activity of imidazole. The transition state for imidazole carbamate formation can be expected to be destabilized by loss of the aromatic resonance involving the nitrogen atom's unshared electron pair.

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The Acid-Catalyzed Hydrolysis of Acyl Phosphates

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Abstract: The rates of acid-catalyzed hydrolysis of a series of aliphatic acyl phosphates with varying steric bulk in the acyl group have been measured in water at 25°. At constant ionic strength, plots of log k_{obsd} *vs.* log HCl concentration, with acid concentration increasing to 4.80 *M*, are linear with slopes deviating slightly from 1.0. At high ionic strength an abnormal order of reactivity is observed, the 3,3-dimethylbutyryl derivative hydrolyzing faster than the other compounds in the series. There is a large positive ionic strength effect with each compound and 3,3-dimethylbutyryl phosphate is affected to the greatest extent. The second-order rate constant for the acid-catalyzed reaction independent of ionic strength effects for 3,3-dimethylbutyryl phosphate is only slightly less than that for acetyl and much larger than that for trimethylacetyl phosphate. Plots of log $(k_{\text{obsd}} + H_0)$ *vs.* log $(C_H + H_0)$ have linear slopes of +0.31 for acetyl phosphate and −0.33 for 3,3-dimethylbutyryl phosphate, while trimethylacetyl phosphate yielded a curved line. Values of k_{D_2O}/k_{H_2O} are between 2.2 and 2.6 for all compounds. The ΔS^* for 3,3-dimethylbutyryl phosphate (+0.6 eu) is more positive than that for acetyl phosphate (−5.1 eu) or trimethylacetyl phosphate (−9.7 eu). Cleavage of the C–O bond was demonstrated for the 3,3-dimethylbutyryl derivative. The rate constants for acid-catalyzed hydrolysis of substituted benzoyl phosphates in 25% dioxane–H_2O at 25° show only a small sensitivity to electronic effects ($\rho = -0.24$) indicating an A2 mechanism for acyl phosphate hydrolysis. Thus with the aliphatic acyl phosphates, there are very likely differences in the importance of bond breaking in the transition state or differences in ground-state and transition-state hydration.

Water-structuring effects have been postulated to be important in determining protein behavior[2] and could explain in part the efficiency of enzymatic catalysis. The observation of effects due to structured water in hydrolytic reactions in liquid water is, therefore, of considerable importance. Alkyl groups will cause water around a molecule to be more highly ordered.[2] Such effects were previously suggested to explain the pronounced differences in the hydrolysis of N-3,3-dimethylbutyrylimidazolium ion and less highly branched N-acylimidazolium ions in moderately concentrated HCl solutions.[3] It was thought that the acid-catalyzed hydrolysis of highly branched acyl phosphates might prove to be of interest in this regard since compounds of this general type are of great biochemical importance. Therefore, the rates of hydrolysis of a series of acyl phosphates with varying steric bulk in the acyl group have been studied as a function of acid concentration and temperature. Although mechanistic studies have been carried out on acyl phosphate monoanion and dianion reactions[4] very little is known about the acid-catalyzed reaction.

Experimental Section

Materials. Dilithium acetyl phosphate was purchased from Cal Biochem Corp. and was used without further purification. All of the remaining aliphatic acyl phosphates were prepared by the method of Lipmann and Tuttle,[5] and isolated as the disodium salts. Infrared spectra of all the compounds were characteristic of acyl phosphates.[6] Thin layer chromatography using 60% isopropyl alcohol–water as the solvent showed the compounds to contain a trace of inorganic phosphate. The compounds were purified for elemental analysis through isolation as the disilver salts and gave the results in Table I.

Dilithium *p*-nitrobenzoyl phosphate was also prepared by the method of Lipmann and Tuttle[5] as modified by Ramponi, *et al.*[7] The remaining benzoyl phosphates were synthesized by the procedure of Avison[8] with the modifications of Di Sabato and Jencks.[4] The barium salts were converted into the disodium salts by stirring in water with an excess of sodium sulfate, and isolation was by precipitation from a water–ethanol–acetone solution. The acyl phosphates were stored in a desiccator at −4°, and fresh samples were prepared periodically.

Dioxane was purified by the method of Fieser[9] and was stored frozen. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories. The remainder of the chemicals were reagent grade.

Kinetic Measurements. The hydroxamic acid assay was used exclusively for the kinetic runs. The neutral technique as described by Di Sabato and Jencks[10] was used for the aliphatic phosphates.

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[1] This study represents part of the work to be submitted by D. R. Phillips in partial fulfillment of the requirements for the Ph.D. degree, University of Southern California, Los Angeles, Calif. 90033.

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[6] W. P. Jencks, C. Moore, F. Perini, and J. Roberts, *Arch. Biochem. Biophys.*, **88**, 193 (1960).

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[10] G. Di Sabato and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4393 (1961).

Table I. Analytical Results for Acyl Phosphates

Compound	Formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
Isobutyryl phosphate	$C_4H_7O_5PAg_2$	12.57	1.83	8.12	12.58	2.11	8.20
Isovaleryl phosphate	$C_5H_9O_5PAg_2$	15.15	2.27	7.84	15.38	2.47	7.62
Trimethylacetyl phosphate	$C_5H_9O_5PAg_2$	15.15	2.27	7.84	15.16	2.33	7.77
3,3-Dimethylbutyryl phosphate	$C_6H_{11}O_5PAg_2$	17.57	2.68	7.57	17.66	2.67	7.38

For the substituted benzoyl phosphates, the alkaline technique of Hestrin[11] as utilized by Di Sabato and Jencks[4] was employed. All rates were run in duplicate to at least 75% completion, with less than 5% deviation between the two rate constants in all cases. Temperature was controlled to ±0.1° by means of a constant-temperature bath regulated with a Precision Scientific thermoregulator. Each run was initiated by adding the acyl phosphate to the pre-equilibrated acid solution making it approximately 10^{-2} *M* in acyl phosphate. Rates did not change when the acyl phosphate concentration was varied 50%. At appropriate time intervals, aliquots were removed and introduced into the hydroxylamine solution. The resulting mixture was then stoppered and shaken. A Hamilton syringe was used to remove the aliquots in the measurement of the faster rates. Development time for complete formation of the hydroxymate was experimentally determined for each compound. At least nine points were employed for a rate determination, and infinity points were taken at ten half-lives. Pseudo-first-order rate constants (k_{obsd}) were calculated with an Olivetti-Underwood Programma 101 using a computer program designed to calculate a least-squares evaluation of the slope and intercept of a plot of ln $((OD_0 - OD_\infty)/(OD_t - OD_\infty))$ *vs.* time.

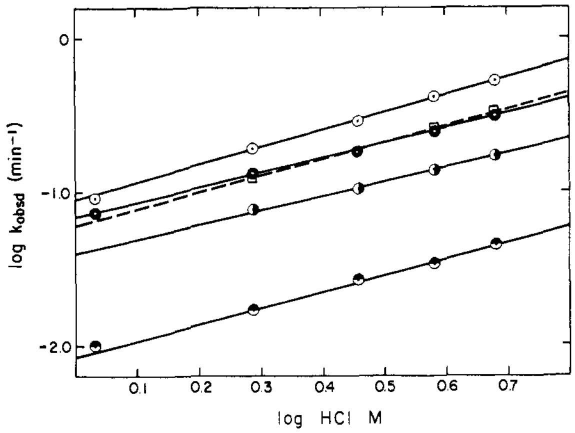

Figure 1. Plot of log k_{obsd} for hydrolysis of 3,3-dimethylbutyryl (⊙), isovaleryl (□), acetyl (●), isobutyryl (◑), and trimethylacetyl phosphate (◓) *vs.* log HCl concentration at 25° and $\mu = 4.80$ *M* with LiCl.

$H_2{}^{18}O$ Experiments. 3,3-Dimethylbutyryl phosphate was dissolved in 4.69 *M* HCl with 1.03 atom % excess $H_2{}^{18}O$ at 25°. At ten half-lives the reaction was stopped by cooling to 0° and was neutralized to pH 8 with NaOH. Inorganic phosphate was then precipitated as the barium salt by the addition of 100% excess equivalents of $BaCl_2$. The mixture was then filtered, and the precipitate was washed and dried. An identical procedure was followed for inorganic phosphate, which was the control for this experiment. That no organic material was precipitated in the 3,3-dimethylbutyryl phosphate experiment was confirmed by the lack of any carboxyl or carbonyl peaks in the infrared spectrum and, indeed, an identical spectrum with that from the control experiment was obtained. Oxygen-18 analyses were carried out by West Coast Technical Service Inc., San Gabriel, Calif.

Product Analysis. Disodium 3,3-dimethylbutyryl phosphate (1.01 g) was dissolved in 20 ml of 5.29 *M* HCl. After complete hydrolysis (ten half-lives) an oil layer formed which was isolated and combined with the ether extracts of the aqueous phase. After removal of the ether, the residue was treated successively in dry benzene with thionyl chloride and aniline. Upon evaporation of the solvent, 0.5 g of the crude anilide (65% yield) was obtained. After two crystallizations from ethanol-water the melting point was 130.5–132°. An authentic sample of 3,3-dimethylbutyranilide melted at 131–131.5°[12] and a mixture melting point revealed no depression (mmp 131–132°). The major reaction products from the acid hydrolysis of 3,3-dimethylbutyryl phosphate are therefore 3,3-dimethylbutyric acid and inorganic phosphate.

Results

Table II presents the rate constants at various HCl concentrations for hydrolysis of five acyl phosphates, ionic strength being held constant at 4.80 *M* at 25°. The logarithms of the rate constants are plotted in Figure 1 *vs.* the logarithms of the concentration of HCl. It can be seen that in the case of the 3,3-dimethylbutyryl derivative, branching at the β-carbon has given rise to faster rates of hydrolysis than seen with the other compounds in the series. The plots are linear, and the slopes approach unity as determined from a least-squares program although some deviation does occur with each compound. The values of the slopes are acetyl phosphate, 0.99; isobutyryl phosphate, 0.86; trimethylacetyl phosphate, 0.99; isovaleryl phosphate, 1.05; 3,3-dimethylbutyryl phosphate, 1.15.

The effect of allowing ionic strength to vary with acid concentration is seen in Table III and Figure 2. The rate constant, k_H', for the acid-catalyzed reaction at a specified ionic strength, is dependent upon the ionic strength of the medium with a very pronounced positive salt effect being observed. Equation 1, where b is a constant for a particular salt and μ is the ionic strength, appears to be valid,[13] and was used to calculate the curved lines in Figure 2.

$$k_{obsd} = (k_0) + (k_H(H^+))10^{b\mu} \qquad (1)$$

The rate constant for hydrolysis of the neutral species of acyl phosphates, k_0, is not significant since k_{obsd} approaches zero with decreasing acidity for all the compounds studied. Values for the acid-catalyzed reaction rate constants, k_H, and b were calculated from eq 1 for HCl solutions and are given in Table IV.

Plots of log k_{obsd} for hydrolysis reactions in acid solutions with no added salt *vs.* $-H_0$ are linear as shown in Figure 3. However, the slopes deviate greatly from unity with values of 0.77 for acetyl phosphate, 0.76 for trimethylacetyl phosphate, and 1.23 for 3,3-dimethylbutyryl phosphate. Since there is a large salt effect and since the slopes are not close to one, mechanistic interpretations cannot be made from these plots.

Rate constants for hydrolysis of the acyl phosphates at a constant HCl concentration of 2.97 *M* and with

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[11] S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

[12] M. Hommelen, *Bull. Soc. Chim. Belg.*, **42**, 243 (1933).

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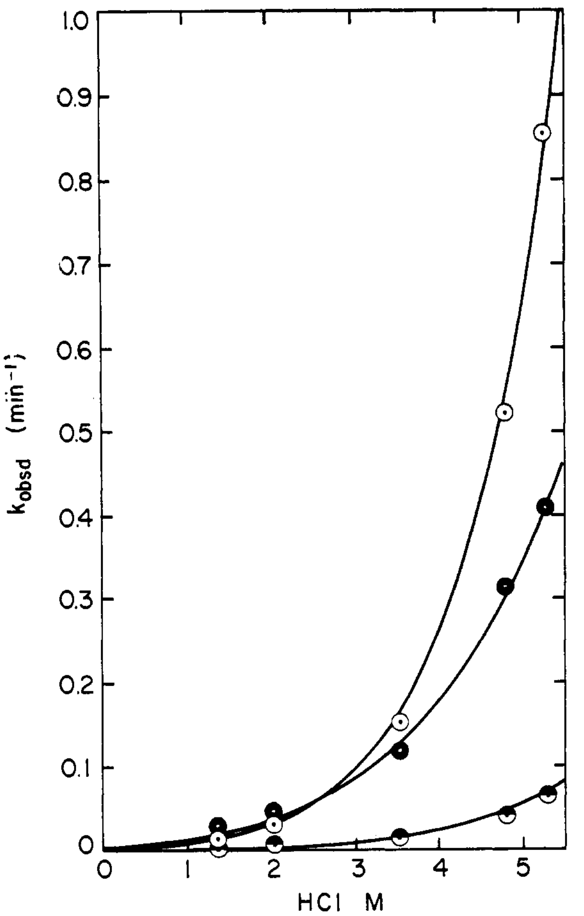

Figure 2. Plot of k_{obsd} for hydrolysis of 3,3-dimethylbutyryl (⊙), acetyl (●), and trimethylacetyl phosphate (◒) *vs.* HCl concentration at 25° (ionic strength not held constant).

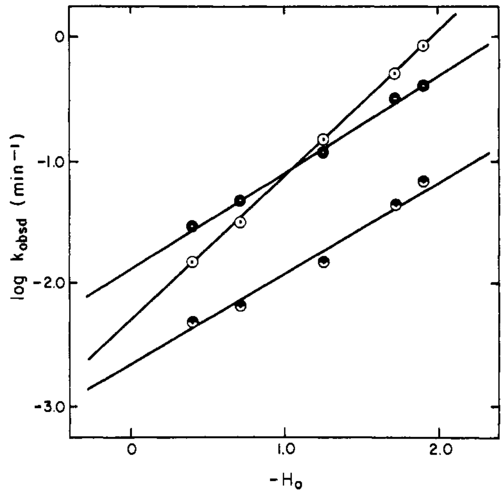

Figure 3. Plot of log k_{obsd} for hydrolysis of 3,3-dimethylbutyryl (⊙), acetyl (●), and trimethylacetyl phosphate (◒) in various HCl solutions *vs.* $-H_0$ at 25°.

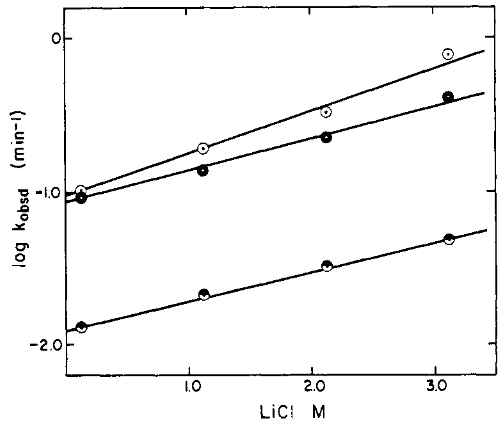

Figure 4. Plot of log k_{obsd} for hydrolysis of 3,3-dimethylbutyryl (⊙), acetyl (●), and trimethylacetyl phosphate (◒) *vs.* LiCl concentration at a constant concentration of HCl of 2.97 *M* at 25°.

varying amounts of LiCl are presented in Table V. The logarithms of k_{obsd} are plotted *vs.* LiCl concentration in Figure 4. The *b* constants were also calculated in these HCl–LiCl solutions (0.13–3.13 *M* LiCl). The lithium salt was employed since lithium ion has nearly the same effect on the activity of water as hydrogen ion.[14] For the HCl and HCl–LiCl solutions the cal-

Table II. Rate Constants for the Hydrolysis of Aliphatic Acyl Phosphates at 25° and μ = 4.80 *M* with LiCl

Acyl group	HCl, *M*	k_{obsd}, min^{-1}	k_H', l. mol^{-1} min^{-1}
Acetyl	1.08	0.070	
	1.94	0.132	0.064
	2.87	0.184	
	3.82	0.246	
	4.80	0.315	
3,3-Dimethylbutyryl	1.08	0.088	
	1.94	0.192	0.117
	2.87	0.289	
	3.82	0.412	
	4.80	0.522	
Isovaleryl	1.94	0.124	0.069
	2.87	0.181	
	3.82	0.253	
	4.80	0.318	
Isobutyryl	1.94	0.078	0.032
	2.87	0.105	
	3.82	0.137	
	4.80	0.169	
Trimethylacetyl	1.08	0.010	
	1.94	0.017	0.0093
	2.87	0.027	
	3.82	0.035	
	4.80	0.044	

Table III. Rate Constants (k_{obsd}[a]) for Hydrolysis of Acyl Phosphates in Various HCl Solutions with No Added Salt at 25°

HCl, *M*	Acetyl	Trimethylacetyl	3,3-Dimethylbutyryl
1.36	0.030	0.0049	0.015
2.03	0.048	0.0066	0.032
3.53	0.120	0.015	0.151
4.80	0.315	0.044	0.522
5.29	0.409	0.068	0.855

[a] Units are min^{-1}.

Table IV. Rate Constants and *b* Values for Hydrolysis of Acyl Phosphates at 25° in HCl Solutions

Acyl group	$k_H \times 10^3$, l. mol^{-1} min^{-1}	*b*(HCl)	*b*(LiCl)
Acetyl	7.58	0.191	0.215
Trimethylacetyl	0.776	0.230	0.193
3,3-Dimethylbutyryl	4.07	0.302	0.289

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[14] R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth and Co. Ltd., London, 1959, p 483.

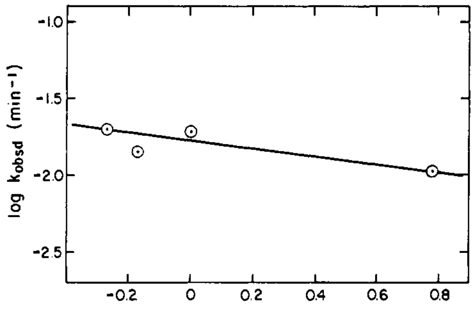

Figure 5. Plot of log k_{obsd} for hydrolysis of *para*-substituted benzoyl phosphates in 25% dioxane-water (v/v) and 3.91 *M* HCl at 25° *vs.* σ, the Hammett substituent constant.

culated values of the constants were quite similar. The values of *b* obtained for acetyl phosphate, trimethylacetyl phosphate, and 3,3-dimethylbutyryl phosphate are given in Table IV.

Table V. Rate Constants (k_{obsd}[a]) for Hydrolysis of Acyl Phosphates at a Constant HCl Concentration of 2.97 *M* and at 25° with Variable Ionic Strength Made Up with LiCl

LiCl, *M*	Acetyl	Trimethylacetyl	3,3-Dimethylbutyryl
0.13	0.091	0.013	0.101
1.13	0.137	0.021	0.190
2.13	0.226	0.032	0.377
3.13	0.402	0.048	0.775

[a] Units are min^{-1}.

The acid-catalyzed hydrolysis of acetyl phosphate has been shown to take place predominantly with C–O bond cleavage.[15] 3,3-Dimethylbutyryl phosphate was analyzed by a similar procedure as outlined in the Experimental Section. The results, expressed in atom % excess oxygen-18 in $Ba_3(PO_4)_2$ above that normally occurring in H_2O, were 0.008 in the control and 0.000 for the complete hydrolysis of 3,3-dimethylbutyryl phosphate. It is readily apparent that in 4.69 *M* HCl, extensive incorporation of ^{18}O into the inorganic phosphate product has not taken place. Predominantly C–O bond cleavage must be occurring, as is also the case for acetyl phosphate.

In Table VI are given rate constants in D_2O–DCl solutions. DCl in deuterium oxide increases the rates of hydrolysis compared to the rates obtained with an equal concentration of HCl in water. The ratios of k_D/k_H are between 2.2 and 2.6 for all compounds studied.

Table VI. Rate Constants for Hydrolysis of Aliphatic Acyl Phosphates in 4.72 *M* HCl[a] in H_2O and 4.72 *M* DCl in D_2O at 25°

Acyl group	H_2O k_{obsd}, min^{-1}	D_2O k_{obsd}, min^{-1}	k_D/k_H
Acetyl	0.284	0.627	2.21
3,3-Dimethylbutyryl	0.487	1.11	2.28
Isobutyryl	0.166	0.371	2.24
Trimethylacetyl	0.0413	0.106	2.56

[a] The rate constants in 4.72 *M* HCl were obtained by interpolation of the plots of log k_{obsd} *vs.* HCl concentration.

The rate constants for acid-catalyzed hydrolysis of substituted benzoyl phosphates are given in Table VII. As shown in Figure 5, a ρ value close to zero (−0.24) is obtained when the logarithms of the rate constants are plotted *vs.* σ, Hammett's substituent constants;[16] 25% dioxane–H_2O (v/v) was chosen as the solvent for the reaction since this was the best compromise between solubility of the reactant and the reaction product. *p*-Chlorobenzoic acid was insoluble in this solution and, therefore, the rate of hydrolysis of *p*-chlorobenzoyl phosphate could not be determined. It is assumed that the substituted benzoyl phosphates all have the same *b* value.

Table VII. Rate Constants for Hydrolysis of *para*-Substituted Benzoyl Phosphates at 25° in 25% Dioxane–H_2O (v/v) with an HCl Concentration of 3.91 *M*

para substituent	k_{obsd}, min^{-1}
OCH_3	0.0200
CH_3	0.0143
H	0.0194
NO_2	0.0107

In Table VIII are reported rate constants for hydrolysis of the aliphatic acyl phosphates in 2.87 *M* HCl and at various temperatures. Values of ΔH^* and ΔS^* are also given in Table VIII. It can be seen that the ΔS^* for 3,3-dimethylbutyryl phosphate is 5.7 eu more positive than that for acetyl phosphate and 10.3 eu more positive than the ΔS^* for hydrolysis of trimethylacetyl phosphate.

Table VIII. Rate Constants for the Hydrolysis of Aliphatic Acyl Phosphates in 2.87 *M* HCl at Various Temperatures with μ = 4.80 *M* Made Up with LiCl, and the Activation Parameters for the Hydrolysis Reactions

Acyl group	Temp, °C	k_{obsd}, min^{-1}	ΔH^*, kcal/mol	ΔS^*,[a] eu
Acetyl	10	0.026		
	15	0.049		
	25	0.184	21.2 ± 0.1[b]	−5.1 ± 0.5
	30	0.341		
	35	0.595		
3,3-Dimethylbutyryl	10	0.034		
	15	0.066		
	25	0.289	23.2 ± 0.2	+0.6 ± 0.7
	30	0.561		
	35	1.011		
Trimethylacetyl	15	0.0080		
	25	0.027	21.2 ± 0.3	−9.7 ± 1.2
	30	0.058		
	35	0.097		
	40	0.162		

[a] Calculated at 25° employing values of k_H (l. mol^{-1} sec^{-1})
[b] Errors were calculated from the standard error of plots of log k_{obsd} *vs.* $1/T$.

Rate constants were also determined in 25% dioxane–H_2O (v/v) at 25° and are given in Table IX. Dioxane has a retarding effect on the rate in all cases, but the

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(15) J. H. Park and D. E. Koshland, Jr., *J. Biol. Chem.*, **233**, 986 (1958).

(16) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

Table IX. Rate Constants for Hydrolysis of Aliphatic Acyl Phosphates in 25% Dioxane–H_2O (v/v) at 25° and an HCl Concentration of 3.91 M

Acyl group	H_2O k_{obsd}[a]	Dioxane–H_2O k_{obsd}	$k_{dioxane}/k_{H_2O}$
Acetyl	0.164	0.132	0.80
3,3-Dimethylbutyryl	0.213	0.146	0.69
Trimethylacetyl	0.0211	0.0191	0.91

[a] The rate constants in 3.91 M HCl were obtained by interpolation of the plots of log k_{obsd} *vs.* HCl concentration.

effect is much greater for the 3,3-dimethylbutyryl derivative than for acetyl or trimethylacetyl phosphate.

In Table X rate constants are given for hydrolysis of the acyl phosphates in perchloric acid. It can be seen that the rates of hydrolysis of 3,3-dimethylbutyryl phosphate and trimethylacetyl phosphate are greater in perchloric acid than with an equal amount of HCl. The values of b were calculated in perchloric acid and were found to be 0.307 for trimethylacetyl phosphate and 0.389 for 3,3-dimethylbutyryl phosphate. Thus b is greater in perchloric acid than hydrochloric acid, a result which eliminates the possibility of nucleophilic attack by the anion since halogens are much better nucleophiles than perchlorate. The value of b could not be determined for acetyl phosphate in perchloric acid since that compound is insoluble in the solution.

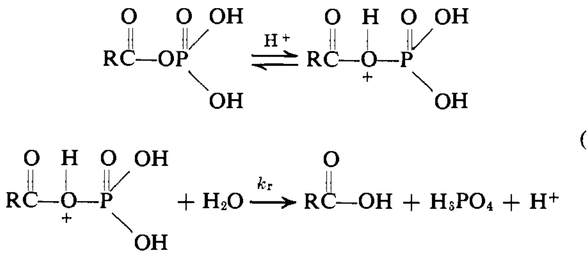
Table X. Rate Constants for Hydrolysis of Aliphatic Acyl Phosphates in Perchloric Acid at 25°

Acyl group	$HClO_4$, M	k_{obsd}, min^{-1}
3,3-Dimethylbutyryl	0.964	0.0088
	1.88	0.0362
	2.91	0.144
	4.20	0.738[a]
Trimethylacetyl	4.20	0.0635[b]

[a] In comparison the rate constant in 4.20 M HCl, obtained by interpolation of a plot of log k_{obsd} *vs.* HCl concentration, was 0.286 min^{-1}. [b] The rate constant in 4.20 M HCl is 0.0263 min^{-1}.

Discussion

For the compounds studied, the reaction can be described in terms of an A2 mechanism involving attack of solvent on the protonated acyl phosphate as shown in eq 2. Water very likely attacks as a nucleophile at the carbonyl carbon as indicated by the lack of sensitivity to electronic effects ($\rho = -0.24$) in the acid-catalyzed hydrolysis of substituted benzoyl phosphates. The finding of C–O bond cleavage shows that attack of water is at the carbonyl carbon and not at phosphorus, and the D_2O solvent isotope effects ($k_D/k_H = 2.2$–2.6) are consistent with the occurrence of a preequilibrium protonation step. The small ρ value observed for substituted benzoyl phosphate hydrolysis can be explained by invoking compensating effects; increased electron withdrawal in the benzoyl group will decrease the equilibrium concentration of protonated intermediate but will increase the ease of attack of water at the carbonyl carbon. Partial cancellation of these effects should give a ρ close to zero. An A1 reaction in which an acylium ion was formed, however, might be expected to show correlation with σ^{+}[17] with a highly negative value of ρ as in the acid-catalyzed hydrolysis of substituted 2,6-dimethylbenzoate esters.[18]



$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}O\overset{O}{\overset{\|}{P}}(OH)_2 \overset{H^+}{\rightleftharpoons} R\overset{O}{\overset{\|}{C}}{-}\underset{+}{\overset{H}{O}}{-}\overset{O}{\overset{\|}{P}}(OH)_2}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}\underset{+}{\overset{H}{O}}{-}\overset{O}{\overset{\|}{P}}(OH)_2 + H_2O \xrightarrow{k_r} R\overset{O}{\overset{\|}{C}}{-}OH + H_3PO_4 + H^+} \qquad (2)$$

At high ionic strength the rates of hydrolysis of the α-branched compounds, trimethylacetyl phosphate and isobutyryl phosphate, are slower than the rate for acetyl phosphate, but the rates for the β-branched compounds, 3,3-dimethylbutyryl phosphate and isovaleryl phosphate, are faster than that for acetyl phosphate. Increased steric bulk at the reaction center should not increase the equilibrium concentration of protonated intermediate, and the rate of nucleophilic attack by water should be decreased. A change in mechanism to A1 for the 3,3-dimethylbutyryl derivative might account for the abnormal steric order of reactivity, although it would naturally be expected that the mechanism would be the same for all the compounds studied since the acylium ion that would be produced in an A1 reaction should be a highly unstable intermediate. However, the data are in accord with an A1 mechanism for 3,3-dimethylbutyryl phosphate and therefore this must be regarded as a possibility.

The rate differences at high acidity are at least partially due to ionic strength effects as seen from the larger value of b reported in Table IV for 3,3-dimethylbutyryl phosphate than for acetyl or trimethylacetyl phosphate. All of the compounds are subject to a marked positive salt effect, and at constant HCl concentration, increasing concentrations of LiCl have a greater effect in the hydrolysis of the 3,3-dimethylbutyryl derivative than in the hydrolysis of acetyl or trimethylacetyl phosphate.

In addition to salt effects, however, other factors are influencing the observed relative rate ratios. The values of k_H reported in Table IV also show differences that would not be expected if increased bulk in the acyl group were simply influencing the reaction by steric hindrance to approach of an attacking water molecule. 3,3-Dimethylbutyryl phosphate has a k_H that is only 1.9 times less than that for acetyl and which is 5.2 times greater than that for trimethylacetyl. On the basis of steric hindrance the 3,3-dimethylbutyryl acyl group should produce a large reduction in rate compared to acetyl and should also give a slower rate than trimethylacetyl since its steric effects constant, E_s, is more negative (-1.74 compared to -1.54).[19] The rate constants for hydroxide ion catalyzed hydrolysis of these compounds show pronounced rate retardations due to increased steric hindrance; the relative rate ratios being acetyl 1.0, trimethylacetyl 0.0073, and 3,3-dimethylbutyryl 0.0064.[20] The mechanism for the hydroxide

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(18) M. L. Bender and M. C. Chen, *J. Am. Chem. Soc.*, **85**, 37 (1963).

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(20) D. R. Phillips and T. H. Fife, unpublished data.

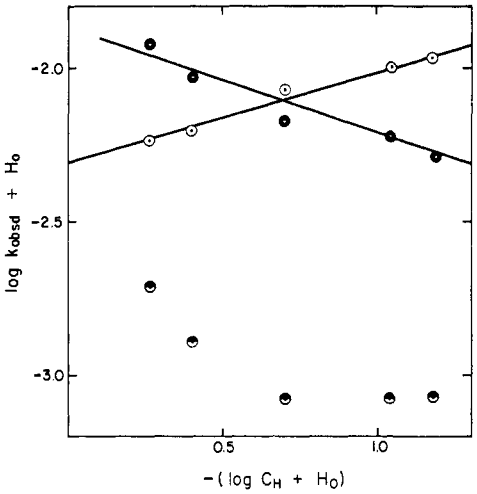
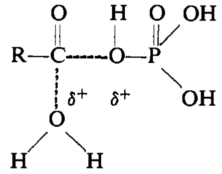


Figure 6. Plots of log ($k_{obsd} + H_0$) *vs.* log ($C_H + H_0$) for hydrolysis of 3,3-dimethylbutyryl (⊙), acetyl (●), and trimethylacetyl phosphate (◓) in various HCl solutions at 25°.

ion catalyzed reaction undoubtedly involves nucleophilic attack by hydroxide ion at the carbonyl group of the dianionic species.

Possible insight into the problem of the abnormal order of reactivity in acid might be realized through use of Bunnett's linear free energy relationships.[21] These relationships can serve as an indication of the involvement of water in the reaction but do not necessarily yield conclusive evidence for the mechanism involved. Problems encountered in this regard have been discussed previously.[22] The degree of water involvement, ϕ, is obtained from the slope of log (k_{obsd} + H$_0$) *vs.* log ($C_H + H_0$). From known reactions, Bunnett suggested that for water not involved in the rate-limiting step, ϕ is less than zero; for water involved as a nucleophile, ϕ = 0.22–0.56; and for water involved as a proton-transfer agent, ϕ is greater than 0.58. As seen in Figure 6, linear slopes are obtained with values of 0.31 for acetyl phosphate and −0.33 for 3,3-dimethylbutyryl phosphate, while trimethylacetyl phosphate yields a curved line with a slope approaching zero as the acid concentration is increased. From Bunnett's empirical criteria, therefore, water should act as a nucleophile in the hydrolysis of the conjugate acid of acetyl phosphate, should not be involved in the hydrolysis of 3,3-dimethylbutyryl phosphate and may or may not be involved in the hydrolysis of trimethylacetyl phosphate. In the latter case the curved plot could indicate a mechanism change as acid concentration is increased. Plots (not shown) of log ($k_{obsd} + H_0$) *vs.* log a_{H_2O} had slopes, *w*, that would be interpreted in the same manner,[23] *w* being +1.8 with acetyl phosphate and −2.3 in the case of 3,3-dimethylbutyryl phosphate. Interpretation of the observed acid effects in terms of either the Zucker–Hammett hypothesis[24,25] or the Bunnett modifications[21,23] is obviously difficult, and neither of these treatments can be employed with great confidence as criteria of mechanism.

A concerted reaction, as shown in eq 3, in which the reaction becomes progressively more unimolecular with increased branching in the acyl group, would be in accord with the observed acid effects. The facilitation in rate produced by the highly branched acyl group might then be due to relief of strain upon stretching the C–O bond in the transition state. If this were occurring, however, it might reasonably be expected that trimethylacetyl phosphate would hydrolyze more rapidly than 3,3-dimethylbutyryl which is not the case. It should be pointed out that it is not known whether ^{18}O exchange between water and the carbonyl oxygen of acyl phosphates takes place in the acid-catalyzed reactions, and therefore, evidence is lacking as to whether tetrahedral intermediates might occur.



(3)

If the mechanism is the same for all the compounds then the Bunnett values may be simply indicating that there is much less change in hydration upon going from the ground state to the transition state for 3,3-dimethylbutyryl phosphate than for acetyl phosphate, and that for trimethylacetyl phosphate this change is also not as pronounced.

The rate expression for an A2 acyl phosphate hydrolysis reaction is

$$k_{obsd} = (k_r/K_{SH^+})a_H a_{H_2O}^{\ n}(f_s/f_\pm) \tag{4}$$

where f_s and $f_\pm$ are the activity coefficients for substrate and transition state and *n* is the formal order with respect to water.[25] Ions that salt out the substrate more than the transition state will raise its activity coefficient and thereby increase the rate[26,27] if, of course, the activity coefficient effects can overcome the adverse effects of high salt concentration on the activity of water. These considerations have previously been applied to anhydride solvolysis where acid effects are also complicated.[28] The increased rates and *b* values for 3,3-dimethylbutyryl phosphate in perchloric acid compared to HCl are surprising since perchlorate generally salts in to a greater extent than chloride ion,[27,28] but it was found that in the A2 hydrolysis of acetic anhydride, perchloric acid at concentrations above 1.5 *M* was a better catalyst than HCl although the reverse was true in the case of trimethylacetic anhydride.[28]

The faster rate for the 3,3-dimethylbutyryl derivative in 2.87 *M* HCl with an ionic strength of 4.80 is due solely to a more favorable ΔS^*, which might again indicate that with 3,3-dimethylbutyryl phosphate there is more unimolecular character or much less difference in hydration between the ground state and the transition state than with acetyl phosphate or trimethylacetyl phosphate. It is perhaps surprising that the ΔS^* values are in general as positive as was found. However, Kugel and Halmann[29] obtained a ΔS^* of −6.0 eu for the acid-catalyzed hydrolysis of ethyl phosphate, a compound which hydrolyzes by an A2 mechanism. Therefore, ΔS^* is not expected to be highly negative,

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and the high ionic strength may make it even more positive.

Steric hindrance to solvation of the transition state would not be expected to lead to the rate facilitation seen with 3,3-dimethylbutyryl phosphate. Therefore, if there is smaller hydration change upon going from ground state to transition state with the 3,3-dimethylbutyryl acyl group it must be because of increased ground-state hydration as is also probable in the case of N-3,3-dimethylbutyryl imidazolium ion.[3] The rates of acid-catalyzed hydrolysis measured in 25% dioxane–water are consistent with solvent ordering in the ground state for 3,3-dimethylbutyryl phosphate since its rate was decreased much more than that of the two other compounds studied. This could be due to preferential solvation of the highly branched acyl group by the dioxane component of the solvent.

It would thus appear that the values of k_H for the acyl phosphates, which show a smaller sensitivity to steric bulk in the acyl group and a faster rate for 3,3-dimethylbutyryl phosphate than expected for an A2 reaction, and the unusual differences brought about by increasing acid concentrations can be explained either by increasing unimolecular character in the rate-determining step as branching in the acyl group increases, or smaller differences in hydration between ground state and transition state with greater acyl group branching, possibly due to the ability of alkyl groups to structure water around them in the ground state. These effects are not mutually exclusive and it is possible that both types of effects are important.

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Ethyl Vinyl Ether Hydrolysis in Dimethyl Sulfoxide as Solvent[1a]

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Abstract: When water, strong acid, and ethyl vinyl ether are all solutes in DMSO the rate of hydrolysis of the vinyl ether is still controlled by the rate of proton transfer to carbon. This rate is dissected, giving rate constants for the DMSO-solvated proton, k_H, and the monohydrated proton, k_{H_3O}, the former being about twice as large as the latter. This shows that direct proton transfer from strong acid to a carbon atom is possible, without an intervening water molecule and other evidence suggests that this is the predominant mechanism even when water is the solvent. If isotope effects on k_{H_3O} are assumed to be the same as those in water, reasonable and internally consistent isotope effects on k_H can be estimated. The variation in rate as a function of solvent composition is analogous to that for A1 reactions, and quite different from that for A2 reactions.

In a number of previous papers[2–4] detailed studies of proton transfers from aqueous acid to organic substrates have been reported. In none of these has it been possible to prove, definitively, the value of n in Figure 1. No evidence requiring that it be greater than zero has been developed, but, similarly, no evidence requiring that it be identically zero has been produced. In a recent paper[5] Goodall and Long have inferred that $n = 0$ for protonation of nitroalkane anions. Their inference, however, depends on assumptions about the transition state which, although reasonable, lack experimental support. It does not seem likely that definitive evidence on this point will be forthcoming for aqueous solutions.

The present paper reports results obtained in dilute solution in dimethyl sulfoxide (DMSO) with water present as a solute. The reaction chosen for study was ethyl vinyl ether cleavage (eq 1) which has already been

$$CH_2{=}CHOEt + H_2O \longrightarrow CH_3CH{=}O + EtOH \qquad (1)$$

extensively studied in aqueous solution. The results rigorously demonstrate that n equals zero in at least one case. While they apply directly only to the system actually studied, certain features of the results strongly suggest that the conclusions apply to aqueous solutions as well.

Results

Equilibrium Constants. If water is added to DMSO containing a small concentration of dissociated acid a series of hydrates, $H^+(H_2O)_m$, should be formed. In the limit, at very low water concentration, the equilibrium for the formation of the first of these (eq 2) can

$$H^+ + H_2O \overset{K_H}{\rightleftharpoons} H\cdot H_2O^+ \qquad (2)$$

be studied. (All the species in eq 2 are DMSO solvated.) In the presence of an acid–base indicator

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(1) (a) Supported, in part, by the National Science Foundation through GP-7915. (b) National Science Foundation Postdoctoral Fellow, 1966–1967.

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