Transition State Activity Coefficients in the Acid-Catalyzed Hydrolysis of Esters

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Abstract: The transition state activity coefficient for an acid-catalyzed reaction can be calculated from rate, substrate activity coefficient, and substrate basicity data, coupled with recently available values of proton activity for nondilute acids. This approach is applied to the hydrolysis reactions in sulfuric acid of a series of acetate esters and is shown to be successful in predicting mechanistic behavior. In particular, two distinct types of medium dependence of log $f^*_{S^\ddagger}$ are observed for each ester, a region of pronounced salting-out of $S^\ddagger$ in moderately concentrated acids, associated with an A_{Ac}-2 reaction, giving way at some higher acidity strongly dependent on the structure of the ester to a region of much smaller salting-out, attributable to a changeover to an A_{Al}-1 mechanism. *tert*-Butyl acetate is an exception; this ester shows only the latter behavior in accord with its hydrolysis solely by the unimolecular route. The log $f^*_{S^\ddagger}$ variations with medium are further compared with log f^*_+ values of various types of stable cationic species and are completely consistent with the expected transition state structures. The approach has also been applied to two examples of acid-catalyzed aromatic exchange (*p*-cresol and anisole), and log $f^*_{S^\ddagger}$ values for these reactions are found to be very sensitive to transition state solvation. The advantages of this method over other approaches are discussed.

The interpretation of the variation in the rates of acid-catalyzed reactions with changing acidity in the nondilute acid region has presented a considerable challenge, particularly as a guide for the complete understanding of the detailed mechanism of such reactions. For a reaction written in the following general terms

$$S + H^+ \underset{\text{slow}}{\overset{\text{fast}}{\rightleftharpoons}} SH^+$$

$$SH^+ (+H_2O) \xrightarrow{\text{slow}} S^\ddagger$$

transition-state theory gives the rate equation

$$v = \frac{k_0}{K_{SH^+}} \frac{f_S a_{H^+}}{f_{S^\ddagger}} [S]$$

where k_0 is the rate constant for the slow step and K_{SH^+} is the dissociation constant for the protonated substrate. These reactions normally follow pseudo-first-order kinetics ($v = k_\psi$ [S]) so that[1]

$$k_\psi = \frac{k_0}{K_{SH^+}} \frac{f_S a_{H^+}}{f_{S^\ddagger}}$$

Thus the acidity dependence of k_ψ is determined by that of three essentially independent variables, f_S, a_{H^+}, and $f_{S^\ddagger}$, at least one of which ($f_{S^\ddagger}$) is experimentally inaccessible. A number of different approaches[2-6] have been developed for the analysis of the acidity variations of k_ψ. Despite some successes, a number of uncertainties and ambiguities remain in each treatment, principally because of various assumptions made concerning cancellation of the activity coefficient terms, particularly $f_{S^\ddagger}$.

Recently,[7] a treatment was proposed which circumvents this problem by calculating $f_{S^\ddagger}$ directly. Rearrangement of the above equation yields

$$\log (f^*_{S^\ddagger}/k_0) = -\log k_\psi - \log K_{SH^+} + \log f_S + \log a^*_{H^+} \quad (1)$$

in which the transition state activity coefficient is expressed in terms of potentially measurable quantities. In this equation, k_ψ is the observed pseudo-first-order rate constant, K_{SH^+} can be obtained from ionization ratio measurements, and f_S is the substrate activity coefficient. These are experimentally determinable, although problems may arise when the reaction is extremely rapid. The final term in $a^*_{H^+}$ represents the activity of the proton relative to the standard ion (tetraethylammonium, TEA^+); values of $a^*_{H^+}$ in several different aqueous acids have recently been determined.[7] The transition state activity coefficient in eq 1 is thus also relative to TEA^+ ($f^*_{S^\ddagger} = f_{S^\ddagger}/f_{TEA^+}$)[8] and initially is calculated relative to k_0. This term can, however, be separated because log $f^*_{S^\ddagger}$ must approach zero in dilute acid solutions so that the intercept of a plot of log ($f^*_{S^\ddagger}/k_0$) vs. acid concentration gives the value of $-$log k_0. Hence it should be possible to estimate the medium variation of the transition state activity coefficient (relative to a standard ion) for any acid-catalyzed reaction.

This approach was illustrated in our previous paper[7] using the example of methyl *o*-toluate hydrolysis, and the result obtained was in full agreement with previous conclusions concerning hydrolysis mechanisms.[4,9] In the present paper, the approach is applied to the hydrolysis of a number of acetate esters. In this way, we hope to illustrate its application to a series of closely related (and well studied[3,4]) reactions. In particular, we will describe its sensitivity to mechanism and mechanistic changes and moreover, by comparing the behavior of log $f^*_{S^\ddagger}$ and log f^*_+ (for stable cationic species), we will attempt to show how the structural characteristics and solvation requirements of the transition state are reflected in its activity coefficient behavior.

Results and Discussion

For the purpose of determining the transition state activity coefficient, it is necessary to measure three quantities, namely rate constants, basicity constants, and substrate activity coefficients. We will therefore consider each of these separately before turning to the more general problem.

Rate Constants. In Table I are listed pseudo-first-order rate constants for four acetate esters as a function of acidity. Along with values previously obtained for benzyl acetate,[3] isopropyl acetate,[3] and *tert*-butyl acetate,[10] these are displayed graphically in Figure 1. Widely divergent behavior is shown in these rate–acidity profiles; this, however, is not unexpected[4] and, as will be shown later, is entirely consistent with the structure of these various esters.

Basicity of Esters. The protonation of a number of esters, including alkyl acetates, has recently been reported by Lee and Sadar.[11] Since no benzyl acetates were included in this study, we have applied the same NMR approach to study the protonation of *p*-nitrobenzyl acetate. The differences

Table I. Acetate Ester Hydrolysis Rates in Sulfuric Acid at 25°

% H_2SO_4	10^4k_ψ [a, b] p-Nitrobenzyl	p-Chlorobenzyl	p-Methoxybenzyl	Cyclopropylcarbinyl
10			1.80	1.45
15			3.30	2.60
20			6.10	4.00
25			13.70	5.80
30			36.7	8.05
35	5.80	6.34	84.0	10.70
40	7.10	9.00		13.5
45	8.70	11.30		16.7
50	11.40	13.40		21.6
55	12.05	14.00		35.0
60	12.00	13.60		72.2
65	10.05	14.60		295
70	6.90	28.6		1200
75	3.85	100		
80	1.50			
85	2.05			
90	7.00			

[a] Pseudo-first-order rate constant, $\sec^{-1}$. [b] Values interpolated to common acidities.

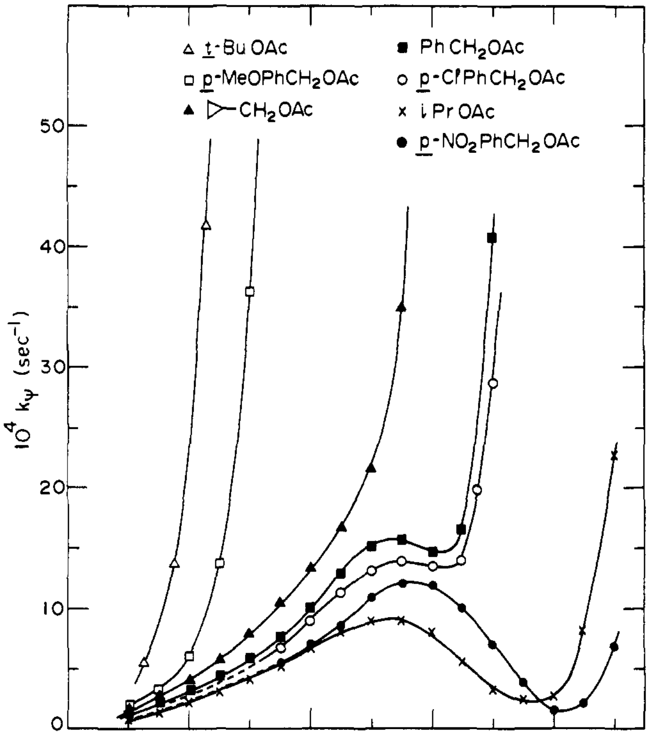


Figure 1. Rate profiles for hydrolysis of acetate esters.

Table II. Chemical Shift Data for p-Nitrobenzyl Acetate

% H_2SO_4	$\Delta\delta$, ppm	Log I[a]
60.95	5.27	
65.66	5.26	
71.09	5.24	−0.86
78.14	5.21	−0.57
81.27	5.15	−0.19
85.21	5.10	+0.08
90.50	5.03	+0.49
92.41	4.99	+0.86
94.46	4.97	
97.0	4.96	

[a] Log $(5.28 - \Delta\delta)/(\Delta\delta - 4.95)$.

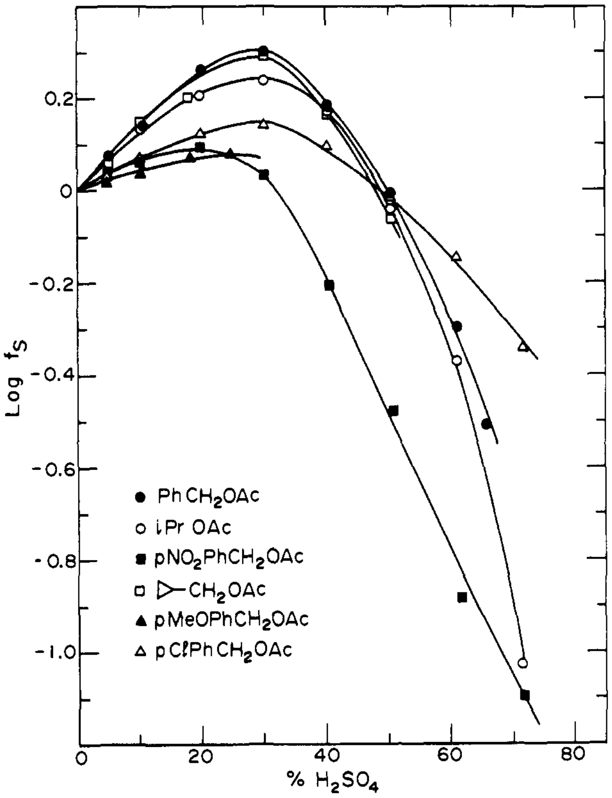


Figure 2. Activity coefficient variation for acetate esters.

($\Delta\delta$) in the chemical shifts of the acetate protons and the high-field aromatic protons were measured in various sulfuric acid solutions (Table II). A sigmoidal titration curve is obtained, and values of log I are given in the same table. The plot of log I vs. $-H_0$ is reasonably linear ($r = 0.995$) with a slope of 0.43 and gives a pK_{BH^+} of -3.48.[12] This is very similar to the values (-3.2 to -3.8) found by Lee and Sadar for various alkyl acetates, and it can therefore be assumed that, in all these esters, structural variations in the alcohol moiety have little effect on the basicity. In consequence, a single value of $pK_{BH^+} = -3.5$ has been used in all calculations.

Activity Coefficient Data. The distribution method[13] was employed to determine activity coefficients, in all cases using cyclohexane as the organic solvent. For each ester, above some concentration of sulfuric acid, hydrolysis was sufficiently fast to interfere with the measurements. In these cases, various shaking periods (1-3 min) were used and the results extrapolated to zero time. The distribution technique is ideally suited for this since equilibration is achieved in a very short period of time.[14]

The activity coefficients determined for six acetate esters at different concentrations of sulfuric acid are listed in Table III and represented graphically in Figure 2. These curves in general exhibit the behavior that is normally observed for neutral molecules containing polar groups,[15] an initial salting-out followed at some acidity by a fairly pronounced salting-in. (The terms "salting-out" and "salting-in" refer to positive and negative variations in log f values, respectively, and arise from the solubility behavior of the species, e.g., positive log f means lower solubility.) Certain variations are observed. The nitro substituent of p-nitrobenzyl acetate exerts its well-known salting-in effect.[13,15] The other three benzyl esters also behave slightly differently. Interestingly, the order observed with these is significantly different from that of benzene, chlorobenzene, and anisole.[13] In other words, the effect of substituents on f_S be-

Table III. Activity Coefficients of Acetate Esters in Sulfuric Acids at 25.0°

% H_2SO_4	Log f_S Benzyl	*p*-Nitrobenzyl	*p*-Chlorobenzyl	*p*-Methoxybenzyl	Cyclopropylcarbinyl	Isopropyl
4.72	0.08	0.03		0.01	0.06	
10.10	0.13	0.07	0.07	0.03	0.15	0.13
18.11				0.08^a	0.19	
19.96	0.26	0.10	0.12			0.21
24.87				0.08^a		
30.28	0.30	0.03	0.14		0.30	0.24
40.53	0.19	−0.20	0.10		0.16	0.17
50.66	−0.01^a	−0.48	−0.02		−0.07^a	−0.04
60.95	−0.30^a	−0.89^a	−0.15			−0.37^a
65.66	−0.51^a					−1.03
71.09		−1.10^a	−0.35^a			

^{a}Obtained by extrapolation to zero time.

Table IV. Transition State Activity Coefficients for Acetate Ester Hydrolysis in Sulfuric Acid Solutions at 25°

% H_2SO_4	Log $f^*_{S\ddagger}$ Benzyl	*p*-Chlorobenzyl	*p*-Methoxybenzyl	*p*-Nitrobenzyl	Cyclopropylcarbinyl	Isopropyl	*tert*-Butyl
5	0.5	0.4	0.4	0.4	0.2	0.3	0.1
10	0.8	0.7	0.8	0.7	0.5	0.7	0.3
15	1.4	1.2	1.1	1.3	1.0	1.2	0.5
20	1.8	1.6	1.5	1.7	1.4	1.6	0.6
25	2.1	2.0	1.7	2.0	1.8	2.0	0.7
30	2.6	2.5	1.9	2.5	2.3	2.5	0.8
35	3.1	3.1	2.1	3.0	2.8	3.0	
40	3.7	3.7	2.4	3.6	3.4	3.6	
45	4.4	4.3		4.1	4.0	4.3	
50	5.0	5.1		4.8	4.6	5.0	
55	5.8	5.9		5.5	5.2	5.8	
60	6.7	6.9		6.4	6.0	6.7	
65	7.6	7.9		7.4	6.0	7.7	
70	8.0	8.6		8.4		8.7	
75	8.5	9.0		9.6		9.7	
80	8.8			11.2			
85				11.9			

havior appears to be a function of the other groups present in the molecule.

In addition activity coefficients for two alkyl acetates, isopropyl acetate and cyclopropylcarbinyl acetate, were measured, and again the same trends are observed. In fact these two exhibit remarkably similar behavior to that of benzyl acetate. Previous studies on alkyl acetates have been carried out with ethyl acetate[14,16] and *n*-butyl acetate[16] and again show this pronounced salting-in in moderately concentrated acids. These results imply that the variations in activity coefficients are not due to the aromatic ring which has normally been present in such studies but rather are a basic feature of the behavior of organic molecules in sulfuric acid solutions.

Log $f^*_{S\ddagger}$ as a Mechanistic Criterion. Transition state activity coefficients obtained from eq 1 using the data discussed in the previous sections are given in Table IV. In most cases, a slight extrapolation (over less than 10% H_2SO_4) was required in order to obtain log f_S values in the more concentrated acids. The justification for this lies in the very similar behavior observed with all the acetates, indeed with most neutral substrates. In any event, the error introduced by this procedure (perhaps ±0.1 log unit) is small compared with the overall variations in log $f^*_{S\ddagger}$. For the same reasons, activity coefficient values for isopropyl acetate were used in the calculations on *tert*-butyl acetate. For this ester, the high rate of hydrolysis even in dilute acids makes direct f_S measurement difficult, if not impossible.

In Figures 3 and 4, values of log $f^*_{S\ddagger}$ are plotted as a function of acidity. With every ester, a continual salting-out is observed with increasing acidity. Unlike the simple rate-acidity profiles for these esters, a common pattern of behavior can be detected. With the exception of *tert*-butyl acetate, these esters initially exhibit very similar curves in the dilute acid region, showing a pronounced salting-out effect on $f^*_{S\ddagger}$. At some acidity strongly dependent on the ester structure, a break from this behavior is observed, to a curve showing a considerably smaller salting-out effect.[17] The *tert*-butyl ester differs in that only this latter behavior is seen, even in dilute acids.

Thus there are two distinct types of behavior in the log $f^*_{S\ddagger}$ values, characterized by a different rate of salting-out with increasing acidity. This implies that there are two different hydrolysis reactions occurring. Furthermore, the break in the log $f^*_{S\ddagger}$ curves from one salting-out behavior to the other strongly suggests that there has been a change from one mechanism to the other, particularly when it is realized that these breaks do not occur at a common acidity but are extremely sensitive to the structure of the acetates. These are precisely the same conclusions that have been reached in previous studies of ester hydrolysis. In general most acetates are found to hydrolyze by the A_{Ac}-2 mechanism in dilute acids, with a changeover at some acidity to one of the two A-1 mechanisms, the position of the changeover and the type of A-1 mechanism being strongly dependent on the structural characteristics of the ester. With the exception of simple primary alkyl acetates and phenyl ace-

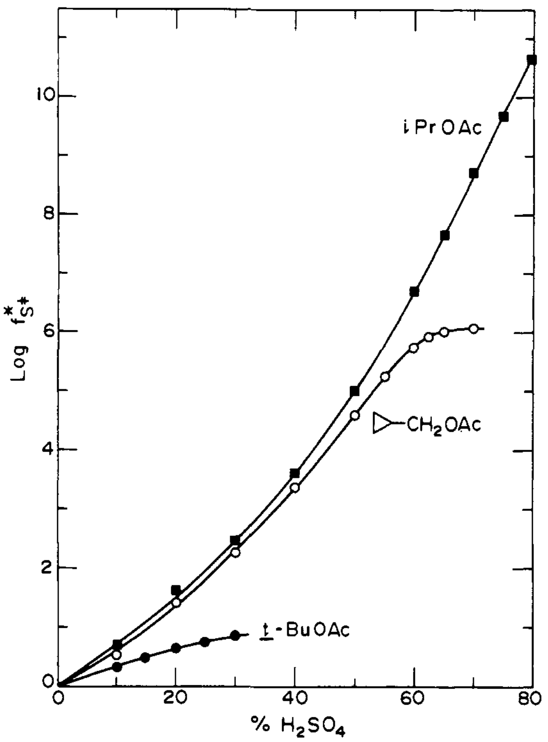


Figure 3. Transition state activity coefficients for benzyl acetate hydrolysis in sulfuric acid solutions.

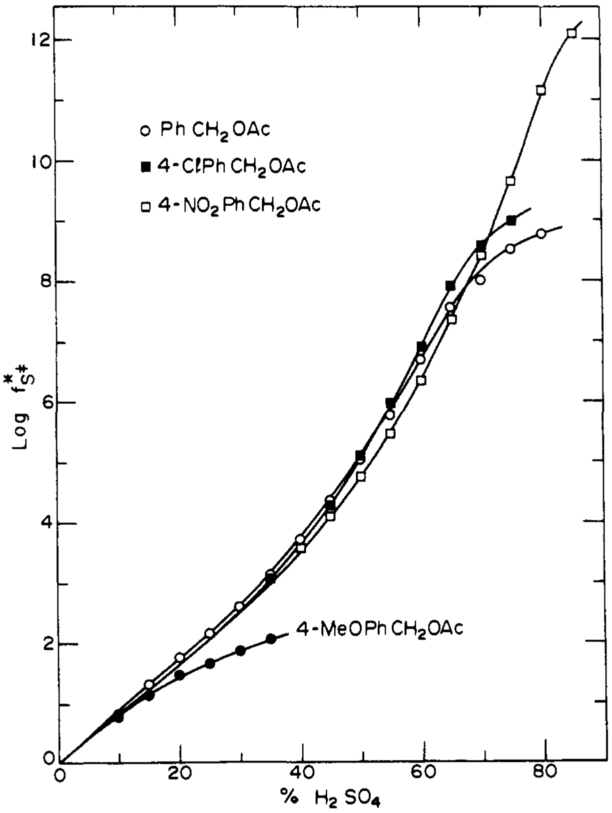


Figure 4. Transition state activity coefficients for alkyl acetate hydrolysis in sulfuric acid solutions.

tates, it is the A_{Al}-1 mechanism that takes over, and moreover it is generally found that the acidity where this occurs is directly determined by the stability of the intermediate carbonium ion so produced.

The log $f^*_{S‡}$ curves can be seen to be reflecting these same trends. The common behavior observed in the dilute acids is due to the A_{Ac}-2 hydrolysis. At some acidity, the A_{Al}-1 reaction becomes important; this is shown by a break in the log $f^*_{S‡}$ curve to a less pronounced salting-out behavior characteristic of this reaction. (We will show later that this type of behavior is what one might expect for the two reactions.) With *tert*-butyl acetate, there is only the A_{Al}-1 hydrolysis so that no break in the curve is obtained.

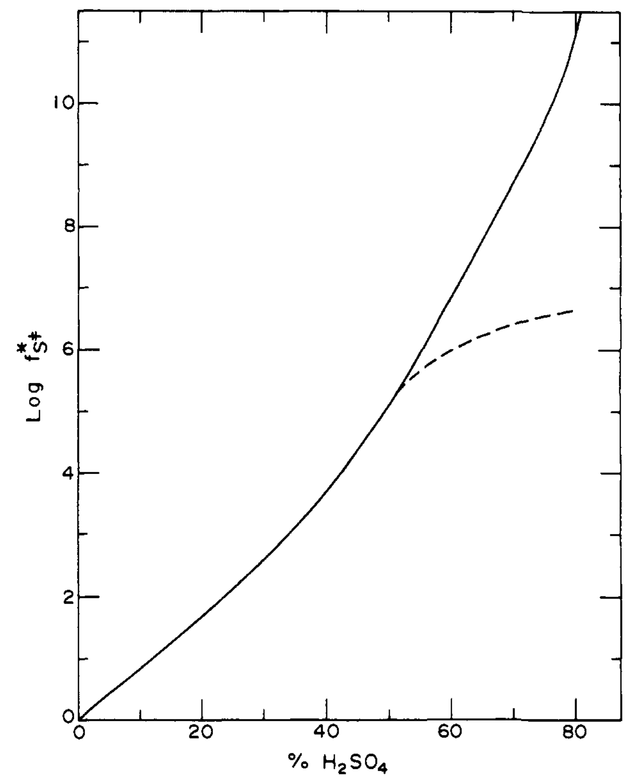


Figure 5. Generalized transition state activity coefficient behavior for acetate ester hydrolysis. Solid line represents the curve which would be obtained if only A_{Ac}-2 hydrolysis were occurring. Dashed line represents the curve which is actually observed about 50% H_2SO_4 due to the changeover in mechanism.

These points are illustrated in Figure 5, using the data for cyclopropylcarbinyl acetate. The solid line represents the log $f^*_{S‡}$ values which would be obtained if there were no break, i.e., only the A_{Ac}-2 hydrolysis. The dashed line represents the observed values above 55% H_2SO_4, caused by the changeover to the unimolecular hydrolysis. Simply by shifting this dashed line up or down the solid line, the entire family of curves obtained with these acetates can be generated. This shifting corresponds to decreasing or increasing carbonium ion stability, and indeed the variation in the acidities where the unimolecular reaction becomes important is consistent with what would be expected for the relative order of stability of the carbonium ions which would be produced by these esters.[18]

$$t\text{-Bu}^+ > p\text{-MeOC}_6\text{H}_4\text{CH}_2^+ > \triangle\text{CH}_2^+ > \text{C}_6\text{H}_5\text{CH}_2^+ >$$
$$p\text{-ClC}_6\text{H}_4\text{CH}_2^+ > i\text{-Pr}^+ > p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2^+$$

Log $f^*_{S‡}$, Comparison with "r" Treatment. In the past, we have used the "r" hydration model[4] for acid-catalyzed reactions as a major criterion of mechanism. This treatment predicts that plots of $\log k_2 = \log k_\psi - \log\{[SH^+]/([S] + [SH^+])\}$ should be linear in log a_{H_2O}, with a slope "r" equal to the difference in hydration between the transition state and the protonated substrate. In Figure 6 "r" plots for the seven esters are shown; these exhibit the same type of behavior previously observed for other acetate esters, namely

Table V. Position of Mechanistic Changeover (A_{Ac}-2 to A_{Al}-1) Based on Log $f^*_{S\ddagger}$ Values and "r" Plots

	Region of acidity of mechanistic change, % H_2SO_4		
Acetate	Log $f^*_{S\ddagger}$ prediction	"r" plot prediction	Other criteria
p-Methoxybenzyl	10–20	0[a]	See text
Benzyl	60–65	60–65	Subst effect[b]
p-Chlorobenzyl	65–70	65–70	Subst effect[b]
p-Nitrobenzyl	>80	75–80	Subst effect[b]
Isopropyl	>80	75–80	^{18}O exchange[c]
tert-Butyl	0[a]	0[a]	$\Delta S\ddagger$,[d] $\Delta V\ddagger$,[e] cleavage[f]
Cyclopropylcarbinyl	55–60	55–60	

[a] Predicts no A_{Ac}-2 reaction. [b] Little effect of varying substituent on A_{Ac}-2; very pronounced effect on A_{Al}-1. [c] Reference 4. [d] P. Salomaa, *Suom. Kemistil. B*, 32, 145 (1959). [e] A. R. Osburn and E. Whalley, *Can, J. Chem.*, 39, 1094 (1961). [f] C. A. Bunton and J. L. Wood, *J. Chem. Soc.*, 1522 (1955); S. G. Cohen and A. Schneider, *J. Am. Chem. Soc.*, 63, 3382 (1941).

Table VI. Relative Contributions of the A_{Ac}-2 and A_{Al}-1 Mechanisms in the Hydrolysis of *p*-Methoxybenzyl Acetate in H_2SO_4 at 25°

% H_2SO_4	A_{Ac}-2, %	A_{Al}-1, %
10	72	28
15	64	36
20	52	48
25	33	67
30	17	83
35	10	90

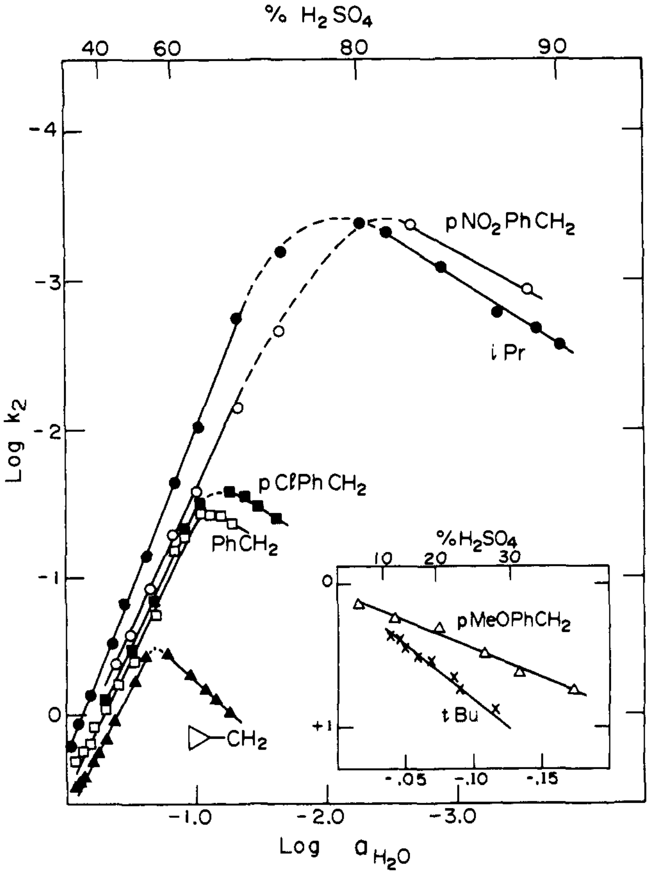


Figure 6. "r" hydration plots for hydrolysis of acetate esters (ROAc) in sulfuric acids. (Note different log a_{H_2O} scale in insert.)

a region of strong positive log a_{H_2O} dependence (A_{Ac}-2), followed by a changeover to a weaker and negative dependence (A-1). *tert*-Butyl acetate and *p*-methoxybenzyl acetate show only a negative log a_{H_2O} dependence.

In Table V, the predictions based on the two approaches are compared. In general they arrive at the same conclusion, both with respect to the mechanistic type and the position of mechanism changeover. Moreover as also shown in this table, these predictions are reinforced by other criteria which can be applied to these reactions.

There is one serious disagreement, that for *p*-methoxybenzyl acetate. The "r" plot shows only a negative log a_{H_2O} dependence and therefore suggests there is no A_{Ac}-2 hydrolysis region. The log $f^*_{S\ddagger}$ values, however, initially follow the curve generated by the other benzyl acetates (Figure 4), implying that there is a substantial contribution from the bimolecular hydrolysis. This ester would give a considerably stabilized benzylic carbonium ion, and hence it is not surprising that the A_{Al}-1 reaction is important even in dilute acids. However, there are two pieces of evidence which suggest that it is the log $f^*_{S\ddagger}$ approach which gives the correct prediction and not the "r" hydration hypothesis.

Firstly the position of cleavage was investigated for hydrolysis in 4.9% H_2SO_4. An ether labeled ester containing 1.2 ^{18}O produced an alcohol of 0.96% ^{18}O enrichment (on hydrolysis in unlabeled solvent), implying 73% acyl carbon-oxygen cleavage. Furthermore this must represent a lower limit since, under conditions identical with those of the hydrolysis, a sample of labeled *p*-methoxybenzyl alcohol exchanged to a similar extent (1.24 → 1.00%). That is, the alcohol obtained in the hydrolysis experiment probably has had some depletion of label caused by exchange after its formation.

The second piece of evidence is based on the substituent effect on A_{Ac}-2 benzyl acetate hydrolysis. In 10% H_2SO_4, the parent benzyl acetate hydrolyses (A_{Ac}-2) at a rate of 0.00012 sec^{-1}. Using a ρ value of -0.1,[19] *p*-methoxybenzyl acetate should have an A_{Ac}-2 hydrolysis rate of ca. 0.00013 sec^{-1}. The observed value is 0.00018 sec^{-1} which can be dissected on the basis of the above rate into contributions of 72% A_{Ac}-2, and only 28% A_{Al}-1. Table VI reports the results of such an analysis at all acidities. Although the unimolecular hydrolysis is occurring throughout, it does not become dominant until greater than 20% H_2SO_4.

In summary the transition state activity coefficient approach gives the same type of information regarding mechanism and mechanism changes as provided by the "r" hydration treatment and, in one instance, is in closer accord with other mechanistic criteria. This approach also avoids a further problem of the "r" treatment, namely the frequently encountered large positive and large negative "r" values which cannot be interpreted in any physical sense and probably are caused by a break-down of the basic assumptions of the treatment.[20] On the other hand as we will show in the following discussion, the $f^*_{S\ddagger}$ variations can be interpreted in a perfectly reasonable manner. The log $f^*_{S\ddagger}$ approach moreover presents a unified picture for the hydrolysis of these esters, in terms of a common curve for the A_{Ac}-2 hydrolysis, giving way to the curve for the A_{Al}-1 hydrolysis at some acidity dependent on the structural characteristics of the ester, namely the stability of the carbonium ion derived from the alcohol moiety. This conclusion cannot be reached on simple examination of the "r" plots, or indeed the rate profiles themselves.

Log $f^*_{S\ddagger}$ for A_{Al}-1 Hydrolysis. Before proceeding further, it should be pointed out that the log $f^*_{S\ddagger}$ values which have been attributed to the A_{Al}-1 reaction are not the true values (with the exception of *tert*-butyl acetate). The reason for

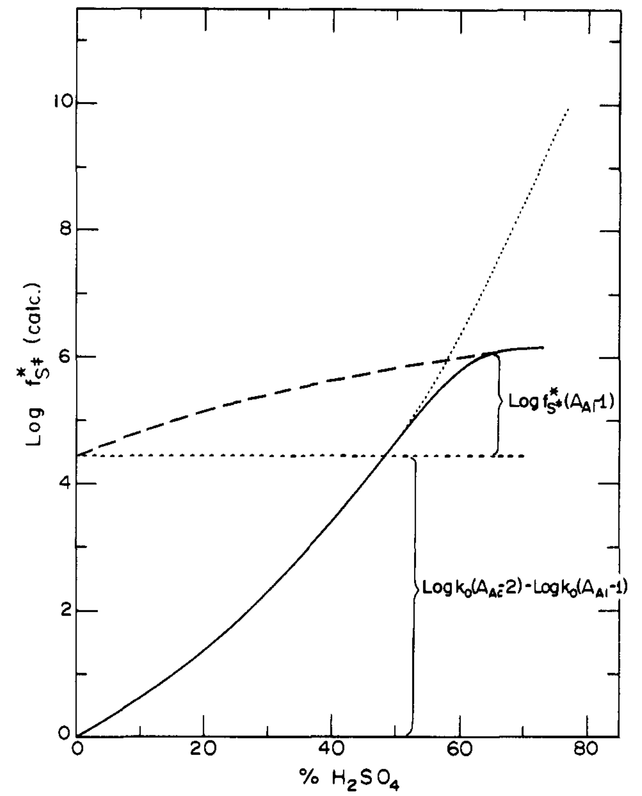


Figure 7. Bimolecular and unimolecular components to transition state activity coefficients. (—) Experimental curve; (. . .) curve due to A_{Ac}-2 which would be obtained above 50% H_2SO_4 if there were no change in mechanism; (- - -) $\log f^*_{S\ddagger}(A_{Al}\text{-}1) + \log k_0(A_{Ac}\text{-}2) - \log k_0(A_{Al}\text{-}1)$, obtained by extrapolation.

this lies in the fact that the calculations based on eq 1 actually give $\log (f^*_{S\ddagger}/k_0)$, and $\log f^*_{S\ddagger}$ is only obtained after extrapolation to zero concentration to estimate $-\log k_0$. However, for all of the esters except *t*-BuOAc, this extrapolation gives $-\log k_0$ for the A_{Ac}-2 hydrolysis. The $\log f^*_{S\ddagger}$ values for the A_{Al}-1 hydrolysis are thus offset from the correct value by a constant equal to $\log k_0(A_{Ac}\text{-}2) - \log k_0(A_{Al}\text{-}1)$. The true values will only be obtained if that section of the curve corresponding to A_{Al}-1 hydrolysis is extrapolated to zero concentration. This is shown in Figure 7 for cyclopropylcarbinyl acetate. The extrapolation must be regarded as being very approximate due to the distance involved and the limited number of data points for the A_{Al}-1 hydrolysis.

In any event, the behavior of the curves representing bimolecular and unimolecular pathways strikingly demonstrates the reason that there is a mechanism changeover in the more concentrated acids, namely the much more pronounced salting-out of the A_{Ac}-2 transition state.

Log $f^*_{S\ddagger}$ and Transition State Structure. In Figure 8, the $\log f^*_{S\ddagger}$ for the two ester hydrolysis reactions are compared with activity coefficients of selected cationic species (also of the form $f^*_+ = f_+/f_{TEA^+}$). Values of $\log f^*_{RO^+H_2}$ were obtained from the alcohol acidity function, H_{ROH},[21] and alcohol activity coefficients,[13] using the relationship

$$h_{RO^+H_2} = \frac{a^*_{H^+} f_{ROH}}{f^*_{RO^+H_2}}$$

Strikingly varied behavior is observed; in 70% H_2SO_4, there is a range of 11 log units in the $\log f^*_+$ values. The A_{Ac}-2 transition state exhibits the greatest salting-out yet observed for a cationic species (other than the proton), even greater than that of a protonated alcohol, RO^+H_2. The

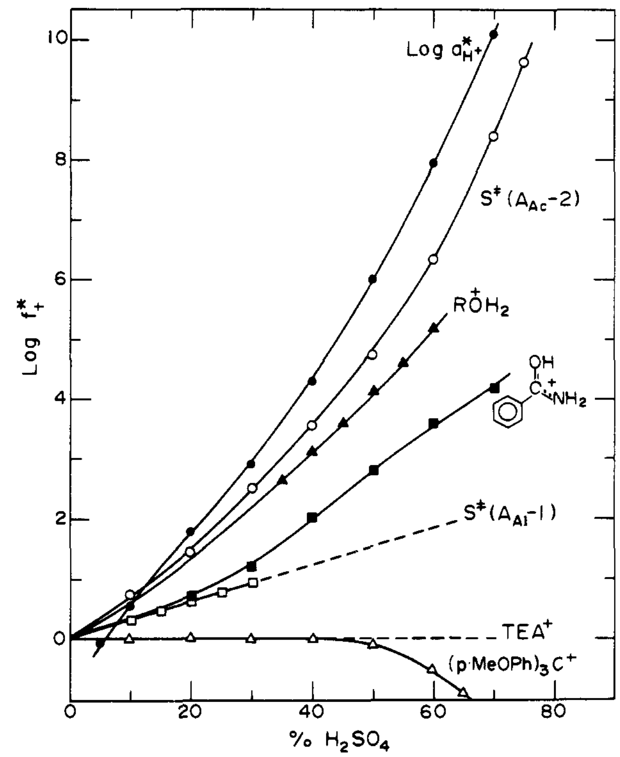
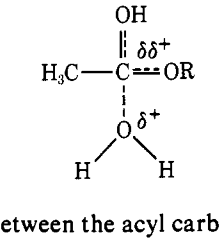


Figure 8. Activity coefficients of cationic molecules and transition states (relative to TEA^+). Benzamidonium and tris(*p*-methoxyphenyl) carbonium, from ref 13; RO^+H_2, from H_{ROH} (see text); log $a^*_{H^+}$, from ref 7.

A_{Al}-1 transition state is salted-in relative to the protonated onium ion species but is still considerably salted-out as compared with stabilized carbonium ions such as the tris(*p*-methoxyphenyl) carbonium ion.

In a recent review,[13] we summarized the factors that can be said to qualitatively affect activity coefficient behavior of cationic species. For our purposes here two such factors appear important, namely the extent of delocalization of the charge and the presence of hydrogen bonding interactions of the type $^+O\text{-}H \ldots OH_2$, in which water acts as a hydrogen bond acceptor. For the former, increased delocalization results in less salting-out since the overall need for solvation is lower. With the latter, increasing acidity results in the removal of the available water molecules (decreasing water activity) and therefore causes a fairly pronounced salting-out.

The behavior of the A_{Ac}-2 transition state can be explained by postulating a structure which fairly closely resembles the tetrahedral intermediate:

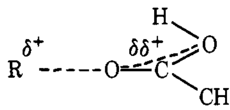


$$\begin{array}{c} OH \\ \| \;\delta\delta^+ \\ H_3C\text{—}C\text{=---}OR \\ \vdots \\ O^{\delta^+} \\ H \quad\; H \end{array}$$

That is, the bond between the acyl carbon and the oxygen of the attacking water is almost fully formed, and the majority of the positive charge resides on this oxygen ($\delta^+ > \delta\delta^+$). This is reasonable on the basis of the Hammond postulate since such species are unstable intermediates along the hydrolysis pathway. This structure would be expected to show the observed marked salting-out. The positive charge is fairly localized (dependent on the degree of advancement of

C-O bond making), but more importantly there is a requirement for a number of hydrogen-bonding interactions of the type $O^+-H\cdots OH_2$. Moreover these interactions must be particularly significant in the system; there are three electronegative oxygens attached (or being attached) to the same carbon, and these must tend to destabilize the positive charge that resides in their vicinity. In other words, the cation is forced to seek solvent stabilization of the above type and hence must be strongly salted-out as the solvent capacity for performing this is decreased. This can be seen more clearly if the transition state is imagined to be fully like the tetrahedral intermediate. In this case, one is dealing simply with a species of the type RO^+H_2, in which the group attached to the oxygen is considerably electron withdrawing because of the two additional oxygens. In consequence, we would expect an activity coefficient behavior similar to that of protonated alcohols, with some additional salting-out due to the greater inherent instability introduced by the electron-withdrawing group, and consequent stronger demand for external stabilization, mainly in the form of hydrogen bonding to water.[22]

We turn now to the A_{Al}-1 transition state for which a considerably smaller salting-out is observed. This transition state can be written in the form



in which there is a substantial amount of carbonium ion character. This structure then contains a considerably delocalized positive charge. (The carbonium ion would not be formed in the first place if it were not stabilized by such a delocalization.) In addition there is a far smaller requirement for the type of hydrogen bonding interactions so important in the bimolecular reaction. The positive charge is being removed from the O-H group as the reaction proceeds and placed on carbon (or in a delocalized system). On both of these counts, a much smaller salting-out is expected.

On the other hand, this transition state is still salted-out relative to long-lived carbonium ions. This is not surprising, even if we consider the extreme case in which the transition state is the fully developed carbonium ion. The carbonium ions involved in these ester hydrolysis are still not nearly as delocalized as, for example, the tris(*p*-methoxyphenyl) carbonium ion. Furthermore, an acetic acid molecule is still present and cannot be ignored. Carboxylic acids are known to be considerably salted-out, at least up to 60% H_2SO_4,[13] and there must still be some interaction with the carbonium ion, if only in the form of an ion-dipole attraction.[23] This would result in a small amount of positive charge being still present in the acid position and subsequently some demand for hydrogen bonding.

Log $f^*_{S\ddagger}$ for A_{SE}-2 Reactions. The transition state activity coefficient approach is not limited to acid-catalyzed reactions involving preequilibrium protonation; it can also be applied in cases of slow proton transfer, i.e., A_{SE}-2 reactions. Log $f^*_{S\ddagger}$ values are then determined from the equation

$$\log f^*_{S\ddagger}/k_0 = \log a^*_{H^+} + \log f_S - \log k_\psi$$

where the symbols have the same meaning as before.

To illustrate this, we have chosen two examples of acid-catalyzed aromatic exchange for which there is sufficient rate data available in aqueous H_2SO_4, namely the dedeuteration of anisole at the para position[24] and *p*-cresol at the ortho position.[25] Activity coefficient data for anisole are available;[13] for *p*-cresol, values previously obtained for phenol[13] have been used. The results are plotted in Figure 9 and show that these two systems differ considerably.

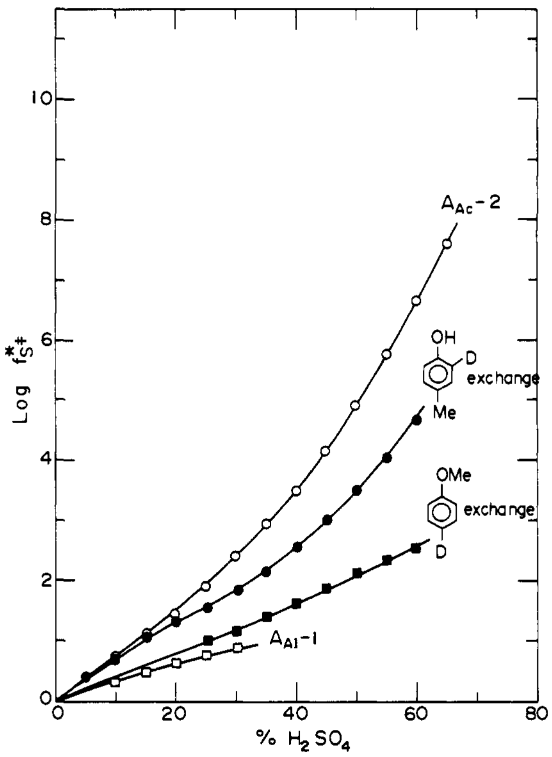
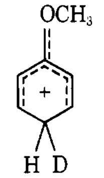


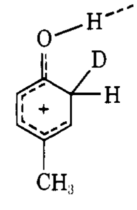
Figure 9. Transition state activity coefficients for A_{SE}-2 aromatic exchange.

The anisole exchange process follows fairly closely the behavior of the A_{Al}-1 transition state. This is reasonable in terms of the transition state that is expected for this reaction, a cationic species approaching in structure the Wheland intermediate:



In fact this species is similar in many respects to the carbonium ion intermediate obtained in the unimolecular hydrolysis of *p*-methoxybenzyl acetate.

The *p*-cresol transition state on the other hand is considerably more salted-out. In both molecules, there is a significant amount of positive charge being built up on the attached oxygen but, with the phenol, this results in a possibility for hydrogen bonding to water:



This additional feature would then account for the increased salting-out. In fact such an interaction has been postulated as being responsible for the greater activating effect of O-H over $O-CH_3$[26,27] in electrophilic aromatic substitution, and the results here serve to further confirm its importance. These examples illustrate the ability of the log $f^*_{S\ddagger}$ approach to detect subtle changes in transition state behavior. In this case, the change does not involve the actual structure but rather solvation.

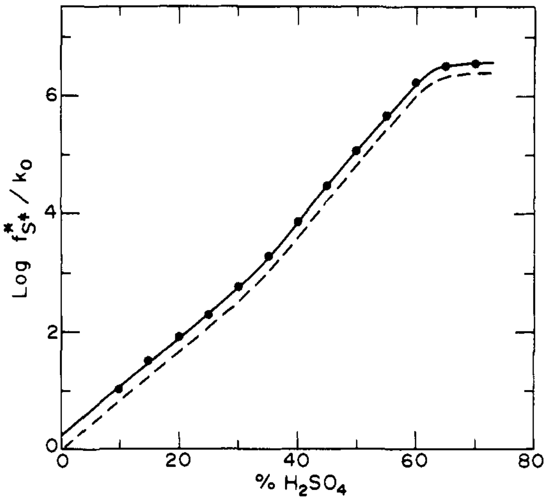


Figure 10. Extrapolation of log $f^*_{S\ddagger}/k_0$ to zero acid concentration. Dashed line represents log $f^*_{S\ddagger}$ values.

Conclusions

The advantage of the present treatment of kinetic acidity dependence is that it avoids the major difficulties inherent in previous treatments. It is more straightforward in that it is not a hydration-parameter treatment. Thus no water activity data are needed, and no assumptions need be made about the separation and cancellation of activity coefficients. Furthermore the acidity is not represented by any Hammett-type acidity function, which eliminates the problem of deciding which function is most appropriate for substrate protonation, or best represents the acidity of the reaction medium.

The transition state activity coefficients derived, and their medium dependence, are entirely reasonable in terms of the structures expected for the various mechanisms, and the positions of mechanistic changeover frequently observed. In at least one case, the treatment gives a result which is more in accord with other evidence than that obtained by a hydration treatment. The method appears to be applicable to reactions other than ester hydrolysis, and work is currently under way to determine whether it can be usefully extended to a wide variety of acid-catalyzed organic reactions.

Experimental Section

Materials. Sulfuric acid solutions were prepared and standardized as previously described.[15] Isopropyl acetate and *p*-nitrobenzyl acetate were commercially available and were purified by distillation and recrystallization, respectively. Cyclopropylcarbinyl acetate, benzyl acetate, *p*-chlorobenzyl acetate, and *p*-methoxybenzyl acetate were obtained from the alcohol, by treatment with acetyl chloride. A sample of *p*-methoxybenzyl acetate-*ether*-^{18}O was prepared by exchange of *p*-methoxybenzaldehyde with ^{18}O water (1.3%, Miles Laboratories), followed by sodium borohydride reduction and acylation.

Rate Determinations. For the substituted benzyl acetates, the previously described[3] ferric chloride-acetohydroxamic acid complex technique was employed. With cyclopropylcarbinyl acetate, the kinetics were followed from the change in uv absorption at 210 nm (on a Cary 16 spectrophotometer equipped with an external recorder). Both methods gave good linear plots of log $(A - A_\infty)$ vs. time from which the pseudo-first-order rate constants were evaluated.

With cyclopropylcarbinyl acetate, NMR spectroscopy showed some decomposition of the product cyclopropylcarbinol in solutions above 55% H_2SO_4. The excellent first-order plots obtained with the ester suggested, however, that this was not interfering with the kinetics. This is reasonable since the uv change that is being followed is acetate to acetic acid, the alcohol being transparent at this wavelength.

Activity Coefficient Measurements. All activity coefficients were determined by the distribution method. From 1 to 2 ml of a 10^{-1}-10^{-2} *M* solution of the acetate in cyclohexane (ACS Spectroanalyzed Grade) was shaken mechanically with 1-10 ml of water or aqueous sulfuric acid for 1-3 min in a thermostatically controlled (25 ± 0.2°) box.[15] For the benzyl acetates, the aqueous layer and, for the alkyl acetates, the cyclohexane layer was transferred to a uv cell and the spectrum recorded on a Cary 14 spectrophotometer. For the benzyl acetates, wavelengths corresponding to the absorbance maximum in the region 250-275 nm were used; for the alkyl acetates, a wavelength of 213 nm was used. Distribution coefficients were calculated from the observed absorbances, and values of the activity coefficient could then be obtained from the ratio of the distribution coefficients in water and the given acid solution. Various control experiments were carried out to check the reliability of these measurements. Using systems where hydrolysis is not a problem, namely the acetates in the more dilute acids, and benzene and 4-nitrobenzene in the more concentrated acids, it was established that the distribution coefficient was independent of (i) the time of shaking, from 30 sec to 20 hr and (ii) the time of separation, from 1 min to 20 hr. These experiments establish (i) that equilibration between the two phases was rapid and complete and (ii) that the two phases were being separated without emulsification. In those cases where hydrolysis interferes, various shaking periods from 1-3 min were employed, and the observed absorbances were extrapolated to zero shaking time.

Basicity of *p*-Nitrobenzyl Acetate. All spectra were obtained using a Varian T60 spectrophotometer. Approximately 5×10^{-2} *M* solutions of the acetate in aqueous solutions of sulfuric acid were prepared, and the solution was immediately transferred to an NMR tube and the spectrum recorded. Since only the difference in chemical shift is required, no internal standard was used.

Position of Cleavage of *p*-Methoxybenzyl Acetate. A solution of 0.3 ml of ether labeled ester in 100 ml of 4.9% H_2SO_4 was placed in a thermostated water bath at 25° for 6 hr (ca. 3 half-lives of hydrolysis). The alcohol was recovered by extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent, followed by preparatory gas chromatography. The ^{18}O content was determined on an AEI MS-902 mass spectrometer, by analysis of the intensity ratio of the ions at *m/e* 140 and 138. In a control experiment, a sample of labeled alcohol was subjected to the same reaction conditions as above, followed by recovery and analysis in an identical manner.

Log $f^*_{S\ddagger}$ Values. These were calculated from eq 1 using the rate, basicity, and activity coefficient data along with the hydronium ion activity.[7] The initial calculation gives log $f^*_{S\ddagger}/k_0$, and k_0 is calculated by extrapolation to zero acid concentration. This is illustrated in Figure 10. What is essentially involved in the determination of true log $f^*_{S\ddagger}$ values is simply a lateral shift of the calculated log $f^*_{S\ddagger}/k_0$ curve so that it passes through the origin.

Acknowledgments. The financial support of the National Research Council of Canada is gratefully acknowledged.

References and Notes

(1) This expression applies to the case where the substrate is substantially unprotonated. In cases of partial protonation, it is necessary to replace k_ψ by $k_\psi(1 + I)$, where I is the ionization ratio $[SH^+]/[S]$.

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(8) (a) Since they refer to single ions, a_{H^+} and $f_{S\ddagger}$ are not directly accessible but can be obtained relative to another cation. TEA^+ has commonly been used for this purpose.[8b] (b) R. H. Boyd, *J. Am. Chem. Soc.*, **85**, 1555 (1963).

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(14) J. N. Anderson, Ph.D. Thesis, University of Pittsburgh, 1974.
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(17) Both isopropyl acetate and *p*-nitrobenzyl acetate show such a break around 80% H_2SO_4. However, the calculations at these acidities are based on f_S values obtained on extrapolation over a considerable range of acidity and are therefore not as reliable.
(18) (a) This study again shows the powerful stabilizing effect of a cyclopropyl group adjacent to a carbonium ion center, even stronger than the corresponding effect of a phenyl group.[20b] (b) D. G. Garratt, A. Modro, K. Oyama, G. H. S. Schmid, T. T. Tidwell, and K. Yates, *J. Am. Chem. Soc.*, **96**, 5295 (1974), and references therein.
(19) This is the ρ value based on the A_{Ac}-2 hydrolysis of the other benzyl acetates of this study and also agrees with a literature value for hydrolysis in aqueous acetone.[19b] (b) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).
(20) The failure of the "*r*" treatment for *p*-methoxybenzyl acetate lies in the substantially negative "*r*" value for A_{Al}-1 hydrolysis in dilute acids (−9 for *t*-BuOAc). Even in a region of relatively small contribution of this mechanism, it therefore has an overriding effect on the value of the slope in the "*r*" plot.
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(22) An alternative way of looking at this is in terms of the acidity of the $^+$O–H bond. The $^+$O–H bond in the tetrahedral intermediate is considerably more acidic than that of a protonated alcohol and thus is capable of forming stronger hydrogen bonds with water.
(23) (a) For example, in Kurz's calculations of transition state $pK_a(\ddagger)$ values[23b] for S_N2 reactions, even in the extreme cases in which he assumes a fully product-like or reagent-like transition state, the additional molecule that is present has a significant influence. (b) J. L. Kurz, *Acc. Chem. Res.*, **5**, 1 (1972).
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(26) See, for example: R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", Elsevier, Amsterdam, 1965, pp 140, 237, 242.
(27) (a) It has been suggested[27b] that, in certain cases, the phenolic hydrogen is being removed during the electrophilic attack, with the resultant formation of a neutral quinoid intermediate. (b) P. B. D. de la Mare, A. Singh, T. G. Tillett, and M. Zeltner, *J. Chem. Soc. B*, 1122 (1971).

Transition State Structure for Peracid Epoxidation. Secondary Deuterium Isotope Effects

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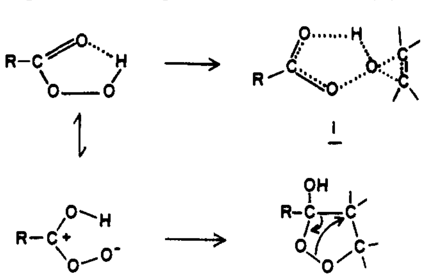
Abstract: Kinetic deuterium isotope effects have been measured for the epoxidation of *p*-phenylstyrene (**3**) and three deuterated derivatives (α-*d* (**4**); β,β-d_2 (**5**); α,β,β-d_3 (**6**)) with *m*-chloroperbenzoic acid in 1,2-dichloroethane at 0°. The isotope effects (k_H/k_D) observed for **4**, **5**, and **6** are 0.99, 0.82, and 0.82, respectively; for *p*-nitrostyrene and its α-*d* analog k_H/k_D at 25° was 0.98. The peracid isotope effect for epoxidation of **3** with *m*-$ClC_6H_4COOOH(D)$ at 0° was $k_H/k_D = 1.17$. These data suggest that in the transition state for epoxidation there is substantial C_β-O bond formation, but negligible change in the bonding or hybridization at C_α of the olefin. Epoxidation mechanisms suggested previously cannot accommodate these findings, thus an alternate transition state structure has been proposed. It is characterized by (1) sp^2 geometry and partial positive charge at C_α of the olefin, (2) extensive C_β-O bond formation but with retention of some π bonding between C_α and C_β, (3) a nearly equal amount of partial negative charge on the peracid carboxylate, and (4) little change in the bonding of the peracid proton.

The epoxidation of olefins by peracids is a familiar and synthetically useful reaction. As summarized in recent reviews,[1] numerous mechanistic studies of this reaction have centered around two proposed mechanisms. The first of these was proposed by Bartlett[2] and involves the symmetrical transfer of an oxygen atom to the olefin from the internally hydrogen bonded peracid monomer (**1**). Kwart and Hoffman[3] later proposed a 1,3-dipolar addition mechanism involving a 1,2-dioxolane intermediate (**2**). Recent arguments based on Hammett correlations and solvent effect studies[4] support the former mechanism more readily than the latter.



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Peracid epoxidation has also been proposed[5,6] as a possible "model" reaction for certain enzymatic epoxidations, probably because both reactions are stereospecific and appear to involve an attack on the olefin by an electrophilic reagent. In our attempts to elucidate the nature of the attacking species in the enzymatic epoxidation, we sought to extend, and if possible to quantitate, the similarity of enzymatic, peracid, and other types of epoxidations by means of Hammett correlations and kinetic deuterium isotope effects. While there have been several Hammett[7-9] studies of peracid epoxidation, this reaction had not been previously studied by kinetic isotope effect methods. We therefore undertook such a study and have found that neither of the two mechanisms mentioned above can adequately accommodate our results. Rather, our data suggest that the transition state for peracid epoxidation has an open chain structure with a large degree of charge separation as shown in Figure 1.

Experimental Section

***p*-Phenylstyrene (3) and *p*-Phenylstyrene-α-*d* (4).** 4-Acetylbiphenyl (Aldrich) was purified by column chromatography and reduced with $LiAlH_4$ (or $LiAlD_4$) in ether to give 4-(1-hydroxyethyl)biphenyl in 88% yield: mp 95–96° (lit.[10] 97°). Dehydration of this alcohol by heating for several hours in DMSO with small amounts of $KHSO_4$ and hydroquinone at 190° under nitrogen, followed by dilution with water, extraction with hexane, and chromatography of the hexane extract on active silica gel, gave an 82%