Transition States as Acids and Bases

JOSEPH L. KURZ

Department of Chemistry, Washington University, St. Louis, Missouri 63130

It is common practice to propose structures for "transition states"[1] with the same freedom that structures are proposed for stable molecules. However, the problem of structure proof is far more difficult for an activated complex than for an isolable species.[2]

Since it can be shown (vide infra) that the pK_a of an acidic activated complex can be measured by a simple rate constant ratio, it is tempting to try to apply our knowledge of the relation between acidity and structure to this problem. Before plunging into a discussion of our attempts to do that, let us briefly review the context of the concept, "transition state," so that we shall have fresh in our minds both the reasons why we wish to know those structures and any possible restrictions on the reality of the structures which we may deduce.

Why Transition States? Attempts to explain the origins of observed rate differences comprise a major fraction of the chemical literature. Questions such as "why" some particular reaction proceeds preferentially to form one out of a multitude of thermodynamically possible products are most often questions about relative rates rather than about relative product stabilities. In regard to the latter, theory provides an exact outline for calculating the position of equilibrium from observable properties of reactants and products; if we have sufficient knowledge of the structures of reactants and products, then statistical mechanics tells us, in principle, how to calculate the equilibrium constant and its variations in response to changes in structure or environment.

Unfortunately, no such exact theory exists for predicting rates. Even if we knew all details of the structures of reactants and of the various thermodynamically possible products, we would not know, even in principle, how those structures should be used to predict which products will be formed or how fast the reaction will proceed. In order to predict rates, additional information is required—information about the structures of reacting molecules which are in states intermediate between reactants and products. The sequence of these intermediate states constitutes the mechanism of the reaction.

For very simple reactions (e.g., $H + H_2^+$), very real progress has been made in calculating complete potential surfaces from first principles.[3] Such surfaces, when calculable, provide a precise description of the mechanism which is independent of observations of structure. However, reactions of interest to most experimental chemists occur between complex molecules in solution, and the exact calculation of potential surfaces for such reactions lies far beyond the present state of the art.

For semiquantitative discussions of rates and mechanisms of reactions in solution, an admittedly approximate theory has come into general use and enjoyed great success. This theory assumes that in order to define the rate for any single-step reaction, the structure of only one intermediate state need be given. That state is postulated to be at the saddle point which lies between reactants and products on the potential surface. The concentration of activated complexes in that transition state is further assumed to be maintained at its equilibrium value with respect to the concentration of reactants.[4] For any assumed structure of the activated complex, this equilibrium assumption allows the concentration of those activated complexes to be expressed in terms of the same statistical mechanical formalism known to be correct for treating equilibria between stable molecular species. The rate can then

Joseph Kurz was born in 1933. He did his undergraduate and graduate work at Washington University in St. Louis, and spent the succeeding 2 years doing postdoctoral work with Frank Westheimer at Harvard. After 3 years in industry he returned to his alma mater, where he is now Associate Professor. His research interests center around the kinetics and mechanisms of reactions in solution and transition state structures.

(1) The terms "transition state" and "activated complex" are often used as if they were synonymous. For the remainder of this Account, we shall maintain a useful distinction and speak of the activated complex as being in the transition state in the same sense that the reactants are said to be in the initial state.

(2) It should be noted that, while activated complexes are in principle nonisolable (since one of their degrees of freedom lies at a maximum in energy), they are not in principle nonobservable. Since the time that each complex spends in the neighborhood of the transition state is of the order of $h/kT \sim 10^{-13}$ sec, they should be spectroscopically observable with radiation whose period is shorter than this (uv and much of the ir). Such direct observation of activated complex structure is prohibited only by the experimental difficulty of extracting the signals arising from the activated complexes from those arising from the vastly more populous other species present in a reacting system.

(3) M. Krauss, Annu. Rev. Phys. Chem., 21, 39 (1970).

(4) For recent critical discussions of the basic assumptions underlying the transition state theory from two rather different viewpoints, see (a) H. S. Johnston, "Gas Phase Reaction Rate Theory," Ronald Press, New York, N. Y., 1966, particularly pp 122–129, 133–136, 244–245; (b) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, particularly pp 62–73, 109.

be obtained by multiplying that concentration by the frequency with which activated complexes pass through the transition state.

The consequences of assuming a single critical state to be rate determining had been under study for two decades[5] when, in 1935, Wynne-Jones and Eyring[6] published their now familiar expression for the rate constant, k'.

$$k' = \kappa \frac{kT}{h} K^{\ddagger}$$

$$= \kappa \frac{kT}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R}$$

The general problem of predicting rates from structures of reactants and products is thus, within the context of transition state theory, equivalent to the problem of using those two observable structures to predict the structure and standard free energy of the activated complex. Qualitatively, such a prediction is implicit whenever curved arrows or dotted bonds are used to "rationalize" the formation of some particular product during a reaction.

Since Leffler's[7] pioneer formulation of the problem in 1953, physical-organic chemists have been making those predictions ever more explicit.[8-11] Although our present level of understanding limits us to qualitative predictions of the variations in activated complex structure which result from changes in solvent or substituents, our ability to test that understanding through experimental determination of the predicted structures remains similarly qualitative. Quantitative measurements are required to guide the development of precise predictive theories.

This Account discusses an approach to the experimental determination of activated complex structure which may permit the assignment of quantitative structural parameters.

Definition of $pK_a(\ddagger)$

General Relationship of $pK_a(\ddagger)$ to Observable Rate Constants. For many reactions it is possible to measure two rate constants: one for the reaction (eq 1) of a substrate, S, and a second for the reaction (eq 2) of SH^+, the conjugate acid of S. Let those two rate constants be denoted by k_S and k_{SH}, respectively. For a

$$S + X + \cdots \xrightarrow{k_S} [S^{\ddagger}] \rightarrow products \tag{1}$$

$$SH^+ + X + \cdots \xrightarrow{k_{SH}} [SH^{\ddagger}] \rightarrow products \tag{2}$$
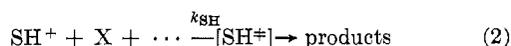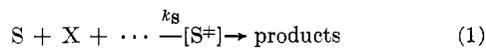
system which contains both S and SH^+ in kinetically

significant concentrations, the total rate of production of products, V, will be given by eq 3. The virtual

$$V = (k_S[S] + k_{SH}[SH^+])[X] \cdots \tag{3}$$

equilibrium constant, $K_a(\ddagger)$, for dissociation (eq 4) of the acidic activated complex, $SH^{\ddagger}$, to give $S^{\ddagger}$ as its conjugate base may then be formally defined in the same way as it would if $SH^{\ddagger}$ and $S^{\ddagger}$ were a stable conjugate acid–base pair.[12,13] Thus for eq 4

$$SH^{\ddagger} + H_2O \underset{}{\overset{K_a(\ddagger)}{\rightleftharpoons}} H_3O^+ + S^{\ddagger} \tag{4}$$
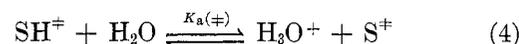
the equilibrium constant is given by eq 5.

$$K_a(\ddagger) = \frac{a_H a_S{}^{\ddagger}}{a_{SH}{}^{\ddagger}} \tag{5}$$

Although $K_a(\ddagger)$ is a virtual equilibrium constant in the sense that the lifetime of an activated complex is not sufficiently long to permit establishment of a direct dynamic equilibrium between $SH^{\ddagger}$ and $S^{\ddagger}$,[4a] the value of $K_a(\ddagger)$ may be related to observable quantities *via* the thermodynamic cycle (eq 6), which

$$H^+ + S + X + \ldots \underset{}{\overset{K_S^{\ddagger}}{\rightleftharpoons}} [S^{\ddagger} + H^+] \rightleftharpoons$$

$$\left\Vert K_a(SH^+) \qquad \right\Vert K_a(\ddagger)$$

$$SH^+ + X + \ldots \underset{}{\overset{K_{SH}^{\ddagger}}{\rightleftharpoons}} [SH^{\ddagger}] \rightleftharpoons \tag{6}$$
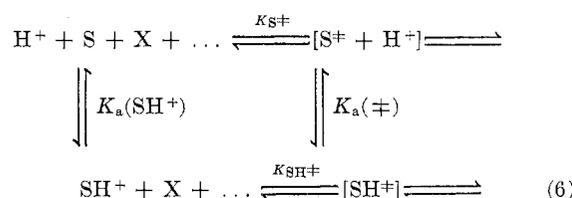
leads to eq 7, where $K_S^{\ddagger}$ and $K_{SH}^{\ddagger}$ are the equilibrium

$$K_a(\ddagger) = \frac{K_S^{\ddagger}}{K_{SH}^{\ddagger}} K_a(SH^+) \tag{7}$$

constants for the conversion of S and SH^+ into their respective activated complexes, $S^{\ddagger}$ and $SH^{\ddagger}$, and $K_a(SH^+)$ is the acid dissociation constant for SH^+. Since $K_S^{\ddagger}$ and $K_{SH}^{\ddagger}$ are related to the observed rate constants, k_S and k_{SH}, by eq 8 and 9,[6,14] it follows that

$$k_S = \kappa \frac{k_b T}{h} K_S^{\ddagger} \tag{8}$$

$$k_{SH} = \kappa \frac{k_b T}{h} K_{SH}^{\ddagger} \tag{9}$$

$$K_a(\ddagger) = \frac{k_S}{k_{SH}} K_a(SH^+) \tag{10}$$

and

$$pK_a(\ddagger) = pK_a(SH^+) + \log \frac{k_{SH}}{k_S} \tag{11}$$

(5) *E.g.*, A. Marcelin, *Ann. Phys. (Leipzig)*, **3**, 158 (1915); W. H. Rodebush, *J. Amer. Chem. Soc.*, **45**, 606 (1923); H. Pelzer and E. Wigner, *Z. Phys. Chem., Abt. B*, **15**, 445 (1932); M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).

(6) W. F. K. Wynne-Jones and H. Eyring, *J. Chem. Phys.*, **3**, 492 (1935).

(7) J. E. Leffler, *Science*, **117**, 340 (1953).

(8) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(9) C. G. Swain and E. R. Thornton, *ibid.*, **84**, 816 (1962).

(10) E. R. Thornton, *ibid.*, **89**, 2915 (1967).

(11) J. C. Harris and J. L. Kurz, *ibid.*, **92**, 349 (1970).

(12) J. L. Kurz, *ibid.*, **85**, 987 (1963).

(13) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, pp 138–140.

(14) It is implicitly assumed in this discussion that the solutions used for measurement of the rate constants are sufficiently dilute to permit all activity coefficients to be set equal to unity. If this is not true, then the value of $pK_a(\ddagger)$ which is derived from the observed rate constants can be approximately corrected to a reference state of infinite dilution by use of the same methods for estimating values of activity coefficients as are commonly applied in analogous measurements of pK_a values for stable acids (*e.g.*, ref 15).

(15) C. W. Davies, "Ion Association," Butterworths, London, 1962, Chapter 3.

The other thermodynamic parameters which characterize equilibrium 4 are similarly given in terms of the activation parameters corresponding to k_S and k_{SH} by equations of the form

$$\Delta S^\circ(\ddagger) = \Delta S^\circ(SH^+) + \Delta S_S{}^\ddagger - \Delta S_{SH}{}^\ddagger \quad (12)$$

Hydrogen Ion Catalysis. A frequently encountered special case of these general relationships exists when the concentration of SH^+ is not explicitly known and the rate law is written in terms of the total substrate concentration, $[S]_T = [S] + [SH^+]$. Under those conditions, the general expression for the empirically observed rate law corresponding to the mechanism given in eq 1 and 2 will be

$$V = \left(\frac{k_0 + k_H[H^+]}{1 + K[H^+]}\right) [S]_T[X] \ldots \quad (13)$$

where the empirical constants, k_0, k_H, and K, are related to the mechanistic constants by eq 14–16. When the

$$k_0 = k_S \quad (14)$$

$$k_H = k_{SH}/K_a(SH^+) \quad (15)$$

$$K = 1/K_a(SH^+) \quad (16)$$

fraction of the substrate which is protonated is low (*i.e.*, $K[H^+] \ll 1$), the general equation, (13), becomes the commonly observed linear rate law for hydrogen ion catalysis.

$$V = (k_0 + k_H[H^+])[S]_T[X] \ldots \quad (17)$$

When the observed rate law is given by either eq 13 or 17, eq 11 and 12, which give $pK_a(\ddagger)$, $\Delta S^\circ(\ddagger)$, etc., in terms of observed parameters, may be combined with eq 14 and 15 to give particularly simple expressions

$$pK_a(\ddagger) = \log \frac{k_H}{k_0} \quad (18)$$

$$\Delta S^\circ(\ddagger) = \Delta S_0{}^\ddagger - \Delta S_H{}^\ddagger \quad (19)$$

where the subscripts 0 and H in eq 19 indicate that the activation parameters correspond to k_0 and k_H, respectively.

It can be shown that eq 18 and 19 are also valid for reactions which obey rate eq 17, but proceed by way of a mechanism in which the rate-determining step corresponding to k_H is proton transfer from H_3O^+ to give SH^+ (so that the prior equilibrium between S and SH^+, which is assumed in the above derivation, is not present). The proton to whose ionization pK_a ($\ddagger$) refers is then not the one being transferred, but is one of the remaining pair on the H_3O^+.

Hydroxide Ion Catalysis. A second common special case arises when the roles of SH^+ and S are played respectively by solvent and the conjugate base of solvent. For example, if a reactant, X, in basic aqueous solution reacts both with H_2O and with OH^-, eq 3 for the observed rate may be written in either of two forms, eq 20a or 20b. Some confusion is then

$$V = (k_1 + k_2[OH^-])[X] \ldots \quad (20a)$$

$$V = (k_1'[H_2O] + k_2[OH^-])[X] \ldots \quad (20b)$$

possible concerning the value to use for $pK_a(H_2O)$ when eq 11 is used to calculate a value of $pK_a(\ddagger)$ for the ionization of the H_2O moiety in the activated complex of the k_1 reaction.[16]

Equations 20a and 20b differ in the standard state chosen for water; eq 20a uses a *mole fraction* basis for that standard state while eq 20b uses a *molarity* basis. The corresponding values of $pK_a(H_2O)$ are respectively the conventional pK_w (14.00 at 25°) and $pK_w + \log[H_2O]$ (15.74 at 25°). The correct value of $pK_a(\ddagger)$ can be calculated from the parameters of either eq 20a or 20b together with the value of $pK_a(H_2O)$ which uses the same standard state convention for H_2O. Thus eq 11 becomes either eq 21a or 21b.

$$pK_a(\ddagger) = \log \frac{k_1}{k_2} + pK_w \quad (21a)$$

$$pK_a(\ddagger) = \log \frac{k_1'}{k_2} + pK_w + \log[H_2O] \quad (21b)$$

When a deduction about the structure of an activated complex is drawn from a comparison of the value of $pK_a(\ddagger)$ from eq 21 to $pK_a(H_3O^+)$ and $pK_a(H_2O)$, the correct values of these latter two constants are those for which a molar basis is chosen for the standard state of those H_2O molecules which act either as the conjugate base of H_3O^+ or as the conjugate acid of OH^-; thus at 25°, $pK_a(H_3O^+) = -1.74$ and $pK_a(H_2O) = 15.74$.[17]

Qualitative Interpretation of $pK_a(\ddagger)$

Mechanistic arguments based on rate constant ratios related to those which are here identified with $K_a(\ddagger)$ have occasionally been made by earlier workers. For example, in the pioneer investigations of hydrolysis mechanisms by Ingold and his collaborators, several such ratios were used, a detailed argument based on k_H/k_{OH} for carboxylate esters being given as early as 1930. However, a wealth of further information is unlocked from the data once the simple relationship between such ratios and $pK_a(\ddagger)$ is recognized. As an illustration of this, consider the k_1/k_2 ratio of rate constants for the uncatalyzed and lyate ion catalyzed hydrolyses of alkyl halides; the magnitude of this ratio for a particular alkyl halide has commonly been considered diagnostic of whether k_1 refers to an S_N1-

(16) An example of such confusion is provided by this author's first paper on $pK_a(\ddagger)$.[12] The standard state convention discussed therein is only partially correct.

(17) This conclusion follows from the fact that both the value of $K_a(\ddagger)$ calculated from eq 21 and the value of a_{H^+} carry units of moles/liter.[18] It is therefore necessary that the units of $a_{S\ddagger}$ and $a_{SH\ddagger}$ in the definition of $K_a(\ddagger)$ (eq 5) be identical. Any other K_a whose numerical value is compared to that of $K_a(\ddagger)$ must thus also have identical standard states for its conjugate acid and base; since H_3O^+ and OH^- concentrations are almost universally expressed as molarities in kinetic work, the same units must therefore be used for the concentration of H_2O.

(18) We are using the convention governing assignment of units to activity and activity coefficient which is recommended by G. N. Lewis, M. Randall, K. S. Pitzer, and L. Brewer, "Thermodynamics," 2nd ed, McGraw-Hill, New York, N. Y., 1961, p 251.

Table I

Difference between the Acidity of H₂O in the Transition State for R₁R₂CHOSO₃⁻ Hydrolysis and in the Initial State

R₁, R₂	Temp, °C	k_2/k_1, M^a	$(pK_a(H_2O) - pK_a(\ddagger))^b$
H, H	138	60	3.5
CH₃, H	138	20	3.0
(CH₃)₂CH, H	138	5.2	2.4
CH₃, CH₃	99	0.8	1.5
CH₃CH₂, CH₃	99	0.4	1.3

^{a} References 19 and 20. ^{b} Both K_a values have units of M, so that this difference is given (via eq 21) by log [H₂O] + log (k_2/k_1).

like or SN2-like process. When that ratio is shown to be proportional to the factor by which the acidity of a solvent molecule is changed upon transfer from bulk solvent into the activated complex for the uncatalyzed hydrolysis, it becomes possible to draw conclusions about bonding and charge distributions in the activated complexes for both the k_1 and the k_2 processes. The key which unlocks those conclusions is the mass of both empirical data and theoretical interpretations which connect the acidity of a molecule with its structure (and particularly with its internal charge distribution).

A detailed, quantitative interpretation of these k_1/k_2 ratios is outlined later in this Account. Such a detailed analysis is not required if all that is desired is a qualitative insight into the structure of the activated complex and into the relation between that structure and the rate constant ratio. To illustrate such a qualitative approach, let us apply eq 21 to calculate values of $pK_a(\ddagger)$ from the measured k_1/k_2 ratios for one of the classic examples[19,20] of how that ratio varies with the structure of R in the solvolysis of RX.

Alkyl Sulfate Hydrolysis. The data of Calhoun and Burwell[19] show that monoalkyl sulfate ions hydrolyze in basic aqueous solution via alkyl–oxygen cleavage and obey the rate law expressed in eq 20a. The activated complex thus has the structure[21]

$$(H)-\overset{\delta+}{O}\cdots\cdots\overset{\overset{R_1}{|}}{\underset{\overset{/}{H}\overset{}{R_2}}{C}}\cdots\cdots OSO_3^{(1+\delta)-}$$
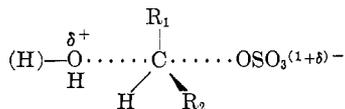
where the parenthetical proton is present in the k_1 reaction but absent in the k_2 reaction. Table I lists values of $pK_a(H_2O) - pK_a(\ddagger)$, which measure the increase in acidity of the parenthetical proton which occurs when the water molecule which bears that proton is transferred from the bulk solution into the activated complex for hydrolysis of R₁R₂CHOSO₃⁻.

When H₂O is bound into this activated complex, the principal contributions to the change in its acidity

should come from the charges in whose fields the dissociating proton is now located. The $\delta+$ on the nucleophilic oxygen will decrease $pK_a(\ddagger)$ (i.e., increase the acidity). If no bond had yet been formed between O and C at the transition state, then there would be no contribution from this source; if a full single bond between O and C were present, then δ would be unity and the decrease in $pK_a(\ddagger)$ would be approximately equal to the difference, $pK_a(H_2O) - pK_a(H_3O^+)$, which is 15.2 pK units at 138° and 15.7 pK units at 99° (on the molar scale). The charge distribution on the leaving group will also affect $pK_a(\ddagger)$. However, the effect of a SO₃⁻ substituent on acid strength is known to be complicated, and available data[22] suggest only that the total effect of the leaving group on $pK_a(\ddagger)$ probably lies in the range -2 to $+1$ pK units if $\delta \approx 0$ and in a range perhaps one or two pK units more positive than this if $\delta \approx 1$. In any event, the value of $pK_a(\ddagger)$ is much less sensitive to the effect of the leaving group than it is to the magnitude of the charge on the nucleophilic oxygen.

The numbers in Table I show that none of the five activated complexes has a large value of $\delta+$. Even methyl sulfate ion appears to have no more than about 20% bond making in its transition state. As the extent of alkyl substitution on the central carbon increases, the acidity of the H₂O in the activated complex decreases until it falls in the range expected if no bond making at all were present. Such a decrease in nucleophilic interaction accompanying alkyl substitution is in agreement with current theories[10,11] describing the structure of SN2 activated complexes.

Benzyl Fluoride Hydrolysis. The preceding example has illustrated how the presence of an acidic site in a nucleophile allows measurement of a $pK_a(\ddagger)$ value which is sensitive to the extent of nucleophile–carbon bond making in the activated complex. A $pK_a(\ddagger)$ value with the complementary sensitivity order can be measured analogously for any leaving group which contains an acidic site. A simple example of such a leaving group is HF.

Benzyl fluoride hydrolyzes in acidic aqueous solution by two kinetically distinguishable paths,[23] one uncatalyzed (F⁻ as leaving group) and the other catalyzed by hydrogen ion (HF as leaving group). The observed rates obey eq 17, so that the thermodynamic parameters for ionization of the HF moiety in the activated complex are given by eq 18 and 19. Table II[12] lists some of those parameters together with the corresponding known values for HF (approximately corresponding to an activated complex in which C–F bond breaking was complete) and the estimated values for RFH⁺ (approximately corresponding to an activated complex in which a full C–F single bond was present). The data in Table II strongly suggest that the activated complex has a C–F bond which is nearly broken.

(19) G. M. Calhoun and R. L. Burwell, Jr., J. Amer. Chem. Soc., **77**, 6441 (1955).

(20) A. Streitwieser, Jr., Chem. Rev., **56**, 571 (1956).

(21) As written, this structure implicitly assumes that no charge is built up on the central carbon during the activation process (i.e., that total bond order to the central carbon is conserved). This assumption is shown to be correct for some related substrates in later sections of this Account.

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

(23) C. G. Swain and R. E. T. Spalding, J. Amer. Chem. Soc., **82**, 6104 (1960).

Table II[12]

Thermodynamic Parameters for Ionization at 50°

	HF	$C_6H_5CH_2F$ solvolysis activated complex	RFH^+
pK_a	3.4	1.8	< -10
$\Delta S°$, eu	-17.7	-15.0	~ 0
$\Delta H°$, kcal/mole	-0.8	-2.1	< -15

Relation between $pK_a(\ddagger)$ and the Brønsted β. In the first approximation, estimation of bonding parameters for activated complexes from $pK_a(\ddagger)$ values is equivalent to the familar[24] estimation of such parameters from slopes of linear free energy correlations. For example, if the rate constants for proton transfer from an acid, HA, to H_2O and to OH^- are both known, the acidity of the parenthetical proton in the activated complex

$$
\overset{\delta+}{(H)\!-\!O}\cdots\cdots\overset{}{H}\cdots\cdots\overset{\delta-}{A}
$$
$$\underset{H}{}$$
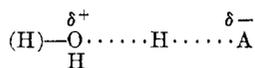
is given by eq 21.[12] Estimation of an approximate value of δ by linear interpolation between the acidities of H_3O^+ and H_2O then gives eq 22. If a value of the

$$
\delta = \frac{pK_a(H_2O) - pK_a(\ddagger)}{pK_a(H_2O) - pK_a(H_3O^+)} \tag{22}
$$

Brønsted β (which may be identified with δ)[24] is calculated from the same two rate constants which were used to calculate $pK_a(\ddagger)$, then that β is given by eq 23. Substitution of log (k_1'/k_2) from eq 21 into

$$
\beta = \frac{\log k_2 - \log k_1'}{\log [K_a(H_2O)] - \log [K_a(H_3O^+)]} \tag{23}
$$

eq 23 shows that this β is identical with the first approximation value of δ which is calculated from the pK_a values via eq 22.

An advantage of the $pK_a(\ddagger)$ formulation becomes evident when an attempt is made to correct this approximate first estimate of δ for the substituent effect of the A^- moiety in the activated complex. A qualitative illustration of such a correction was given in the alkyl sulfate example above. Such corrections are easily made more quantitative (vide infra) since the major contributions to substituent effects on acid strength are well understood. The difficulty of formulating such a correction within the usual context of the identification of δ with β is demonstrated by the extreme rarity in the literature of even the simple recognition that such corrections might be important.

A More Rigorous Interpretation of $pK_a(\ddagger)$

The introduction of substituents into an activated complex is expected[9-11] to change the bond orders and bond lengths of the "reacting bonds"[9] which are present. That such changes can be significant is suggested by many experimental observations, including

the existence of substituent effects on kinetic isotope effects and the curvature commonly observed in various kinds of linear free energy plots. The protonation of a site in an activated complex is equivalent to a major change in substituent, and hence might lead to a large change in such bond orders, particularly if the atom being protonated participates directly in a reacting bond. It is, for example, frequently observed that the points for H_3O^+ and OH^- fall off of the Brønsted correlation lines for general-acid- and general-base-catalyzed reactions, particularly when those lines have been defined by much weaker acids or bases.

The definition (eq 5) of $pK_a(\ddagger)$ shows that this quantity depends on the properties of *two* activated complexes. Since those two species differ in that one is protonated and the other is not, the discussion in the preceding paragraph implies that they are likely to be characterized by two different values of the reacting bond order parameter, δ. The probable existence of such differences was not explicitly considered in our approximate discussions of the transition states for alkyl sulfate and benzyl fluoride hydrolyses given above.

An intuitively appealing interpretation of a δ value derived from a $pK_a(\ddagger)$ would be that it is a *mean* of the true δ values for the two activated complexes. Let us examine a class of reactions for which this intuitive interpretation can be proven to be correct. Consider a pair of activated complexes in each of which only one reacting bond is present; for example, suppose that an alkyl fluoride, RF, undergoes acid-catalyzed and uncatalyzed solvolyses, both by S_N1 mechanisms. Let $R^{\delta+}\cdots FH^{(1-\delta)+}$ represent the actual bonding in one activated complex and $R^{\delta'+}\cdots\cdots F^{\delta'-}$ represent the actual bonding in the other $(\delta' > \delta)$.[25] The process to which the measured $pK_a(\ddagger)$ value refers is then the diagonal in the following thermodynamic cycle (eq 24) in which the subscript on each equilibrium constant indicates the direction of the reaction for which that constant is written (i.e., K_{AC} is for A → C).

$$
\begin{array}{ccc}
R^{\delta+}\cdots FH^{(1-\delta)+} & \underset{\text{hypothetical}}{\overset{K_{AB}}{\rightleftharpoons}} & R^{\delta+}\cdots F^{\delta-} + H^+ \\
A & & B \\
\Big\Updownarrow K_{AC} \text{ observed} & \searrow K_a(\ddagger) & \Big\Updownarrow K_{BD} \\
R^{\delta'+}\cdots FH^{(1-\delta')+} & \underset{\text{hypothetical}}{\overset{K_{CD}}{\rightleftharpoons}} & R^{\delta'+}\cdots F^{\delta'-} + H^+ \\
C & & D
\end{array} \tag{24}
$$
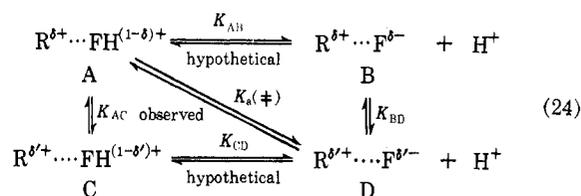
A sufficient condition for the validity of our intuitive interpretation of δ(obsd) as a mean of δ and δ' is that for each reaction the maximum in standard free energy, $G°$, occurs at the same point along the reaction coordinate as does the maximum in potential energy, E_0, which defines the transition state. Since A has been defined as the actual activated complex for the catalyzed path, the coincidence of $G°_{max}$ and $E_{0,max}$ re-

---

(24) *E.g.*, see ref 4b, Chapter 6.

(25) This ordering of the magnitudes of δ and δ' is incorporated into our symbology in eq 24 (by showing the reacting bond in structure A to be shorter than that in B) in anticipation of the conclusion of the following derivation.

quires A to have a higher $G°$ than does C (because C differs from A only in having a different reacting bond order and therefore also lies on the reaction coordinate). Similarly, D must have a higher $G°$ than does B. Therefore, $K_{AC} > 1$, $K_{BD} < 1$, and

$$pK_{CD} > pK_a(\neq) > pK_{AB} \qquad (25)$$

Thus the observed value of $pK_a(\neq)$ is a mean of the values which correspond to the two hypothetical pairs of mechanisms in which the reacting bond order is the same in both activated complexes. The relative weights of pK_{CD} and pK_{AB} in that mean will depend on the exact forms of the two $G°$ plots as functions of the reaction coordinates, but the important conclusion is that $pK_a(\neq)$ *and* δ *(obsd) are correctly interpreted as limits;* δ(obsd) *is an upper limit on bond breaking in* $R^{\delta+}\cdots FH^{(1-\delta)+}$ (i.e., $\delta < \delta$(obsd), *and a lower limit on bond breaking in* $R^{\delta+}\cdots\cdots F^{\delta'-}$ (*i.e.*, $\delta' > \delta$(obsd)).

The conclusion that $\delta' > \delta$ is of particular interest. Let us compare the argument by which we have obtained this conclusion to previous theories which lead to the same conclusion.[9,10] In general, this ordering of the δ values is a necessary consequence of the assumption that the transition states are the states of maximum standard free energy along their respective reaction coordinates. Our present argument may be expressed verbally as follows. In the derivation of eq 25, the assumption that A and D lie at maxima in $G°$ was shown to imply that A is a stronger acid than C ($pK_{AB} < pK_{CD}$); since the acidic site in A and C becomes less positively charged as the R–F bond length increases, it follows that the bond is shorter in A than in C. A parallel argument may be phrased in the context of Thornton's general discussion[10] of the structures of activated complexes as follows. The normal mode which corresponds to the reaction coordinate contains only one reacting bond; the basic end of that bond becomes less basic when it is protonated, so that such protonation makes stretching that reacting bond easier; therefore, by Thornton's rules 1, 2, and 4, that bond will be shorter when protonated. The assumption about the location of the maximum in standard free energy which we have pointed out above is implicit in Thornton's first rule.

If more than one reacting bond is present in an activated complex, the interpretation of $pK_a(\neq)$ is more complicated. In particular, arguments such as that which proved that $K_{AC} > 1$ in the preceding case are no longer generally true since the presence of a second variable reacting bond in C lifts the requirement that C lie on the reaction coordinate for the reaction in which A is the activated complex. In order to prove that the value of any bonding parameter derived from the observed value of $pK_a(\neq)$ does lie between the corresponding real values for the two activated complexes, additional assumptions must be introduced. For example, in an S_N2 activated complex, $X\cdots R\cdots Y$, if it is assumed that the total bond order is conserved

(*i.e.*, that X–R bond making has proceeded to the same extent as has R–Y bond breaking), then the observed value of $pK_a(\neq)$ for the dissociation of a proton from X, R, or Y can be shown to be a mean value in exactly the same sense as is that for an activated complex with a single reacting bond.

Even though it cannot be proven in the general case that $pK_a(\neq)$ and the structural parameters derived from it are correctly regarded as mean values, the weight of experimental evidence suggests strongly that such an interpretation is valid. We are not aware of any reaction for which mechanistic conclusions based on this interpretation of $pK_a(\neq)$ are inconsistent with conclusions based on other criteria which are commonly regarded as reliable. In some instances, it has been possible to subject this interpretation to direct experimental test; in systems involving more than one acidic proton it is sometimes possible to use successive $pK_a(\neq)$ values to estimate both upper and lower limits on the order of a reacting bond. One such reaction is the permanganate oxidation of fluoral hydrate to trifluoroacetic acid; this reaction occurs by four kinetically distinct paths differing formally only in the numbers of protons in the four activated complexes.[26] Application of the mean value interpretation of the three successive $pK_a(\neq)$ values for the parenthetical protons in the hydride-transfer activated complex

$$F_3C—\overset{\displaystyle O(H)}{\underset{\displaystyle O(H)}{\overset{|}{\underset{|}{C}}}}{}^{\delta+}\cdots H\cdots OMnO_3(H)^{\delta'-}$$
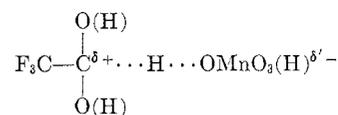
has been shown[27] to lead to the following conclusions. (a) The value of δ increases when each of the hydroxyl protons is removed from the fluoral hydrate. (b) For the dianionic activated complex (from $CF_3CH(OH)O^-$ + MnO_4^-), $0.38 > \delta > 0.29$; the calculated limits are in the correct order and differ by only 9% of a full bond. (c) The two independently estimated parameters, δ and δ', are approximately equal for the singly charged activated complex (observed mean values of 0.29 and 0.28, respectively), suggesting conservation of bond order to the hydride ion. These conclusions show that such interpretations of $pK_a(\neq)$ are, at the very least, highly internally consistent.

An Approach to a Quantitative Interpretation of $pK_a(\neq)$

The future importance of the $pK_a(\neq)$ method for characterizing the structures of activated complexes will depend on its success in assigning *quantitative* values to bonding parameters. In the preceding sections of this Account, we have given examples which illustrate the qualitative conclusions which can be deduced from observed values of $pK_a(\neq)$ and have demonstrated that the first approximations to quantitative bonding parameters which can be derived from

(26) R. Stewart and M. M. Mocek, *Can. J. Chem.*, **41**, 1160 (1963).
(27) J. L. Kurz, *J. Amer. Chem. Soc.*, **86**, 2229 (1964).

$pK_a(\ddagger)$ values are essentially identical with the values obtained *via* more common arguments based on linear free energy slopes.

Attempts to derive more accurate values for bonding parameters are subject to the limitations associated with the interpretation of δ as a mean value for the two activated complexes (*vide supra*). The quantitative significance of those limitations can be determined only through extensive application of the $pK_a(\ddagger)$ method of analysis to experimental data. The remainder of this Account will illustrate one such application by describing the current status of some of our attempts to apply this method to data for nucleophilic displacement reactions. Our purpose in this application has been dual; to seek detailed information about the mechanism of these reactions and to explore the range of validity of the $pK_a(\ddagger)$ approach.

Structure–Acidity Correlations. A key assumption which is implicit in the following discussion is that, for ionic reactions in solution, the bond order of a reacting bond is linearly related to the charges on the atoms which participate in that bond; *i.e.*, that bond cleavages in such reactions are perfectly heterolytic. This assumption allows us to deduce the orders of reacting bonds by using our knowledge of how changes in acidity are related to changes in the distribution of charge within an acid. Such field effects on the pK_a values of stable acids are well understood. Both empirical correlations[28,29] and direct electrostatic calculations[30] have been successful, and for many types of stable acids the uncertainty in a predicted value of pK_a is no more than a few tenths of a pK unit.

When such methods for predicting pK_a values are applied to activated complexes, a new complication arises; activated complexes have unusual geometries in the sense that bond lengths and angles which involve reacting bonds are often different from those present in the stable molecules for which the predictive techniques have been designed. In order to cope with this problem in our investigations of nucleophilic displacements on alkyl halides, we have adopted an empirical approach. The effect of a charge on the pK_a of an acid is well correlated with the distance between that charge and the acidic site by eq 26, where ΔpK_a

$$\log \Delta pK_a = 1.231 - 0.212 r_{rms} \qquad (26)$$

is the shift in pK_a (corrected for contributions from changes in symmetry) which results from introducing a charge on an atom at a root mean square distance (assuming free rotation), r_{rms}, from the atom which bears the acidic proton. The parameters in eq 26 are those which give the best fit for 15 dibasic acids
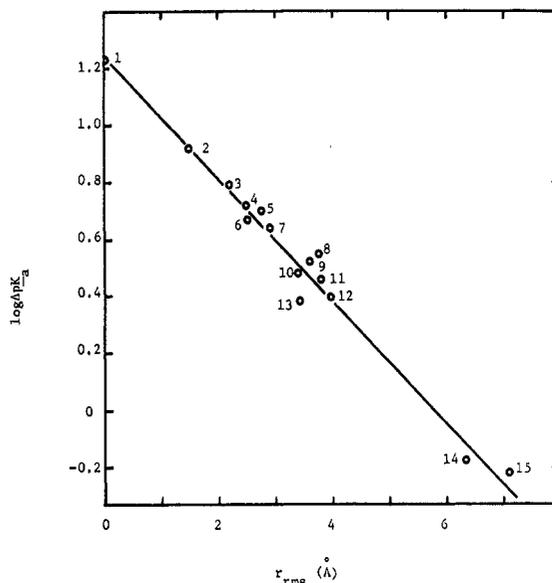

Figure 1. Log ΔpK_a (symmetry corrected) for dibasic acids as a function of r_{rms}. The line shown is that given by eq 26. Statistical parameters and definitions of symbols are given in the text. The points correspond to: (1) H_3O^+, (2) $NH_3{}^+NH_3{}^+$, (3) H_2CO_3, (4) $HN^+(CH_2CH_2)_3N^+H$, (5) H_2SeO_4, (6) H_3PO_4, (7) H_3AsO_4, (8) $H_2N^+(CH_2CH_2)_2N^+H_2$ (chair), (9) $H_2N_2O_2$, (10) *cis*-1,2-cyclohexanediammonium ion, (11) *trans*-1,2-cyclohexanediammonium ion (diaxial), (12) $H_3N^+CH_2CH_2N^+H_3$, (13) $(CO_2H)_2$, (14) $(CH_3)_3N^+C(CH_2CH_2)_3CCO_2H$ *vs.* $(CH_3)_2NC(CH_2CH_2)_3CCO_2H$, (15) $HO_2CC(CH_2CH_2)_3CCO_2H$.

(Figure 1); the standard deviations of the slope, the intercept, and a point from the line are, respectively, ± 0.04, ± 0.01, and ± 0.08 (corresponding to $\pm 20\%$ in ΔpK_a). Alternate definitions of r can lead to equally good correlations;[29] the one given here[31] was chosen for convenience of application to S_N2 activated complexes.

A similar empirical correlation between the acid-strengthening effect of a carbon–halogen bond dipole and the distance, orientation, and moment of that dipole is given by eq 27, where μ is the magnitude of

$$\log\left(\frac{\Delta pK_a}{\mu \cos \theta}\right) = 1.250 - 0.383r \qquad (27)$$

the dipole moment of the corresponding methyl halide, θ is the angle between the bond dipole and the line joining the midpoint of that dipole to the basic site (for carboxylic acids, the point on the axis of the adjacent C–C bond at a distance of 0.7 Å from the carbonyl carbon; for other acids, the atom bearing the ionizing proton)[30] in the extended conformation, and r is the distance between the midpoint of the dipole and the basic site in that same conformation. The extended conformation model was adopted in preference to the theoretically preferable one in which rms values or r and $\cos \theta$ are used because it gives an equally good correlation and avoids the difficult calculation of $\overline{\cos^2 \theta}$. The data upon which eq 27 is based are shown in Figure 2.

(28) *E.g.*, (a) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1941, Chapter 6; (b) J. C. McGowan, *J. Appl. Chem.*, **10**, 312 (1960).

(29) J. L. Kurz and J. I. Coburn, *J. Amer. Chem. Soc.*, **89**, 3528 (1967).

(30) *E.g.*, (a) F. H. Westheimer and M. W. Shookhoff, *ibid.*, **61**, 555 (1939); (b) C. Tanford, *ibid.*, **79**, 5348 (1957); (c) C. F. Wilcox, Jr., and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965); (d) H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **86**, 5188 (1964).

(31) J. C. Harris, Ph.D. Thesis, Department of Chemistry, Washington University, 1970.
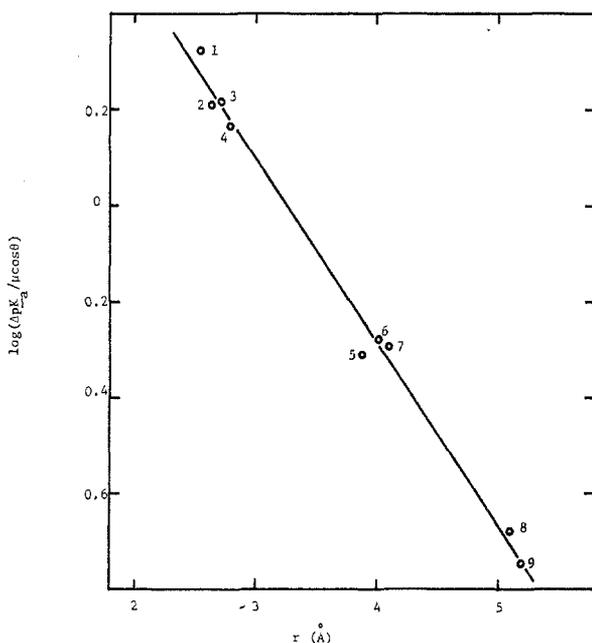
Figure 2. Log $(\Delta pK_a/\mu \cos \theta)$ for ω-halo straight-chain carboxylic acids as a function of r. The line shown is that of eq 27. Definitions of symbols are given in the text; standard deviations of slope, intercept, and a point from the line are ± 0.05, ± 0.01, and ± 0.04 (corresponding to $\pm 10\%$ in ΔpK_a). The points correspond to: (1) FCH_2CO_2H, (2) $ClCH_2CO_2H$, (3) $BrCH_2CO_2H$, (4) ICH_2CO_2H, (5) $ClCH_2CH_2CO_2H$, (6) $BrCH_2CH_2CO_2H$, (7) $ICH_2CH_2CO_2H$, (8) $ClCH_2CH_2CH_2CO_2H$, (9) $BrCH_2CH_2CH_2CO_2H$.

Equations 26 and 27 can be used directly to calculate substituent effects on $pK_a(\neq)$ for any geometry and charge distribution assumed for an activated complex. A procedure which we believe to be more accurate is to choose a stable acid which resembles the activated complex as closely as possible, measure the substituent effect (i.e., ΔpK_a) for that stable model, and then use that model ΔpK_a to estimate a correction to the value predicted by eq 26 and 27.

Methyl Halide Hydrolyses. Let us demonstrate the application of these methods by discussing the hydrolysis of a particularly simple substrate, CH_3Cl. Almost identical conclusions result from analogous analyses[31] of data for CH_3F, CH_3Br, and CH_3I. Literature values for k_1[32] and k_2[33] in eq 20a give, via eq 21a, $pK_a(\neq) = 11.7$ at 25° for the virtual ionization, eq 28, where δ

$$\begin{array}{c} H \\ \diagdown \\ O^{\delta+}\cdots CH_3^{(\delta'-\delta)+}\cdots Cl^{\delta'-} \rightleftharpoons H^+ + O^{(1-\delta)-}\cdots \\ \diagup \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad H \\ H \qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_3^{(\delta'-\delta)+}\cdots Cl^{\delta'-} \quad (28) \end{array}$$
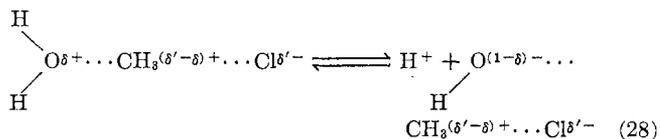
and δ' are mean values. However, k_1 and k_2 were measured at ionic strengths of, respectively, 0.1 and 0; estimation of activity coefficients from the Davies equation[15] gives a corrected value of $pK_a(\neq) = 11.9$.

Suppose that the mean activated complex was very product-like and had a structure near $H_2O^+-CH_3,Cl^-$.

In this limiting structure, the C–Cl bond length is that characteristic of zero covalent bond order and may be estimated from the equilibrium distance for the corresponding two-atom noble gas cluster ($r = 3.46$ Å for Ne, Ar).[34] The substituent effect of the Cl^- on $pK_a(\neq)$ will thus be that of a negative charge at a distance equal to 3.46 Å plus the O–C single bond length (1.47 Å). A rough estimate of $\Delta pK_a = 1.5$ can be obtained from eq 26. A more reliable estimate of $\Delta pK_a = 1.3$ results from correcting this rough value by using the value of $\Delta pK_a = 2.50$ (vs. 3.00 predicted by eq 26) for a charge at $r_{rms} = 3.54$ Å in a model compound[35] in which the charge is located on RS^- (isoelectronic with Cl^-). For this limiting product-like structure, we therefore predict $pK_a(\neq)$ to be equal to the pK_a of $CH_3OH_2^+$ (-2.2)[36] plus 1.3 (e.g., -0.9). It is thus clear that the mean activated complex does not resemble products.

Suppose that the mean activated complex was very reactant-like and had a structure near H_2O,CH_3Cl. For this limiting structure, the $pK_a(\neq)$ would be equal to $pK_a(H_2O)$, 15.7, plus a ΔpK_a arising from the CH_3Cl dipole moment. Assuming the O–C distance to be that of the Ne,Ne cluster (3.19 Å)[34] and using the observed relationship (eq 27) between ΔpK_a and the distance, orientation, and moment of a carbon–halogen dipole give $\Delta pK_a = -0.9$. For this limiting structure, we thus predict $pK_a(\neq) = 14.8$, just 2.9 pK units higher than the observed value.

The internal charge distribution in the mean activated complex must therefore be quite similar to that in the reactants, $H_2O + CH_3Cl$. In fact, only ca. 1% covalent overlap between the nucleophilic oxygen and the methyl carbon need be assumed in order to account for the observed value of $pK_a(\neq)$. Thus a bond order of 0.01 would imply, via Pauling's rule,[34] an O–C bond length of 2.6 Å which would, from eq 27, imply a substituent effect from the CH_3Cl dipole of -3.5 pK units. The positive charge of 0.01 protonic unit transferred to the H_2O would add a ΔpK_a given approximately by $0.01(pK_a(CH_3OH_2^+) - pK_a(H_2O))$ $= -0.18$. Our assumption of $\delta = 0.01$ thus predicts $pK_a(\neq) = 12.0$ in agreement with the observed value of 11.9. A more cautious interpretation would be that, since $\delta = 0.01$ is expected to lie between the correct δ values for the two activated complexes in eq 28, in at least one of those activated complexes there is no more than 1% nucleophile–substrate bond formation.

In the preceding discussion, it has been assumed that bond making and bond breaking occur synchronously so that the total bond order to the CH_3 group is conserved (i.e., that $\delta = \delta'$). Unfortunately, the observed value of $pK_a(\neq)$ does not distinguish between that model and one in which bond breaking precedes bond making so that the CH_3 bears a full positive charge

(32) R. E. Robertson, Progr. Phys. Org. Chem., **4**, 213 (1967).
(33) E. A. Moelwyn-Hughes, Proc. Roy. Soc., Ser. A, **196**, 540 (1949).

(34) Reference 4a, Chapter 4.
(35) J. L. Kurz and J. C. Harris, J. Org. Chem., **35**, 3086 (1970).
(36) E. M. Arnett, Progr. Phys. Org. Chem., **1**, 223 (1963).

in the rate-determining transition state. Such a carbonium ion type activated complex (H_2O,CH_3^+,Cl^-) is required either by a classical S_N1 mechanism or by Sneen's ion-pair mechanism for S_N2 reactions.[37,38] In such an activated complex, the ΔpK_a's arising from the CH_3^+ at the Ne,Ne distance and the Cl^- at twice that distance are predicted by eq 26 to be, respectively, -3.6 and $+0.7$. The predicted $pK_a(\ddagger)$ is thus 12.8, which could easily be made to match the observed value by making small adjustments in bond lengths.

This question of the charge on the central carbon must be answered before we can claim to have any significantly detailed knowledge of the mechanism of nucleophilic displacement reactions. It can be answered through the expedient of placing an acidic group on that carbon. Thus for the hydrolysis of chloroacetic acid, the activated complex has the general structure

$$
\begin{array}{c}
\quad\quad CO_2(H) \\
H \quad | \\
(H)O\cdots CH_3 \cdots Cl \\
\delta + \quad (\delta'-\delta)+ \quad \delta' -
\end{array}
$$
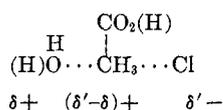
and contains *two* dissociable protons (shown in parentheses).[39] The carboxyl proton is particularly sensitive to the magnitude of the difference, $\delta - \delta'$. The carboxyl proton also has the advantage that the atom to which it is bonded does not participate in any reacting bond, so that structural differences between the two activated complexes should be minimized and the calculated δ should be a good approximation to the correct δ for both activated complexes. The presence of two dissociable protons has yet a further virtue: it allows us to check for errors arising from our mean

value assumption. Accordingly, in order to test the validity of our assumption that the mean structure deduced from the $pK_a(\ddagger)$ of the H_2O moiety is not far from the correct structures corresponding to attack by H_2O and by OH^-, we can deduce *two* mean structures from the $pK_a(\ddagger)$ values for ionization of the CO_2H group: one from ionization of CO_2H when H_2O is the nucleophile and a second, independent structure from ionization of CO_2H when OH^- is the nucleophile.

It has been shown[37] for such haloacetate substrates that: (a) the $pK_a(\ddagger)$'s for CO_2H ionization imply $\delta - \delta' \approx 0$ for attack of both H_2O and OH^-; (b) the $pK_a(\ddagger)$'s for H_2O ionization imply $\delta \approx 0$ for attack on both $XCH_2CO_2^-$ and XCH_2CO_2H.

This recurring conclusion that the internal charge distribution in activated complexes for hydrolysis of alkyl halides and related compounds is essentially unchanged from that present in the reactants strongly suggests that the rate-determining process for such reactions is a change in *solvent configuration* rather than a change in internal structure. Similar proposals have been made in the past[32,33,40] but appear not to have been generally accepted.

One of the possible extensions of the $pK_a(\ddagger)$ method could be to attempt to investigate the role of the solvent in such reactions by measuring ΔS°, ΔV°, and ΔC_p° for the ionization of activated complexes. The corresponding parameters for the ionization of stable acids are commonly interpreted in terms of the behavior of the medium. The available data are too sparse to allow such an approach to be tested at present, and, in closing, a word of caution may be in order. Since extrema in G° do *not* generally coincide with extrema in S°, V°, or C_p°, application of the mean value assumption to these parameters would be significantly more speculative than was its application to $pK_a(\ddagger)$.

(37) J. L. Kurz and J. C. Harris, *J. Amer. Chem. Soc.*, 92, 4117 (1970).

(38) R. A. Sneen and J. W. Larsen, *ibid.*, 91, 6031 (1969).

(39) It is here assumed that there is no participation by the carboxylate group in the uncatalyzed hydrolysis of $ClCH_2CO_2^-$. This assumption is supported by the large difference between the values of $\Delta S^{\ddagger}$ observed for these haloacetate hydrolyses and those observed for halopropionate hydrolyses in which such participation is well established (*e.g.*, J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, pp 142–144). For example, consider the following $\Delta S^{\ddagger}$ values for hydrolysis: $ClCH_2CO_2^-$, $\Delta S^{\ddagger} = -10$ eu and $BrCH_2CO_2^-$, $\Delta S^{\ddagger} = -11$ eu (both negative); however, $BrCH(CH_3)CO_2^-$, $\Delta S^{\ddagger} = 11$ eu (positive).[31]

(40) C. D. Ritchie, G. A. Skinner, and V. G. Badding, *J. Amer. Chem. Soc.*, 89, 2063 (1967).