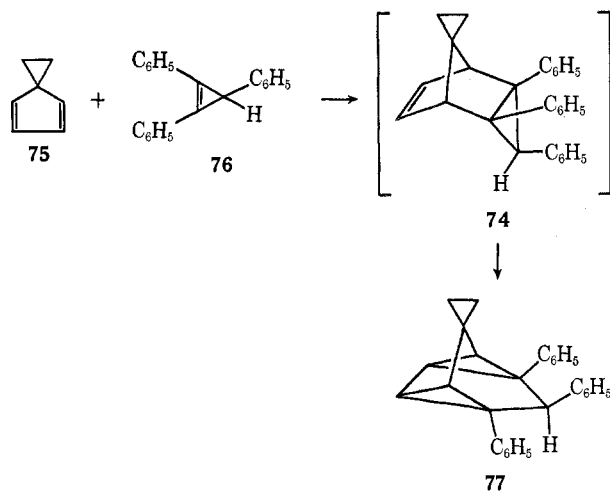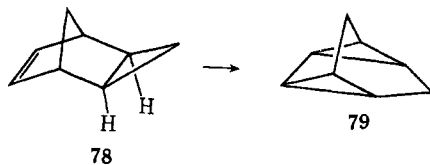mediate in the reaction of **75** with **76** to give **77**. Presumably, the thermal intramolecular cycloaddition required for the conversion of **74** into **75** occurs at relatively low temperatures.


75   **76**

74

77

Metal-Catalyzed Additions

Metal-catalyzed intermolecular additions of carbon–carbon multiple bonds to strained carbocyclics are yet to be observed. However, intramolecular reactions of this type are known. Rhodium on carbon and various coordination complexes of rhodium readily transform **78** into **79**.[39,40] Some mechanistic details of this reaction have been reported.[39]

78   **79**

A related curiosity involves the conversion of **1** into **80** in the presence of maleic anhydride and rhodium dicarbonyl chloride dimer.[41] Although it has been

$[Rh(CO)_2Cl]_2$

1

80   **81**
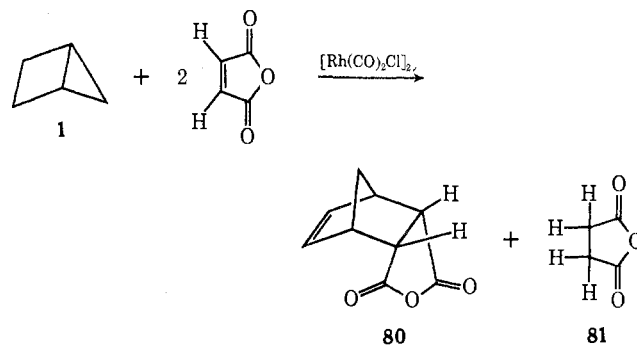
found[41] that **1** is rapidly isomerized to cyclopentene in the presence of the catalyst and that cyclopentene reacts with maleic anhydride in the presence of the catalyst to yield a mixture of **80** and **81**, we have yet to establish all the details of this particular set of reactions.

Summary

The addition of electron-deficient carbon–carbon multiple bonds to strained carbocyclics has been shown to be a general reaction. Mechanistic evidence indicates that the rate-determining step involves the formation of a diradical in the simple $_\pi2 + {}_\sigma2$ additions.

(39) T. J. Katz and S. A. Cerefice, *J. Amer. Chem. Soc.*, **91**, 2405 (1969); **91**, 6519 (1969).

(40) H. C. Volger, H. Hogeveen, and M. Gaasbeek, *ibid.*, **91**, 218 (1969).

(41) P. G. Gassman, J. T. Lumb, and T. J. Atkins, unpublished work.

Kinetics of Ester Hydrolysis in Concentrated Acid

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Of the many organic reactions which are acid catalyzed, ester hydrolysis has been one of the most frequently studied. Many kinetic investigations have dealt with the dilute acid region, where activity coefficient variation of reaction species can be either ignored or reasonably treated using Debye–Hückel-type approximations. However, in dilute acids, reactions often proceed at inconveniently slow rates, and it is also difficult to achieve much variation in the concentration (or activity) of one important reaction species, water, unless more concentrated acids are used.

On the other hand, in more concentrated solutions,

these difficulties are replaced by other serious problems, which are largely concerned with the theoretical interpretation of results. Some of these arise from the use of acidity functions to represent variations in the acidity of a reaction medium. Because of these difficulties this field of reaction mechanisms has been in an uncertain state for many years.[1] The intent of this Account is to illustrate and examine these difficulties, using recent results on ester hydrolysis, in an attempt to show that nonetheless valuable mechanistic information can

(1) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

be obtained from study of kinetics in concentrated acids.

Acidity Functions

An acidity function, H_X, is defined as the quantitative measure of the ability of a medium to protonate a particular type of base X. For neutral Brønsted bases the equilibrium

$$X + H^+ \rightleftharpoons XH^+$$
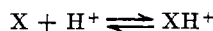
and the thermodynamic dissociation constant K_{XH^+}

$$K_{XH^+} = a_X a_{H^+}/a_{XH^+} = (a_{H^+} f_X/f_{XH^+})(c_X/c_{XH^+})$$

are used to define acidity according to

$$h_X = a_{H^+} f_X/f_{XH^+}$$
$$-\log h_X = H_X = pK_{XH^+} + \log (c_X/c_{XH^+})$$

where c is a stoichiometric concentration, a is an activity, and f is a molar activity coefficient. Thus h_X and H_X are extensions of the [H^+] and pH scales into concentrated acids where f's are no longer approximately equal to unity. The subject of acidity functions has recently been thoroughly reviewed;[2] it is now well recognized that no one acidity function, such as H_0,[3] based on primary aniline indicators,[4] is generally applicable to the protonation behavior of neutral bases of different structural classes, such as typical organic substrates in acid-catalyzed reactions.

The Zucker–Hammett Hypothesis

The first quantitative attempt to treat rate–acidity dependence in nondilute acids was made by Zucker and Hammett.[5] Based on the data then available, they grouped reactions into two categories, depending on whether the logarithm of the pseudo-first-order rate constant (k_ψ) was linear with approximately unit slope in either $-H_0$ or $\log c_{H^+}$. The hypothesis was that reactions of the first type involved rate-determining unimolecular decomposition of protonated substrate (A1) and those of the second type rate-determining attack on protonated substrate by a water molecule (A2).

For A1 reactions, represented as

$$S + H^+ \rightleftharpoons SH^+$$
$$SH^+ \xrightarrow{\text{slow}} \ddagger \longrightarrow \text{products}$$
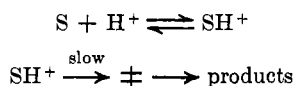
the Brønsted rate expression which results if acidity is represented by H_0 (or h_0) is given by eq 1, where B

$$k_\psi = k h_0 \left[\frac{f_S f_{BH^+}}{f_{\ddagger} f_B} \right] \tag{1}$$

and BH^+ refer to typical Hammett indicators. Thus for $\log k_\psi$ to be linear in $-H_0$ with unit slope requires the bracketed term to be essentially medium invariant.

Table I

H_2SO_4, M	Log c_{H^+}	$-H_0$	$-\text{Log}$ a_{H_2O}	Log $(c_{H^+}/h_0 a_{H_2O})$
1.0	0.0	−0.26	0.02	−0.24
5.0	0.7	−2.27	0.22	−1.35
10.0	1.0	−4.94	0.97	−2.97

For A2 reactions

$$S + H^+ \rightleftharpoons SH^+$$
$$SH^+ + H_2O \xrightarrow{\text{slow}} \ddagger \longrightarrow \text{products}$$
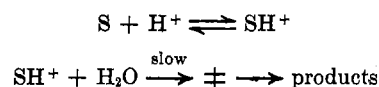
the corresponding expression for the rate constant is given by eq 2. Again, linearity of $\log k_\psi$ in $\log c_{H^+}$

$$k_\psi = k c_{H^+} \left[\frac{f_S f_{H^+} a_{H_2O}}{f_{\ddagger}} \right] \tag{2}$$

with unit slope requires the medium invariance of the bracketed term.

As rate constants of more reactions were obtained, some were found to be linear in either $-H_0$ or $\log c_{H^+}$ but with nonunit slopes; others were not linear in either function of acidity. Despite ensuing severe criticisms of this hypothesis and recommendations that it be discarded as a serious criterion of mechanism, it has been remarkable for its durability. Its basic difficulty as a dual criterion of mechanism lies in the two necessary but unjustifiable parallel assumptions of constancy of the two activity coefficient ratios. For example, in a reversible reaction which reacts A1 in the forward sense (S_1) and A2 in the reverse sense (S_2) and obeys the dual criteria,[6] the two assumptions require the equality

$$\frac{f_{S_2}}{f_{S_1}} = \frac{f_{BH^+}}{f_B f_{H^+} a_{H_2O}} = \frac{c_{H^+}}{h_0 a_{H_2O}}$$

This equality arises because the two cases of the Zucker–Hammett hypothesis both require the relevant activity coefficient ratio to be constant, including under conditions of infinite dilution in water, where each is unity. Therefore the two ratios can be equated, and since S_1 and S_2 react through a common transition state $f_{\ddagger}$ cancels. The term on the right-hand side of this equality can be calculated from available data, and logarithmic values at selected H_2SO_4 concentrations are given in Table I. Thus pairs of neutral substrates for all such reactions obeying the hypothesis would be required to exhibit the same large and anomalous activity coefficient ratio variation,[7] which is unreasonable.

The Bunnett Hydration Parameter Treatment

Bunnett found empirically that, for a large number of organic reactions,[8] plots of $\log k_\psi + H_0$ are linear or very nearly linear in $\log a_{H_2O}$ of the reaction medium. The slopes, w, of these plots vary over a wide range, and

(2) C. H. Rochester, "Acidity Functions," Academic Press, London, 1970.

(3) L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.*, **54**, 2721 (1932).

(4) M. J. Jorgenson and D. R. Hartter, *ibid.*, **85**, 878 (1963).

(5) L. Zucker and L. P. Hammett, *ibid.*, **61**, 2791 (1939).

(6) Bunnett has considered this problem in some detail in the specific case of the γ-butyrolactone–γ-hydroxybutyric acid interconversion: J. F. Bunnett, *ibid.*, **83**, 4978 (1961).

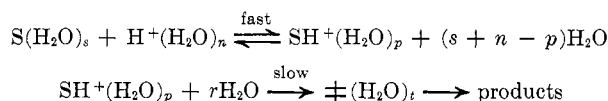(7) R. W. Taft, N. C. Deno, and P. S. Skell, *Annu. Rev. Phys. Chem.*, **9**, 287 (1958).

(8) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

Table II

Role of water in rate-determining step	Range of w values
None	$\leqslant 0$
Nucleophile	$+1.2$ to $+3.3$
Proton transfer agent	$> +3.3$

on the basis of comparisons with reactions of known mechanism it was possible to group reactions into three types according to the magnitude of the w parameter[9] and the role of water in the rate-determining step, as shown in Table II.

To give these empirical relationships a theoretical basis, Bunnett considered the following general equations[10] describing an acid-catalyzed process in terms of fully hydrated species

$$S(H_2O)_s + H^+(H_2O)_n \overset{fast}{\rightleftharpoons} SH^+(H_2O)_p + (s + n - p)H_2O$$

$$SH^+(H_2O)_p + rH_2O \overset{slow}{\longrightarrow} \ddagger(H_2O)_t \longrightarrow products$$

Redefining H_0 also in terms of fully hydrated species

$$B(H_2O)_b + H^+(H_2O)_n \rightleftharpoons BH^+(H_2O)_a + (b + n - a)H_2O$$

and substituting for $a_{H^+(H_2O)_n}$ in the rate equation in terms of the redefined h_0 yields for the pseudo-first-order rate constant

$$k_\psi = \frac{k_0}{K_{SH^+}} h_0 a_{H_2O}{}^{r+(p-s)-(a-b)} \left(\frac{f_{S(H_2O)_s} f_{BH^+(H_2O)_a}}{f_{B(H_2O)_b} f_{\ddagger(H_2O)_t}} \right)$$

On making the extreme assumption that activity coefficients for all species of like charge show the same medium dependence, the term in parentheses cancels, and on taking logarithms

$$\log k_\psi + H_0 = [r + (p - s) -$$
$$(a - b)] \log a_{H_2O} + constant$$

Thus the theoretical interpretation of w is that it is a measure of the transition-state hydration requirement (r) on a scale relative to the difference in hydration changes between protonating a substrate molecule $(p - s)$ and a Hammett indicator base $(a - b)$.

Modified Hydration Parameter Treatment

The Bunnett treatment has been modified by Yates and coworkers[11] in an attempt to minimize the seriousness of the necessary approximations and to simplify the interpretation of observed water activity dependence. The basic approach is the same, but acidity is defined in terms of a function, H_X, strictly appropriate to the type of substrate being investigated. In this case it is reasonable that $(p - s) \simeq (a - b)$ and also that $f_{S(H_2O)_s} \simeq f_{X(H_2O)_b}$ in a given medium. For example, if the amide-based acidity function H_A[12] is used for

amide hydrolysis, both types of term refer to very similar processes or species. If it is then assumed that, since the transition state and XH^+ will be of similar structure, charge, and size, the ratio $f_{XH^+(H_2O)_a}/f_{\ddagger(H_2O)_t}$ will be approximately medium independent, the Bunnett expression simplifies to

$$\log k_\psi + H_X = r \log a_{H_2O} + constant$$

Now the water activity dependence r corresponds more closely to the number of water molecules required to convert a protonated substrate molecule to transition state, or the approximate "order" of the reaction in water.

Ester Hydrolysis in Concentrated Sulfuric Acids

Because acid-catalyzed ester hydrolysis has been so widely studied and the general mechanistic possibilities are so well recognized, we have attempted a systematic study of their rate dependence on structure, acidity, and water activity for two reasons: to provide further insight into detailed mechanisms and their domains and to test the described theoretical treatments of rate–medium dependence. Although the kinetics of a few ester hydrolyses have previously been studied in concentrated acids,[13] the present discussion deals mainly with results from the writer's laboratory, some of which have been reported previously.[14]

Rate Profiles. The esters so far investigated are all acetates, chosen so as to vary one structural parameter at a time, and the rates have been measured over the widest range of acid experimentally practicable.[15] The rate dependence (k_ψ) of all these esters on acid concentration was found to fit into one of four basic categories, as shown in Figure 1. Type I is characterized by an initial steady rate increase with acid concentration, passing through a local maximum (at about 50–60% H_2SO_4), followed by a rate decrease almost to zero, then a final modest increase in highly concentrated (>90%) acids. As shown in Table III this behavior is typical of primary alkyl acetates, which give very similar profiles. Type II resembles this somewhat, except that the rate maximum occurs at significantly lower values of k_ψ, whereas the final rate increase occurs much earlier, is much sharper, and is strongly structure dependent. This has been found typical of secondary alkyl, benzyl (except p-methoxy-), and allyl acetates as shown in Table III. Type III differs from the previous cases in that there is no observable rate maximum, although rate increases in the moderately concentrated acid region are very similar to those found for types I and II. However the rates continue to increase until they are too fast to follow by conventional methods by about 70% H_2SO_4. This behavior has been found for vinyl and substituted-phenyl acetates. Finally type IV re-

(9) This criterion of mechanism was originally advanced with some qualification, especially as stated in the last paper of ref 8.

(10) The symbolism used here is somewhat different from that in the original papers by Bunnett.[8]

(11) K. Yates and J. B. Stevens, *Can. J. Chem.*, **43**, 529 (1965); K. Yates and J. C. Riordan, *ibid.*, **43**, 2328 (1965).

(12) K. Yates, J. B. Stevens, and A. R. Katritzky, *ibid.*, **42**, 1957 (1964).

(13) C. A. Lane, *J. Amer. Chem. Soc.*, **86**, 2521 (1964); D. Jaques, *J. Chem. Soc.*, 3874 (1965); J. A. Leisten, *ibid.*, 1572 (1956).

(14) K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, **89**, 2686 (1967).

(15) The main limitation in the case of some substrates is the occurrence of side reactions, such as sulfonation.
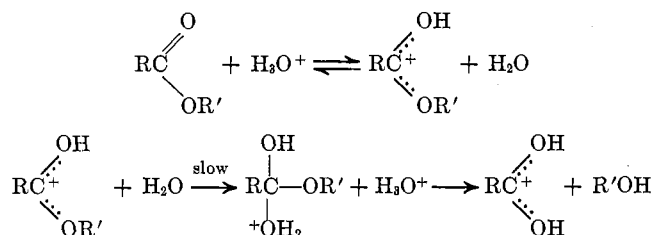
Table III

Ester Hydrolysis Rate Behavior in Concentrated Sulfuric Acids

Acetate	Type of rate profile	Local rate max, % H$_2$SO$_4$	Start of final rate increase, % H$_2$SO$_4$	Initial r value	Final r value	Region of changeover, % H$_2$SO$_4$	Assigned mechanisms
Methyl[a]	I	59	90	1.92	−0.2	75–90	A$_{Ac}$2 → A$_{Ac}$1
Ethyl[b]		54	90	2.10	−0.2	75–85	A$_{Ac}$2 → A$_{Ac}$1
n-Propyl[a]		53	90	2.05	−0.2	75–90	A$_{Ac}$2 → A$_{Ac}$1
Isopropyl[a]	II	53	80	2.15	−0.6	70–80	A$_{Ac}$2 → A$_{Al}$1
sec-Butyl[a]		52	75	2.20	−0.7	70–75	A$_{Ac}$2 → A$_{Al}$1
Allyl[c]		60	80	1.93	−0.6	70–80	A$_{Ac}$2 → A$_{Al}$1
Benzyl[a]		53	60	1.96		60–65	A$_{Ac}$2 → A$_{Al}$1
p-Chlorobenzyl[c]		56	65	2.03	−0.8	65–70	A$_{Ac}$2 → A$_{Al}$1
p-Nitrobenzyl[c]		57	85	1.85	−0.7	70–80	A$_{Ac}$2 → (A$_{Al}$1)
Vinyl[c]	III		Dilute	2.30	−0.3	40–55	A$_{Ac}$2 → (A$_{SE}$2)
Phenyl[a]			Dilute	1.92		>60	A$_{Ac}$2 → A$_{Ac}$1
p-Chlorophenyl[a]			Dilute	∼1.4		>65	A$_{Ac}$2 → A$_{Ac}$1
p-Nitrophenyl[a]			Dilute	1.82	−0.2	60–70	A$_{Ac}$2 → A$_{Ac}$1
o-Nitrophenyl[c]			Dilute	1.95	−0.4	60–70	A$_{Ac}$2 → A$_{Ac}$1
p-Carboxyphenyl[c]			Dilute	1.65	−0.4	60–75	A$_{Ac}$2 → A$_{Ac}$1
o-Carboxyphenyl[c]			Dilute	1.56	−0.8	50–65	A$_{Ac}$2 → A$_{Ac}$1
tert-Butyl[d]	IV		Dilute	−8.91			A$_{Al}$1
p-Methoxybenzyl[c]			Dilute	−4.12		Dilute	(A$_{Ac}$2) → A$_{Al}$1

[a] Reference 14. [b] Reference 13. [c] K. Yates and R. A. McClelland, unpublished results. [d] C. A. Bunton, J. H. Crabtree, and L. Robinson, J. Amer. Chem. Soc., **90**, 1258 (1968).

sembles the previous case in that there is only a monotonic rate increase with acidity, but this is much sharper than all other esters studied, and is extremely rapid even in fairly dilute acids. This behavior was found only for tert-butyl and p-methoxybenzyl acetates.

Hydrolyses Exhibiting Rate Maxima. This diversity of rate–acidity dependence makes it clear that all acetates are not reacting by the same mechanism and also that mechanism changes are occurring for individual esters with changing medium conditions. The early rate maxima for types I and II are easily understandable in terms of the "normal" A$_{Ac}$2 mechanism, which in simplified form is

$$RC\overset{O}{\underset{OR'}{\big\langle}} + H_3O^+ \rightleftharpoons RC\overset{OH}{\underset{OR'}{\big\langle}}{}^+ + H_2O$$

$$RC\overset{OH}{\underset{OR'}{\big\langle}}{}^+ + H_2O \xrightarrow{slow} RC\overset{OH}{\underset{+OH_2}{\big|}}-OR' + H_3O^+ \longrightarrow RC\overset{OH}{\underset{OH}{\big\langle}}{}^+ + R'OH$$

since at about 60% H$_2$SO$_4$ further increases in concentration of the reactive ester conjugate acid brought about by increasing acidity are more than offset by the rapidly decreasing availability of water required for the bimolecular hydrolysis step. (This resembles the rate maxima observed for amide hydrolysis,[16] which occur at lower acidity because of the higher basicity of amides.) However the final rate increases in still more concentrated acids where a_{H_2O} is extremely small (i.e., $a_{H_2O} = 2.2 \times 10^{-4}$ at 90% H$_2$SO$_4$) strongly suggest that gradual transitions to predominant A1 processes must be occurring quite generally.

Confirmation of this was obtained from exchange

(16) J. T. Edward and S. C. R. Meacock, J. Chem. Soc., 2000, 2009 (1957).
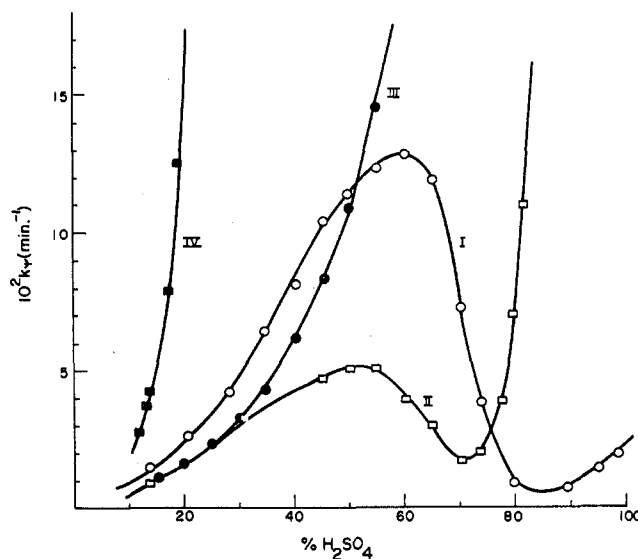

Figure 1. Typical rate profiles for acetate hydrolysis: type I, methyl; II, sec-butyl; III, phenyl; IV, tert-butyl.

studies on ^{18}O-labeled esters of types I and II at various acidities, as illustrated in Figure 2. At acidities both above and below the rate maxima [18]O exchange concurrent with hydrolysis is occurring at about one-fifth of the hydrolysis rate for both primary and secondary alkyl esters, consistent with the accepted A$_{Ac}$2 mechanism involving a symmetrical tetrahedral immediate in which both oxygens become equivalent.[17] However, in regions where the final rate increase is observed, the ratio of exchange to hydrolysis has fallen significantly, with k_E/k_H about 0.1–0.01. Also consistent with a change from A$_{Ac}$2 to a predominant A1 mechanism are the activation parameters for ethyl acetate hydrolysis given in Table IV.

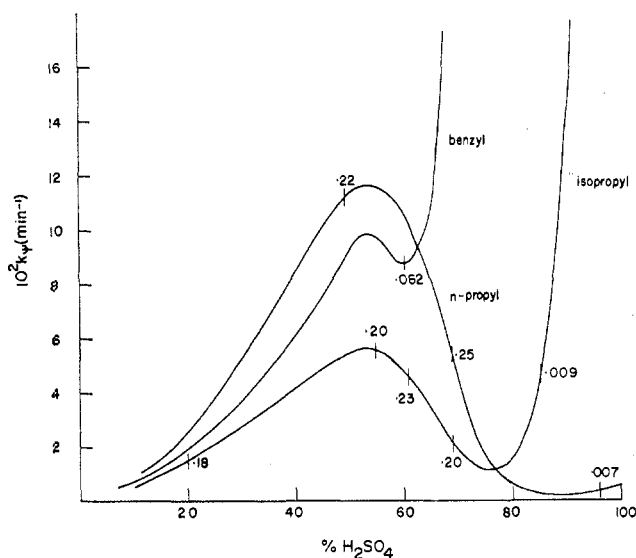(17) M. L. Bender, J. Amer. Chem. Soc., **73**, 1626 (1951).

Figure 2. Rate profiles for n-propyl, isopropyl, and benzyl acetate hydrolysis showing values of k_{exch}/k_{hydr} at selected acidities.

Table IV
Activation Parameters for Ethyl Acetate Hydrolysis

% H_2SO_4	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
40.2	16.9	−15.3
55.9	16.5	−15.7
62.5	16.3	−17.0
71.8	18.3	−12.4
98.4	23.7	+2.3

In the concentrated region where the mechanism is presumed to have changed from A2 to A1, $\Delta H^{\ddagger}$ has increased significantly and $\Delta S^{\ddagger}$ has changed sign from the negative values typical of A2 reactions to a small positive value more typical of an A1 process. Although these $\Delta S^{\ddagger}$ values are based on pseudo-first-order rate constants, which themselves are dependent on acidity, the observed medium dependence of $\Delta S^{\ddagger}$ over the range 40–72% acid would not be expected to lead to such a drastic change by 98%, unless a mechanism change were involved.

The most reasonable conclusion is that the hydrolysis of primary esters changes over from a predominant $A_{Ac}2$ mechanism below 90% H_2SO_4 to a predominant $A_{Ac}1$ mechanism in more concentrated acids.[18] This is consistent with the close similarity of rate profile for all three primary esters, since all would generate the same acylium ion. However, the secondary, benzyl, and allyl esters presumably change over from $A_{Ac}2$ to $A_{Al}1$. This is consistent with the fact that their rate profiles are more structure dependent. The acidity at which the final sharp rate increase occurs corresponds roughly to the order of stability of the carbonium ions being generated in an $A_{Al}1$ process, i.e., benzyl > p-chlorobenzyl > sec-butyl > allyl ~ isopropyl > p-nitrobenzyl, in order of increasing acidity.

Hydrolyses Exhibiting Monotonic Rate Increases.
Despite that fact that their rate profiles are monotonic,

it is very probable that the type III esters also undergo changes in mechanism at higher acidities. Assuming that phenyl acetates are also hydrolyzed initially by the $A_{Ac}2$ process, as seems reasonable, the fact that their rates continue to increase ever more sharply even when a_{H_2O} becomes extremely small cannot be explained by a dominant $A_{Ac}2$ process over the whole acid range. Eventually protonation of the neutral esters would approach completion, and rates would either level off or decrease as the a_{H_2O} factor assumed control. Thus the continued increases in rate must be due to the onset of another process which does not have the same water requirement.

Of the two possibilities $A_{Al}1$ can be ruled out since phenyl carbonium ions are inherently unlikely, leaving the $A_{Ac}1$ process. Consistent with this is the fact that the observed order of reactivity of substituted phenyl acetates in the 0–50% acid region (phenyl > p-chlorophenyl > p-carboxyphenyl > p-nitrophenyl) is exactly reversed in the more concentrated acids (>70% H_2SO_4) where the final sharp rate increases are occurring. Dependence of approximate ρ values on acidity shows a change in sign from −0.2 to +0.5 in the 50–70% H_2SO_4 range, consistent with a changeover from $A_{Ac}2$ to $A_{Ac}1$ in the region. Unfortunately, experimental difficulties have so far prevented a confirmation of this changeover by ^{18}O exchange, but the fact that it appears to occur much earlier for phenyl than primary alkyl acetates (although both types would yield the same acylium ion) is consistent with the greater electron-withdrawing abilities of phenyl over alkyl groups. Although vinyl acetate formally resembles the phenyl acetates, recent evidence[19] makes it highly likely that any mechanistic change for this ester would be from $A_{Ac}2$ to $A_{SE}2$.

Of the remaining esters, tert-butyl acetate probably reacts by an $A_{Al}1$ mechanism over the whole acidity range, since Bunton and Wood[20] have demonstrated by ^{18}O-exchange studies that tert-butyl benzoate reacts by an $A_{Al}1$ mechanism even in dilute mineral acid. In the present case several typical acetates labeled with ^{18}O in the ether oxygen have been hydrolyzed and the recovered alcohol products analyzed for ^{18}O content. Alkyl-oxygen fission was confirmed for tert-butyl acetate as shown in Table V, all other esters investigated showing acyl-oxygen fission in the moderately concentrated (<80%) acid region.

Unlike the other benzyl acetates, p-methoxybenzyl resembles tert-butyl closely in its rate profile, suggesting that the stability of the p-methoxybenzyl cation is sufficient to give rise to $A_{Al}1$ hydrolysis even in fairly dilute acids. However, in the most dilute acid studied (4.9%), the p-methoxybenzyl alcohol formed derives about 80% of its oxygen from starting ester, showing that, as with the other benzyl esters, the hydrolysis at least initially has a large $A_{Ac}2$ component.

The benzyl acetate series is very interesting in that

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(18) This conclusion has been arrived at previously by Leisten for ethyl acetate hydrolysis.[13]

(19) D. S. Noyce and R. M. Pollack, J. Amer. Chem. Soc., 91, 119 (1969).

(20) C. A. Bunton and J. L. Wood, J. Chem. Soc., 1522 (1955).

Table V

| | | —————¹⁸O content, %————— | | | Posi- |
Acetate	% H_2SO_4	Start-ing ester	Product alcohol	Un-labeled alcohol[a]	tion of cleav-age
tert-Butyl	20.7	1.12	0.30	0.26	Al
p-Methoxybenzyl	4.9	1.24	0.96		Ac
Benzyl	60.9	1.25	1.20		Ac
n-Butyl	63.1	1.13	1.01		Ac
sec-Butyl	63.1	1.13	1.34		Ac
sec-Butyl	84.0	1.13	0.21	0.20	Al

[a] Recovered from hydrolysis of unlabeled substrates.

structural changes produce a continual variation from type IV almost to type I behavior as the stability of the incipient carbonium ion in an $A_{Al}1$ process is varied by changing the nature of the substituent. This is illustrated in Figure 3.

Quantitative Treatment of Hydrolysis Rates. In the case of esters, no general acidity function, H_S, appropriate to this type of base has been established, nor because of their chemical properties is one likely to be. However, it has been shown empirically[13,14] that the function $H_S = mH_0$, with $m = 0.62$, is a good approximation to the ionization behavior of several representative acetates. Thus the equation used to treat the medium dependence of ester hydrolysis is

$$\log k_\psi + mH_0 = r \log a_{H_2O} + \text{constant}$$

In regions where the fraction of substrate protonated becomes significantly large, the more general equation[21]

$$\log k_\psi - \log \frac{h_0{}^m}{K_{SH^+}{}^m + h_0{}^m} = r \log a_{H_2O} + \text{constant}$$

must be used. Approximate values of K_{SH^+} have been obtained for representative acetates, and these appear to show little dependence on the structure of R in CH_3-COOR (see later on this point).

Using the above treatment, all esters studied give one of the four typical r plots shown in Figure 4. For the type I esters there is an extensive linear region, showing a strong positive water activity dependence ($r \simeq 2$), followed by a sharp break at about 85% H_2SO_4, and a final short linear portion with a small negative dependence ($r \simeq -0.2$) in the most concentrated acids. The two linear regions and the sharp break are consistent with the earlier qualitative conclusion that a change in mechanism from $A_{Ac}2$ to $A_{Ac}1$ occurs for these primary acetates at about 85% acid. The r plots of the type II esters are similar, with an initial long linear region with $r \approx 2$, except that the position of the break is strongly dependent on structure and the final negative water activity dependence is steeper ($r \simeq -0.6$). This is consistent with the earlier conclusion that changes from $A_{Ac}2$ to $A_{Al}1$ occur at acidities dependent on stability of the incipient carbonium ion being formed in an $A_{Al}1$ process, when a_{H_2O} is too low to support an A2 process. That the final slope is not the same for

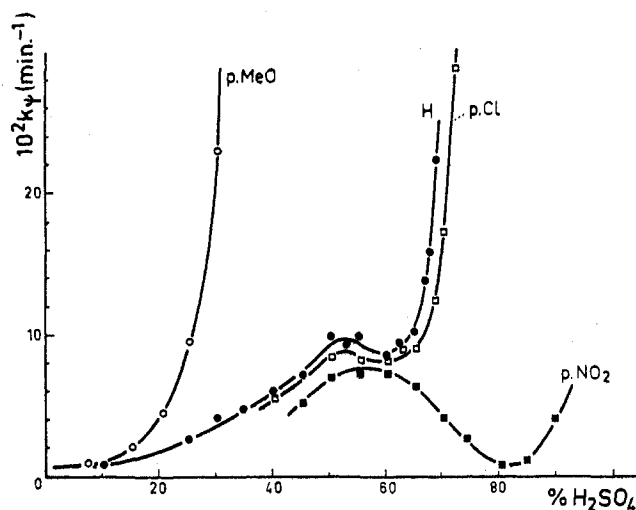(21) W. M. Schubert and H. K. Latourette, *J. Amer. Chem. Soc.*, **74**, 1829 (1952).

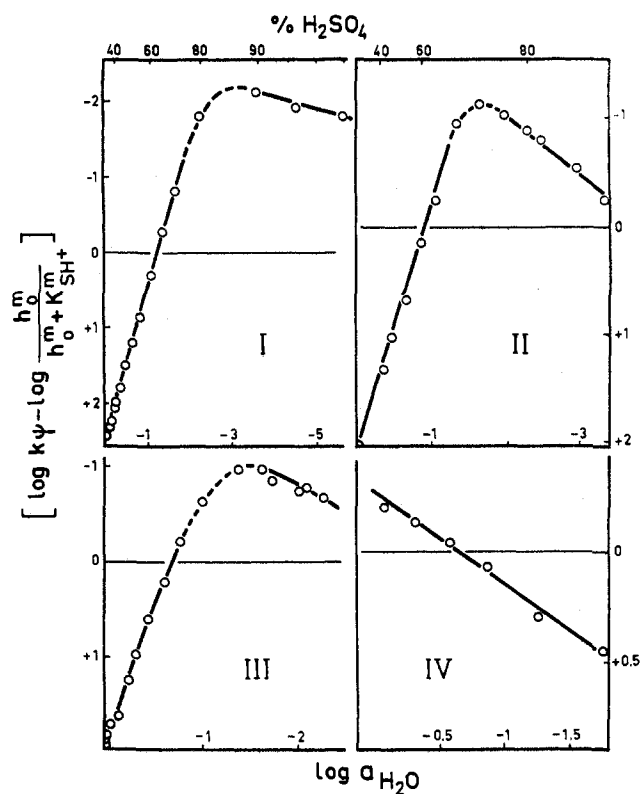Figure 3. Variation in rate profile for benzyl acetate hydrolyses with changing substituents.

Figure 4. Typical r-plots for acetate hydrolysis: type I, methyl; II, *sec*-butyl; III, *p*-nitrophenyl; IV, *p*-methoxybenzyl.

the secondary, benzyl, and allyl esters as it is for the primary esters is not unexpected since the new mechanism taking over is different.

The phenyl and vinyl esters of type III show similar breaks in the r plots, with a change from an initial strong water activity dependence to a final weak negative dependence. This is despite their failure to show local maxima in their simple rate profiles and is further evidence that mechanistic changes are occurring nonetheless. However, the plots are less linear initially and of somewhat lower slope (see Table III), although r does approach 2 initially. Also the changeover region is

broader than for the previous cases. This may be due partly to the fact that aryl-type esters are sufficiently different structurally that the previous approximations regarding pK_{SH^+} and m are less valid. However, it is probably also due to the fact that the onset of the A1 mechanism occurs in a region where a_{H_2O} is not negligible, and hence the A2 component is still contributing significantly to the total rate. Thus a sharp changeover in mechanism may not occur.

Finally, the r plots for type IV esters are quite different from all others studied. The a_{H_2O} dependence is always negative, with a particularly large value for *tert*-butyl acetate. This is not inconsistent with hydrolyses where the mechanism is virtually A1 throughout the whole acidity range.

Theoretical Significance of the r Values. The theoretical interpretation of the slopes of linear dependences found in strongly acid solutions is always made somewhat uncertain by the inherent difficulty in trying to allow for activity coefficient behavior in these far from "ideal" solutions. Nevertheless, the following interpretation has been placed on the r values by the author and his coworkers.[14] Firstly, r values of approximately 2 are associated with the rate-determining step of the $A_{Ac}2$ process in which two water molecules on the average are involved in conversion of a protonated ester molecule to the transition state. This can be visualized as
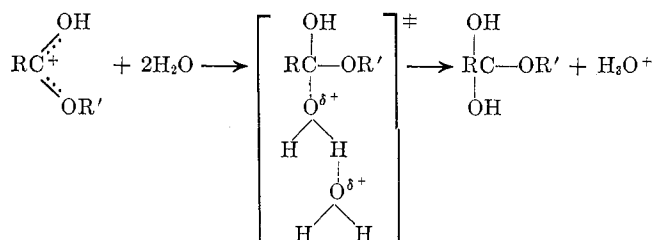

In this step, one water molecule acts as a nucleophile and the second acts in a hydrogen-bonding role. This allows some dispersion of the positive charge developed on the oxygen of the first water molecule and also situates the second one ideally for complete proton transfer to give the neutral tetrahedral intermediate as progress is made along the reaction coordinate. In fact, Kirby,[22] in a recent review, has concluded from a detailed consideration of all the evidence available that the formation of the widely accepted tetrahedral intermediate involves *both* nucleophilic attack and general base catalysis by water. Thus the incipient proton transfer pictured above may have significantly progressed at the transition state. In line with this is the fact that ester hydrolyses have the typically high values of the Bunnett w and ϕ parameters[23] associated empirically with a proton-transfer role by water. However, these high values are partly due to the fact that w and ϕ measure the *sum* of the hydration effects involved in the preequilibrium protonation step and the actual hydroly-

sis step, whereas the r parameter refers only to the latter process.

The simple conclusion that a log a_{H_2O} slope of 2 indicates that $A_{Ac}2$ hydrolysis is "bimolecular" in water is supported by the conclusions of independent investigations. Lane[13] has drawn a similar conclusion from a parallel study of the kinetic dependence of hydrolysis and [18]O exchange on water activity, although he postulates a cyclic transition state. Laidler and Landskroener[24] found agreement with a theory of solvent effects on reaction rates when they used a model for the ester hydrolysis transition state involving molecules of ester, water, and hydronium ion. Although their structure differs in detail from either of the above, its basic constitution is the same (ester + proton + H_2O). Further, Long and coworkers[25] had previously reported that the variation of ester hydrolysis rate in H_2O–D_2O mixtures can be accounted for most accurately if at least five, rather than three, exchangeable hydrogens are available in the transition state.

The final negative slopes of approximately -0.2 (associated with the $A_{Ac}1$ mechanism) and -0.6 (associated with $A_{Al}1$) are more difficult to interpret. Naively it might have been expected that truly A1 processes would be completely independent of log a_{H_2O} since formally water is neither consumed nor released in the rate-determining step. However, despite the approximations involved in the r-parameter equation, which presumably become less valid in the most concentrated region, the observed final negative a_{H_2O} dependence for most esters appears to be real. This is seen from the observation that the final overall reaction rates increase even more rapidly with acidity after protonation has become essentially complete, and log a_{H_2O} is becoming increasingly negative.

The interpretation which has been given to these negative slopes both by the author[14] and more recently and succinctly by Ingold[26] is that the acylium ions or carbonium ions (and more particularly the transition states from which they are derived) are on the average less hydrated than the starting esterium ions. This is not
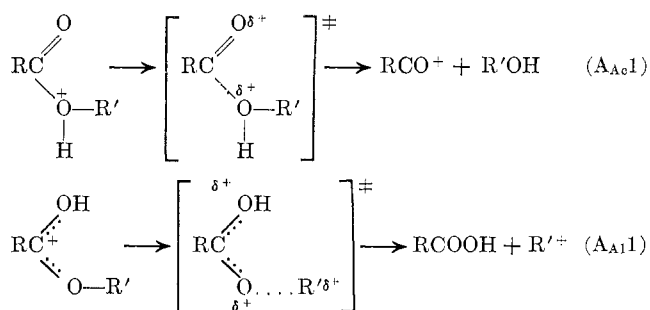
unreasonable since carbonium ions in particular are almost certainly less strongly hydrated than oxonium ions because they have fewer if any specific sites for

(22) A. J. Kirby, *Compr. Chem. Kinetics*, 10, in press.
(23) J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, 44, 1917 (1966).

(24) K. J. Laidler and P. A. Landskroener, *Trans. Faraday Soc.*, 52, 200 (1956).
(25) P. Salomaa, L. L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, 86, 1 (1964).
(26) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, Chapter XV.

hydrogen bonding. What is more difficult to understand is why formation of an $A_{Ac}1$ transition state, which resembles an acylium ion plus alcohol, should undergo less of a hydration change than an $A_{Al}1$ transition state, resembling a carbonium ion and an acid. One possibility is that the two transition states are generated from different esterium ions, as shown above, which have different hydration requirements. An alternative explanation is that the incipient R'OH in the $A_{Ac}1$ process may retain solvated water more strongly than the RCOOH being formed in the $A_{Al}1$ process.

The most serious difficulty in interpreting these negative r values comes from the very large values observed for *tert*-butyl and *p*-methoxybenzyl acetates in dilute acid solution. These numbers can hardly be ascribed to the approximate molecularity of water in the rate-determining steps in the same way as previously. The main difficulty is that rates increase rapidly, even in very dilute acid solutions where log a_{H_2O} is scarcely changed with acid concentration. However, there is no doubt that their initial water activity dependence is quite different from that of the other esters investigated and qualitatively resembles the final behavior of the latter in much more concentrated acids.

Fundamental Problems in Strong Acid Kinetics

There are several basic difficulties inherent in all attempted treatments of kinetic acidity dependence. I shall examine these critically both in general and in the light of the above results on ester hydrolysis.

Acidity Dependence of Substrate Protonation. Except where substrates are completely protonated in the region of kinetic interest, it is necessary to have quantitative knowledge of their ionization behavior for reactions where a preequilibrium proton-transfer step is involved. However, attempts to determine true thermodynamic dissociation constants, K_{SH^+}, for weak organic bases have not as yet generally been quantitatively successful. This is largely because of the necessity of extrapolating results obtained in concentrated acids, where ionization is measurable, to the region of a dilute aqueous standard state, where as yet it is not. In fact, because of the frequently discordant results obtained for a given weak base using different methods, Arnett[27] has recently concluded that weak base pK's are still not even operationally defined. However, this is an extreme viewpoint, and concordant results *can* be obtained by different methods[23] if care is taken with both experimental data and operational definitions. Since substrates do not in general obey any one acidity function in their ionization, it is necessary to determine a specific function (H_S) that a particular substrate does obey or else the empirical value (m) of its ionization dependence on some known acidity function. Until the problem of determining valid thermodynamic pK's is solved, uncertainties must remain,

and the only reasonable approach at present is to determine a "pK" value as carefully as possible, by the acidity function method, and a corresponding m value for the variation of measured ionization ratio with some available acidity function.

The magnitude of the uncertainty introduced by the "pK" and "m" values used above for ester hydrolysis is difficult to assess. However, two points lend some confidence that it is not critical. One is that the observed rate maxima, resulting from the opposing factors of increasing protonation and decreasing water activity, occur at about the same acidity for nine different esters, suggesting that their pK values are not in fact very structurally dependent. The other is that use of trial m values (both higher and lower than the empirically determined one) leads to distinct curvature of the extensive linear portions of the r plots.

Transition-State Activity Coefficient Behavior. Since there is no possible way of measuring terms like $f_\pm$ directly, their medium dependence must be taken account of by assuming some form of cancellation with another activity coefficient term in the rate equation. To minimize the seriousness of this approximation one approach is to select a reasonable model for the indicator conjugate acid in the hope that, because of the similar charge and structure of the two species, the ratio $f_{InH^+}/f_\pm$ will be fairly insensitive to medium changes. There is obviously no guarantee that this will always be effective,[28] but at least in the case of ester hydrolysis the initial linear portions of the r plots lend some confidence that approximate cancellation is occurring. These extend over very wide ranges of acid concentration with generally very high correlation coefficients (>0.999); despite the fact that the approximation appears to be less valid for the phenyl esters, 16 different esters give very similar slopes with $r = 1.92 \pm 0.22$.

Activity Coefficients for Hydrated Species. It can be shown that, when the same sets of equilibria and rate equations are treated either in terms of formal species, as is usual, or in terms of fully hydrated species (as in the Bunnett and Yates treatments), the relationship between the two types of activity coefficient is as follows. For a species X which is specifically hydrated by h water molecules

$$f_{X_{formal}} = f_{X_{hydrated}} a_{H_2O}^{-h}$$

However, only $f_{X_{formal}}$ is accessible to direct measurement, and whether the terms on the right-hand side can be treated *separately* as an effectively electrostatic part, $f_{X_{hydrated}}$, and a water-activity-dependent part, $a_{H_2O}^{-h}$, although reasonable, has not been shown to be rigorously justified. The validity of such separations is implicit in hydration parameter treatments, since assumptions are made with respect to cancellation of the $f_{hydrated}$ terms, leaving the net water-activity dependence

(27) E. M. Arnett, Abstracts, International Conference on the Mechanisms of Reactions in Solution, Canterbury, England, 1970, p 6.

(28) For example, similar kinetic treatments of amide hydrolysis, using the amide-based H_A function, which if anything should be superior to the present treatment, almost invariably give less linear r plots.

Table VI

	r values			
	Low acidity		High acidity	
Acetate	H_2SO_4	$HClO_4$	H_2SO_4	$HClO_4$
Ethyl	2.10	1.63	−0.2	−0.2
Isopropyl	2.15	1.70	−0.6	−0.8
tert-Butyl	−8.9	−14.1		

of all hydrated species involved to represent the overall rate dependence on a_{H_2O}. The occurrence of so many linear Bunnett-type plots makes it entirely reasonable that the f_{formal} terms for the various species are in fact separable into two parts, one of which gives *some* measure of hydration as a simple power term in a_{H_2O}. However, whether these terms are always exactly as represented by the above equation is not clear; hence a further source of uncertainty may exist in the interpretation of w or r values.

Dependence of Hydration Parameters on the Nature of Catalyzing Acid. Since none of the previously described kinetic treatments takes any specific account of the counterion of the catalyzing hydronium ion species, results obtained in different mineral acids should yield similar values of hydration parameters such as w. (It seems inherently unlikely that the presence of different counterions such as HSO_4^-, ClO_4^-, and Cl^- could alter the basic mechanism to such an extent that the role of water in the rate-determining step would be significantly changed.) Further, since all strong mineral acid solutions eventually exhibit the same activity coefficient behavior, all w or r plots for a given hydrolysis in different acids should extrapolate to the same point in dilute acid.

Unfortunately, neither of these conditions is in general closely obeyed. The r values obtained for the same reaction in different acids have been frequently found to be very similar,[8,12] although not identical, and results obtained in $HClO_4$ for some typical acetate hydrolyses in Table VI illustrate this.

The simple rate profiles for all three esters in $HClO_4$ are qualitatively very similar to those in H_2SO_4, as are the derived r values. If it is assumed that similar mechanistic changes occur in both acids, a breakdown of the overall rates indicates that A1 reactions are faster in $HClO_4$ and A2 reactions are faster in H_2SO_4. Clearly, the hydration parameter treatment is completely neglecting a contribution of the counterion,[29] either in specifically stabilizing particular types of transition states or in altering the nature of the water molecules in the immediate region of the transition state. What is more difficult to understand is why the r plots do not extrapolate to the same point in dilute acid. Differences of more than 0.5 log unit are sometimes obtained. Both of these discrepancies remain as deficiencies[30] of any simple hydration model which neglects the possible role of the counterions.

Temperature Dependence of Protonation Equilibria and Water Activity. Although most available data on

weak base pK's and water activity have been measured at 25°, pseudo-first-order rate constants are usually measured at temperatures most convenient for kinetic measurements. In Bunnett's original compilation of available data, kinetic temperatures ranged from 0 to 130°; of over 150 sets of rate data, only about half were at 25°. It has been suggested by the writer[11] that use of data obtained at different temperatures, as in the equation

$$(\log k_\psi)_t + (H_S)_{25} = r \log (a_{H_2O})_{25} + \text{constant}$$

will not affect the magnitude of the slope r. However, this is only true if $\Delta H^{\neq}$ for the reaction is medium independent over the acidity range studied. It has also been suggested by Kirby[22] that w values are not significantly affected if pK and a_{H_2O} used in calculations are not based on the same temperature as k_ψ. However, recent results on amide hydrolysis in the writer's laboratory[31] show quite clearly that this is not generally true. A large number of amide hydrolysis rate constants, as well as the temperature dependence of pK_{SH^+} and a_{H_2O}, have been measured over the temperature range 25–85°. Use of the correct equation

$$(\log k_\psi)_t + (H_S)_t = r \log (a_{H_2O})_t + \text{constant}$$

results in significantly different values of r from those obtained using the previous equation. Discrepancies in slope of the order of one unit can result if the temperature dependence of $\log a_{H_2O}$ and K_{SH^+} is neglected. Such neglect could result in incorrect mechanistic interpretations; thus it is recommended that all treatment of kinetic acidity dependence be based only on sets of data all at the same temperature.

Conclusion

Although some of the fundamental difficulties in interpreting kinetic acidity dependence are not likely to be quickly resolved, approaches based on the hydration treatment still remain the most satisfactory presently available. They are much more widely applicable than other treatments and have clearly demonstrated the singular importance of water activity as a reaction variable. Also, despite some of their difficulties in a purely numerical sense, they can be very useful to chemists in drawing qualitative and sometimes quantitative conclusions about the nature of reaction mechanisms in a more chemically descriptive way than perhaps more mathematical treatments would do. In addition to providing additional and useful complementary mechanistic criteria to go with others such as $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta V^{\neq}$, and ^{18}O exchange and kinetic isotope effects, continued testing of hydration parameter treatments may in future lead us to more satisfactory solutions to the complex problems of reaction kinetics in concentrated acids.

(29) See Table III, footnote d.
(30) V. C. Armstrong and R. B. Moodie, *J. Chem. Soc. B*, 934 (1969).
(31) K. Yates and C. R. Smith, unpublished results.