stants is $-(5.20 \pm 0.18) \times 10^3$, in good agreement with the calorimetric prediction.

Estimation of ΔC_p. The values of ΔH_h for 0.5 and 24.9° derived above imply an average value of ΔC_p for that interval of -10 ± 5 cal/mole deg. The uncertainty in this number was estimated from the known 90% confidence limits for ϵ_0, $(x\Delta H_h)_{0.5°}$ and $(x\Delta H_h)_{24.9°}$, and from the larger value for the uncertainty in ϵ_∞ discussed above. Errors in temperature were assumed negligible. If the error in ϵ_∞ is also assumed negligible, the 90% confidence interval for the average value of ΔC_p becomes 10 ± 4 cal/mole deg. The uncertainty in ΔC_p is appreciably smaller than the individual uncertainties in the two values of ΔH_h might at first suggest. This is due to the cancellation of a large part of the uncertainty in ΔH_h which arises from the uncertainty in ϵ_0 when the difference is taken. If the calorimetric data of Bell and Clunie[15] are combined with the values of K_h found in this work, the resulting value of ΔC_p is -9 cal/mole deg.

This value of ΔC_p clearly implies that the net contribution of solvation changes to ΔC_p for the hydration is small. The assumption made by Kohnstam[1] that the contribution to $\Delta C_p^{\ddagger}$ arising from covalent binding of the elements of water into an activated complex will be significantly smaller than the corresponding contribution to $\Delta S^{\ddagger}$ thus now has experimental support for reactions occurring in pure water as solvent. The failure of his mechanistic criterion for reactions in that solvent must therefore be due to large effects on $\Delta C_p^{\ddagger}$ and/or $\Delta S^{\ddagger}$ arising from solvation changes associated with charge separation rather than to any peculiar effects associated with covalent bond formation.

The calorimetric data also imply that for the solution of unhydrated CH_3CHO in water, $\Delta C_p = +20 \pm 3$ cal/mole deg. The data of Bell and Clunie imply $\Delta C_p = +13$ cal/mole deg. These positive values are about what would be anticipated for solution of a low molecular weight uncharged solute in water.

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The Hydration of Acetaldehyde.
II. Transition-State Characterization

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Abstract: Kinetic data on the hydrogen ion, hydroxide ion, and water-catalyzed hydration of acetaldehyde in aqueous solution have been analyzed by the $pK_a^{\ddagger}$ method and the following inferences drawn. The hydronium ion catalyzed reaction does not proceed *via* a mechanism involving rate-determining carbon–oxygen bond formation; it thus presumably involves rate-determining proton transfer. The data are consistent with a concerted mechanism for the other two catalytic paths in which the transition state is defined by rate-determining carbon–oxygen bond formation and all protons lie at potential minima. Assuming that the transition state for the hydroxide-catalyzed path has structure I, there are two approximately equally stable structures for the water-catalyzed transition state: II and III. (Hydrogen-bonded water molecules are omitted from all these structures.) The most probable average value of δ in the hydroxide- and water-catalyzed transition states lies between 0.5 and 0.6. The water-catalyzed transition state contains at least two strongly hydrogen-bonded water molecules (*i.e.*, this reaction probably proceeds *via* a push–pull mechanism), but the positions of the protons in the hydrogen bonds remain such that the charge distribution in the transition state closely approximates that shown in II and III.

The formally "uncatalyzed" or water-catalyzed hydration of acetaldehye

$$CH_3CHO + H_2O \longrightarrow CH_3CH(OH)_2$$

is in many ways analogous to the uncatalyzed hydrolysis of carboxylate esters, which is currently under investigation in these laboratories. Both show large solvent isotope effects ($k_{H_2O}/k_{D_2O} = 3.6$ for acetaldehyde dehydration at 0°,[1] and 3.8 for ethyl trichloroacetate hydrolysis at 20° [2]), both have very low entropies of activation [$\Delta S^{\ddagger} =$ *ca.* -38 eu for acetaldehyde hydration (Tables I and II) and -43 eu for ethyl trichloroacetate hydrolysis[2]], both involve addition of water to a carbonyl group, and both additions are subject to acid and base catalysis. Since the transition states for the hydronium ion, hydroxide ion, and water-catalyzed hydration reactions differ stoichiometrically only in the numbers of protons and water molecules which they contain, it should be possible to characterize these transition states by the $pK_a^{\ddagger}$ approach.[3] Such an analysis for the aldehyde transition state should be simpler than that for the ester transition state, since there is one less oxygen atom which could serve as a site for protonation, and hence was attempted first.

The pseudo-first-order rate constant for acetaldehyde hydration in an aqueous solution containing the acidic

$$k = k_0 + k_H[H^+] + k_{OH}[OH^-] + k_{HA}[HA] + k_A[A^-] \qquad (1)$$

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(1) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

(2) J. L. Kurz and M. E. DeBlois, unpublished observations.

(3) J. L. Kurz, *J. Am. Chem. Soc.*, 85, 987 (1963).

Table I. Rate Constants for the Catalyzed Hydration of Acetaldehyde

Temp, °C	k_H,[a] M^{-1} sec^{-1}	10^3k_0,[a] sec^{-1}	$10^{-4}k_{OH}$,[a] M^{-1} sec^{-1}	Ref
0.0	115 (A)	1.7 (E)	0.97 (K)	*b, g*
0.0	131 (B)			*c, g*
0.3	125 (C)	2.3 (F)		*d*
0.4		2.1 (G)	0.59 (L)	*e*
25.0	930 (D)	7.9 (H)	8 (M)	*f*
24.8		9.1 (I)		*d*
25.1		9.0 (J)	2.65 (N)	*e*

[a] The letters in parentheses will be used to indicate the particular values of k taken for subsequent calculations. [b] Reference 4. [c] Reference 5a. [d] Reference 38. [e] This work. [f] Reference 15. [g] To facilitate comparison with other results, the values of k quoted in these sources have been multiplied by ln 10.

Table II. Activation Parameters for Acetaldehyde Hydration[a]

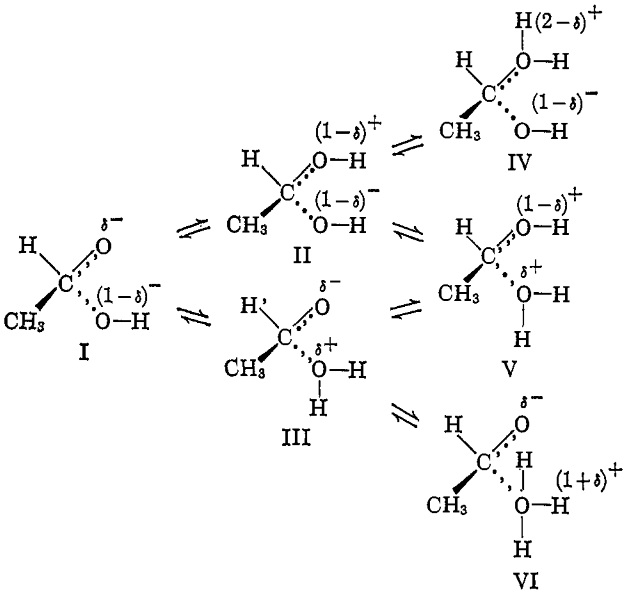
Catalyst	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu
Hydronium ion	12.1 (B, D)	−4
Water	9.4 (E, H)	−37
	8.5 (F, I)	−39
	8.9 (G, J)	−38
Hydroxide ion	13.1 (K, M)	+8
	9.3 (L, N)	−7

[a] Values of rate constants used in calculating $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are indicated by parentheses which refer to the data in Table I.

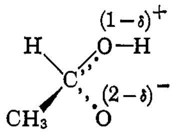
and basic species, HA and A^-, may be expressed as in eq 1. Bell and Darwent[4] concluded that the rate-determining steps in the mechanisms corresponding to the terms in eq 1 must be termolecular, involving the addition of water to the carbonyl group with the concerted transfer of a proton to or from the catalyzing base or acid. Most subsequent investigators[5–8] have also favored such a concerted mechanism. However, simple rate-determining proton transfer to either acetaldehyde itself[9] or an acetaldehyde–water adduct formed in a prior equilibrium step[1] also has been proposed, and such a mechanism cannot be excluded on the basis of any available evidence.

According to the "solvation rule" recently proposed by Swain, Kuhn, and Schowen,[10] if the rate-determining step in a reaction involves the formation of a bond to carbon, then any proton whose transfer between oxygen atoms accompanies reaction must lie in a stable potential at the transition state for that step. According to this rule, there are thus two distinct possible mechanisms for each term in eq 1. The mechanism could be either rate-determining proton transfer with the carbon–oxygen bond between the nucleophile and the carbonyl carbon remaining either completely formed or completely broken, or a concerted mechanism in which the carbon–oxygen bond is only partially formed at the transition state and translation of the proton being transferred does not contribute to motion along the reaction coordinate through the transition state.

Unhydrated Transition-State Configuration. First, let it be assumed that the concerted mechanism is correct. Then for the pathways corresponding to k_0, k_H, and k_{OH} in eq 1, if hydrogen-bonded water molecules are excluded from consideration, the number of possible transition-state configurations which must be examined is small. For k_{OH}, only one unhydrated structure, I, is acceptable.



The alternative possible structure VII corresponds to the transition state which would result from attack of oxide ion on protonated acetaldehyde. Such a path for its formation can be excluded, since it can be shown to require a rate constant many orders of magnitude greater than the encounter-controlled limit. However, as pointed out by Swain and Worosz[11] for a similar case, such an argument does not rigorously exclude the structure as a possible transition state since it might be formed *via* a different path. Nevertheless, structure VII, *per se*, can be ruled out by the following argument. In both I and VII, translation along the reaction coordinate through the transition state corresponds to forming the C···O bond. Since this is assumed to be the rate-determining process, I and VII must each correspond (for some value of δ) to the transition state which would be present if the indicated proton distribution were correct; neither could lie off of the corresponding reaction coordinate. The value of δ would in general be different in each of these two possible transition states; however, the oxygen atom bearing the $(2-\delta)^-$ charge in VII would be more basic than the former carbonyl oxygen in I, which bears a δ^- charge, for all pairs of δ values except when both δ's are unity, in which case I and VII are identical. A transition state with the proton distribution of VII would thus



VII

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[4] R. P. Bell and B. deB. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950).

[5] (a) R. P. Bell and J. C. Clunie, *Proc. Roy. Soc.* (London), **A212**, 33 (1952); (b) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

[6] M. Eigen, *Angew. Chem.*, **75**, 489 (1963).

[7] M. L. Ahrens and H. Strehlow, *Discussions Faraday Soc.*, **39**, 112 (1965).

[8] H. H. Huang, R. R. Robinson, and F. A. Long, *J. Am. Chem. Soc.*, **88**, 1866 (1966).

[9] R. Gibert, *J. Chim. Phys.*, **51**, 372 (1954).

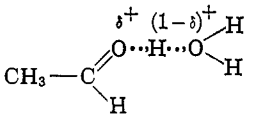
[10] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, **87**, 1553 (1965).

[11] C. G. Swain and J. C. Worosz, *Tetrahedron Letters*, 3199 (1965).

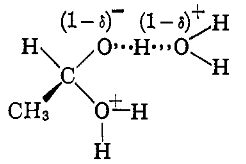
always have a higher standard free energy than one with structure I in which the proton is on the other oxygen, and hence could not be the transition state through which the majority of reactants passed.

The unhydrated structures of the possible transition states corresponding to k_0 and k_H may now be written by adding one or two protons, respectively, to I. This gives rise to two possible structures, II and III, corresponding to k_0, and three possible structures, IV, V, and VI, corresponding to k_H. Structures IV and VI can be ruled out by thermodynamic stability arguments analogous to that used to exclude VII. Structure V therefore represents the most stable proton distribution for an unhydrated, concerted transition state corresponding to k_H. Unfortunately, no such argument can be used to rule out either member of the pair of possible transition states for k_0; if the transition state resembles products (δ large), II will be more stable, while if it resembles reactants (δ small), III will be more stable.

If proton transfer, rather than carbon–oxygen bond formation, were rate determining, a different set of possible transition-state structures would have to be considered. This type of mechanism has been suggested specifically for the acid-catalyzed hydration,[1,9] and two possible rate-determining transition states corresponding to such a mechanism for k_H are VIII and IX.



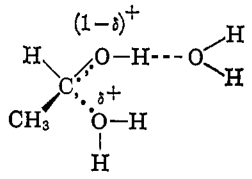
VIII



IX

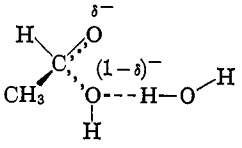
Hydrated Transition-State Configuration. Recent workers[5b,6–8,12] have tended to favor mechanisms, frequently cyclic, in which one or more water molecules act as acids or bases in addition to the catalyst appearing explicitly in the rate law. However, Bell and Clunie[5a] had earlier applied Swain's[13] argument to show such push–pull mechanisms[14] to be unlikely for these reactions; if it is assumed that the relative catalytic effectiveness of any two acids is independent of the base with which they are paired in the push–pull mechanism, then it can be predicted that a term in [HOAc][OAc$^-$] should be easily observable, and it is not. This assumption of independence has since been shown to be valid for at least one general-acid- and -base-catalyzed reaction, the enolization of acetone.[3]

Whether or not a cyclic push–pull mechanism is followed, strong hydrogen bonding of water molecules to the unhydrated transition-state structures shown above appears to be probable. The observed value of log k_H is within 0.2 of the value predicted by the Brønsted correlation based on catalysis by carboxylic acids and phenols.[15] This observation suggests that catalysis by hydronium ion follows a mechanism closely analogous to that followed when weaker acids act as catalysts, and thus that the H_2O moiety present in H_3O^+ must be included in the transition state. If proton transfer is rate determining, then structure VIII or IX would meet this requirement. However, if the concerted mechanism is correct, a water molecule would have to be added to V, giving Va.[16]

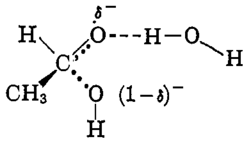


Va

Similarly, the observed value of log k_{OH} lies close to the Brønsted line defined by the carboxylate and phenolate anions. However, the scatter in the defining points is sufficiently large that such agreement might be fortuitous. If the agreement were real, it would suggest a mechanism for hydroxide which was analogous to that followed by the weaker bases and thus that a water molecule was bound into the activated complex to give a structure such as Ia or Ib.



Ia



Ib

For the water-catalyzed term, the observed value of log k_0 is 1.6 units higher than predicted by the general acid Brønsted correlation.[15] It also appears to be more than 2 units higher than the value predicted by the general base Brønsted correlation; again, however, the scatter in that plot makes this conclusion uncertain. This high catalytic activity of the water implies a special mechanism, differing in some major respect from that followed by other acids and bases. This implication, when combined with the abnormally low value of $\Delta S^{\ddagger}$ for k_0 (discussed below), suggests that the mechanism for k_0 involves the rearrangement of a comparatively large number of water molecules from the solvent structure which is normal in the vicinity of an acetaldehyde molecule into a more ordered structure. Any such highly ordered structure which would lead to the observed rate increase should involve both the carbonyl oxygen and the attacking water molecule in strong hydrogen bonds, *i.e.*, the mechanism would be push–pull with two water molecules acting as acid and base in cooperation with an uncertain number of other waters in a restructured solvent shell. Such structures, corresponding to the unhydrated structures II and III, are shown as IIa and IIIa. Only the two waters acting as acid and base catalysts are shown; a third water could be included in either structure by using it to bridge the first two and complete the ring to give the transition state for an Eigen-type[6,12] mechanism.

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(12) M. Eigen, *Discussions Faraday Soc.*, **39**, 7 (1965).

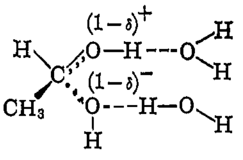
(13) C. G. Swain, *J. Am. Chem. Soc.*, **72**, 4578 (1950).

(14) In this paper, the term *push–pull* will be used to denote mechanisms in which both an acid and a base are present in the transition state, while the term *concerted* (which often has been used as a synonym for push–pull) is meant only to designate that strong hydrogen bonding to the acid or base catalyst is present in a transition state for which progress along the reaction coordinate corresponds to making a carbon–oxygen bond.

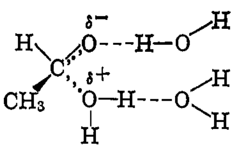
(15) (a) R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956); (b) R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc.* (London), **A197**, 141 (1949).

(16) In this and later structures, the convention will be adopted that a *dotted* line represents a "reacting bond"[17] while a *dashed* line represents a hydrogen bond in which the proton must[10] lie in a potential minimum.

(17) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 817 (1962).



IIa



IIIa

Transition-State Characterization

Transition-State Acidities. In terms of the constants defined in eq 1, it may be shown[3] that the two successive values of $pK_a^{\ddagger}$ (for the ionization of the hydrogen ion catalyzed transition state to give the uncatalyzed transition state and the ionization of the latter to give the hydroxide-catalyzed transition state) are given by eq 2 and 3. The values of these two virtual dissociation

$$pK_1^{\ddagger} = \log (k_H/k_0) \qquad (2)$$

$$pK_2^{\ddagger} = \log (k_0/k_{OH}) + pK_w \qquad (3)$$

constants at 25° are given in Table III. It may be noted that, although the observed values of k_0, k_H, and k_{OH} are sums of the corresponding constants for the forward and reverse reaction, the ratios of these observed constants appearing in eq 2 and 3 must be equal to the corresponding ratios for either the forward or reverse reaction alone.

Table III. Thermodynamic Parameters for Proton Dissociation from the Transition States

Dissoc	$pK_a^{\ddagger}$,[a,b] 25.0°	$\Delta H°$,[c] kcal/mole	$\Delta S°$, eu
pK_1	5.1 (D, H)	−2.7 (E, H–B, D)	−33
	5.0 (D, I)	−3.6 (F, I–B, D)	−35
	5.0 (D, J)	−3.2 (G, J–B, D)	−34
pK_2	7.0 (H, M)	17 (K, M–E, H)	+26
	7.5 (I, N)	14 (L, N–F, I)	+13
	7.5 (J, N)	14 (L, N–G, J)	+12

[a] Values of rate constants used in calculating $pK_a^{\ddagger}$ are indicated by parentheses which refer to the data in Table I. [b] All rate constants were corrected to 25.0°. [c] The parentheses designate the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table II) used to calculated each $\Delta H°$ and $\Delta S°$.

Method of Estimation of Bonding in the Transition State. If the mechanisms for k_H, k_0, and k_{OH} all involved rate-determining proton transfer, it can be shown that the $pK_a^{\ddagger}$ approach[3] to the characterization of the transition state would be equivalent to the interpretation[18] of the Brønsted slope in terms of the extent of proton transfer in the transition state. If the two members of either pair of observed rate constants used to calculate a value of $pK_a^{\ddagger}$ did not correspond to mechanisms with the same rate-determining step, then no interpretation of that $pK_a^{\ddagger}$ in terms of bond formation in the transition states could be made. For example, if the rate-determining transition state corresponding to k_H were VIII or IX (proton transfer) while that corresponding to k_0 were II or III (C···O bond formation), then the two transition states would have different reacting bonds, and no unique interpretation of $pK_1^{\ddagger}$ in terms of parameters characterizing the two independent sets of reacting bonds would be possible.

If it is assumed that the concerted mechanism is correct for all three terms, then $pK_1^{\ddagger}$ and $pK_2^{\ddagger}$ can be used to estimate the extent of carbon–oxygen bond formation in the three transition states. For each possible conjugate acid–base pair of transition states, the value of $pK_a^{\ddagger}$ may be estimated for the two limiting cases of 100 and 0% displacement along the reaction coordinate. In order to obtain an expression for the value of $pK_a^{\ddagger}$ at intermediate displacements as a function of that displacement, an electrostatic model for the transition state will be used. Charges will be assigned to the various atoms in the activated complex in terms of its fractional displacement, δ, along the reaction coordinate from the reactant or intermediate just preceding the transition state to the first product following it.

For the atom bearing the proton to whose ionization $pK_a^{\ddagger}$ refers, δ will measure the magnitude of the difference in formal charge between the transition state and the reactants. In order to assign charges to other atoms in the activated complex, it is necessary to make specific assumptions about bonding. It will be assumed here that in an addition reaction, the atom being attacked has the same total bond order in the transition state as in the reactants. For example, if a neutral nucleophile, N, adds to a carbonyl group and the fraction of N–carbon bond formation in the transition state is δ, the charge distribution (relative to the reactants) will be assumed to be $+\delta$ protonic charge units on N, $-\delta$ on the carbonyl oxygen, and zero on the carbonyl carbon. The value of δ may thus be taken, not only as a measure of σ bond making between the carbonyl carbon and the nucleophile, but also of the fraction of π bond breaking in the carbonyl group.

This assumption of conservation of bond order is analogous to Johnston's assumption in his treatment of hydrogen-transfer reactions.[19] If it fails slightly for attack at carbon, the error in the final calculation of δ for the reaction considered here should be small, since the *total* magnitude of the effect on $pK_a^{\ddagger}$ of a *full* unit charge at the position for which this assumption is invoked is *ca.* 5 pK units out of a total range of *ca.* 15–20 units.

In terms of this model, the value of $pK_a^{\ddagger}$ calculated from the observed rate constants may be set equal to the value of pK_a for either of the limiting cases, $\delta = 1$ or $\delta = 0$, plus a sum of correction terms which are functions of δ. The resulting equation may then be solved for δ. Because of the special assumptions about hydrogen bonding of water molecules to the various transition states under consideration here, it is necessary also to include a term for the effect of that hydrogen bonding on $pK_a^{\ddagger}$. The complete equation may be written in the form

$$pK_a^{\ddagger} = pK_a(\delta = 0) + \Delta pK_h \Delta m + \Sigma(z_i - z_i(\delta = 0))\Delta pK_i(z = 1) \qquad (4)$$

where $pK_a(\delta = 0)$ is the pK_a of the reactant species in the potential minimum just preceding the transition state, Δm is the difference between the number of water molecules strongly hydrogen bonded to the acid form of the transition state and the corresponding number for the conjugate base transition state, and ΔpK_h is the average change in $pK_a^{\ddagger}$ per water molecule lost on ionization. The summation is taken over all formal

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(18) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 238.

(19) H. S. Johnston, *Advan. Chem. Phys.*, 3, 140 (1961).

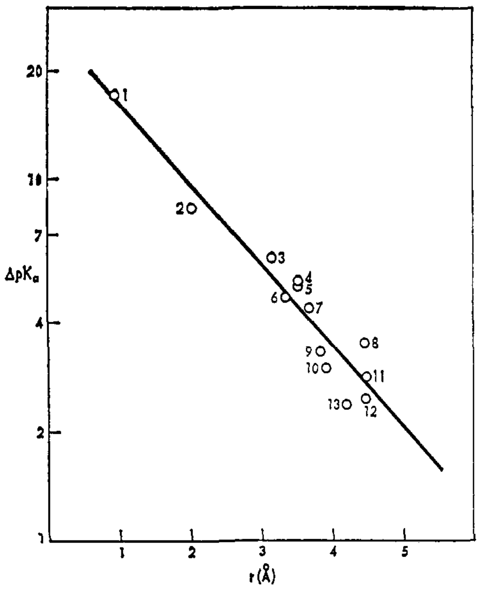

Figure 1. Log ΔpK_a (symmetry corrected) for dibasic acids as a function of r, the extended conformation distance between the second proton and the atom from which the first proton dissociates. The line is the linear least-squares line of best fit. The points are for: (1) H_3O^+, (2) $N_2H_6^{2+}$, (3) H_2CO_3 (corrected for hydration equilibrium), (4) $HN^+(CH_2CH_2)_3NH^+$, (5) H_2SeO_3, (6) H_3PO_4, (7) H_3AsO_4, (8) $H_2N^+(CH_2CH_2)_2NH_2^+$, (9) $H_2N_2O_2$, (10) *cis*-1,2-cyclohexanediammonium ion, (11) *trans*-1,2-cyclohexanediammonium ion, (12) $H_3N^+CH_2CH_2NH_3^+$, and (13) $(CO_2H)_2$.

charges in the activated complex; $z_i - z_i(\delta = 0)$ is the difference, in protonic units, between the charge on an atom in the transition state and the charge on the same atom in the species to which $pK_a(\delta = 0)$ refers, and $\Delta pK_i(z = 1)$ is the shift in $pK_a{}^{\ddagger}$ which would arise from placing a unit positive charge on the atom in question. When estimating the value of $\Delta pK_i(z = 1)$, it is convenient to include the effect of any substituent group (absent at $\delta = 0$ but present at $\delta = 1$) whose introduction produces the change in charge in question. This, however, does introduce the further assumption that coulombic and noncolumbic substituent effects vary with δ in the same way.

In previous applications[3,20] of $pK_a{}^{\ddagger}$ to the estimation of δ, a more simple approach was used: pK_a values were estimated for $\delta = 0$ and $\delta = 1$, and a first approximation to δ was estimated by linear interpolation of the observed value of $pK_a{}^{\ddagger}$ between those limits, after correction for symmetry differences. A correction for the effect of charges present in the activated complex but not present in either limit was then made by using this first approximation to δ to estimate those charges. Changes in the value of δ were not significant after one iteration of this procedure. In the present example, use of eq 4 was found to be preferable due to the large charge correction and to its more convenient inclusion of hydration and symmetry effects. [Since the symmetry contribution to $pK_a{}^{\ddagger}$ will not vary with δ, such effects need be included only in the estimation of $pK_a(\delta = 0)$.]

Method of Estimation of $\Delta pK(z = 1)$. In the activated complexes under consideration here, there are two atoms which bear charges: the oxygen of the nucleophile and the carbonyl oxygen. The effect on $pK_a{}^{\ddagger}$ of a unit positive charge being placed on the atom which bears the proton to whose ionization $pK_a{}^{\ddagger}$ refers may be estimated from the known pK_a values for model compounds. The choice of models becomes more difficult when the charge whose effect is sought lies on the other oxygen. Model compounds with the same charge–proton distance, steric factors, etc., are usually not available. In previous applications, the one closest analog was chosen as a model. Except when that model is unusually close in structure to the transition state, the following procedure is probably more reliable.

For dibasic acids in which the protons are located on oxygen or nitrogen and the interprotonic distance is less than about 5 A, it is found empirically that the value of ΔpK_a is given by eq 5 with a standard deviation of a single point from the line of 0.45 pK unit. In this equation, r is the extended-chain distance in the monodissociated acid between the second proton and the center of the atom which bore the first proton, while ΔpK_a is the observed value of $pK_2 - pK_1$ after correction for symmetry effects. This correlation and the acids used in establishing it are shown in Figure 1.

$$\log \Delta pK_a = 1.438 - 0.223r \qquad (5)$$

The acids used to establish this correlation cover a range of r values (1–4.5 A) which includes those of interest in most transition states. In the present calculation, the distance between the proton to which $pK_a{}^{\ddagger}$ refers and the charged oxygen atom whose effect on pK_a is being estimated will vary with δ. To estimate this r as a function of δ, all bond angles were assumed to be tetrahedral. The length of the former carbon–oxygen double bond was assumed to vary linearly with δ between the limits of 1.21 A (its value in acetaldehyde) and 1.43 A (its value in methanol). The length of the bond being formed between the nucleophilic oxygen and the carbonyl carbon was estimated by extrapolation of the Pauling bond order–bond length relation[21] in the form

$$D(\delta) = 1.43 - 0.7 \log \delta$$

The oxygen–hydrogen bond length was taken as 0.96 A. From these assumptions, together with an assumed extended conformation of the HOCO sequence in the transition state, it follows that any reasonable choice of δ leads to an r which corresponds to the same value of ΔpK (within the uncertainty of eq 5). For $0.2 < \delta < 1.0$, that equation predicts that $\Delta pK(z = 1) = -5.2 \pm 0.3$, and that value has been used in all calculations of $pK_a{}^{\ddagger}$.

Estimation of ΔpK_h. Since it has been assumed that the transition state for the uncatalyzed hydration of acetaldehyde is more strongly hydrogen bonded to solvent than those for hydronium or hydroxide ion catalysis, and since this difference is not compensated for in the models used to estimate the other terms in eq 4, the $\Delta pK_h \Delta m$ term must be introduced explicitly. Each of the virtual equilibria between the possible transition states for the three reactions may be reformulated as the sum of the corresponding equilibrium involving the unhydrated structures and steps for forming the hydrogen bonds to the activated complexes involved. Thus if m_V and m_{II} were the numbers of water

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(20) J. L. Kurz, *J. Am. Chem. Soc.*, **86**, 2229 (1964).

(21) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 239.

molecules strongly hydrogen bonded to structures V and II, then the equilibrium between the hydrated structures would have the form

$$\mathrm{V}\cdot m_{\mathrm{V}}\mathrm{H_2O} \longrightarrow \mathrm{II}\cdot m_{\mathrm{II}}\mathrm{H_2O} + \Delta m\mathrm{H_2O} + \mathrm{H^+}$$

which is the sum of

$$\mathrm{V} \longrightarrow \mathrm{II} + \mathrm{H^+}$$

and

$$\mathrm{V}\cdot m_{\mathrm{V}}\mathrm{H_2O} + \mathrm{II} \longrightarrow \mathrm{II}\cdot m_{\mathrm{II}}\mathrm{H_2O} + \mathrm{V} + \Delta m\mathrm{H_2O}$$

where $\Delta m = m_{\mathrm{II}} - m_{\mathrm{V}}$.

The magnitude to be expected for the shift in $\mathrm{p}K_a^{\ddagger}$ arising from the hydration equilibrium may be estimated from the known equilibrium constants for hydrogen-bond formation between stable species. Since hydrogen-bonding equilibria in aqueous solution are really *transfer* reactions in which a hydrogen bond between two water molecules is broken for each one formed between a water molecule and the substrate, one might expect the value of $\Delta F°$ for simple hydrogen-bond formation to be near zero. That such is generally the case is suggested by the available data. Thus for formic acid dimerization, the association constant is 1.5 at 25°[22] while the constant for association of fluoride ion with HF is 3.9.[23] That the value of $\Delta F°$ resulting from the assumed solvent reorganization is also near zero is suggested by the thermodynamic parameters observed for hydrophobic bond formation.[22,24] Since the hydrogen bond in bifluoride ion is the shortest known and also has the largest known formation constant, it will be assumed that $-\log 3.9$ may be taken as an estimate of an upper limit on $\Delta \mathrm{p}K_h$. This value will be used for $\Delta \mathrm{p}K_h$ in calculations of δ, and, for reasonable values of Δm, will lead to no qualitative change in the conclusions drawn from the observed values of $\mathrm{p}K_1^{\ddagger}$ and $\mathrm{p}K_2^{\ddagger}$.

Calculation of δ. The extent of carbon–oxygen bond formation in the transition states may be estimated only if it is assumed that all three catalytic paths involve a concerted mechanism. If this is assumed, the interpretation of the $\mathrm{p}K_a^{\ddagger}$ values depends on whether II or III is assumed to be the correct unhydrated structure for the activated complex in the uncatalyzed reaction. If it first is assumed that II is correct, then $\mathrm{p}K_1^{\ddagger}$ corresponds to the equilibrium, $\mathrm{V} \rightleftharpoons \mathrm{II} + \mathrm{H^+}$, and the proton ionizes from the nucleophilic water moiety in the transition state. The value of $\mathrm{p}K_a(\delta = 0)$ will thus be 14.0, the value for an unperturbed water molecule with a molecule fraction standard state.[25] As previously concluded, $\Delta \mathrm{p}K(z = 1) = -5.2$ for the charge on the former carbonyl oxygen. For the charge on the oxygen bearing the ionizing proton, $\Delta \mathrm{p}K(z = 1)$ is the difference in $\mathrm{p}K_a$ between a species with the structure $\mathrm{CH_3CH(OH)OH_2^+}$ and unperturbed water. (The effect of the $\mathrm{CH_3CH(OH)}$ substituent as well as of the positive charge is included when $\Delta \mathrm{p}K(z = 1)$ is defined in this way.) The $\mathrm{p}K_a$ for the former species may be estimated by comparison to $\mathrm{(CH_3)_2CHOH_2^+}$ for which $\mathrm{p}K_a = -3.2$.[26] The effect of substitution of a hydroxyl for the methyl group may be approximated from $\sigma^*_{\mathrm{OH}} = +1.28$[5a] (this value is taken in preference to the older value of $+1.34$[27] since it was derived from measurements on *gem*-diols) and the assumption that ρ^* for the ionization of $\mathrm{R_3COH_2^+}$ is the same as for the ionization of $\mathrm{R_3COH}$, or $\mathrm{R_2C(OH)_2}$ for which $\rho^* = 1.42$.[5b,28] Since the symmetry factors for the ionizations of $\mathrm{(CH_3)_2CHOH_2^+}$ and $\mathrm{CH_3CH(OH)OH_2^+}$ are identical, these numbers imply that the latter acid has a $\mathrm{p}K_a$ of -5.0. By comparison to the acidity of $\mathrm{H_2O}$, this number in turn leads to a value of -19.0 for $\Delta \mathrm{p}K(z = 1)$ when the charge lies on the nucleophilic oxygen. Substitution of these terms into eq 4 leads to

$$\mathrm{p}K_1^{\ddagger} = 8.8 - 13.8\delta - 0.6\Delta m \qquad (4a)$$

If the assumptions that the concerted mechanism is followed and that II, rather than III, is correct are continued, $\mathrm{p}K_2^{\ddagger}$ corresponds to the ionization equilibrium, $\mathrm{II} \rightleftharpoons \mathrm{I} + \mathrm{H^+}$, and the proton ionizes from the former carbonyl oxygen. For $\delta = 0$, the transition state would have the structure of the conjugate acid of acetaldehyde, $\mathrm{CH_3CHOH^+}$. The value of $\mathrm{p}K_a^{\ddagger}$ for this species may be estimated by assuming that the difference in $\mathrm{p}K_a$ between the conjugate acids of acetophenone and benzaldehyde is the same as that between the conjugate acids of acetone and acetaldehyde. For $\mathrm{C_6H_5C(CH_3)OH^+}$, $\mathrm{p}K_a = -6.2$,[29] for $\mathrm{C_6H_5CHOH^+}$, $\mathrm{p}K_a = -7.1$,[30] and for $\mathrm{(CH_3)_2COH^+}$, $\mathrm{p}K_a = -7.2$,[31] thus implying that $\mathrm{p}K_2(\delta = 0) = -8.1$. This estimate agrees with those of Arnett[32] and of Ahrens and Strehlow,[7] both of whom estimate *ca.* -8 for this species. The value of $\Delta \mathrm{p}K(z = 1)$ for the charge on the former carbonyl oxygen may be estimated as -22.0 from this value of -8.1 in combination with the value of $\mathrm{p}K_a$ for $\mathrm{CH_3CH(OH)_2}$ (13.6[33]) and a correction of log 2 for the symmetry difference. This use of acetaldehyde hydrate as a model implicitly includes the effect of the hydroxyl substituent in the calcultion of $\Delta \mathrm{p}K(z = 1)$. Use of these values for $\mathrm{p}K_2(\delta = 0)$ and $\Delta \mathrm{p}K(z = 1)$ together with $\Delta \mathrm{p}K(z = 1) = -5.2$ for the effect of a unit charge on the nucleophilic oxygen gives eq 4b.

$$\mathrm{p}K_2^{\ddagger} = -2.9 + 16.8\delta - 0.6\Delta m \qquad (4b)$$

Calculations based on the alternate assumption that III rather than II is correct may be carried out analogously, using the same models for estimation of $\mathrm{p}K$ values as are described above. Application of eq 4 then leads to the result that the equilibrium, $\mathrm{V} \rightleftharpoons \mathrm{III} + \mathrm{H^+}$, corresponds to

$$\mathrm{p}K_1^{\ddagger} = -8.1 + 16.8\delta - 0.6\Delta m \qquad (4c)$$

and for $\mathrm{III} \rightleftharpoons \mathrm{I} + \mathrm{H^+}$, the result is that

$$\mathrm{p}K_2^{\ddagger} = 14.0 - 13.8\delta - 0.6\Delta m \qquad (4d)$$

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(22) E. E. Schrier, M. Pottle, and H. A. Scheraga, *J. Am. Chem. Soc.*, **86**, 3444 (1964).

(23) H. H. Broene and T. DeVries, *ibid.*, **69**, 1644 (1947).

(24) G. Némethy and H. A. Scheraga, *J. Phys. Chem.*, **66**, 1773 (1962); H. Schneider, G. C. Kreshick, and H. A. Scheraga, *ibid.*, **69**, 1310 (1965).

(25) If $\mathrm{p}K_a(\delta = 0)$ is taken as 14.0, for consistency it is necessary to take $z_i(\delta = 0)$ as 0 rather than as +1 for the carbonyl oxygen when evaluating eq 4; this convention is equivalent to the assumption that when $\delta = 0$ the water moiety is completely unperturbed by the positive charge on the acetaldehyde moiety. The same final result (eq 4a) is obtained if the opposite convention is adopted so that a correction term of -5.2 is included in $\mathrm{p}K_a(\delta = 0)$ and $z_i(\delta = 0)$ for the carbonyl oxygen is taken as +1.

(26) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 351 (1963).

(27) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(28) P. Ballinger and F. A. Long, *ibid.*, **82**, 795 (1960).

(29) Reference 26, p 378.

(30) Reference 26, p 367.

(31) Reference 26, p 374.

(32) Reference 26, p 296.

(33) R. P. Bell, and D. P. Onwood, *Trans. Faraday Soc.*, **58**, 1557 (1962).

The values of δ which are given by eq 4a–d in combination with the experimental values, $pK_1^{\ddagger} = 5.0$, $pK_2^{\ddagger} = 7.5$, and various assumed values of Δm are given in Table IV. Each of these δ values should be interpreted as an *average* fraction of carbon–oxygen bond making for the two activated complexes participating in the equilibrium for which that δ was calculated.[3,20] Each δ will be an upper limit for bond making in one activated complex and a lower limit for bond making in the other.

Table IV. Fractions of Carbon–Oxygen Bond Making Corresponding to Assumed Proton Distributions and Hydration Numbers

Equilibrium	δ^a for $\lvert\Delta m\rvert^b$ values of 0	2	4
$V \rightleftharpoons II + H^+, pK_1^{\ddagger}$ (eq 4a)	0.28	0.19	0.10
$II \rightleftharpoons I + H^+, pK_2^{\ddagger}$ (eq 4b)	0.62	0.55	0.48
$V \rightleftharpoons III + H^+, pK_1^{\ddagger}$ (eq 4c)	0.78	0.85	0.92
$III \rightleftharpoons I + H^+, pK_2^{\ddagger}$ (eq 4d)	0.47	0.56	0.64

[a] Average extent of C–O bond making for the two transition states in the corresponding equilibrium, calculated from the indicated equation and the experimental values: $pK_1^{\ddagger} = 5.0$, $pK_2^{\ddagger} = 7.5$. [b] $\Delta m \geq 0$ for an ionization of V and ≤ 0 for ionization of II or III.

In principle, it should be possible to decide which transition state has the longer (less made) bond from a consideration of the effect of protonation on the structure of the conjugate base transition state. Thus a strict application of the Swain–Thornton reacting bond rule[17] would appear to lead to the conclusion that the bond being formed between the nucleophile and the carbonyl carbon will always be shortened by coordination of a proton with the activated complex, independently of whether the site of protonation is the nucleophile or the carbonyl oxygen. This conclusion results from the argument that when a nucleophile attacks the *trigonal* carbonyl carbon, its electron pair must interact with one lobe of the π system of the carbonyl group so that in the transition state there is no nucleus which separates the σ bond being formed from the π bond being broken; both thus belong to the same reacting orbital. (Note that the term, "reacting orbital," as used in applications[17] of the Swain–Thornton rule refers to an electron cloud rather than to an individual molecular orbital.) However, there is some question whether the formulation of the reacting bond rule in terms of reacting orbitals is always correct. Thornton[34] has proposed a more general approach to the prediction of the effect of substituent changes on transition-state geometry, which, in this case, leads to the same prediction as would be obtained if the bonds being formed and broken were treated as alternate reacting bonds (as would be done for nucleophilic attack at a tetrahedral carbon). This latter convention is the one used by Swain and Worosz.[11] These two interpretations lead to the same conclusion in two cases: if structure II (rather than III) is correct, then carbon–oxygen bond formation in the transition states corresponding to $pK_1^{\ddagger}$ increases in the order II < V; if structure III is correct, then for the transition states corresponding to $pK_2^{\ddagger}$, bonding increases in the order I < III. For the other two possible pairs of transition states corresponding to the concerted mechanism, these two interpretations lead to opposite conclusions.

Choosing between Alternative Transition-State Structures. An attempt to decide whether II or III represents the correct unhydrated structure of the activated complex in the water-catalyzed reaction may be based on an estimate of the relative thermodynamic stability of these two structures as a function of δ. The value of δ for which the two possible average transition states corresponding to $pK_1^{\ddagger}$ have the same free energy may be estimated by equating the two expressions for $pK_1^{\ddagger}$ which correspond to the two possible assumed structures for the neutral activated complex. Thus, from eq 4a and 4c it follows that these two average transition states are equally stable when $\delta = 0.55$. From the structures of II and III (or from eq 4a and 4c) it is clear that if $\delta \approx 0$, III would be the more stable ($pK_1^{\ddagger}$ smaller) while II would be the more stable if $\delta \approx 1$. The value $\delta = 0.55$ is thus a dividing line, and for $\delta > 0.55$, II would be correct; while for $\delta < 0.55$, III would be correct. Similarly, for the two possible average transition states corresponding to $pK_2^{\ddagger}$, eq 4b and 4d also yield $\delta = 0.55$ as the point of equal stability, above which II would be more stable ($pK_2^{\ddagger}$ larger) and below which III would be more stable.

The values of δ in Table IV may be compared to these predictions. First, consider the criterion based on $pK_2^{\ddagger}$. If II is assumed to be correct, then δ is calculated to be within 10% of 0.55 for $0.4 \leq |\Delta m| \leq 3.6$. If III is assumed to be correct, then δ is within 10% of 0.55 for $0.8 \leq |\Delta m| \leq 3.4$. Either assumption is internally consistent in that it leads to an estimate of δ which is consistent with the assumed structure, and both agree that the two possible transition states are of approximately equal stability. This conclusion implies that significant numbers of transition states exist with each possible proton distribution, which in turn may reflect the operation of an Eigen-type[6,12] cyclic mechanism. The calculated δ values also imply that the magnitude of Δm is not large.

For the pair of transition states corresponding to $pK_1^{\ddagger}$, the value of δ calculated for each assumption about the structure of the uncatalyzed transition state is inconsistent with that assumption. If II is assumed to be correct, then δ ranges from 0.28 to 0.10 as Δm varies from 0 to 4; these low values of δ imply that III would be more stable than II and therefore the correct structure. If III is assumed to be correct, then δ ranges from 0.78 to 0.92 over the same range of Δm, implying that II is correct.

It appears impossible to explain these inconsistencies on the basis of uncertainties inherent in eq 4. The term with the highest probability of being seriously in error should be the ΔpK_h correction. It might be thought possible that the HF_2^- model would seriously underestimate the size of the hydrogen-bonding correction. However, increasing the magnitude of this term would make the inconsistency worse instead of better; for the ΔpK_h term to remove the inconsistency, the hydronium ion catalyzed transition state would have to be more strongly hydrogen bonded than the uncatalyzed transi-

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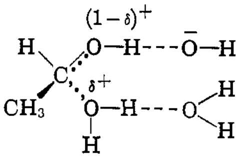
(34) E. R. Thornton, private communication.

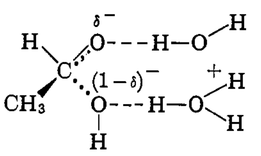
tion state by at least 5.3 kcal/mole. This would be inconsistent with the arguments based on $\Delta S^{\neq}$, k_H/k_D, and the Brønsted correlation which lead to the conclusion that the uncatalyzed transition state must be the more strongly hydrogen bonded of this pair. For the other terms in eq 4, it seems unlikely that an over-all uncertainty greater than 1 pK unit would be present, whereas an error of at least 4 pK units would be required for removal of the inconsistency.

Since the observed value of $pK_2^{\neq}$ does lead to consistent and reasonable estimates of δ, the inconsistency in those derived from $pK_1^{\neq}$ strongly suggests that the assumed structure of the transition state corresponding to k_H is grossly in error, *i.e.*, that the hydronium ion catalyzed reaction does *not* follow the concerted mechanism. The only other reasonable path would be rate-determining proton transfer; such a mechanism would be consistent with the observed $pK_1^{\neq}$, although no unique δ value could be calculated. The simple fact that the reaction follows an alternative mechanism would require the transition state for that alternative mechanism to have a lower free energy than that for the concerted mechanism. Its pK_a would therefore be higher, so that the true value of $pK_1^{\neq}$ corresponding to the previously assumed concerted mechanism with V as its transition state would be lower than the experimentally observed value. A value of $pK_1^{\neq}$ lower than 1.1 (instead of the 5.1 observed) would have been required for consistency with the concerted mechanism.

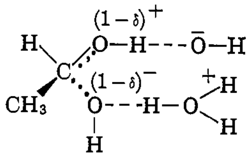
One question concerning the structure of the activated complex for the uncatalyzed reaction still must be considered. The arguments used to rule out the concerted mechanism for the k_H term and to conclude that II and III were of nearly equal stability were based on the specific charge distributions shown for these latter two structures. When the hydrogen-bonded structures IIa and IIIa were written, that charge distribution was retained. If, however, the positions of the protons in the hydrogen bonds were different from those shown, the charge distribution might be perturbed and the value of $pK_a^{\neq}$ changed. For example, for structure III there are four possible limiting cases for the positions of the protons. That shown for IIIa is one; the others are IIIb, IIIc, and IIId.



IIIb



IIIc



IIId

The Swain solvation rule[10] predicts that the proton in each hydrogen bond will be closer to the more basic oxygen; an estimate of the relative basicity of the two oxygens in each hydrogen bond will thus predict which of the four limiting hydrated structures shown for III is most nearly correct.

First consider the hydrogen bond involving the former carbonyl oxygen. The proton is bound between a hydroxide ion and a species which in IIIa and IIIb is identical with III. In estimating the pK_a of each conjugate acid (water and V, respectively) the perturbations due to charges on oxygen atoms other than that to which the proton is bonded must be considered. The magnitudes of these perturbations may be estimated from eq 5, the internuclear distances being calculated from a model in which $\delta = 0.55$, all bond angles (except for hydrogen bonds) are 109° 28′, hydrogen bond angles are 180°, and a fully extended conformation is assumed. In IIIa and IIIb, the pK_a of water is equal to 15.7 plus a correction term due to the negative charge on the former carbonyl oxygen in III and minus a correction for the positive charge on the nucleophilic oxygen. The pK_a of V will be given by eq 4c, in which $\delta = 0.55$ and $\Delta m = 0$, plus a correction for the negative charge on hydroxide. The values of pK_a thus estimated are 17.5 for the water moiety and 9.6 for V; since the former carbonyl oxygen is the weaker base by 7.9 pK units, the Swain solvation rule predicts that IIIa is a better approximation to the correct structure than is IIIb.

An analogous calculation may be made for the hydrogen bond involving the nucleophilic oxygen. In structures IIIa and IIIc (which have the more stable hydrogen bond to the former carbonyl oxygen) the proton is bound between a water molecule and a species identical with I. The pK_a of the water will be perturbed by the charges on I and be equal to +3.7. The pK_a of the appropriate conjugate acid of I is given by eq 4d as +6.4 ($\delta = 0.55$ and $\Delta m = 0$). The nucleophilic oxygen is thus more basic than the water molecule by 2.7 pK units and the proton lies nearer to the nucleophilic oxygen. It may therefore be concluded that the charge distribution shown in IIIa is correct. Similar calculations lead to the conclusion that the charge distribution shown in IIa is correct for the hydrated structure corresponding to II.

Possible failure of the Swain solvation rule has been predicted by Reimann and Jencks[35] on the grounds that association with the catalyst may perturb the reacting bond from the length used for prediction of the proton's position by that rule. For the reaction under consideration here, the required low value of Δm implies that either both unhydrated transition states corresponding to $pK_2^{\neq}$ interact with solvent by hydrogen bonding to the same extent (which seems unlikely), or that the free-energy change resulting from hydrogen bonding to solvent is small. Such a conclusion combined with the large estimated differences in basicity between the groups competing for the proton in each hydrogen bond suggests that coupling between the free-energy changes associated with stretching reacting bonds and forming hydrogen bonds to solvent cannot be large enough in these examples to invalidate the prediction of the solvation rule. By starting with structures which have the catalyzing proton already attached and then applying only the small perturbation due to association with solvent, this source of failure appears to have been avoided.

Other Criteria of Transition-State Structure. The enthalpies and entropies of activation for the three

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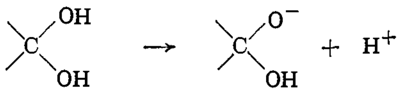
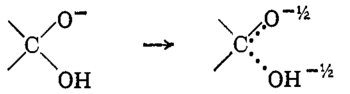
[35] J. E. Reimann and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3973 (1966).

catalytic paths are given in Table II, and the corresponding parameters for the virtual equilibria between transition states in Table III. The small negative values of $\Delta S^{\ddagger}$ corresponding to hydronium ion and hydroxide ion catalysis (−4 and −7 eu, respectively) are consistent with the assumed transition-state structures. The very large negative value of $\Delta S^{\ddagger}$ corresponding to k_0 (−38 eu) requires a special explanation. This conclusion becomes even more obvious upon inspection of the values of $\Delta S°$ given in Table III for virtual equilibria between the transition states. Thus the transition state for the water-catalyzed reaction may be obtained from that for the hydronium ion catalyzed path by ionizing a proton and rearranging reacting bonds. Neither ionization of a proton from a positively charged acid nor simple bond stretching and compression could account for the loss of 34 eu in that transformation. A major reorganization of solvent structure, as has been postulated above, would be required.

Semiquantitative estimates of the magnitude of the entropy change arising from this special solvent reorganization may be made by comparison of the tabulated values of $\Delta S°$ to those for model equilibria. For example, the value of $\Delta S°$ for the equilibrium, II → I + H^+, between nonspecially hydrated activated complexes would be equal to the sum of the $\Delta S°$ values for reactions 6–8. The value of $\Delta S°$ for eq 6 may be estimated to be about −30 eu (the value for ionization of a sugar hydroxyl group[36]). If contributions from bond stretching are assumed to be negligible, eq 7 corresponds to dispersing the negative charge over two oxygens, and hence should be approximately equal to the difference between $\Delta S°$ for ionization of a carboxylic acid (charge dispersed over two oxygens in the product) and for ionization of an alcohol (localized charge). For the former, $\Delta S°$ is near −20 eu,[37] while for the latter, $\Delta S°$ is near −30 eu.[36] The value of $\Delta S°$ for eq 8 may be estimated from a simple electrostatic argument to be about equal to that for the reverse of eq 7 or to slightly less than half of that expected for complete charge separation (as in the ionization of an uncharged acid). Either estimate suggests a value of about −10 eu. For the over-all process, II → I + H^+, $\Delta S°$ is thus predicted to be about −10 eu. An alternate estimation would regard the ionization to be of a charge type halfway between the ionization of a positively charged acid [*e.g.*, the conjugate acid of ethanolamine or tris(hydroxymethyl)aminomethane, which has $\Delta S° = -1$ and 0, respectively[37]] and an alcohol, and thus would predict −15 eu. The observed value of +12 eu thus implies that about 25 eu must be attributed to solvent reorganization.



(6)



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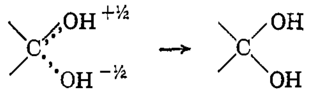

(8)

Data for the solvent deuterium isotope effect on k_H and k_0 are also available and are given in Table V. These effects were shown by Pocker[1] to be consistent with rate-determining proton transfer. However, they also could be rationalized as secondary isotope effects if the concerted mechanism were assumed. For example, Huang, Robinson, and Long[8] have measured the rate of mutarotation of tetramethylglucose in H_2O–D_2O mixtures and have calculated the average fractionation factor ϕ (defined as the equilibrium constant for the exchange reaction: SH + $^1/_2D_2O$ → SD + $^1/_2H_2O$) for all exchangeable protons in each of the various possible transition states for a concerted mechanism. They concluded that the data were consistent with such mechanisms if the transition states were assumed to contain two or more strongly hydrogen-bonded water molecules. The observed values of k_H/k_D, and presumably the reverse mechanisms, for acetaldehyde hydration are almost identical with those for tetramethylglucose mutarotation.

Table V. Relative Rate Constants and Corresponding Average Fractionation Factors for Acetaldehyde Hydration in H_2O and D_2O

Catalyst	Temp, °C	k_{H_2O}/k_{D_2O}	ϕ $m^b = 0$	$m = 1$	$m = 2$
Hydronium ion	0	1.3[a]	0.59	0.72	0.80
Water	0	3.6[a]	0.52	0.72	0.81

[a] Reference 1. [b] $m \equiv$ number of water molecules of hydration.

The analogous average fractionation factors for the exchangeable protons in the transition states for acetaldehyde hydration are listed in Table V. In calculating those factors, the value of ϕ^3 for H_3O^+ was taken to be $(0.64)^3$ at 0°. This value was estimated from the known 25° value by the approximate method of Swain and co-workers.[10] It is seen that if at least one water of hydration is assumed to be present, the values of ϕ are not unreasonable when compared to those for H_3O^+ and OH^- (0.47 at 0°, estimated from the 25° value).

Experimental Section

Pseudo-first-order rate constants for the hydration were measured by the calorimetric method previously described, using acetaldehyde from the same batch as that used for the calorimetric measurements.[38] Rate constants were measured for hydration in 2,4,6-trimethylpyridine–2,4,6-trimethylpyridinium perchlorate buffers at four different total buffer concentrations ranging from 0.005 to 0.02 *F*, at each of two buffer ratios (acid: base = 2.86 and 0.72) and each of two temperatures (24.9 and 0.4°). The pH of each buffer was measured at the same temperature as that of the corresponding kinetic run, and the molarity of the hydroxide ion calculated from the measured pH, pK_w (14.000 at 24.9°, 14.927 at 0.4°),[39] and the Davies equation[40] for the activity coefficient. For each buffer ratio at a given temperature, the value of log [OH^-] was assumed to be constant and equal to the average of the values

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determined for the four buffers. The scatter of those values implies an uncertainty of about ±2% in the value of [OH⁻]. Each set of four observed first-order rate constants was plotted as a function of total buffer concentration, and the rate constant for zero buffer concentration (assumed to be $k_0 + k_{OH}[OH^-]$ for the corresponding average value of [OH⁻]) obtained by linear extrapolation. The values of k_0 and k_{OH} for each temperature were then calculated from the two corresponding extrapolated rate constants.

2,4,6-Trimethylpyridinium perchlorate was prepared from Matheson Coleman and Bell *s*-collidine and perchloric acid, and recrystallized from absolute ethanol to obtain white needles; neutralization equivalent (by titration to the potentiometric inflection point with 0.1 *N* sodium hydroxide): 221.2, 221.6 (calcd: 221.6). Buffers were prepared from weighed quantities of this salt and the calculated amount of standard 0.1 *N* sodium hydroxide.

The values of k_0 and k_{OH} obtained and the corresponding values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are shown in Tables I and II along with comparable values from the literature. The values obtained for k_0 from the measured hydration rates in these collidine buffers are in good agreement with those from reactions run in dilute perchloric acid.[38] The new values obtained for k_{OH} give $\Delta S^{\neq} = -7$ eu, which is in better agreement with expectation than the old value of +8 eu.

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General Acid and General Base Catalysis for the Methoxyaminolysis of Phenyl Acetates[1]

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Abstract: Investigation of the dependence of second-order rate constants for the reaction of a series of substituted phenyl acetates with methoxyamine in aqueous solution at 25° on the concentration of methoxyamine and on pH reveals these reactions to be subject to both general base catalysis, by a second molecule of amine, and general acid catalysis, by a molecule of the conjugate acid of the amine. In addition, these reactions have been found to be subject to general base catalysis by carboxylate anions and to general acid catalysis by carboxylic acids and by other ammonium ions. The following values of ρ have been measured: for the uncatalyzed (or water-catalyzed) methoxyaminolysis, 1.6; for general base catalysis by methoxyamine and acetate, 1.0 and 0.8, respectively; for general acid catalysis by methoxyammonium ion and acetic acid, 0.45 and 0.8, respectively. Thus, general acid and general base catalysis becomes of increasing importance as the reactivity of the substrate decreases, a conclusion consistent with earlier results. The third-order rate constants for general base catalysis of the methoxyaminolysis of *p*-nitrophenyl acetate by a series of carboxylate anions are correlated by a straight line in a Brønsted plot with a slope, β, of 0.45. Third-order rate constants for general acid catalysis of this reaction fall into two categories. In the case of catalysis by carboxylic acids, the rate constants are substantially independent of the acidity of the catalyst ($\alpha = 0$), a result interpreted tentatively in terms of bifunctional catalysis by these species, while in the case of catalysis by ammonium ions, the rate constants decrease with decreasing acidity of the catalyst. The reaction of *p*-nitrophenyl acetate with N,O-dimethylhydroxylamine is also subject to both general acid and general base catalysis. Values of ρ for the reaction of substituted phenyl acetates with piperidine (2.1), ethylenediamine (1.9), morpholine (2.6), and glycine ethyl ester (2.2) were determined.

General acid–base catalysis for nucleophilic reactions at the acyl carbon atom is a well-established phenomenon. The earliest such example is provided by the observation of Kilpatrick in 1928 that acetate ion functions as a general base catalyst for hydrolysis of acetic anhydride.[3] General base catalysis has subsequently been established for hydrolysis of acyl-activated esters,[4] nonactivated esters,[5,6] acetylimidazolium ion,[7] and ethyl trifluorothiolacetate.[8] General acid–base catalysis for those reactions at acyl carbon involving nitrogen nucleophilic reagents is particularly well studied. Seminal studies include the observation of general acid and general base catalysis for phenyl acetate aminolysis in water,[9] general base catalysis for ammonolysis of phenyl acetates in water,[10] and general base catalysis for *n*-butylaminolysis of ethyl formate in ethanol.[11] Subsequently, such catalysis has been established for a variety of esters,[12–15] lactones,[16] thiol esters,[17–20] and thiolactones.[21] A detailed summary

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