

molecules are the reactants, careful evaluation of the relaxation kinetics of the reactants must precede any interpretation of the total mechanism. For example, in the case of  $\text{CH}_3\text{F}$  and  $\text{Cl}_2$  reaction,<sup>27</sup> the  $\text{CH}_3\text{F}$  was excited to its C-F stretching mode and the reaction products were found to be  $\text{CH}_2\text{FCl}$  and  $\text{HCl}$ . Questions regarding intramolecular V-V transfer and intermolecular V-V transfer into the C-H manifold under multiphoton absorption conditions must still be settled before a final mechanism can be deduced.

The value of the energy-transfer information is perhaps best exemplified in recent experiments involving laser isotope separation.<sup>28</sup> If one envisages a reaction driven by laser excitation, a number of immediate constraints on the possible selectivity come to mind. The V-T/R deactivation time of the excited reactant must be longer than the total reaction time. Just as obviously the V-V isotope scrambling rate must

be slower than the reaction rate. Therefore, it seems to us that a total understanding, as well as a large data base, of vibrational energy transfer rates in polyatomic species is of import to understanding collisional phenomena in general and to the new and exciting field of laser-induced chemistry. We expect that most polyatomic species will follow the general pattern of energy transfer observed here. Numerous studies on the other systems tend to bear out this expectation. While these may not bear quantitative comparisons with results reported here, we do believe that insights concerning parameters which are significant in vibrational relaxation will retain considerable validity over a very wide range of systems.

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## Transition-State Activity Coefficients—A New Mechanistic Tool in the Investigation of Acid-Catalyzed Reactions

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The interpretation of the variation in the rates of acid-catalyzed reactions with changing acidity has presented a considerable challenge to physical organic chemists, particularly as a guide to the complete understanding of the detailed mechanism of such reactions. Various general kinetic treatments have been proposed for investigating the kinetics and mechanisms of such organic reactions in nondilute (i.e., nonideal) acid solutions. Since the kinetic-acidity dependence of acid-catalyzed reactions in dilute to concentrated acid region can be quite variable and complex, even for apparently simple reactions, these general treatments have not been uniformly successful in providing reliable mechanistic criteria. The four main approaches which have been used are the Zucker-Hammett method,<sup>1</sup> the Bunnett hydration parameter treatment,<sup>2</sup> the Yates modification or *r*-parameter treatment,<sup>3</sup> and the Bunnett-Olsen approach.<sup>4</sup>

Keith Yates was born in England and emigrated to Canada in 1948. He was educated at the University of British Columbia where he received a B.A., M.Sc., and Ph.D., and at Oxford University where he took the D.Phil. degree. In 1961 he joined the Department of Chemistry at the University of Toronto, where he is now Professor and Chairman. His main research interests are in physical and theoretical organic chemistry.

Tomasz A. Modro was born and educated in Poland, receiving the Ph.D. degree in 1962 and the degree of Habilitated Doctor in 1969. Postdoctoral work at the University College, London, was followed by an academic appointment at the University of Gdansk. In 1973 he joined the University of Toronto where he is now Assistant Professor of Chemistry. His research is concentrated in structure-reactivity dependence in organophosphorus compounds, aromatic reactivity, and catalysis in strongly acidic media.

Each of these approaches suffers from similar disadvantages and difficulties. The disadvantages are that each method requires (different) assumptions leading to the cancellation of important activity coefficient terms. Each is heavily dependent on the use of Hammett-type acidity functions, with their attendant uncertainties. Each method also depends heavily on the existence of linear log-log relationships, involving some function of the rate constant, the acidity, and possibly the water activity of the reaction medium. The difficulty here is twofold. One is that linear log-log plots are almost legion in physical-organic chemistry, since they are frequently easy to obtain, and it is often difficult to evaluate the statistical significance of such relationships. The second is that, having obtained these linear relationships, the mechanistic interpretation of the slope values (e.g., unity,  $\omega$ ,  $w$ ,  $r$ , or  $\phi$ ) is also fraught with difficulty.

A simpler treatment has been proposed which is based on transition-state theory; it uses hydronium ion activities directly. This approach does not involve any assumptions concerning the acidity function behavior of a particular substrate, nor does it involve the water activity of the medium, since it is not a hydration parameter treatment. No cancellations of important

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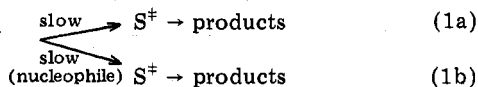
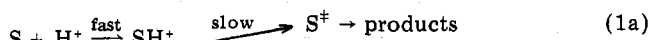
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activity coefficient ratios are involved, and the method is not dependent on the existence of linear logarithmic relationships. The approach to be described in this Account simply involves the determination of the transition-state activity coefficient (TSAC), and examination of its variation as a function of acidity, in comparison with the corresponding behavior of model transition states and stable ions.

### Outline of the Approach

With respect to the position of the proton-transfer step on the reaction coordinate, acid-catalyzed reactions can be divided into two main classes—with the proton transfer occurring before or during the overall rate-determining step of the reaction: Mechanism 1, in-



cluding a fast, preequilibrium protonation step, is expected to apply mainly to substrates containing oxygen or nitrogen atoms as the basic center, because rates of proton transfers to these sites are known to be very rapid.<sup>5</sup> Slow, rate-determining proton transfers (eq 2) are more likely to be characteristic of reactions involving carbon atoms as the basic site of the molecule (protonation of such bases is known to be a slow process<sup>6</sup>), and such reactions can be considered as an electrophilic attack of the proton (A-S<sub>E</sub>2 mechanism).

Equation 1 basically comprises two possible mechanisms: a rate-determining, unimolecular reorganization of the substrate conjugate acid SH<sup>+</sup>, with no nucleophilic (solvent) participation except on a simple solvation level (A1 mechanism, eq 1a), or the stoichiometric involvement of a nucleophile (most frequently a water molecule) in the rate-determining step (A2 mechanism, eq 1b). All these forms of acid-catalyzed reactions are well-known, and examples of each mechanistic type will be discussed in this article in terms of the TSAC approach.

For reactions described by eq 1, application of transition-state theory gives the rate equation 3, where

$$\nu = \frac{k_0}{K_{SH^+}} a_{H^+} \frac{f_S}{f_{S^{\ddagger}}} [S] \quad (3)$$

$k_0$  is the rate constant for the slow step,  $K_{SH^+}$  is the dissociation constant for the protonated substrate (both these quantities being medium independent by definition),  $f_S$  is the substrate activity coefficient, and  $f_{S^{\ddagger}}$  represents the activity coefficient of the activated complex for the given reaction. The same holds for reactions described by eq 2, the only difference being that the  $K_{SH^+}$  term disappears from eq 3. Acid-catalyzed reactions of interest (eq 4, where  $k_\psi$  is the ob-

$$\nu = k_\psi [S] \quad (4)$$

served pseudo-first-order rate constant) are usually carried out in media of effectively constant acidity, that is under conditions of pseudo-first-order kinetics. This expression applies to cases where the substrate is es-

entially unprotonated stoichiometrically, i.e.  $[S] \gg [SH^+]$ . If this condition is not met, the term  $k_\psi$  must be corrected for partial protonation by replacing it by  $k_\psi(1 + I)$ , where  $I$  is the substrate ionization ratio  $[SH^+]/[S]$ . From (3) and (4) it follows that

$$k_\psi = \frac{k_0}{K_{SH^+}} \frac{f_S}{f_{S^{\ddagger}}} a_{H^+} \quad (5)$$

Rearrangement of eq 5 yields eq 6, in which the log-

$$\log (f_{S^{\ddagger}}/k_0) = \log a_{H^+} - \log k_\psi + \log f_S \quad (-\log K_{SH^+}) \quad (6)$$

arithm of the activity coefficient of the transition state (relative to the rate constant  $k_0$ ) is expressed as a sum of the logarithmic values of the proton activity, observed rate constant, substrate activity coefficient, and the  $pK_a$  value of substrate conjugate acid. The quantities  $f_{S^{\ddagger}}$  and  $a_{H^+}$  refer to ionic species—the activated complex involving a fully or partially bonded proton and the solvated proton or hydronium ion itself. Since activity coefficients of all single ions are experimentally inaccessible, they are expressed as relative to the standard reference ion X<sup>+</sup>, using the Boyd approach:<sup>7</sup>

$$f_{Z^+}^* \equiv f_{Z^+}/f_{X^+} \quad (7)$$

The generally accepted reference ion is the tetraethylammonium ion (Et<sub>4</sub>N<sup>+</sup>) which is believed to be relatively free of specific medium-dependent solute-solvent interactions; this assumption has been recently supported<sup>8</sup> by medium effects upon <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts for tetraalkylammonium ions in aqueous solutions of strong acids. As a consequence, the starred quantities can only be determined relative to the activity coefficient of Et<sub>4</sub>N<sup>+</sup>, i.e.

$$\begin{aligned} f_{S^{\ddagger}}^* &\equiv f_{S^{\ddagger}}/f_{Et_4N^+} \\ a_{H^+}^* &\equiv a_{H^+}/f_{Et_4N^+} \end{aligned} \quad (8)$$

and eq 6 has the final form

$$\log f_{S^{\ddagger}}^* - \log k_0 = \log a_{H^+}^* - \log k_\psi + \log f_S \quad (-\log K_{SH^+}) \quad (9)$$

The left side of eq 9 is therefore expressed in terms of experimentally accessible quantities, three of which ( $a_{H^+}^*$ ,  $k_\psi$ , and  $f_S$ ) are a function of the composition (acidity) of the reaction medium. By estimating the medium variation of these quantities, it should be possible to determine the variation of  $\log (f_{S^{\ddagger}}^*/k_0)$  as a function of reaction medium composition. The  $k_0$  term can next be separated, since  $\log f_{S^{\ddagger}}^*$  must approach zero in dilute acid solution, so that a short extrapolation of a monotonic plot of  $\log (f_{S^{\ddagger}}^*/k_0)$  vs. acid concentration gives the value of  $-\log k_0$  as intercept. In conclusion, by determining the experimentally available (at least in principle) quantities of the right side of eq 9, and their variation with the acidity of the reaction medium, it should be possible to characterize the medium variation of the transition-state activity coefficient (relative to that of a suitable reference ion) for any acid-catalyzed reaction. The behavior of  $\log f_{S^{\ddagger}}^*$

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as a function of some parameter of the reaction medium (e.g., acid concentration or activity of water) should then reflect the solvation requirements or characteristics of the transition state. This behavior can then be interpreted in terms of possible transition-state structures, and thus provide important mechanistic information. The structural description of a given transition state can be proposed by comparison of the actual  $\log f_{S^{\ddagger}}$  behavior with that of the activity coefficient of a known, stable cationic species of related structure.

To plot the  $\log f_{S^{\ddagger}}$  values against the medium composition, several quantities have to be determined for each reaction system. Reactions discussed in this Account involve strongly acidic media—usually aqueous solutions of mineral acids of medium to high concentrations. The hydronium ion activities  $a_{H^+}^*$  used in the TSAC approach were derived from the acidity function  $H_{GF}$ , established by Janata and Jansen<sup>9</sup> by a combined polarographic-glass electrode method, with the ferrocene-ferricenium ion couple as reference. This function has been corrected for variations of the ferrocene and ferricenium ion activity coefficients, and values of proton activity ( $a_{H^+}^*$ ) are available for several aqueous acid systems, covering a wide range of concentrations.<sup>10</sup>

Pseudo-first-order rate constants,  $k_{\psi}$ , are usually determined by conventional methods; the present method is not as directly applicable for highly reactive systems whose rates are in the stopped-flow range.

Substrate activity coefficients,  $f_S$ , can be obtained by either the solubility or the distribution technique.<sup>11</sup> Experimental difficulties are encountered if the reaction of the substrate with the acidic medium is rapid. If at high acidities extensive protonation of a substrate takes place, a correction for the fraction of substrate unionized is necessary.

Dissociation constants for the substrate conjugate acids,  $K_{SH^+}$ , are evaluated from determination of the variation of the ionization ratio  $[SH^+]/[S]$  as a function of acidity; UV and NMR spectroscopy are the most frequently used techniques.<sup>12</sup> Again, in case of acid-labile compounds, determinations may be difficult over the full range of acidities. Also for very weakly basic substrates  $K_{SH^+}$  value may be less reliable. However, this term in eq 9 is a constant, and possible errors are incorporated into the  $\log k_0$  (intercept) value and do not affect the behavior of  $\log f_{S^{\ddagger}}$  as a function of acidity.

### Acid-Catalyzed Carbon-Oxygen Bond Cleavage

Ester hydrolysis probably represents the most important and most frequently studied reaction of this class. The mechanistic problems involved and possible approaches to their solution have been discussed previously.<sup>13</sup> The reaction follows eq 1 and, depending upon the substrate structure and reaction conditions, two mechanistic pathways are possible for the rate-determining collapse of the ester conjugate acid. According to the A2 mechanism, nucleophilic attack of

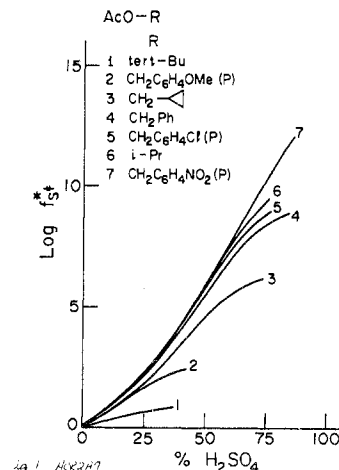
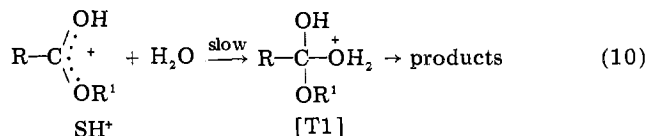
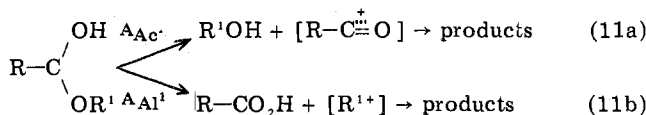


Figure 1. Transition-state activity coefficients for hydrolysis of acetate esters in sulfuric acid solutions.

water results in rate-determining formation of the tetrahedral intermediate (T1). In the alternative, A1,



mechanism the unimolecular cleavage of either the acyl-oxygen (A<sub>Ac</sub>1) or alkyl-oxygen (A<sub>Al</sub>1) bond occurs, and the intermediate acylium or carbonium ion is formed in the rate-determining step (eq 11). Acidic



hydrolysis of esters makes a particularly suitable reaction system for the illustration of the TSAC approach. In the A2 and in both A1 mechanistic models, the rate-determining transition states can be visualized as systems immediately preceding the corresponding intermediate, hence structurally resembling these intermediates. In the case of the bimolecular mechanism A2, the intermediate (and transition state) has the character of an oxonium ion, with the carbon atom bonded to three oxygen atoms; that is a structure for which an exceptionally high demand for the hydration (hydrogen bonding) stabilization would be expected. On the other hand, both A1 pathways produce intermediates of a carbonium ion character, i.e., systems of low hydration requirements.<sup>14</sup> Consequently, activity coefficients of the A2 and A1 type transition states, considered as a measure of the free energy of transfer of a species from pure water to a given aqueous acid, would be expected to exhibit significant differences in their response to the change in the reaction medium composition. For the oxonium ion-like A2 transition state (eq 10), the decrease in the availability of water (increase in acid concentration) should result in a profound destabilization of the system ("salting-out" effect), i.e., a rapid increase of the  $\log f_{S^{\ddagger}}$  value (relative to the  $\text{Et}_4\text{N}^+$  ion). The activated complex characterizing the A1 hydrolysis pathway (eq 11), lacking sites for specific hydrogen-bonding interactions, should show

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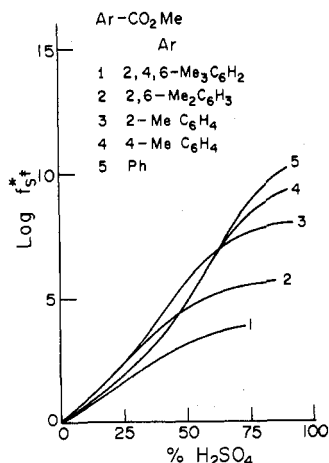


Figure 2. Transition-state activity coefficients for methyl benzoates in sulfuric acid solutions.

much lower sensitivity to the changes in medium composition, and therefore a weaker "salting-out" effect should be observed. The TSAC approach has been used in mechanistic studies of the two classes of esters in aqueous  $\text{H}_2\text{SO}_4$ , namely a series of acetate esters<sup>15</sup> and ring-methyl-substituted methyl benzoates.<sup>16</sup> The plots of  $\log f_{\text{S}}^{\ddagger}$  as a function of  $\text{H}_2\text{SO}_4$  concentration are presented for both ester systems in Figures 1 and 2. For acetates (Figure 1), with the exception of *tert*-butyl acetate, a common pattern of behavior is observed in the dilute acid region, that is, a pronounced salting-out effect on  $f_{\text{S}}^{\ddagger}$ . At some acidity, dependent upon the ester structure, a break from this behavior is observed, to a curve showing a considerably smaller salting-out effect. The *tert*-butyl ester differs in that only this latter behavior is seen, even in dilute acids. These results have been interpreted in terms of different mechanisms operating in the various hydrolyses and in terms of mechanistic changes that take place at some acidity characteristic of each individual substrate. In dilute acids, most acetates hydrolyze by the  $\text{A}_{\text{Ac}2}$  mechanism, which corresponds to a region of a strong salting-out effect due to the rapid increase of the relative free energy of the oxonium ion-like transition state as a consequence of the removal of water from the reaction medium. At some acidity a mechanistic changeover occurs, and the  $\text{A}_{\text{Al}1}$  reaction becomes important; this is shown by a break in the plot to a less pronounced salting-out behavior. The position of this change depends on the relative stability of the carbonium ion being formed in the rate-determining step of the  $\text{A}_{\text{Al}1}$  mechanism (eq 11b). With *tert*-butyl acetate, only the  $\text{A}_{\text{Al}1}$  hydrolysis pathway is operating, even in the dilute acid region. The observed variation in the acidities at which the unimolecular reaction becomes predominant allows one to arrange the carbonium ions which would be produced by these esters in the relative order of stability:  $t\text{-Bu}^+ > p\text{-MeOC}_6\text{H}_4\text{CH}_2^+ > c\text{-C}_3\text{H}_5\text{CH}_2^+ > \text{PhCH}_2^+ > p\text{-ClC}_6\text{H}_4\text{CH}_2^+ > i\text{-Pr}^+ > p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2^+$ . This order is consistent with known structural effects upon carbonium ion stability.

$\log f_{\text{S}}^{\ddagger}$  plots for the hydrolysis of methyl-substituted benzoates (Figure 2) provide information about the

sensitivity of the reacting system to steric effects operating in the substrate molecule. All benzoates studied initially show a strong salting-out effect on the  $f_{\text{S}}^{\ddagger}$  value, consistent with a bimolecular  $\text{A}2$  type of reaction. For each system, at some acidity, a change to a weak salting-out behavior is observed; this can be interpreted as a mechanism changeover to the  $\text{A}_{\text{Ac}1}$  scheme characterized by rate-determining unimolecular formation of an acylium ion (eq 11a). Polar effects are similar in the benzoate esters investigated, but there is a significant difference in steric hindrance around the reaction center (acyl carbon atom). The formation of the tetrahedral intermediate (mechanism  $\text{A}2$ ) is followed by an increase of steric crowding at the protonated carbomethoxy function. On the contrary, unimolecular collapse of the conjugate acid to the acylium ion (and alcohol) should be associated with the relief of steric strain in a sterically crowded system. Consequently, the  $\text{A}_{\text{Ac}1}$  mechanism would be expected to be more important for the more sterically hindered substrates and should be observed to operate in more dilute acids. This is exactly what is observed in Figure 2; the positions of the mechanistic  $\text{A}2/\text{A}1$  changeovers correspond to the following order of the decreasing importance of the unimolecular hydrolysis pathway for the methyl benzoate derivatives: 2,4,6-trimethyl > 2,6-dimethyl > *o*-methyl > *p*-methyl > unsubstituted.

It is instructive to compare the  $\log f_{\text{S}}^{\ddagger}$  behavior, ascribed to the distinctive reaction mechanisms (and the corresponding transition-state structures), with the behavior of the activity coefficients of stable cations of structure related to the postulated structure of the transition states. Such a comparison is made in Figure 3a, where the  $\log f_{\text{S}}^{\ddagger}$  plots for the  $\text{A}2$  (illustrated by the behavior of *p*-nitrobenzyl acetate) and  $\text{A}1$  (illustrated by data for *tert*-butyl acetate) type hydrolysis are presented together with the variation of  $\log f_{\text{Z}}^{\ddagger}$  values for the protonated alcohols<sup>11,15,17</sup> (oxonium ion, model for the  $\text{A}2$  transition state) and the triphenylcyclopropenium ion<sup>18</sup> (stable carbonium ion, model for the  $\text{A}1$  type of transition state). The oxonium ion-like transition states of the  $\text{A}2$  reactions show very similar (and even slightly greater) destabilization with the decrease in the availability of solvating water, as does the alcohol conjugate acid. The carbonium ion-like transition state ( $\text{A}1$  mechanism) is, on the other hand, salted-out only to a slightly greater degree than the particularly stable triphenylcyclopropenium ion.

The transition-state activity coefficient approach has been applied recently in studies of the effect of  $\text{H}_2\text{SO}_4$  concentration on the rates of hydrolysis of ethyl benzoate and ethyl esters of isomeric thiolbenzoic and thionbenzoic acids.<sup>19</sup> The authors found that while ethyl thiolbenzoates hydrolyze by an  $\text{A}_{\text{Ac}2}$  mechanism in the more dilute acid region and change to an  $\text{A}_{\text{Ac}1}$  hydrolysis in more concentrated acids, the corresponding thionesters hydrolyze entirely via an  $\text{A}_{\text{Ac}2}$  mechanism over the whole acidity region (30–99%  $\text{H}_2\text{SO}_4$ ). These interesting results demonstrate the greatly superior stability of the acylium ion ( $\text{Ar-CO}^+$ ) over that of the thioacylium ion ( $\text{Ar-CS}^+$ ), due to the less effective  $^3p\pi\text{-}^2p\pi$  conjugation of sulfur as compared

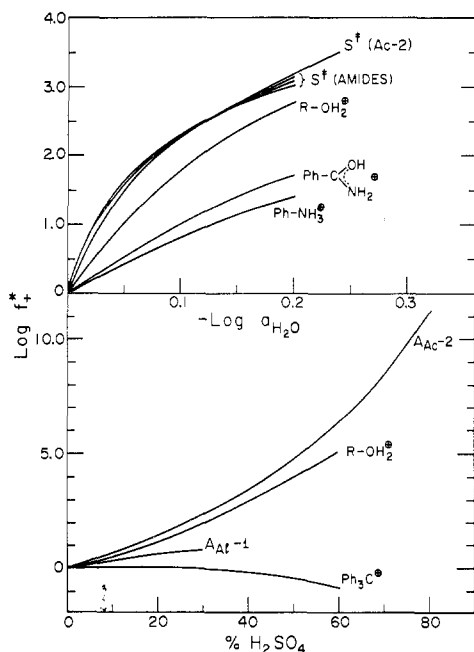
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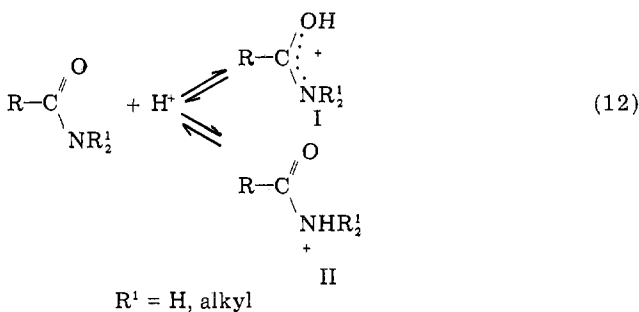


**Figure 3.** Activity coefficients of cationic molecules and transition states: (a, lower) of ester hydrolysis (relative to  $\text{Et}_4\text{N}^+$ ); (b, upper) of amide and ester hydrolysis (relative to  $\text{Et}_4\text{N}^+$ ).

with the  ${}^2p\pi$ - ${}^2p\pi$  effect of oxygen.

### Acid-Catalyzed Carbon-Nitrogen Bond Cleavage

The principal example of this class is the acidic hydrolysis of amides and related systems.<sup>20</sup> One of the fundamental problems associated with the behavior of amides in acidic media is the structure of the conjugate acid itself (eq 12). Although the question of proton-



ation site seems to be presently resolved in favor of oxygen protonation (structure I),<sup>21</sup> the N-protonated form (II) has been also advocated.<sup>22</sup> Considering the two possible conjugate acids (eq 12), there are principally four distinct mechanistic schemes that have been taken into account. Three of them involve bimolecular rate-determining nucleophilic attack of water on the substrate conjugate acid (A2 mechanism); the fourth represents unimolecular rate-determining cleavage of the acyl-nitrogen bond (A1 mechanism). For the special case of *N-tert*-alkyl-substituted amides, reactions involving the initial alkyl-nitrogen bond cleavage has been observed.<sup>23</sup> This hydrolysis pathway is currently under investigation in this laboratory.

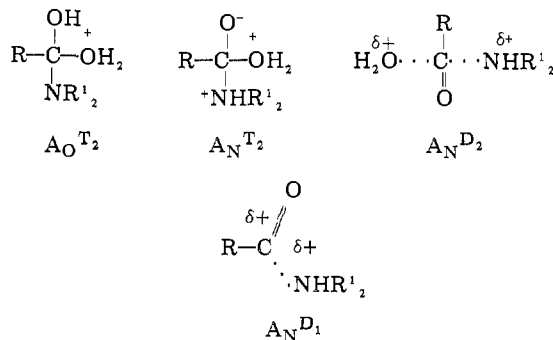
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The first of the A2 reactions (designated as  $\text{A}_0\text{T}_2$ )<sup>24</sup> involves rate-determining formation of the tetrahedral intermediate from the O-protonated substrate; in the second ( $\text{A}_\text{N}\text{T}_2$ ), such an intermediate is formed from the N-protonated substrate. The third mechanism ( $\text{A}_\text{N}\text{D}_2$ ) involves a rate-determining, synchronous displacement of ammonia (or amine) by water from the N-protonated conjugate acid, and the last scheme ( $\text{A}_\text{N}\text{D}_1$ ) consists of an unimolecular rate-determining cleavage of the N-protonated species to give ammonia (or amine) molecule and an acylium ion. The possible transition states or the intermediates which directly follow the transition states for these four mechanistic schemes can be represented by the following structures:



The  $\text{A}_0\text{T}_2$  scheme corresponds closely to the  $\text{A}_\text{Ac}2$  mechanism of ester hydrolysis, and the behavior of the transition state should resemble that of the esters'  $\text{A}_\text{Ac}2$  hydrolysis, i.e., should exhibit a marked salting-out effect when the availability of water in the reaction medium is decreased. By contrast, in the  $\text{A}_\text{N}\text{D}_2$  and  $\text{A}_\text{N}\text{D}_1$  mechanisms, the corresponding transition states are characterized by significant charge dispersal and at least partial ammonium ion character. This should result in much lower hydration requirements and therefore in lower sensitivity to changes in the composition of the reaction medium. It is difficult to predict the behavior of the transition state corresponding to the polycharged intermediate in the  $\text{A}_\text{N}\text{T}_2$  process. At any rate, it should be quite different from that for the  $\text{A}_0\text{T}_2$  mechanism, for which a close resemblance to the  $\log f^*_{\text{S}^+}$  profile obtained for the bimolecular ester hydrolysis is expected.

The TSAC approach has been applied to hydrolysis of benzamide and some of its *N*-alkyl derivatives in aqueous sulfuric acid.<sup>25</sup> Values of  $\log f^*_{\text{S}^+}$  as a function of decreasing water activity in the aqueous  $\text{H}_2\text{SO}_4$  solution have been determined for benzamide and its *N*-methyl, *N,N*-dimethyl, and *N*-isopropyl derivatives. The plots are presented in Figure 3b, together with the related plots of  $\log f^*_{\text{S}^+}$  for the  $\text{A}_\text{Ac}2$  hydrolysis of esters and of  $\log f^*_{\text{Z}^+}$  of oxonium ions derived from alcohols<sup>11,15,17</sup> and of benzamidonium ion.<sup>26</sup>

Figure 3b shows the remarkable similarity in  $\log f^*_{\text{S}^+}$  values for all amides studied, despite the very large variation in observed rates of hydrolysis, which implies a uniformity of mechanism. It appears that the number of hydrogen atoms present at nitrogen is not important in determining the solvation requirements of the transition state; this indicates that only a minor fraction of the positive charge is localized on nitrogen in the

(24) C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, 94, 8811 (1972).

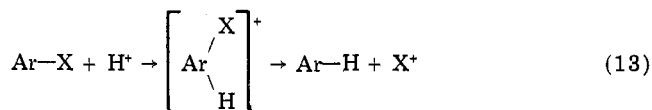
(25) T. A. Modro, K. Yates, and F. Beaufays, *Can. J. Chem.*, 55, 3050 (1977).

(26) L. M. Sweeting and K. Yates, *Can. J. Chem.*, 44, 2395 (1966).

transition state. The values of  $\log f_{S^\ddagger}^*$  for amides parallel very closely the plots characteristic for the  $A_{Ac}2$  mechanism of ester hydrolysis. This leads to the obvious conclusion that for both systems the transition states must resemble each other in solvation requirements and in the degree of development of oxonium ion character—a result only compatible with the  $A_O T_2$  mechanistic pattern of amide hydrolysis.

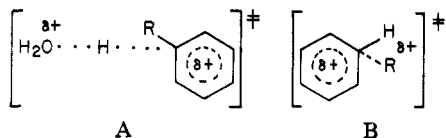
### Aromatic Substitution

Reactions involving displacement of an aromatic substituent by hydrogen in strongly acidic media can be treated as acid-promoted reactions, since hydrogen ions are consumed in the process, according to eq 13.



Aromatic hydrogen exchange is the best known example of reaction 13, although in principle X can represent almost any substituent, replaceable by a proton under suitable conditions.<sup>27</sup> These reactions, involving the proton as the effective electrophile, have been classified<sup>28</sup> as  $A-S_{E2}$  processes, where proton transfer to the aromatic takes place in the rate-determining step, and the alternative A1 or A2 mechanisms have been rejected. The  $A-S_{E2}$  mechanism has been demonstrated for such reactions as protodesilylation and protodegermylation (substitution of  $\text{SiR}_3$  and  $\text{GeR}_3$  groups),<sup>29</sup> but it seemed reasonable to expect that in some systems the rate of the second step (removal of a leaving group from the Wheland intermediate) could become rate determining and that a mechanism change from  $A-S_{E2}$  to A1 might take place.

Acid-promoted  $C_{\text{arom}}-C_{\text{aliph}}$  bond cleavage (eq 13, X = alkyl) is known, particularly for systems where X represents an alkyl group capable of leaving as a relatively stable carbonium ion. If reaction 13 proceeds via the  $A-S_{E2}$  mechanism, the rate-determining transition state involves only a partially transferred proton (structure A); if the second step becomes rate-deter-



mining (A-1 mechanism), the positive charge is delocalized over the ring and the departing carbonium system (structure B).

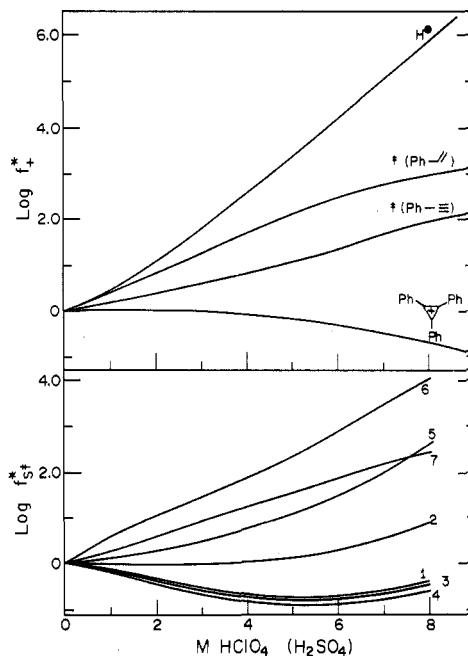
Following the arguments presented before, the alternative transition states (A and B) should differ markedly in their hydration requirements, and thus should produce different  $\log f_{S^\ddagger}^*$  behavior over some range of acidity. The aromatic protodealkylation has been studied in aqueous  $\text{HClO}_4$  and the  $\log f_{S^\ddagger}^*$  values have been determined for protode-*tert*-butylation (eq 13, X = *t*-Bu) and protodetrylation (eq 13, X =  $\text{CPh}_3$ ) reactions.<sup>30</sup> Transition-state activity coefficient behavior for the *tert*-butyl and trityl derivatives of phenol and anisole (OH and OMe groups served as activating

(27) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds", Elsevier, Amsterdam, 1965, Chapter 9.

(28) R. Taylor in "Comprehensive Chemical Kinetics", Vol. 13, C. H. Bamford and C. F. H. Gripper, Ed., Elsevier, Amsterdam, 1972.

(29) Reference 28, Chapters 9.6 and 9.7.

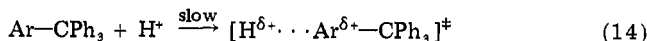
(30) T. A. Modro and K. Yates, *J. Am. Chem. Soc.*, **98**, 4247 (1976).



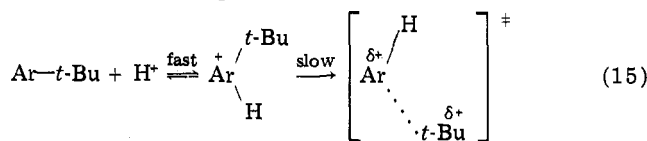
**Figure 4.** (a, lower) Transition-state activity coefficient for: protodealkylation in aqueous  $\text{HClO}_4$ —(1) *p*-*tert*-butylphenol, (2) *o*-*tert*-butylphenol, (3) *p*-*tert*-butylanisole, (4) *o*-*tert*-butylanisole, (5) *p*-triphenylmethylphenol; protode deuteration in aqueous  $\text{H}_2\text{SO}_4$ —(6) *p*-cresol-2-*d*, (7) anisole-4-*d*. (b, upper) Activity coefficients of cationic species and transition states of hydration in sulfuric acid solutions (relative to  $\text{Et}_4\text{N}^+$ ).

substituents) is presented in Figure 4a, together with plots of the  $\log f_{S^\ddagger}^*$  for the protode deuteration reaction,<sup>31</sup> taken as an example of the well-established  $A-S_{E2}$  type of substitution.

$\log f_{S^\ddagger}^*$  profiles in Figure 4 can be divided into two families—curves 1–4 (*tert*-butyl derivatives), which show very small variations with acidity and even show salting-in (stabilization) at some acidities, and curves 5–7 (the trityl compound and deuterated derivatives), which show a strong and continuous salting-out effect over the whole range of acidity. It has been concluded that the protodetrylation reaction falls into the category of the “normal”  $A-S_{E2}$  mechanistic pattern, involving a transition state of the high hydration requirements:



For the protode-*tert*-butylation, a completely different type of dependence was obtained; the  $\log f_{S^\ddagger}^*$  behavior is what would be expected if carbon-carbon bond cleavage occurs at the transition state and the formation of *tert*-butyl carbonium ion is highly advanced (mechanism A1, eq 15). These mechanistic conclusions



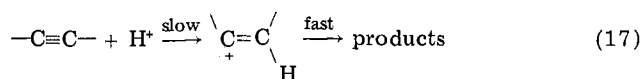
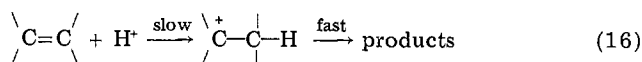
have been fully supported by the observed solvent kinetic isotope effects for these reactions.<sup>30</sup>

### Acid-Catalyzed Hydration of Alkenes and Alkynes

These reactions provide an example of a slow, rate-determining proton transfer to an  $\text{sp}^2$  or  $\text{sp}$  carbon

(31) V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 3619 (1955).

atom, resulting in the formation of carbonium ions or vinyl cations.<sup>32</sup>



The transition states for the hydration reaction would be naturally expected to resemble the corresponding carbonium (or vinyl) ions and, depending upon the degree of the proton transfer, retain some hydrated proton character. Examination of the  $\log f^*_{\text{S}}$  behavior for these reactions, relative to the (known) behavior of carbonium ion systems and the proton itself, can therefore be taken as a probe of the position of the rate-determining transition state along the reaction coordinate.

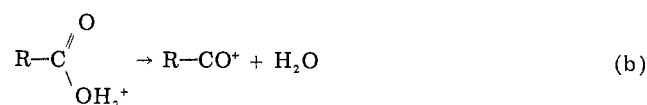
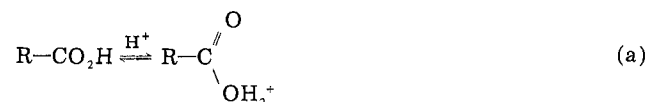
The interesting feature of hydration reactions is that, in spite of the known higher difficulty of formation of vinyl cations relative to the corresponding carbonium ions,<sup>33</sup> reactions 16 and 17 usually proceed with similar rates.<sup>34</sup> By investigating the solvent effects upon rates of electrophilic additions (including acid-catalyzed hydration) to structurally related alkenes and alkynes it has been concluded<sup>35</sup> that solvation effects in aqueous acids are responsible for the cancellation of the expected difference in reactivities resulting from the difference in stabilities of the cationic intermediates. This view has recently been criticized by Modena et al.<sup>36</sup> who have analyzed the rate of hydration of styrene and phenylacetylene derivatives in aqueous  $\text{H}_2\text{SO}_4$  in terms of their linear free energy relationship approach. On the basis of the values of the "solvation parameter"  $\phi_t$ , they concluded that hydration effects for both types of unsaturated systems are small and similar in magnitude. Transition-state activity coefficients for the hydration of styrene and phenylacetylene can be calculated using rate and  $f_{\text{S}}$  data from ref 36. These are presented as a function of  $\text{H}_2\text{SO}_4$  concentration in Figure 4b, together with the variation of  $\log f^*_{\text{S}}$  for the proton itself<sup>10</sup> and the carbonium (triphenylcyclopropenium<sup>11</sup>) ion species serving as "limiting" structural models of the two types of transition states. In agreement with the generally accepted view about "late" transition states for hydration reactions<sup>37</sup> Figure 4b demonstrates very mild salting-out effects for both  $f^*_{\text{S}}$  plots, consistent with the low hydration requirements of the carbonium (or vinyl) ion-like transition states.

However, Figure 4b reveals also that solvation effects upon both transition states cannot be considered to be identical. Over the whole range of the acidity the  $\log f^*_{\text{S}}$  values show higher destabilization (by ca. one logarithmic unit) of the transition state corresponding to the formation of the benzylic carbonium ion relative to that leading to the phenylvinyl cation. This can be taken as an indication that the relative stabilities of the two structural types of carbon ions in the gas phase do

not necessarily have to parallel their relative stabilities in solution.

### Concluding Remarks

We believe that by the use of the TSAC approach our knowledge of the detailed mechanism of various types of acid-catalyzed reactions could be significantly increased. There are of course numerous other reactions than those described in this Account, where the application of the TSAC approach would be a potential source of valuable mechanistic information. To mention only a few, for example, the Wallach rearrangement<sup>38</sup> of azoxyarenes requires the use of moderately concentrated acid, which is a medium far from being considered as ideally behaved. The TSAC approach could in this case provide evidence supporting the postulated rate-determining second proton transfer to the conjugate acid of the azoxy compound to produce a diprotonated intermediate. Similarly, the mechanism of the Fischer-Hepp rearrangement of *N*-alkyl-*N*-nitrosoanilines studied in acid solutions up to 12 M acid and involving rate-determining proton transfer from an aromatic substrate to the solvent<sup>39</sup> could be tested in terms of the TSAC behavior. Hydrolysis of ethers in strong acids<sup>40</sup> represents another reaction system in which possible A2 and A1 reaction pathways could be examined by the TSAC approach. Decarbonylation of various carboxylic acids in concentrated  $\text{H}_2\text{SO}_4$  is a well-known reaction. According to Hammett,<sup>41</sup> the mechanism of this process can be represented by the following sequence:



Kinetic and isotope effect evidence is consistent either with a rate-determining C-O bond cleavage (step b) or with a concerted C-O and C-R bond breaking (steps b and c).<sup>42</sup> Solvation requirements of the cationic species involved in steps b and c should be sufficiently different to produce distinguishable behavior of the rate-determining transition-state activity coefficient as a function of reaction mechanism.

The TSAC approach can be in principle applied to any reaction system for which a medium effect upon a reaction rate is observed. Variations in reaction medium properties (e.g., polarity) would modify solvent-transition-state interactions in a manner depending upon the solvation requirements of the particular transition state. This effect could be measured in terms of the TSAC approach, and the stabilization (or destabilization) of the rate-determining transition state could be determined relative to some reference state, as well as being directly compared with the behavior of suitable stable model structures.

(38) E. Buncel, *Acc. Chem. Res.*, **8**, 132 (1975).

(39) I. D. Biggs and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 601 (1976).

(40) Reference 12, p 183.

(41) L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1940.

(42) Reference 12, pp 254-259.

(32) V. Nowlan and T. T. Tidwell, *Acc. Chem. Res.*, **10**, 252 (1977).

(33) G. Modena and V. Tonellato, *Adv. Phys. Org. Chem.*, **9**, 185 (1971).

(34) P. B. D. de la Mare and R. Bolton, "Electrophilic Addition to Unsaturated Systems", Elsevier, London, 1966, pp 211-212.

(35) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H. W. Leung, and R. McDonald, *J. Am. Chem. Soc.*, **95**, 160 (1973).

(36) G. Modena, F. Rivetti, G. Scorrano, and U. Tonellato, *J. Am. Chem. Soc.*, **99**, 3392 (1977).

(37) D. S. Noyce and M. D. Schiavelli, *J. Am. Chem. Soc.*, **90**, 1020 (1968); **90**, 1023 (1968).