_a(PhOH;H_2O)}{K_a(PhOD;D_2O)} \qquad (5)$$

course, a value comparable to those calculated separately in different experiments.

It has been suggested earlier that uncatalysed hydrolysis may be incorporated in the Brønsted relation, in the form of the acidity constant for the phenol corresponding to the leaving group in the reaction.[5] Application of this to reactions in isotopically different waters leads to the expression presented here, equation (5), rather than to the isotopic rate–equilibrium relationship suggested for the uncatalysed hydrolysis of phenyl dimethyl orthoformates.[11] The accord of the α coefficient obtained by this imperfect relation with the experimental Brønsted α value is due to a solvent deuterium isotope effect very close to unity for the oxonium ion catalysed hydrolysis for phenyl dimethyl orthorformates.[20]

The presented treatment of transition-state acidities in concerted proton transfers gives a short cut to the Brønsted coefficient α. The more general validity of the treatment in the hydrolysis of different compounds and the accord with the conventional value for buffer solutions will be tested in further work.

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