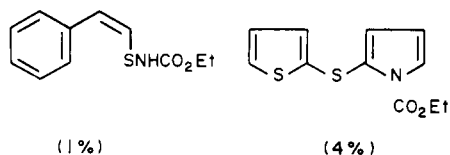


Chart I.
Ylide-Derived Products from the Reaction of Thiophene
and Ethyl Azidoformate



When ethyl azidoformate was thermolyzed in methylene chloride solution containing acenaphthylene and a variety of thiophenes, fluoranthenes or their dihydro-derivatives (51) were indeed isolated in yields from 3–26%. Thus thiophene, 2,5-dimethyl-, 2,5-dichloro-, 2,5-dimethoxy-, tetrabromo-, 2,5-dichloro-3,4-dibromothiophene all yielded ylide-derived fluoranthenes, the halo derivatives giving the dihydro compounds (51). Furthermore a more careful investigation of the original literature reaction²⁵ of thiophene with ethyl azidoformate without any trap revealed several fascinating (and unreported) products, clearly derived

by cycloadditions of an intermediate ylide (Chart I).³³ We leave the reader to enjoy solving the mechanistic perambulations involved.

We are of the opinion that hard electrophiles in general attack thiophenes at sulfur commonly. This contentious issue needs investigating.

Future Prospects

Oxycarbonylnitrenes clearly have a Herculean potential, almost untapped, in synthesis. This prospect is especially attractive and in need of exploitation in cyclizations. The biochemical applications referred to of photoaffinity labeling are especially exciting. Furthermore, by use of their remarkable energy, new, interesting, and useful intermediates typified by acyl- and sulfonylthionitroso compounds are rendered readily accessible. This almost virgin field awaits the entrepreneurial nitrene chemist.

I am deeply indebted to all my co-workers indicated in the references in this review, as well as to the Science Research Council, Great Britain, who funded much of the earlier work.

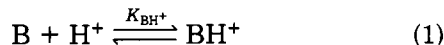
Organic Reactions in Sulfuric Acid: The Excess Acidity Method

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Large numbers of organic reactions take place in aqueous sulfuric and other strong acid media. A not particularly exhaustive list would include: hydrolyses, dehydrations, hydrations, isomerizations, electrophilic substitutions, aromatic rearrangements, carbonyl reactions, and a number of other reactions. Not surprisingly, much attention has been given to the elucidation of reaction mechanisms in acidic solutions.



$$pK_{BH^+} = \log I + pH \quad (2)$$

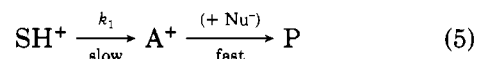
$$pK_{BH^+} = \log I - \log (a_{H^+}f_B/f_{BH^+}) = \log I + H_0 \quad (3)$$

For almost all of these reactions, protonation of the substrate is of critical importance. This can either be the rate-determining step (A-S_E2 mechanism), or a fast preequilibrium process, and the protonated substrate can then give product directly (A-1), or react with a nucleophile or base in the slow step (A-2). Taking as a model the protonation of a weak base B, reaction 1, in the dilute acid region¹ the acid dissociation constant of BH⁺ can be defined in terms of molar concentration C as $K_{BH^+} = C_B C_{H^+} / C_{BH^+}$, which, on taking logarithms and substituting the ionization ratio I for C_{BH^+} / C_B ,

becomes eq 2. In nonideal strong acids activities *a* and/or activity coefficients *f* must be used; $K_{BH^+} = a_B a_{H^+} / a_{BH^+} = (C_B / C_{BH^+}) a_{H^+} (f_B / f_{BH^+})$ and eq 2 becomes eq 3. An acidity function *h*₀ can be defined, following Hammett,² by $h_0 = a_{H^+} f_B / f_{BH^+}$, provided that B is a primary aromatic amine;^{3,4} $H_0 (= -\log h_0)$ in eq 3 is defined in the same way as pH in eq 2.³

H₀ and Reaction Rates

The A-1 mechanism is represented by reactions 4 and 5; fast preequilibrium protonation of the substrate S followed by rate-determining reaction of SH⁺, either to some intermediate A⁺ which subsequently reacts quickly, or to product directly. Reactions in sulfuric



$$k_{\psi}(C_S + C_{SH^+}) = k_1 a_{SH^+} / f_{\psi} = k_1 C_{SH^+} (f_{SH^+} / f_{\psi}) \quad (6)$$

$$\log k_{\psi} - \log (C_S / (C_S + C_{SH^+})) =$$

$$\log (k_1 / K_{SH^+}) - H_0 + \log (f_{BH^+} f_S / f_B f_{\psi}) \quad (7)$$

$$\log k_{\psi} - \log (C_{SH^+} / (C_S + C_{SH^+})) =$$

$$\log k_1 + \log (f_{SH^+} / f_{\psi}) \quad (8)$$

(1) The standard state is a hypothetical acid solution of unit activity, as for pH measurements, and the reference state (unit activity coefficients) is infinite dilution in water.

(2) Hammett, L. P.; Deyrup, A. J. *J. Am. Chem. Soc.* **1932**, *54*, 2721.

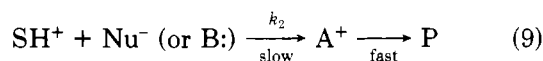
(3) See the extensive discussion and listing of acidity functions in Cox, R. A.; Yates, K. *Can. J. Chem.* **1983**, *61*, 2225.

(4) Jorgenson, M. J.; Hartter, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 878.

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acid are pseudo-first-order, usually, with an observed rate constant k_ψ ; the reaction rate is $k_\psi(C_S + C_{SH^+})$, with the substrate concentration written as a sum because the state of protonation, as well as the observed rate, varies with acidity. Reaction rate theory requires the equality in eq 6. There are now two possible cases. Either the substrate can be essentially unprotonated, becoming partially protonated as the acidity increases, or it can be (partially to) fully protonated in the reaction medium. In the first case, from the definition of K_{SH^+} it follows that $C_{SH^+} = (C_S/K_{SH^+})a_{H^+}(f_S/f_{SH^+})$, and a_{H^+} can be substituted by $h_0 f_{BH^+}/f_B$ from the definition of h_0 . Making these substitutions, gathering terms and taking logarithms produces eq 7. In the second case, eq 8 is easily obtained from eq 6 directly.

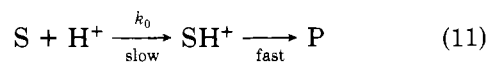
Reactions 4 and 9 describe the A-2 mechanism, rate-determining reaction of the protonated substrate with some other species. Reasoning analogous to that



$$\log k_\psi - \log (C_S/(C_S + C_{SH^+})) = \log (k_2/K_{SH^+}) - H_0 + \log a_{Nu} + \log (f_{BH^+}f_S/f_Bf_+) \quad (10)$$

already given leads to eq 10 for predominantly unprotonated substrates; this is eq 7 with the addition of a nucleophile (or base) activity term. A similar addition to eq 8 gives the rate equation for predominantly protonated substrates.

The A-S_E2 mechanism involves rate-determining substrate protonation, reaction 11; the corresponding



$$\log k_\psi = \log k_0 - H_0 + \log (f_{BH^+}f_S/f_Bf_+) \quad (12)$$

readily derivable⁵ rate equation is eq 12, very similar to eq 7 for the A-1 reaction.

Early Mechanistic Criteria

Provided that the activity coefficient terms are negligible, eq 7 and 12 will give linear plots of $\log k_\psi$ against $-H_0$, the protonation correction term in eq 7 being unimportant for most substrates. Equation 10 will give a curve, due to the presence of the extra nucleophile activity term.

This, essentially, is the Zucker-Hammett mechanistic criterion.^{6,7} Originally it was found that, for A-2 reactions, plots of $\log k_\psi$ tended to be linear in $\log C_{H^+}$ rather than in $-H_0$,⁶ but this is now known to be coincidental more than anything else. For A-1 and A-S_E2 reactions the slopes of the linear plots against $-H_0$ are seldom unity as predicted. The reason for this is that the activity coefficient terms in eq 7, 10, and 12 are seldom negligible; most substrates do not "follow" H_0 ; i.e., f_B and f_S , and f_{BH^+} and f_+ , seldom cancel out exactly. More realistic behavior can be expected if H_0 is replaced by a more appropriate acidity function, H_A for amides,⁸ H_T for thio compounds,⁹ and so on, and this has been

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(6) Zucker, L.; Hammett, L. P. *J. Am. Chem. Soc.* **1939**, *61*, 2791.

(7) Rochester, C. H. *Acidity Functions*; Academic Press: New York, 1970.

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found to be true in practice.^{10,11}

Another mechanistic criterion was proposed by Bunnett.¹² The major nucleophile or base in sulfuric acid should be water,⁵ and a slight rearrangement of eq 10 for A-2 reactions shows that $\log k_\psi + H_0$ should be a linear function of the water activity, provided that the activity coefficient and protonation correction terms are negligible as before. In fact Bunnett found this to be true for almost all reactions, A-1 and A-S_E2 as well as A-2, and he proposed mechanistic criteria based on the observed slopes, w : $w \leq 0$, water not involved in the reaction; $1.2 < w < 3.3$, water acting as a nucleophile; $w > 3.3$, water acting as a proton-transfer agent.¹² The slope is a combination of the number of water molecules kinetically involved in the reaction and the number involved in solvation changes of the various reactants and products.¹²

Subsequently this was modified by Yates, who used the most appropriate acidity function for the substrate, H_S , rather than H_0 , in the expression.¹³ The slope of plots against water activity, now called r , should reflect the actual number of water molecules kinetically involved, solvation changes being factored out by a correct choice of acidity function.¹³

In general, however, problems remain. There is little generality, since individual acidity functions must be used for specific substrates; H_0 does not apply to them all, or even to most of them. Distinguishing between A-1 and A-S_E2 mechanisms is difficult. Additionally, no account is taken of the fact that species in the medium other than water and solvated protons may react with the substrate. These may include sulfate ions, bisulfate ions, and undissociated and protonated sulfuric acid molecules, as well as water and solvated protons, depending on the acid concentration.⁵ For instance, as part of a study of the rearrangement of azoxybenzenes to hydroxyazobenzenes in sulfuric acid, it was found that the rate-determining step was general-acid-catalyzed, involving H_2SO_4 and $H_3SO_4^+$, but not H_3O^+ , as proton donors, the latter not being a strong enough acid species to catalyze this reaction.^{5,14,15} In some cases reaction involving bisulfate ion was postulated.^{14,15} Unmodified acidity function techniques are only capable of detecting reaction with "H⁺" or H_2O .

The Excess Acidity Method

In view of the limitations of the acidity function method, it was decided to use a different approach, based on ones originally developed by Bunnett and Olsen¹⁶ and by Marziano et al.¹⁷ The assumption used up to now, that activity coefficients such as f_B and f_S cancel out (we have called this the zeroth-order approximation³), which is evidently inadequate, is replaced by a less stringent one.

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$$\log I - \log C_{H^+} = pK_{BH^+} + \log (f_{B^+H^+}/f_{BH^+}) \quad (13)$$

$$\log (f_{B^+H^+}/f_{BH^+}) = m^* \log (f_{B^+H^+}/f_{B^*H^+}) = m^*X \quad (14)$$

$$\log I - \log C_{H^+} = m^*X + pK_{BH^+} \quad (15)$$

Making the additional separation of a_{H^+} into C_{H^+} and f_{H^+} , K_{BH^+} in eq 1 can be redefined as $(C_B C_{H^+}/C_{BH^+})(f_{B^+H^+}/f_{BH^+})$, the familiar $K_a = K_C K_f$, which, on taking logarithms and rearranging, gives eq 13 (compare eqs 2 and 3). The new assumption is that activity coefficient ratios like that in eq 13 are linear functions of one another (the first-order approximation³). For simplicity it is convenient to define the activity coefficient ratio for a standard base B^* as X , and slopes against X as m^* , see eq 14. (In Marziano's terminology X is called M_C or $M_C f(x)$ and m^* are the various n_{ij} .¹⁷) Values of pK_{BH^+} and m^* for specific bases can readily be obtained using eq 15, once values of $\log C_{H^+}$ and X are available for a particular acid system. Calculation of X is a reasonably straightforward if tedious process; details will not be given here but may be found in the appropriate references.^{18,19} Values are available for aqueous H_2SO_4 ,¹⁸ $HClO_4$,¹⁸ HCl ,¹⁹ HBr ,¹⁹ and $DClO_4$ ²⁰ media; values of $\log C_{H^+}$ for use with these are simply the log acid molarities for the fully dissociated acids, all of the above except H_2SO_4 , for which values taking into account the partial dissociation of HSO_4^- have been calculated.¹⁸

Taking the definition of H_0 given earlier, eq 3, it is apparent that $-(H_0 + \log C_{H^+}) = \log (f_{Am} f_{H^+}/f_{AmH^+})$, where the subscript Am refers to the primary aromatic amines used in determining H_0 .^{3,4} It is apparent that this definition is almost identical with that of X in eq 14, particularly if $B^* = Am$. This has been shown to be true in practice;²¹ the use of $H_0 + \log C_{H^+}$ in this context is the Bunnett-Olsen method.¹⁶ The only problem is one of definition; to obtain H_0 the zeroth-order approximation must be used, and then the first-order one is used in equations like eq 15. The excess acidity method only involves the latter.¹⁸ In practice, however, $H_0 + \log C_{H^+} \approx -X$,²¹ which is particularly useful for those many acid systems which have a measured H_0 scale but no values of X .³

The assumption of eq 14 has been extensively tested by Marziano's group,²² by ourselves in both acidic^{18,19} and basic²³ media, and by Bunnett and Olsen¹⁶ and the many different groups who have subsequently used their method. The author is aware of no exceptions to linearity that are not readily explicable by special circumstances; this assumption currently has the status of an "empirical fact".²⁴

The assumption of linearity amongst activity coefficient ratios is a linear free energy relationship, as originally observed by Bunnett and Olsen.¹⁶ Recasting eq 15 in terms of K_a and K_C , the expression $\log (K_C/K_a) = -m^*X$ is obtained, where the similarity to equations

like Hammett's $\log (K/K_0) = \rho\sigma^{25}$ is readily apparent.²⁶ Thus the plentiful experience gained with other types of LFER may help with the interpretation of m^* values.²⁶ Also, since X is equivalent to a free energy of transfer from the ideal state to a given acid medium, it becomes very easy to convert X (defined at 25 °C) to different temperatures by multiplying by the absolute temperature ratio, if the transfer ΔS^0 is defined as being zero:²⁷ $X_T = 298.15X/(273.15 + T)$. Thus for instance X has been used in this way to determine the enthalpies and entropies of protonation of 55 different compounds in sulfuric acid, from ionization ratios as a function of acid composition and temperature.²⁷

Rather than simply estimating pK_{BH^+} , as the H_0 method does, the excess acidity method determines m^* as well; X becomes a "universal" acidity function and m^* measures the variability of individual substrates previously expressed as the different acidity functions which they follow. The best interpretation of m^* values is probably in terms of solvation changes; this aspect is the subject of a recent review²⁶ and will not be covered here. Equation 15 is now widely used for the estimation of pK_{BH^+} values;^{17-19,28} an extension to enable extraction of pK_{BH^+} values from spectra with extensive medium effects has been described²⁹ and used.³⁰

Application to Kinetics

The excess acidity method can readily be applied to reaction kinetics.³¹ For the A-1 reaction of unprotonated substrates, substituting a_{H^+} in eq 6 in terms of C_{H^+} and f_{H^+} , rather than using h_0 , produces eq 16.

$$\log k_{\psi} - \log (C_S/(C_S + C_{SH^+})) - \log C_{H^+} = \log (k_1/K_{SH^+}) + \log (f_S f_{H^+}/f_*) \quad (16)$$

$$\log (f_S f_{H^+}/f_*) = m^* \log (f_S f_{H^+}/f_{SH^+}) = m^* m^* X \quad (17)$$

$$\log k_{\psi} - \log (C_S/(C_S + C_{SH^+})) - \log C_{H^+} = \log (k_1/K_{SH^+}) (+ \log a_{Nu}) + m^* m^* X \quad (18)$$

$$\log (f_{SH^+}/f_*) = (m^* - 1) \log (f_S f_{H^+}/f_{SH^+}) = (m^* - 1) m^* X \quad (19)$$

$$\log k_{\psi} - \log (C_{SH^+}/(C_S + C_{SH^+})) = \log k_1 (+ \log a_{Nu}) + (m^* - 1) m^* X \quad (20)$$

$$\log k_{\psi} - \log C_{H^+} = \log k_0 + m^* m^* X \quad (21)$$

The best assumption that can be made regarding the activity coefficient term in eq 16 is that it is a linear function of the term describing the equilibrium protonation of the same substrate S, as in eq 17. This is an extension of the Kresge α -coefficient assumption.³² Since the second term in eq 17 has already been shown to be linear in X (eq 14), the slope parameter is written

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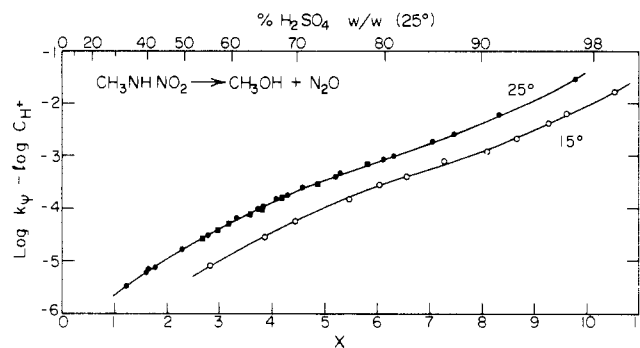


Figure 1. Excess acidity plot for the decomposition of *N*-nitromethylamine in sulfuric acid, assuming an A-1 or A-S_E2 reaction.

as the product, m^*m^* , and eq 16 becomes eq 18. (The Bunnett–Olsen treatment of reaction kinetics,³³ in contrast, uses an additive combination of slope parameters.) For protonated substrates, addition of $\log f_{\text{SH}^+}$ to each side of eq 17 gives eq 19; substitution of this into the logarithmic form of eq 6 gives eq 20. The A-2 mechanism produces equations with an additional nucleophile activity term, in parentheses in eq 18 and 20. The A-S_E2 mechanism gives eq 21, similar to eq 18 but without the protonation correction term; here m^* is identical with α_A as defined by Kresge,³² and varies in value between zero and one, depending on whether the transition state is reactant-like or product-like: $f_* = (f_{\text{SH}^+})^{1-\alpha} (f_{\text{SH}^+})^\alpha$. For A-1 reactions, m^* has been found to be greater than one; for A-2, values of about one seem to be usual.³¹

These equations, and others like them, are easy to use in practice. Firstly, the protonation equilibrium of the substrate should be studied, if this is possible. This provides values of $\text{p}K_{\text{SH}^+}$ and m^* via eq 15, and enables calculation of protonation correction terms such as $\log (C_{\text{S}}/(C_{\text{S}} + C_{\text{SH}^+})) = \log (1/(1 + D))$ for use in eq 18 or 20. If measurement is not possible, due to fast reaction or for other reasons, a reasonable estimate³⁴ is usually sufficient.³⁵ Often the substrate is essentially unprotonated in the acid range under investigation, and sometimes essentially fully protonated, and protonation correction terms are not needed.

Secondly, $\log k_p - \log C_{\text{H}^+}$ ($\log k_p$ for protonated substrates), modified for partial protonation if necessary, is plotted against X . An example of this is shown in Figure 1, which is an excess acidity plot for the decomposition of CH_3NHNO_2 into CH_3OH and N_2O .³⁶ It is apparent from Figure 1 that this reaction is acid-catalyzed, since the rate increases with acidity, and that the reaction mechanism is A-2, since the plot is curved. If it were A-1, the plots would be straight with a steep slope ($m^* > 1$), and if A-S_E2, straight with a shallow slope ($m^* < 1$). This is already a conclusion which the original authors could not reach, since they only had

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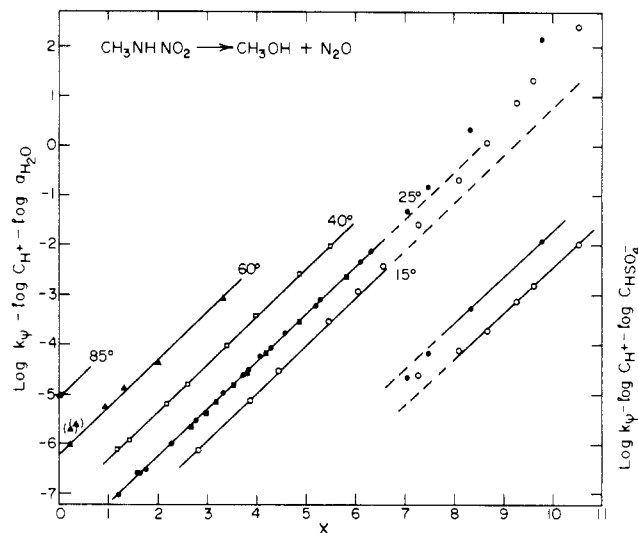
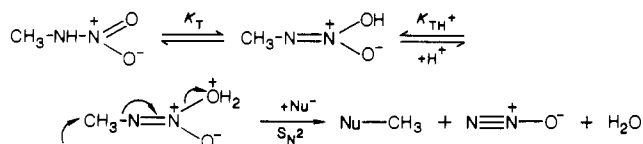


Figure 2. Excess acidity plot for the decomposition of *N*-nitromethylamine in sulfuric acid, assuming an A-2 reaction with one water molecule (left axis, temperature-labeled lines) or with one bisulfate ion (right axis, two rightmost lines).

$-H_0$ correlations available.³⁶

From curved excess acidity plots it is possible to decide exactly what is reacting with the substrate in the slow step, which is the unique feature of the excess acidity method, by using eq 18. This is most easily done by subtracting the log water activity³⁷ from $\log k_p - \log C_{\text{H}^+}$ and plotting the result against X , as is done in Figure 2, left-hand axis. A straight line immediately shows that one water molecule is reacting with the protonated substrate in the slow step. Points above about 85% H_2SO_4 in acidity fall above the line, and these points are replotted, after subtracting the bisulfate ion concentration, on the right of Figure 2; linearity shows that the nucleophile is one bisulfate ion in this region. This is exactly what one would expect; the substrate reacts with water as long as it is available in the medium, which is up to about 85% H_2SO_4 ,⁵ and then with bisulfate ion, which is plentiful above this point.⁵ Bisulfate is some 1000 times worse as a nucleophile than is water, as is shown by the vertical separation of three log units between the lines due to the different species in Figure 2. The reaction mechanism probably involves preliminary tautomerization to the aci-nitro form as well:



Reactions Studied up to Now

Most of the reactions in sulfuric acid that have been examined with the excess acidity method to date have been hydrolyses. The compounds studied include acetals,³¹ acylals and thioacylals,³⁵ *p*-methoxybenzyl acetate,³⁸ sterically crowded benzoates,³⁹ thiol- and thionbenzoate esters and thiobenzoic acids,⁴⁰ benz-

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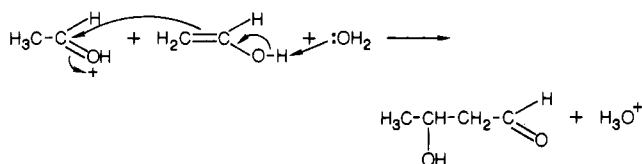
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amides, methylbenzimidatium ions, and lactams,⁴¹ substituted acetamides,⁴² acyl- and benzoylhydrazines,⁴³ episulfoxides,⁴⁴ aryloxatriazoles,⁴⁵ and 3- and 4-(*p*-methoxyphenylazo)pyridines.⁴⁶ Space considerations preclude extensive discussion, but some relevant points can be made. Many compounds start with an A-2 hydrolysis at low acidity, and then switch to an A-1 one at higher acidity, as most carboxylic esters do;¹³ the A-1 process is typified by high m^* values^{31,38,39} and positive entropies of activation.³⁹ The A-2 hydrolysis typically involves more than one water molecule, subtraction of two or three times the water activity being required to achieve linearity against X .⁴⁰ Ester hydrolysis uses two, and it is surmised that one acts as a base towards the second, which is the nucleophile, allowing a neutral tetrahedral intermediate to be formed directly.³⁹ In dilute acid, amides use three water molecules, probably in a cyclic transition state that has one transferring a proton to nitrogen, the second acting as an acid/base, and the third being the nucleophile.⁴¹ In more concentrated acid, where the water activity is lower, a one-water-molecule process takes over.⁴¹ In strong acid, bisulfate ion is the nucleophile.^{41,43}

In contrast to the several water molecules needed for most hydrolyses, for most S_N2 substitutions only *one* appears in the transition state,⁴¹ as in the CH_3NHNO_2 decomposition described above. This probably means minimal charge buildup on the incoming water, and thus possibly an early transition state, in substitution, in comparison to the carbonyl addition involved in hydrolysis processes.⁴¹

Several other reactions have also been studied. Marziano's group is engaged in a continuing study of aromatic nitration processes.⁴⁷ Enolization has been investigated,^{48,49} as has the acidic aldol condensation of acetaldehyde.⁴⁹ The latter reaction is interesting insofar as it involves the extension of the equations given here to include a pseudo-*second-order* reaction.⁴⁹ It also led to the discovery that a water molecule is involved in the rate-determining step here too, probably as a base:⁴⁹



In the same study it was shown that the reversible dehydration of aldol to crotonaldehyde involved water loss or water attack in the rate-determining step, not

proton transfer at carbon.⁴⁹ The same may be true in β -hydroxypropionic acid/cinnamic acid chemistry.⁵⁰

Styrene and phenylacetylene hydrations do involve rate-determining carbon protonation; the resulting $\log k_0$ values lead to Hammett ρ 's which are independent of acidity, in contrast to the situation found for acylal and thioacylal hydrolyses, which give ρ values which increase with acidity.³⁵ Cases in which rate-determining proton transfer occurs from H_2SO_4 molecules rather than from H_3O^+ can be studied using a modified form of eq 21;⁴⁰ a case is found in the hydrolyses of thioesters.⁴⁰

Solvent isotope effects can be determined in the usual way, using D_2SO_4 . Although no X scale in D_2SO_4 has been measured, the H_2SO_4 one can readily be modified by using Noyce's assumption that the medium acidities are equal at equal mole fractions of acid.⁵¹ The results are unsurprising, values of 2-4 being obtained.⁵⁰ Isotope effects on the breakup of the Wheland intermediate in aromatic proton exchange have been found by combining the results of deuterium and tritium exchange experiments; the resulting values were in the range 2.4-9.8.⁵² The m^* (or α_A)³² values for this reaction were between 0.70 and 0.86, indicating a transition state with the proton about three-quarters transferred, with higher values being associated with higher activation energies, as might be expected.⁵²

The k_0 , k_1 , and k_2 values obtained by the excess acidity extrapolation are standard-state values,¹ comparable to ones obtained in aqueous buffers. However, the comparison between extrapolated values themselves, as used in the determination of ρ , ΔH^\ddagger , ΔS^\ddagger , etc., can be somewhat more reliable than the comparison between them and aqueous solution values. For instance, the acid-catalyzed acetophenone enolization rate constant obtained under dilute acid conditions⁵³ is 35% smaller than the one extrapolated from sulfuric acid solutions,⁴⁸ a result which can be attributed to catalysis by sulfate ion in the latter case,⁵³ difficult to detect otherwise.

The above necessarily brief survey should convey at least a flavor of the large amount of work that has been done in this area in the last 7 years. The excess acidity method can now be classified as a proven, reliable technique for the investigation of reaction mechanisms in sulfuric acid and other media, and its usage for this purpose is likely to increase.

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