solid residue was dissolved in absolute ethanol. The resulting Burgundy-colored solution was treated with Darco and filtered. The filtrate, which was still colored, was evaporated to dryness *in vacuo*. The resulting mixture of brown oil and crystals was dissolved in 5 ml. of 10% potassium hydroxide, filtered and acidified with 10% hydrochloric acid. The white precipitate that resulted was collected and dried. It was identified as boronophthalide from its infrared spectrum.

With Benzylamine.—A mixture of 1.0 g. (0.0074 mole) of boronophthalide in 15 ml. of benzylamine was heated to reflux for 25 hr. under nitrogen, during which the boronophthalide dissolved. The solution was allowed to cool and 12 ml. of water was added. Two phases formed. The lower, organic phase was separated and washed with three 10-ml. portions of water. The oil was then suspended in 10 ml. of water and this mixture extracted with three 10-ml. portions of ether. The combined ether extract was dried over magnesium sulfate and the ether evaporated under a stream of nitrogen. The remaining oil, which had a slight odor of benzylamine, was dried *in vacuo* overnight and distilled; b.p. 80–110° (*ca.* 5 mm.). The distillate was identified as benzyl alcohol from its infrared spectrum.

With *o*-Phenylenediamine.[13]—A mixture of 803 mg. (0.0060 mole) of boronophthalide, 648 mg. (0.0060 mole) of *o*-phenylenediamine and 20 ml. of absolute ethanol was heated to reflux for 10 min. While the solution continued to boil, toluene was added in 2-ml. portions during a 30-minute period. At the end of this time all the ethanol had boiled away and the temperature of the refluxing solution was 109°. The total volume was *ca.* 25 ml. Boiling was continued for 10 min., and then the solution was filtered through absorbent cotton. The filtrate was allowed to cool to room temperature, whereupon crystallization occurred. The tan crystals (*ca.* 500 mg.) were collected. The crystals were identified as *o*-phenylenediamine from their infrared spectrum.

Attempted Oxidation of the Methylene Group of Boronophthalide.—A mixture of 1.0 g. (0.0075 mole) of boronophthalide, 0.83 g. (0.0075 mole) of selenium dioxide and 25 ml. of 80% aqueous dioxane was heated under reflux for 12 hr. The solution, which had a yellow color and contained a small amount of black, metallic selenium, was filtered. The selenium weighed only 30 mg.

A second experiment was run using the same solvent and reaction conditions except that 1.66 g. (0.0150 mole) of selenium dioxide was used. No appreciable amount of selenium was precipitated.

URBANA, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

Association Phenomena. I. Specific Cation Effects on the Hydrolysis and Glycinolysis of Acetyl Phosphate[1]

BY JOSEPH L. KURZ[2] AND C. DAVID GUTSCHE

RECEIVED AUGUST 26, 1959

The kinetics of the disappearance of acetyl phosphate in glycine–glycinate buffers has been analyzed in terms of rate constants defined by the equation $-\mathrm{d}[\mathrm{AcPO_4^{=}}]/\mathrm{d}t = (k_\mathrm{w}[\mathrm{H_2O}] + k_\mathrm{OH}a'_\mathrm{OH} + k_\mathrm{HG}[\mathrm{HG}] + k_\mathrm{G}[\mathrm{G^-}])[\mathrm{AcPO_4^{=}}]$, where a'_OH is the *p*H meter-determined hydroxide ion activity and the quantities in brackets are concentrations. The four rate constants have been studied as a function of cation species (tetramethylammonium ion and lithium ion), cation concentration, temperature and solvent. A rationalization of the results is based on the assumption of complex formation between the cation and one or more of the reactants. With the exception of the activation parameters for k_W, the behavior of these specific rates is consistent with these assumptions: (1) in water solution, there is little association between the reactants and the cations, but appreciable association of the cations with the triply charged transition states; (2) in 50% dioxane, there is association of the cations with all the reactant anions, the association constants increasing with the charge and polarizability of the anion; (3) although tetramethylammonium ion associates, it has little ability to polarize the anion with which it associates. Preliminary studies with polymeric quaternary ammonium compounds indicate that these are more effective catalysts than tetramethylammonium ion.

Many reactions occurring in living systems take place in aqueous solution and involve charged reactants. The mode of action of enzymes mediating such processes should involve the same types of forces, electrostatic and otherwise, which are operative in the interactions of simple ions. To gain insight into the nature of these interactions, the reaction of acetyl phosphate with aqueous glycine has been investigated using lithium ion and tetramethylammonium ion as models for the metal ions and quaternary ammonium ion centers which may be involved in comparable enzymatic reactions.

Acetyl phosphate was chosen as a substrate because it is a known component of several biological systems[3] and because it already has received a certain amount of attention from a purely chemical viewpoint. Lynen[4] observed that the hydrolysis of acetyl phosphate is first order at *p*H 7.4; Lipmann and Tuttle[5] studied the hydrolysis rate as a function of *p*H and observed catalysis in acid by molybdate ion and in base by calcium ion; Weil-Malherbe and Green[6] also studied the molybdate-catalyzed hydrolysis; Bentley[7] studied the hydrolysis with H_2O^{18} and also investigated the acetylation of some amines; similarly, Lipmann and Tuttle[8] and Chantrenne[9] studied amine acylation with particular reference to hydroxylamine; and finally, Koshland[10,11] has made an extensive study of both the hydrolysis reaction and the glycinolysis reaction which provided the starting point for the work described in this communication.

Koshland's study of the kinetics of the reaction

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[1] This work was supported, in part, by grant no. A-2398 from the National Institutes of Health.

[2] Du Pont Fellow in Chemistry, 1957–1958; Monsanto Research Associate, summer, 1957.

[3] *Cf.*, for instance, L. P. Hager, D. M. Geller and F. Lipmann, *Fed. Proc.*, **13**, 734 (1954); I. A. Rose, M. Grunberg-Manago, S. R. Korey and S. Ochoa, *J. Biol. Chem.*, **211**, 737 (1954); E. R. Stadtman, *ibid.*, **196**, 527 (1952); B. L. Horecker, E. C. Heath, J. Hurwitz and A. Ginsburg, *Fed. Proc.*, **16**, 198 (1957).

[4] F. Lynen, *Ber.*, **73**, 367 (1940).

[5] F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **153**, 571 (1951).

[6] H. Weil-Malherbe and R. H. Green, *Biochem. J.*, **49**, 286 (1951).

[7] R. Bentley, THIS JOURNAL, **70**, 2183 (1948).

[8] F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 286 (1945).

[9] H. Chantrenne, *Compt. rend. trav. lab. Carlsberg, Ser. chim.*, **26**, 231 (1948).

[10] D. E. Koshland, THIS JOURNAL, **73**, 4103 (1951).

[11] D. E. Koshland, *ibid.*, **74**, 2286 (1952).

of acetyl phosphate with aqueous glycine to yield inorganic phosphate, acetate (hydrolysis) and acetylglycine (glycinolysis) established the rate equation

$$-\mathrm{d}[\mathrm{AcPO_4^{=}}]/\mathrm{d}t = k_1[\mathrm{AcPO_4^{=}}] + k_2[\mathrm{AcPO_4^{=}}][\mathrm{glycine}] \quad (1)$$

To verify and expand this rate expression, the hydrolysis reaction alone was first investigated by studying the rate of disappearance of acetyl phosphate in N,N-dimethylglycine–N,N-dimethylglycinate buffered solutions. When tetramethylammonium ion was the only cation present, *p*H had little effect on the rate of hydrolysis. The rate in 50% dioxane solutions, for instance, only changed from 9.05×10^{-7} to 8.93×10^{-7} when the *p*H was changed from 10.5 to 11.5. In contrast, when lithium ion was the only cation, the hydrolysis rate was a linearly increasing function of the hydroxide ion activity in both solvents. The hydrolysis rate thus may be expressed as the sum of the rates of reaction with water and with hydroxide ion

$$k_1 = k_{\mathrm{W}}[\mathrm{H_2O}] + k_{\mathrm{OH}}a'_{\mathrm{OH}} \quad (2)$$

where a'_{OH} is the *p*H meter-determined hydroxide ion activity. The water concentration in moles/liter is introduced to make k_{W} agree in units with the other rate constants. This formulation implies the unproved assumption that the reaction with water is of the S_N2 type. The above expression, valid both in water and in 50% dioxane, is similar to one obtained by Koshland from a study of the *p*H dependence of the rate of hydrolysis of acetyl phosphate in basic solutions containing alkali metal ions. It differs only in the assumption that the *p*H meter readings measure the activity of hydroxide ion rather than its concentration.

From a knowledge of hydrolysis rates under various conditions, glycinolysis rate constants, k_2, then could be determined from the difference between the over-all rates in glycine buffers and the hydrolysis rates. In both water and 50% dioxane, k_2 proved to be a linear function of the total glycine concentration (glycine concentration varied over range 1–16 $\times 10^{-2}M$), in agreement with the findings of Koshland. In solutions of the basicities under investigation, however, the total glycine concentration is the sum of the glycine zwitterion concentration, [HG], and the glycinate anion concentration, [G⁻], which requires that

$$[\mathrm{Glycine}]k_2 = k_{\mathrm{HG}}[\mathrm{HG}] + k_{\mathrm{G}}[\mathrm{G^-}] \quad (3)$$

This expression is consistent with the assumption that the glycinolysis of acetyl phosphate occurs by two mechanisms: (1) attack by glycine and/or glycine zwitterion, and (2) attack by glycinate anion. The possibility that the k_{HG} term might be due to reaction with the small amount of $H_2NCH_2CO_2H$ in equilibrium with the $H_3N^+CH_2CO_2^-$ may be shown to be improbable by the following considerations. The equilibrium constant for the reaction $H_2NCH_2CO_2H \rightleftarrows H_3N^+CH_2CO_2^-$ has been estimated[12] to be 2.6×10^5 in aqueous solution at 25°. The second-order rate constant for the reaction of neutral glycine with acetyl phosphate would thus have to equal k_{HG} (2.6×10^5) if this reaction were to account for the observed dependence of k_2 on [HG]. Koshland's values[11] of k_2 for benzylamine and for glycine at various *p*H's imply that $C_6H_5CH_2NH_3^+$ reacts with acetyl phosphate and that the value of k_2 for $H_2NCH_2CO_2H$ would have to be 10^4 to 10^5 times as large as k_2 for neutral benzylamine for this to be a significant reactant. While a special mechanism involving carboxyl participation might conceivably account for such a rate factor, the benzylamine data make such a postulation unnecessary.

The over-all first-order rate constant for the disappearance of acetyl phosphate in aqueous glycine may thus be written as

$$k_{\mathrm{T}} = k_{\mathrm{W}}[\mathrm{H_2O}] + k_{\mathrm{OH}}a'_{\mathrm{OH}} + k_{\mathrm{HG}}[\mathrm{HG}] + k_{\mathrm{G}}[\mathrm{G^-}] \quad (4)$$

where k_{T} is defined by the equation $-\mathrm{d}[\mathrm{AcPO_4^{=}}]/\mathrm{d}t = k_{\mathrm{T}}[\mathrm{AcPO_4^{=}}]$. Since pK_2 for acetyl phosphate is *ca.* 4.8,[13] the only species present in kinetically significant concentrations under the conditions of the reactions is the dinegative ion. The four rate constants in eq. 4 have been determined for a variety of reaction conditions as detailed below.

Experimental

Materials.—Distilled water which had been boiled and allowed to cool in an atmosphere free from carbon dioxide was used in all of the kinetic runs. The 50% (by weight) dioxane was prepared volumetrically from dioxane which had been purified by the method of Fieser.[14] Eastman Kodak Co. white label tetramethylammonium hydroxide was freed from carbonate by the method of Davies and Nancollas,[15] and Fisher C.P. lithium hydroxide was found to be carbonate-free and was used without further purification. Glycine (Matheson, Coleman and Bell, ammonia free) was crystallized from water and dried in vacuum over phosphorus pentoxide giving a product whose assay by potentiometric formal titration[16] was 99.8 ± 0.2%. Sodium dimethylglycinate was prepared from sodium chloroacetate and dimethylamine. Neutralization of this material by passage through an Amberlite IRC-50 column in the acid form yielded a sodium-free solution of dimethylglycine. Dilithium acetyl phosphate was prepared by the method of Stadtman and Lipmann,[17] and converted to the disilver salt by metathesis with silver nitrate. The acetyl phosphate solutions were prepared immediately prior to a kinetic run as follows. For the runs in 50% dioxane solution, to 2.00 ml. of a 50% dioxane solution 0.150 *N* in lithium chloride or tetramethylammonium bromide contained in a centrifuge tube was added 0.1 g. of disilver acetyl phosphate. The tube was shaken, and the silver halide and excess silver acetyl phosphate was centrifuged down. For the runs in water, since silver acetyl phosphate is too soluble to permit the use of an excess, 50–60 mg. of the salt was accurately weighed and metathesized with 3.00 ml. of a water solution of the halide as described above. Polydiallyldimethylammonium nitrate was prepared by polymerization[18] of diallyldimethylammonium bromide and then metathesis with silver nitrate. Tetramethylammonium nitrate was prepared by a similar metathesis of tetramethylammonium bromide (Matheson, Coleman and Bell). Fisher certified reagent lithium nitrate was used without further purification.

***p*H Determinations.**—*p*H measurements were made with a Beckman model G *p*H meter equipped with a Beckman 78074 low resistance E-2 bulb glass electrode and a Beckman 1170 calomel reference electrode. Each measurement was made at the same temperature and in the same buffer that was to be used in the run to which it was to apply. The exact significance of the glass electrode-determined *p*H in

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[12] J. T. Edsall and M. H. Blanchard, THIS JOURNAL, **55**, 2337 (1933).

[13] F. Lipmann and L. C. Tuttle, *Arch. Biochem.*, **13**, 373 (1947).

[14] L. F. Fieser, "Experiments in Organic Chemistry," 2nd. ed., D. C. Heath and Co., Boston, Mass., 1941, p. 369.

[15] C. W. Davies and G. H. Nancollas, *Nature*, **165**, 237 (1950).

[16] M. S. Dunn and A. Loshakoff, *J. Biol. Chem.*, **113**, 359 (1936).

[17] E. R. Stadtman and F. Lipmann, *ibid.*, **185**, 549 (1950).

[18] G. B. Butler and R. J. Angelo, THIS JOURNAL, **78**, 4797 (1956).

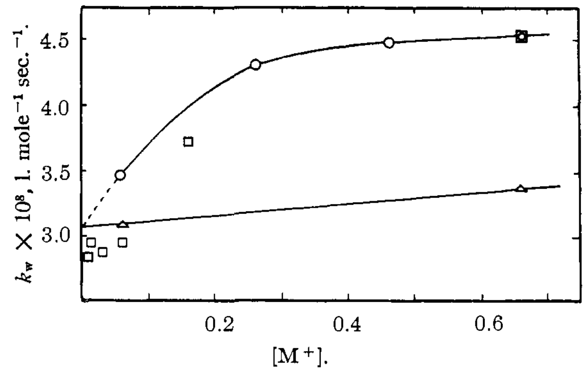

Fig. 1.—k_w as a function of [M^+]: ○, [M^+] = [Li^+]; □, [M^+] = [Li^+] in the presence of 0.063 M TMA$^+$; △, [M^+] = [TMA$^+$].

systems such as the ones under study is not known.[19] There is, however, both theoretical and experimental justification for the assumption that, to a sufficiently good approximation, the observed pH differs from the negative logarithm of the hydrogen ion activity only by an additive constant, as for instance in various dioxane systems.[20] Thus, if a_H represents the hydrogen ion activity on the conventional scale and a'_H the apparent hydrogen ion activity defined as the reciprocal of the antilogarithm of the observed pH, $-\log a_H = -\log a'_H + \log C$ and $a'_H = Ca_H$. This proportionality requires that a rate which is a function of the observed pH be interpreted as the corresponding function of the hydrogen ion activity. The value of a'_{OH} in each buffer was calculated from the measured a'_H and the value of K_W for that particular temperature in pure water.

Kinetic Runs.—To a 25-ml. volumetric flask was added all of the components of the particular run except the acetyl phosphate. The resulting solution was brought to the desired temperature by immersion in a constant temperature bath, and the acetyl phosphate dissolved in the appropriate solvent and brought to the proper temperature then was added. The flask was kept in the constant temperature bath, maintained within ±0.02° of the desired temperature, and 2-ml. aliquots were withdrawn at various intervals. These aliquots were analyzed for acetyl phosphate using Koshland's modification[10] of the method of Lipmann and Tuttle.[8] The optical densities were measured at 540 mμ in a Beckman model DU spectrophotometer.

The rate of disappearance of acetyl phosphate (initial concentrations 2–5 × 10^{-3} M) was pseudo first-order for at least 50% of the reaction in all experiments (initial concentration of glycine in aminolysis runs was 5–15 × 10^{-2} M), and for more than 80% in many experiments. In a typical run, nine or ten aliquots were taken during a time period corresponding to 35–50% of the reaction, and the first-order rate constant with its probable error was calculated by a least square determination of the best linear equation for the acetyl phosphate concentration as a function of time. The average deviation of a single concentration measurement from the line of best fit was *ca.* 1% of the concentration.

The pH dependence of the hydrolysis rate was studied in solutions buffered with N,N-dimethylglycine and N,N-dimethylglycinate, this buffer having been chosen because of its similarity to the glycine–glycinate buffer system present in the glycinolysis experiments.[21] The absence of general base catalysis of the hydrolysis by the buffer species was shown by an unchanged rate when the buffer concentration was doubled. The observed over-all first-order rate constant, k_T, for the disappearance of acetyl phosphate in each glycine buffer was corrected for hydrolysis by subtracting the first-order specific rate of hydrolysis in a system of corresponding pH, salt concentrations, solvent composition and temperature, thus giving the first-order specific rate of glycinolysis. Four separate kinetic runs were made for each selected set of values of temperature, salt concentrations and solvent composition in order to determine the four bimolecular rate constants in eq. 4 for those specific conditions. Thus, two measurements were made in different dimethylglycine buffers to determine k_W and k_{OH}, and two measurements were made in different glycine buffers to determine k_{HG} and k_G. Salts were added as nitrates in all instances to ensure that any specific effects could be attributed to the cation.

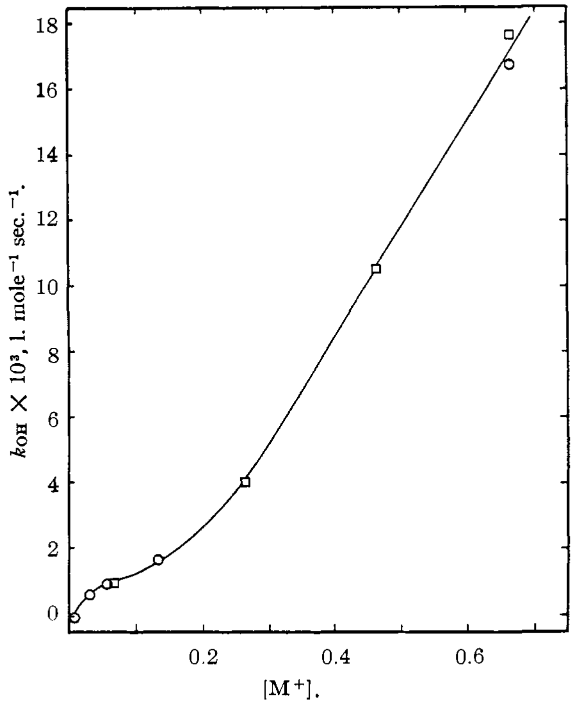

Fig. 2.—k_{OH} as a function of [Li^+]: ○, Li^+ in the presence of 0.063 M TMA$^+$; □, Li^+ alone.

The temperature dependence of the rate constants was determined for the system containing lithium ion or tetramethylammonium ion in 50% dioxane solution. In both instances rates were determined at 0°. For systems containing tetramethylammonium ion the higher temperature determinations were made at 40°, while the higher temperature was reduced to 25° for the systems containing lithium ion because of poor reproducibility at 40°. The enthalpy and entropy of activation for each second-order rate constant at each cation concentration were computed from the data at the two temperatures using the Eyring equation[22] with the assumptions that the transmission coefficient is unity and that the enthalpy and entropy of activation are temperature independent. The probable errors in the activation parameters were calculated from the probable errors in the rate constants.

Discussion

Salt Effects on Rates.—The effect of lithium ion and of tetramethylammonium ion (TMA$^+$) on the individual rate constants for solutions in 50% dioxane at 0° is shown in Figs. 1–4. Similar effects were observed at the higher temperatures. All three constants measurable in the solutions containing no cation other than TMA$^+$ (k_W, k_{HG} and k_G) show a small increase with increasing

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[19] *Cf.*, for example, R. G. Bates, "Electrometric pH Determinations," John Wiley and Sons, Inc., New York, N. Y., 1954.

[20] L. G. Van Uitert and C. G. Haas, THIS JOURNAL, **75**, 451 (1953); E. L. Purlee and E. Grunwald, *ibid.*, **79**, 1372 (1957).

[21] It was assumed that the rate of hydrolysis in a glycine buffer would be the same as in a dimethylglycine buffer at the same pH, temperature, salt concentrations and solvent composition. If a buffer with components of different charge types from those in the glycine system were used for the hydrolysis experiments, such an assumption might be questionable.

[22] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 196.

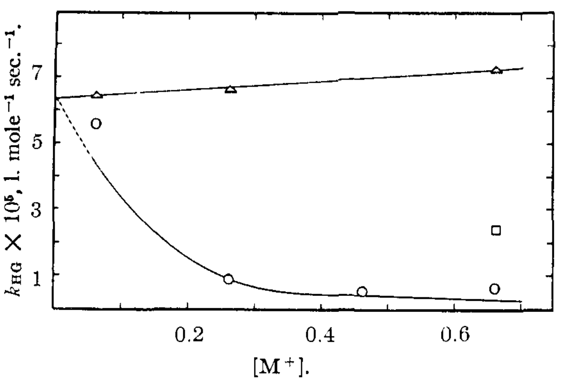

Fig. 3.—k_{HG} as a function of [M$^+$]: ○, [M$^+$] = [Li$^+$]; □, [M$^+$] = [Li$^+$] in the presence of 0.063 *M* TMA$^+$; △, [M$^+$] = [TMA$^+$].

[TMA$^+$] which is linear within experimental error. Lithium ion, on the other hand, is considerably more effective in changing the individual rates and does so in a non-uniform fashion. Thus, increasing [Li$^+$] increases k_W, k_{OH} and k_G, but decreases k_{HG}. The changes in k_W and k_{HG} take place almost entirely before [Li$^+$] has reached 0.263 *M*, whereas no plateau for k_G and k_{OH} is reached in the concentration range studied.

A rationalization of the effects of the cations on the bimolecular rate constants may be formulated in two ways: (1) An alternate path mechanism postulates a new reaction pathway through association of the reactants with the cations, and is the one usually considered for homogeneous catalysis.[23] (2) Alternatively, the effects may be viewed in terms of the Brönsted activity coefficient formulation,[24] which attributes the changes in rate to the differential stabilization of the reactants and transition state through the effect of the cations on the activity coefficients.[25]

In systems such as that under study, in which equilibrium is maintained between associated and non-associated species, the alternate path mechanism merely provides a rationale for that fraction of the activity coefficient product which is due to association. The experimental results presented here are consistent with the assumption that, in the concentration ranges studied, association is the only major factor contributing to changes in the activity coefficient product. Although many of the effects observed are also in qualitative agreement with the predictions based on an ionic strength field mechanism, several effects (such as the variation of k_{OH} with [Li$^+$]) appear to require an association mechanism for their rationalization.

The equivalence of the two formulations may be readily demonstrated for a particular example which fulfills the conditions of association equilibrium and absence of other factors affecting the rates. Consider a reaction between two species, A and B, catalyzed by C which associates only with A. In terms of the Wynne-Jones and Eyring formulation[26] of the Brönsted equation, this may be represented as

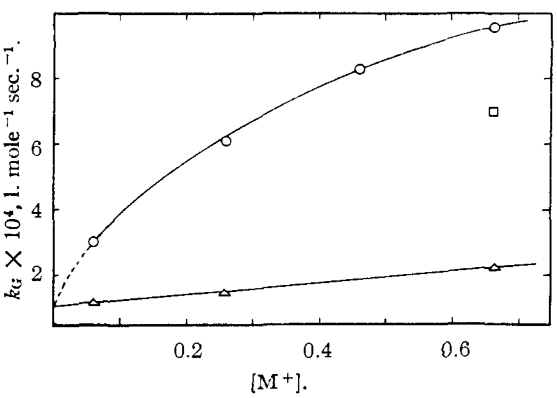

Fig. 4.—k_G as a function of [M$^+$]: ○, [M$^+$] = [Li$^+$]; □, [M$^+$] = [Li$^+$] in the presence of 0.063 *M* TMA$^+$; △, [M$^+$] = [TMA$^+$].

$$\begin{tikzcd}
A + B + C \arrow[r, shift left, "K_1^*"] \arrow[d, shift right] & AB^* + C \arrow[l, shift left] \arrow[r] \arrow[d, shift right] & \text{products} \\
AC + B \arrow[u, shift right, "K_1"'] \arrow[r, shift left, "K_2^*"] & ABC^* \arrow[l, shift left] \arrow[u, shift right, "K_2"'] \arrow[r] & \text{products}
\end{tikzcd}$$

The assignment of an equilibrium constant, K_2, to the association of the transition state is not meant to imply a direct dynamic equilibrium, but only that the associated and non-associated transition states are at their equilibrium concentrations with respect to each other. If the rate law is written as d[products]/dt = k[A][B], then according to the alternate path formulation the rate constant may be split into the sum of two constants each multiplied by the fraction of the total amount of A which is in the form to which that constant applies, *viz.*

$$k = \frac{\kappa T}{h}\left(\frac{(A)}{(A)+(AC)}K_1^* + \frac{(AC)}{(A)+(AC)}K_2^*\right) \qquad (5)$$

However, (A)/((A) + (AC)) = 1/(1 + K_1(C)), (AC/((A) + (AC)) = K_1(C)/(1 + K_1(C)) and $K_2^* = K_1^*K_2/K_1$. Thus, eq. 5 may be written

$$k = \frac{\kappa T}{h} K_1^* \left(\frac{1 + K_2(C)}{1 + K_1(C)}\right) \qquad (6)$$

Alternatively, according to the activity coefficient formulation

$$k = \frac{\kappa T}{h}\frac{y_A y_B}{y^*} K_1^* \qquad (7)$$

where the y's are the molar scale activity coefficients. By the original assumptions, however, $y_B = 1$, y_A = (A)/((A) + (AC)), and y^* = (AB*)/((AB*) + (ABC*)).

Substitution of these relations into eq. 7 gives eq. 6, thus equating the two formulations for the association phenomena. These salt effect formulations are similar to those published by Olson and Simonson.[27]

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[23] See, for example, K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, Chap. 10.

[24] J. N. Brönsted, *J. physik. Chem.*, **102**, 169 (1922); **115**, 337 (1925).

[25] For a similar discussion of the results from a study of the interaction of two inorganic anions, *cf.* A. Indelli and J. E. Prue, *J. Chem. Soc.*, 107 (1959).

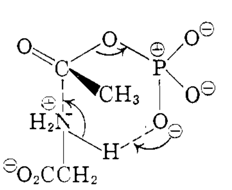
[26] W. F. K. Wynne-Jones and H. Eyring, *J. Chem. Phys.*, **3**, 492 (1935).

[27] A. R. Olson and T. R. Simonson, *ibid.*, **17**, 1167 (1949).

That lithium ion should form a complex with acetyl phosphate is independently suggested not only by Koshland's work on the magnesium ion catalysis of acetyl phosphate hydrolysis, but also by the evidence for the existence of similar complexes of pyrophosphate.[28,29] A chelate structure for the pyrophosphate–alkali metal ion complexes was proposed.[28] A similar structure should be possible with acetyl phosphate and has, in fact, been proposed for the magnesium complex.[11]

For any given mechanism, the charge and polarizability of the transition state relative to the reactants may be estimated. To the extent that these variables determine the association constants, the relative magnitudes of these constants (*e.g.* of K_1 and K_2 in eq. 6), and hence the salt effects due to association, may be predicted.

To explain the apparent nucleophilicity of glycine zwitterion, a quasi-six-membered ring transition state (I) may be postulated in which the nucleophilic character of the nitrogen is increased by transfer of a proton to a phosphate oxygen. Since this transition state should be less easily polarized by a chelated lithium ion than is acetyl phosphate itself, and since it also has a less localized charge, it should form a less stable complex than does acetyl phosphate. Lithium ion should thus decrease k_{HG} by stabilizing the reactants relative to the transition state; *i.e.*, the specific rate of reaction of non-associated acetyl phosphate should be greater than that of associated acetyl phosphate, in agreement with observation. The data suggest that the acetyl phosphate is nearly all in complexed form at $[Li^+]$ above 0.3 M. The effect of $[Li^+]$ on k_W (but not the temperature dependence of k_W; *cf.* later discussion) appears to be consistent with a similar rationale.



I

The large increase in k_G and k_{OH} with increasing $[Li^+]$ is consistent with the expected increase in stability of the complexes upon formation of the triply charged transition state from the doubly and singly charged reactants. The absence of a plateau in the plots of these rate constants *vs.* $[Li^+]$ suggests that the transition state associates with a second lithium ion. Evidence for association of lithium ion with glycinate and hydroxide ions is found in the decrease in the pH of a glycine–glycinate buffer with increasing $[Li^+]$ and in the fact that the activity coefficients of lithium salts of basic anions are known to be abnormally low.[30] Since k_G is still increasing at the highest $[Li^+]$ studied, an appreciable fraction of the glycinate is presumably still unassociated. However, no inferences may be drawn concerning the extent of association of Li^+ with OH^- from the observed linearity of k_{OH} with $[Li^+]$ at the higher lithium ion concentrations. Since k_{OH} is calculated from the observed value of a'_{OH}, rather than from a stoichiometric OH^- concentration, it is required to be a linear function of $[Li^+]$ at lithium ion concentrations in which association of Li^+ and OH^- is the sole factor affecting the rate. The complex variation of k_{OH} with $[Li^+]$ is thus consistent with the rationale that below $[Li^+] = 0.3\ M$, both $AcPO_4^{=}$ and OH^- are increasing their association with Li^+ as the lithium ion concentration increases, while above this concentration the acetyl phosphate is completely complexed and all changes are due to association with OH^-.

The effect of tetramethylammonium ion is much smaller than that of lithium ion in all instances. This might be attributed to: (1) a lack of association with this cation, or (2) a lack of sensitivity of the stability constants of TMA^+ complexes to the polarizability of the anion. That complexes do form and that alternative 1 is probably untenable is suggested by the facts that TMA^+ has been shown to associate with pyrophosphate,[31] and that simple TMA^+ salts often have higher association constants than similar alkali metal salts,[32,33] as well as by the observed decrease in the effectiveness of Li^+ in changing k_{HG} and k_G when TMA^+ is present. Alternative 2 is in agreement with the rationale suggested by Kraus[33] for the dependence of the association constant of TMA picrate on solvent. These facts, together with the nature of the dependence of the rate constants on $[TMA^+]$, support this assumption that the association constants for TMA^+ vary with changes in the charge and not with changes in the polarizability of the anion.

Salt Effects on Enthalpies and Entropies of Activation.—The values of the activation parameters for the four second-order rate constants are given in Table I as functions of cation identity and concentration. Although the changes in ΔH^* and ΔS^* with changes in $[TMA^+]$ are small, those accompanying $[Li^+]$ changes are appreciable and, except for the parameters for k_W, are interpretable in terms of the association model discussed above.

If a transition state is associated to a different extent than the reactants, there should be contributions to ΔS^* and ΔH^* arising from this difference. These contributions would reflect both the binding of the additional particle and the "tighter" structure of the complex having the higher formation constant. Therefore, if the transition state is less associated than the reactants with the result that associating cations decrease the rate, both parameters should increase with increasing cation concentration as was found for k_{HG}. Similarly, if associating cations increase the rate, both parameters should decrease with in-

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(28) S. M. Lambert and J. I. Watters, THIS JOURNAL, **79**, 4262 (1957).

(29) J. R. Van Wazer, E. J. Griffith and J. F. McCullough, *ibid.*, **77**, 287 (1955).

(30) *Cf.* H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolyte Solutions," Reinhold Publishing Corp., New York, N. Y., 1958, p. 514, for a discussion of this phenomenon in relation to ion association and localized hydrolysis.

(31) R. M. Smith and R. A. Alberty, *J. Phys. Chem.*, **60**, 180 (1956).

(32) R. M. Fuoss and C. A. Kraus, THIS JOURNAL, **79**, 3304 (1957).

(33) C. A. Kraus, *J. Chem. Ed.*, **35**, 324 (1958).

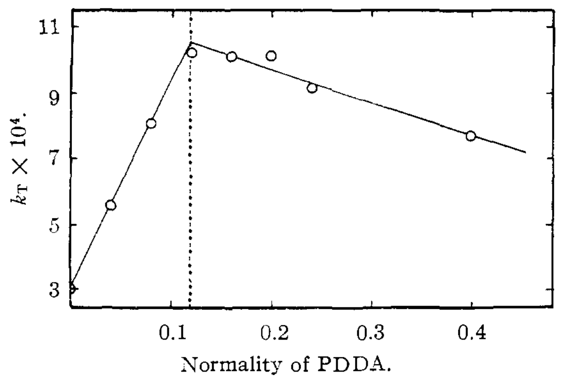

Fig. 5.—k_T as a function of normality of polydiallyldimethylammonium ion: [tetramethylammonium glycinate] = 0.0506 *N*, [HG] = 0.0100 *N*, [$AcPO_4^{=}$] + [$HPO_4^{=}$] = 0.012 *N*.

creasing cation concentration as was found for k_{OH} and k_G. This rationale contains the implicit assumption that any contributions to the changes in the activation parameters arising from the release of solvation accompanying association is small compared to the direct effect of this association. The behavior of the activation parameters for k_W, however, is not consistent with this rationale. Although the changes are small, both ΔS^* and ΔH^* increase, and the effect of the entropy term is dominant. This may indicate that the solvent release contribution is dominant, or simply that the definition of k_W reflects an erroneous view of the mechanism. Another factor which might contribute to the increase in ΔS^* could be a decrease in the entropy of the water due to the structure-forming tendency[34] of lithium ion.

Solvent Effects.—Table II lists rate constants obtained at 0° for water solutions and for 50% dioxane solutions containing either Li^+ or TMA^+ as the sole cation. Two effects are apparent. All rates are slower in water than in 50% dioxane, and the effects of the cations on the rates are smaller in water than in 50% dioxane. This latter effect presumably reflects the expected decrease in electrostatic interactions upon an increase in the dielectric constant. The lower value of k_{HG} in water is in accord with the proposed mechanism in which the charge on the transition state is more highly dispersed than in the reactants. In contrast, the decrease in k_{OH} and k_G is the reverse of that to be expected at infinite dilution. All observed solvent effects are, however, consistent with the association mechanism if two reasonable assumptions are made: (1) in water there is little association of cations with doubly or singly charged anions, although some association with triply charged transition states takes place; and (2) in 50% dioxane there is association with all anions, the association constants varying with the charge and polarizability of the anion and with the identity of the cation as discussed previously. The "inverse" solvent effect on k_G, for example, may be explained by assuming that, due to differential association of reactants and transition state, the transition state is less polar and tighter than the reactants. The low degree of association of $AcPO_4^{=}$ in water is suggested by the lack of lithium ion inhibition of k_{HG}, although the presence of appreciable association with triply charged transition states even in this solvent is suggested by the observed salt effects (*e.g.*, k_G and k_{OH}). It should be pointed out that the comparison of k_{OH} and k_W in the two solvents may not be fully justifiable due to uncertainty as to the relation of the *p*H scales in the two solvents and to the mechanism corresponding to k_W.

TABLE I

TEMPERATURE DEPENDENCE DATA FOR RATES IN 50% DIOXANE

Cation concn., *M*		ΔH^*, kcal. mole^{-1}	ΔS^*, e.u.
		k_W	
(Li^+)	0.063	22.3 ± 0.2	−10.9 ± 0.7
	.263	23.3 ± .4	− 6.7 ± 1.5
	.663	23.5 ± .2	− 6.1 ± 0.7
(TMA^+)	.063	22.1 ± .1	−11.8 ± .3
	.663	22.0 ± .1	−11.9 ± .4
		k_{HG}	
(Li^+)	0.063	14.6 ± 0.4	−24.3 ± 1.5
	.263	23.8 ± 1.9	+ 5.5 ± 6.9
	.663	25.7 ± 6.5	+12 ± 24
(TMA^+)	.063	15.5 ± 0.1	−20.9 ± 0.4
	.263	16.0 ± .2	−18.8 ± .6
	.663	16.1 ± .1	−18.3 ± .5
		k_G	
(Li^+)	0.063	11.3 ± 0.2	−33.1 ± 0.9
	.263	11.3 ± .2	−31.6 ± .5
	.663	9.9 ± .1	−35.8 ± .5
(TMA^+)	.063	11.4 ± .3	−34.7 ± .9
	.263	11.7 ± .2	−33.0 ± .7
	.663	11.2 ± .4	−33.9 ± 1.3
		k_{OH}	
(Li^+)	0.063	27.3 ± 0.8	+27.9 ± 2.7
	.263	21.2 ± .7	+ 8.3 ± 2.6
	.663	19.5 ± .5	+ 4.8 ± 1.8

TABLE II

RATE CONSTANTS AT 0° FOR SINGLE CATION SYSTEMS

	M	*k* (50% dioxane), l. mole^{-1} sec.$^{-1}$	*k* (water), l. mole^{-1} sec.$^{-1}$
k_{HG} in Li^+	0.069	(6.78 ± 0.25) 10^{-5}	(0.47 ± 0.06) 10^{-5}
system	.269	(0.88 ± .25) 10^{-5}	(0.63 ± .02) 10^{-5}
	.669	(0.67 ± .25) 10^{-5}	(1.05 ± .10) 10^{-5}
k_G in Li^+	.069	(3.03 ± .03) 10^{-4}	(0.85 ± .01) 10^{-4}
system	.269	(6.12 ± .04) 10^{-4}	(1.36 ± .02) 10^{-4}
	.669	(9.68 ± .15) 10^{-4}	(1.90 ± .03) 10^{-4}
k_W in Li^+	.069	(3.47 ± .05) 10^{-8}	(0.56 ± .02) 10^{-8}
system	.269	(4.34 ± .06) 10^{-8}	(0.61 ± .02) 10^{-8}
	.669	(4.51 ± .11) 10^{-8}	(0.58 ± .02) 10^{-8}
k_{OH} in Li^+	.069	(0.97 ± .09) 10^{-3}	(1.19 ± .14) 10^{-3}
system	.269	(4.06 ± .26) 10^{-3}	(4.18 ± .27) 10^{-3}
	.669	(17.7 ± .9) 10^{-3}	(11.6 ± .6) 10^{-3}
k_{HG} in TMA^+	.069	(6.57 ± .12) 10^{-5}	(0.68 ± .05) 10^{-5}
system	.269	(6.67 ± .23) 10^{-5}	(.78 ± .08) 10^{-5}
	.669	(7.28 ± .12) 10^{-5}	(.79 ± .04) 10^{-5}
k_G in TMA^+	.069	(1.20 ± .01) 10^{-4}	(.63 ± .01) 10^{-4}
system	.269	(1.49 ± .02) 10^{-4}	(.80 ± .01) 10^{-4}
	.669	(2.27 ± .05) 10^{-4}	(.96 ± .01) 10^{-4}
k_W in TMA^+	.069	(3.11 ± .05) 10^{-8}	(.55 ± .02) 10^{-8}
system	.669	(3.37 ± .07) 10^{-8}	(.54 ± .01) 10^{-8}
k_{OH} in TMA^+	.069	(0.0) 10^{-3}	(.39 ± .11) 10^{-3}
system	.669	(0.0) 10^{-3}	(.61 ± .13) 10^{-3}

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(34) R. W. Gurney, "Ionic Processes in Solution," McGraw-Hill Book Co., Inc., 1953, Chap. 16; H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945).

Effect of a Polyelectrolyte on the Over-all Rate.—The effect of polydiallyldimethylammonium nitrate (PDDANO$_3$) on k_T (see eq. 4) is shown in Fig. 5. No attempt was made to separate the four individual rate constants. The over-all rate increases with increasing polyelectrolyte concentration until the normality of the PDDA$^+$ is equal to the normality of AcPO$_4^=$ + HPO$_4^=$. Further increase in [PDDA$^+$] leads to a decrease in rate and a cloudiness in the solution, the cloudiness disappearing when the polyelectrolyte normality becomes twice that of the bivalent anions. These data suggest that the polyquaternary cation is a more effective catalyst than tetramethylammonium cation, and that association on a one-to-one charge basis takes place. The decrease in rate in the presence of larger amounts of polyelectrolyte may be ascribed tentatively to further complexing and resultant shielding of the AcPO$_4^=$ by the PDDA$^+$.

Preliminary experiments were carried out on a heterogeneous system using a quaternary ammonium type anion exchange resin (Amberlite IR-400) as the added ionic species. After an initial rapid decrease, the acetyl phosphate concentration in the solution phase decreased according to first-order kinetics as in the homogeneous systems. The first-order over-all glycinolysis rate constant appeared to be increased by the resin far more than was the first-order over-all hydrolysis rate constant.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Some Extensions of the Reaction of Trivalent Phosphorus Derivatives with Alkoxy and Thiyl Radicals; a New Synthesis of Thioesters[1]

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A number of new reactions have been investigated. Evidence for a transient tetracovalent phosphoranyl radical is given by the formation of small amounts of toluene in the reaction of benzyl diethyl phosphite with mercaptans. Thiophenol reacts sluggishly with trialkyl phosphites and inhibits the reaction of other mercaptans. The major reaction is a non-radical alkylation of the thiophenol. The reaction of di-*t*-butyl peroxide with triphenylphosphine has been reinvestigated and found to follow the same path as the reaction with phosphites. No *t*-butyl ether is produced. Alkyl disulfides, trialkyl phosphites and CO react to give good yields of thioesters *via* a radical chain. Some *n*-valeraldehyde is produced in the same way when the disulfide is replaced by *n*-butyl mercaptan.

Recent work in this Laboratory[2] has provided evidence that the facile reaction between trialkyl phosphites and mercaptans

$$\mathrm{RSH + P(OC_2H_5)_3 \longrightarrow RH + SP(OC_2H_5)_3} \qquad (1)$$

first described by Hoffmann and co-workers[3] is a radical chain process with the chain-carrying steps

$$\mathrm{RS\cdot + P(OC_2H_5)_3 \longrightarrow RS\dot{P}(OC_2H_5)_3} \qquad (2)$$

$$\mathrm{RS\dot{P}(OC_2H_5)_3 \longrightarrow R\cdot + SP(OC_2H_5)_3} \qquad (3)$$

$$\mathrm{R\cdot + RSH \longrightarrow RH + RS\cdot} \qquad (4)$$

We also have found that, when mercaptan is replaced by disulfide, an alternate chain occurs with (4) replaced by

$$\mathrm{R\cdot + RSSR \longrightarrow RSR + RS\cdot} \qquad (5)$$

Further, alkoxy radicals (*e.g.*, from di-*t*-butyl peroxide) attack trialkyl phosphites in an analogous manner, although by a non-chain process.

$$\mathrm{RO\cdot + P(OC_2H_5)_3 \longrightarrow RO\dot{P}(OC_2H_5)_3} \qquad (6)$$

$$\mathrm{RO\dot{P}(OC_2H_5)_3 \longrightarrow R\cdot + OP(OC_2H_5)_3} \qquad (7)$$

This paper reports some extensions of these reactions which both give further support to the mechanisms proposed earlier and show the possibility of involving additional species in the radical chains.

Reaction of Benzyl Diethyl Phosphite with *n*-Butyl Mercaptan.—The formulation given above implies the formation of a tetracovalent phosphoranyl radical as a transient intermediate formed in reactions 2 or 6. If the four bonds are actually equivalent, it is possible that an alkyl group from the original phosphite rather than the attacking radical will be split off in the subsequent decomposition, reactions 3 or 7. The reactions of benzyl diethyl phosphite present a favorable case, because of the high resonance stabilization of any benzyl radical produced. When benzyl diethyl phosphite was treated with *n*-butyl mercaptan at 60°, approximately 3% of toluene was detected among the products indicating some benzyl radical formation. The balance of the reaction yielded the normal products, *n*-butane and trialkyl phosphorothionate, indicating that cleavage of a C–S bond is the preferred process.[4] Nevertheless, the experiment certainly provides evidence for the existence of the postulated phosphoranyl radical, and higher yields of the "abnormal" cleavage might be expected in other systems.

Reaction of Thiophenol with Triethyl Phosphite.—The reaction sequence 2–4 where R = phenyl (or other aryl group) if successful should provide a novel method of generating phenyl (or other aryl)

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(1) Support of a portion of this work by a grant from the National Science Foundation is gratefully acknowledged.

(2) C. Walling and R. Rabinowitz, THIS JOURNAL, **81**, 1243 (1959).

(3) F. W. Hoffmann, R. J. Ess, T. C. Simmons and R. S. Hanzel, *ibid.*, **78**, 6414 (1956).

(4) Bond dissociation energies for C–S bonds are in general lower than those for corresponding C–O bonds; *cf.* C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 49.