derivative had mp 254–256° (lit.[28b] 225–226°) and was analyzed because of the discrepancy with the literature value. *Anal.* Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22. Found: C, 82.75; H, 6.22. 4,7-Dimethyl-1-naphthyl-*p*-toluenesulfonamide melted at 217.7–220.2° (lit.[28b] 218°). The amine obtained from the Schmidt reaction was converted to the bromo compound by the diazotization procedure of Newman and Wise.[56] 1-Bromo-4,7-dimethylnaphthalene was obtained in 31.9% yield as an oil which boiled at 120–125° (1.0 mm) (lit.[27] 171–172° (15 mm)) and did not solidify. The picrate melted at 120.1–121.5° (lit.[27] 114°). *Anal.* Calcd for $C_{18}H_{14}BrN_3O_7$: C, 46.57; H, 3.04. Found: C, 46.50; H, 2.99. The trinitrobenzene derivative has mp 153.8–155.2°. *Anal.* Calcd for $C_{18}H_{14}BrN_3O_6$: C, 48.23; H, 3.15. Found: C, 48.49; H, 3.40. Gas chromatography of the picrate mixture from the preparative bromination of 1,6-dimethylnaphthalene enriched with the above picrate, showed that this isomer is the one second in retention time of the three formed in preparative bromination.

Kinetic Determinations and Product Analysis. The kinetic determinations were carried out as described previously,[16] and all runs were conducted at least in duplicate. Rate constants were obtained graphically from the integrated form of the second-order rate equation by the method of least squares. The probable errors in the individual rate constants (k_{obsd}) and in the final rate constants, k (eq 1; Table I) were rarely greater than 2%. The kinetic runs were conducted over a period of several years, but with each new compound a previously determined one was usually checked to assure reproducibility of the technique, of the preparations of the solutions, etc.[3] The kinetics of bromination of 1,4-dimethylnaphthalene had the same characteristics as those found in the case of 1,5-dimethylnaphthalene.[16] In 75% acetic acid k_1 is 1.10 l. mol^{-1} sec^{-1}, and the ratio k_{-1}/k_2 has the value 5.93.

For product analysis of the kinetic runs, 100 ml of solution, 0.004 *M* in mono- or dimethylnaphthalene, 0.10 *M* in NaBr, 0.40 *M* in $NaClO_4$ and approximately 0.001 *M* in Br_2 was allowed to stand in brown bottles, thermostated at 25°, for at least ten half-lives of the reaction. Two isolation runs on 2,6-dimethylnaphthalene were also carried out with 0.5 *M* NaBr and no $NaClO_4$ (material balances 92.2 and 98.3%) and another two runs only with 0.1 *M* NaBr (material balances 94.0 and 97.8%). The variations in salt concentrations had no detectable effect on the composition of the product mixtures. The product mixtures were worked up by extraction with five 20-ml portions of petroleum ether, which were washed with four 20-ml portions of water, dried, and analyzed as described before.[2,16] At least two independent kinetic runs were analyzed for products, and between 3 and 8 chromatographs were recorded for each compound. The errors listed in Table II for the products are average deviations.

The results of the calculations of the MO parameters are contained in the Ph.D. dissertation of Kim.[2]

Acknowledgment. This work was supported by National Science Foundation Grant GP-4986, which is gratefully acknowledged. We also acknowledge stimulating discussions with Professor P. B. D. de la Mare.

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(56) M. S. Newman and P. H. Wise, *J. Amer. Chem. Soc.*, **63**, 2847 (1941).

Enol Phosphates of β-Keto Acids. Synthesis and Hydrolysis of Ethyl β-Hydroxy-*trans*-cinnamic Acid Cyclic Phosphate[1]

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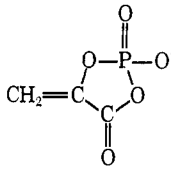
Abstract: The reaction of ethyl phosphoenol benzoylacetic acid (**6**) with N,N′-dicyclohexylcarbodiimide results in formation of the cyclic anhydride **2**. Hydrolysis of **2** in ^{18}O-enriched water indicated carbon–oxygen bond fission. The hydrolysis was subject to catalysis by hydroxide, by hydronium ion, and by general bases.

Since the investigations by Perkow in 1952,[2] a considerable amount of work has been done in the synthesis and reactions of enol phosphates.[3] A number of these enol phosphates have been found to be effective phosphorylating agents.[4,5] Enol phosphates obtained from keto acids, such as phosphoenol pyruvate,[6] are of particular interest, since they may fulfill important biological roles as phosphorylating agents.[7]

The reported[8] formation of an unstable cyclic anhydride of phosphoenol pyruvate (**1**) and its powerful phosphorylating ability led us to investigate the related compound, ethyl β-hydroxy-*trans*-cinnamic acid cyclic phosphate (**2**). Since the evidence for **1** was based primarily on its infrared spectrum, we hoped to produce a more stable compound of this type by taking advantage of the greater stability of six-membered cyclic phosphates.[9]



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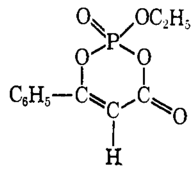

2

Prior to this work only one cyclic anhydride of this type had been reported. Salicoyl cyclic phosphate

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(1) Aided by Grant No. IN57-F from the American Cancer Society.

(2) W. Perkow, K. Ullerich, and F. Meyer, *Naturwissenschaften*, **39**, 353 (1952).

(3) (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 103–109.

(4) F. Cramer and K. Gartner, *Ber.*, **91**, 704 (1958); F. Cramer and R. Wittmann, *ibid.*, **94**, 328 (1961).

(5) H. H. Wasserman and D. Cohen, *J. Org. Chem.*, **29**, 1817 (1964).

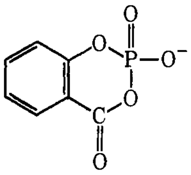
(6) For a recent investigation of phosphoenol pyruvate and ethyl phosphoenol pyruvate see S. J. Benkovic and K. J. Schray, *Biochemistry*, **7**, 4090, 4097 (1968).

(7) V. M. Clark, D. W. Hutchinson, A. J. Kirby, and S. G. Warren, *Angew. Chem. Intern. Ed. Engl.*, **3**, 678 (1964); V. M. Clark and D. W. Hutchinson, *Progr. Org. Chem.*, **7**, 75 (1968).

(8) V. M. Clark and A. J. Kirby, *J. Amer. Chem. Soc.*, **85**, 3705 (1963).

(9) H. G. Khorana, G. M. Tenner, R. S. Wright, and J. G. Moffatt, *ibid.*, **79**, 430 (1957); J. R. Cox, R. E. Wall, and F. H. Westheimer, *Chem. Ind.* (London), 929 (1959); P. C. Haake and F. H. Westheimer, *J. Amer. Chem. Soc.*, **83**, 1102 (1961).

(**3**), which had been considered a possible intermediate in the hydrolysis of salicyl phosphate,[10] was prepared *in situ* from salol phosphate.[10d,11]



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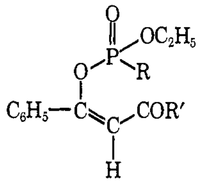
This investigation is concerned with the synthesis and characterization of **2**, together with an investigation of its reactions with nucleophiles. We were particularly concerned whether increasing the ring size would result in loss of the phosphorylating ability present in **1**.

Results and Discussion

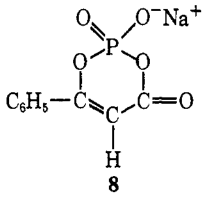
Synthesis of Ethyl β-Hydroxy-*trans*-cinnamic Acid Cyclic Phosphate (2). Both acid- and base-catalyzed hydrolysis of diethyl *trans*-2-carbethoxy-1-phenylvinyl phosphate (**4**)[12] lead to extensive cleavage of the enol phosphate.[3a] This difficulty may, however, be circumvented by monodealkylation of **4** with sodium iodide in butanone.[13] Mild basic hydrolysis of the resulting monohydrogen phosphate (**5**) resulted in the formation of ethyl phosphoenol benzoylacetic acid (**6**). Treatment of **6** with N,N′-dicyclohexylcarbodiimide led to the formation of **2**.



4, $R = R' = C_2H_5O$
5, $R = OH$; $R' = C_2H_5O$
6, $R = R' = OH$
7, $R = OH$; $R' = p\text{-}CH_3C_6H_4NH$

The structure of **2** was established by means of its spectral and chemical properties. The single anhydride carbonyl absorption at 1770 cm^{-1} is particularly characteristic of the mixed anhydride structure,[8,14] and the ultraviolet and proton magnetic resonance (pmr) spectra were also consistent with the proposed structure.

Hydrolysis of **2** allowed determination of the equivalent weight as well as the isolation of **6** in excess of 90% of the theoretical yield. On reaction with *p*-toluidine in acetate buffer the carboxylic amide **7** was obtained. Perhaps the most convincing evidence for the structure is the facile dealkylation of **2** with sodium iodide to the sodium salt **8**, a material which could also be obtained in low yield on the reaction of **6** with sodium iodide.



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Since no other reasonable structure could account for the observed physical and chemical properties, it is clear that the product of the dicyclohexylcarbodiimide reaction has the structure **2**.

Hydrolysis of 2. As a model for nucleophilic reactions, the hydrolysis of **2** was investigated in detail. In water, **2** is rapidly converted to the diacid **6**, and further hydrolysis results in the formation of acetophenone, carbon dioxide, and ethyl dihydrogen phosphate.[15]

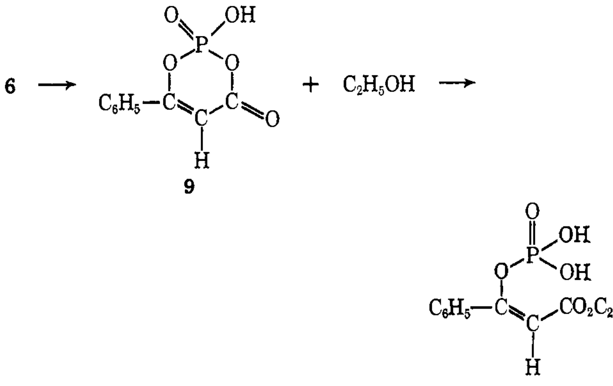
Nucleophilic attack of a water molecule might occur either at phosphorus or at the carbonyl carbon. In an attempt to distinguish between these possibilities the hydrolysis was carried out in water containing 2% ^{18}O. Pyrolysis of **6** obtained from this hydrolysis gave carbon dioxide containing 2.5 times the natural abundance of ^{18}O (Table I), in contrast to the fivefold increase anticipated for exclusive attack at the carbonyl carbon. Although these data might be interpreted as evidence of substantial phosphorus–oxygen bond cleavage on hydrolysis of **2**, the possibility of oxygen scrambling on pyrolysis must be considered.

Table I. ^{18}O-Content of Carbon Dioxide Samples

CO_2 sample	46/44 mass ratio	Atom % ^{18}O
Natural abundance	0.00408[a]	0.20
Equilibration of **6** in 2% $H_2{}^{18}O$	0.0042 ± 0.0002	0.21 ± 0.01
Hydrolysis of **2** in 2% $H_2{}^{18}O$	0.0101 ± 0.0006	0.50 ± 0.03
Hydrolysis of **5** in 2% $H_2{}^{18}O$	0.0164 ± 0.0006	0.82 ± 0.03

[a] This value was used for calibration of the instrument.

The formation of sodium salt **8** on reaction of **6** with sodium iodide suggests the possibility of an equilibrium between the diacid and the anhydride, and if attainment of such an equilibrium occurs more rapidly than decarboxylation, the carbon dioxide obtained from pyrolysis would contain only half the ^{18}O present in the carbonyl of **6**. An equilibrium of this type could also ex-



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(10) (a) J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Amer. Chem. Soc.*, **74**, 4347 (1952); (b) J. D. Chanley and E. M. Gindler, **75**, 4035 *ibid.*, (1953); (c) J. D. Chanley and E. Feageson, *ibid.*, **77**, 4002 (1955); (d) M. L. Bender and J. M. Lawlor, *ibid.*, **85**, 3010 (1963).

(11) The related phosphonate has recently been reported as an intermediate in the hydrolysis of diethyl 2-carboxyphenylphosphonate: G. M. Blackburn and M. J. Brown, *ibid.*, **91**, 525 (1969).

(12) J. C. Craig and M. Moyle, *J. Chem. Soc.*, 3712 (1963).

(13) E. Y. Spencer, A. R. Todd, and F. M. Webb, *ibid.*, 2968 (1958).

(14) D. L. Griffith and M. Stiles, *J. Amer. Chem. Soc.*, **87**, 3710 (1965).

(15) The formation of acetophenone from **6**, however, occurs at a much slower rate than hydrolysis of **2**, having a rate constant of 3.03 × 10^{-6} sec^{-1} at 26° in 0.1 *M* HCl.[16] Therefore, the results reported here are not complicated by this further reaction.

(16) J. F. Marecek, unpublished observations. See also ref 3a.

plain the large amount of ethyl benzoylacetate obtained on pyrolysis by formation of a new anhydride **9**, which could react with ethanol.

As a test of this possibility we have carried out the hydrolysis of **5** in 2% ^{18}O water. The resulting diacid, which should contain somewhat more than 1% ^{18}O as a result of oxygen exchange prior to hydrolysis,[17] was isolated and pyrolyzed. The carbon dioxide obtained in this manner showed significant loss of the ^{18}O label. In light of this observation the ^{18}O results provide no evidence for significant phosphorus–oxygen bond cleavage.

The rate of hydrolysis of **2** was measured in a series of solutions ranging between 1.5 *M* HCl and pH 11.8 (Table II). At zero buffer concentrations the pH–rate profile (Figure 1) is characterized by a broad region between pH 3 and pH 8.5 which is independent of the acidity. Above pH 8.5 the rate of hydrolysis increases rapidly with increasing basicity, and it becomes too rapid to measure accurately by our technique above pH 11. The hydrolysis also shows a significant, though smaller, acid catalysis below pH 2. These results are characteristic of reactions having an observed rate constant of the type shown in eq 1, in which there is a significant contribution due to the uncatalyzed term, k_O.

Table II. The Effect of pH on the Rate of Hydrolysis of **2**[a]

pH[b]	Buffer	10^3k (sec^{-1})
	1.5 *M* HCl	26
	0.5 *M* HCl	13.2
	0.5 *M* $HClO_4$	13.3
1.48	0.05 *M* HCl	6.64
1.60	0.05 *M* $HClO_4$	5.64
2.01	0.005 *M* HCl	5.90
2.11	0.005 *M* $HClO_4$	5.08
2.97	0.0005 *M* HCl	5.83
3.59	Formate	4.69[c]
4.32	Formate	5.04[c]
5.13	Acetate	4.75[c]
6.05	Acetate	5.05[c]
6.50	Acetate	5.10[c]
6.73	Phosphate	5.10[c]
7.38	Sodium formate	4.89[c]
7.77	Phosphate	4.75[c]
8.31	Sodium acetate	4.85[c]
9.59	Sodium bicarbonate	8.31
10.00	Carbonate	11.3
10.80	Carbonate	23
11.45	Carbonate	50
11.50	0.0015 *M* NaOH	76
11.70	Carbonate	70
11.80	0.0025 *M* NaOH	145

[a] 26.0 ± 0.1°; 50% acetonitrile (v/v); ionic strength 0.05 *M*. [b] Observed with a radiometer pH meter, Model 28. Differences between the initial and final pH measurements were ±0.02 pH unit or less. [c] Extrapolated to zero buffer concentration.

$$k = k_O + k_{H_3O^+}(H_3O^+) + k_{OH^-}(OH^-) \qquad (1)$$

The rate in the presence of a number of salts showed a small, but relatively constant, rate enhancement over that measured in pure water (Table III), probably largely the result of an ionic strength effect. This rate increase was smallest when perchlorate was employed, and at high concentrations of KCl the rate of hydrolysis was depressed.

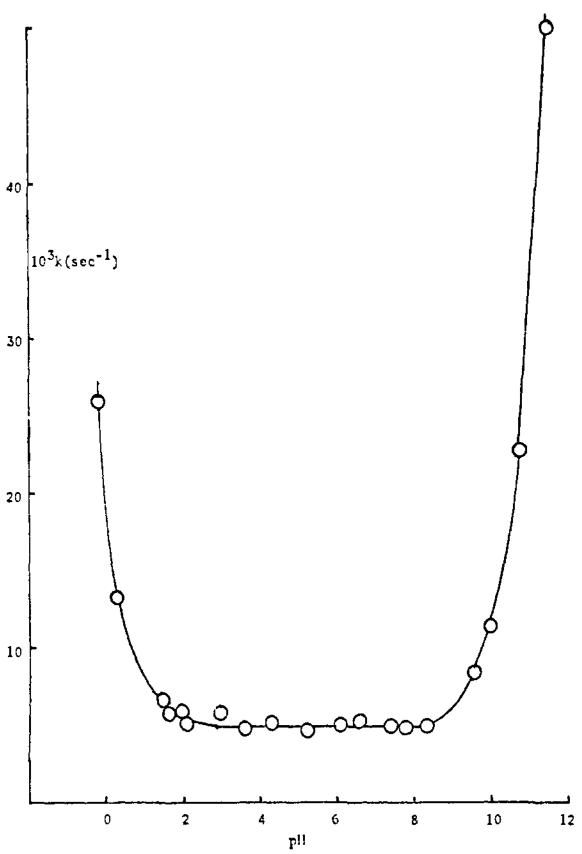

Figure 1. pH–rate profile for hydrolysis of **2**.

In addition to hydroxide and hydronium ion catalysis, the hydrolysis of **2** was also subject to catalysis by the basic forms of the buffer ions. In the pH-independent region the rate constant could be described by eq **2**. The values of k_B for several buffers are sumarized in Table IV. A plot of log k_B *vs.* pK_{BH} (Figure 2) showed good agreement with the Brønsted catalysis law[18] (eq 3) in which the value of β was 0.14.

Table III. Effect of Added Salts on the Rate of Hydrolysis of **2**[a]

Added salt	10^3k (sec^{-1})
None	4.81
0.25 *M* KCl	4.38
0.05 *M* KCl	5.15
0.025 *M* KCl	5.11
0.05 *M* NaCl	5.25
0.05 *M* NaBr	5.15
0.05 *M* $KClO_4$	4.89
0.05 *M* LiCl	5.19
0.033 *M* $MgCl_2$	5.28
0.033 *M* $CaCl_2$	5.30

[a] 26.0 ± 0.1°; 50% acetonitrile (v/v); unbuffered.

$$k = k_O + \Sigma k_B(B^-) \qquad (2)$$

$$\log k_B = \beta pK_{HB} + \log G \qquad (3)$$

Reactions which are subject to general base catalysis normally show solvent isotope effects in the range 2–3, while those involving nucleophilic catalysis are in the

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(17) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *J. Amer. Chem. Soc.*, 83, 4193 (1961).

(18) J. N. Brønsted, *Chem. Rev.*, 5, 231 (1928).

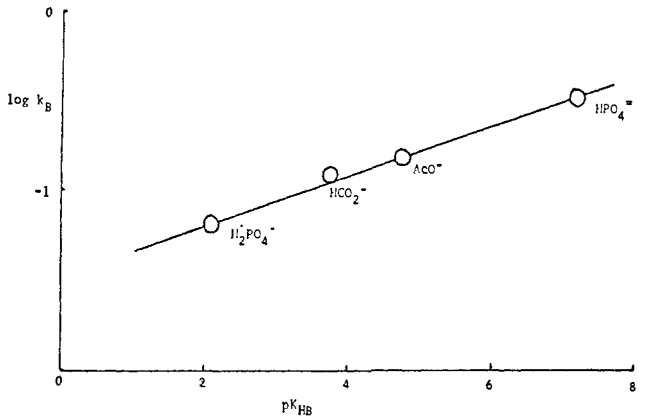

Figure 2. Brønsted plot of catalytic constants for the hydrolysis of **2**.

range between 0.8 and 1.9.[19] The deuterium oxide solvent isotope effect for hydrolysis of **2** in 50% acetonitrile (Table V) was found to be 2.96, a value quite similar to the 2.9 observed for the uncatalyzed hydrolysis of glutaric anhydride in 50% dioxane.[20] Perhaps a better method for distinguishing between nucleophilic and general base catalysis is the measurement of the isotope effect on the base catalytic constant, k_B. Isotope effects of 2 or greater are normally observed if the rate-determining step involves abstraction of a proton by the basic species.[21,22] The ratios of k_B in water and deuterium oxide were evaluated for acetate and formate from the data of Table IV. While the isotope effect of 1.91 for acetate is somewhat ambiguous, the value of 2.38 obtained for formate is clearly consistent with general base catalysis.

Several mechanisms have been proposed to account for general base catalysis.[23,24] Unfortunately, these possibilities are kinetically indistinguishable. By analogy with other highly reactive esters[21,25] and anhydrides,[14] however, it seems probable that nucleophilic attack of water is assisted by removal of a proton by the base (eq 4), resulting in a high energy tetrahedral intermediate.[26]

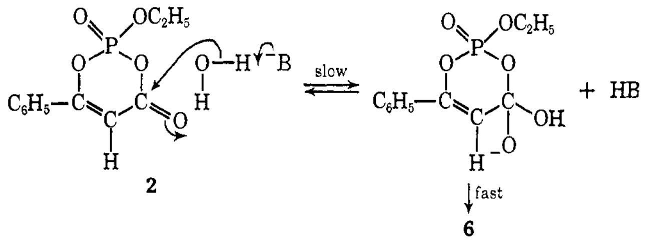

Table IV. Catalysis by General Bases on the Hydrolysis of **2**[a]

Base	Concentration of basic species (mol/l.)	10^3k (sec^{-1})	k_B (l. mol^{-1} sec^{-1})
Water		4.81 (k_0)	
Formate[b]	0.05	10.5	0.114
	0.025	7.76	0.106
	0.01	6.76	0.165
	0.005	5.94	0.166
Formate[c]	0.05	10.2	0.107
Formate[d]	0.05	10.4	0.111
		Av	0.126 ± 0.035
Formate (D_2O)[e]	0.05	4.41	0.058
	0.025	2.97	0.050
Formate (D_2O)[f]	0.05	4.05	0.051
		Av	0.053 ± 0.005
Acetate[g]	0.05	12.2	0.148
	0.025	8.61	0.140
	0.01	6.76	0.165
	0.005	5:79	0.136
Acetate[h]	0.05	12.3	0.149
Acetate[i]	0.05	11.9	0.142
Acetate[j]	0.05	12.1	0.146
		Av	0.147 ± 0.008
Acetate (D_2O)[k]	0.05	5.85	0.085
	0.025	3.62	0.076
	0.01	2.48	0.075
		Av	0.078 ± 0.007
Phosphate[l]	0.041[n]	9.89	
	0.0205[n]	7.49	
	0.0041[n]	5.67	
Phosphate[m]	0.0232[n]	11.0	
	0.0116[n]	7.54	
	0.0023[n]	5.27	
$H_2PO_4^-$			0.066[o]
HPO_4^{2-}			0.337[o]
Hydroxide			*Ca.* 52

[a] 26.0 ± 0.1°; 50% acetonitrile (v/v); ionic strength 0.05 *M*. [b] pH 4.35. [c] pH 3.59. [d] $NaHCO_2$, pH 7.35. [e] pD 4.30. [f] $Na\cdot HCO_2$, pD 7.75. [g] pH 6.07. [h] pH 6.50. [i] pH 5.13. [j] $NaC_2H_3O_2$, pH 8.31. [k] pD 6.28. [l] pH6.71. [m] pH 7.72. [n] $H_2PO_4^-$ + HPO_4^{2-}. [o] Calculated from $k = k_0 + k_{H_2PO_4^-}(H_2PO_4^-) + k_{HPO_4} = (HPO_4^{2-})$.

Table V. Effect of Solvent on the Rate of Hydrolysis of **2**[a]

Solvent	10^3k (sec^{-1})
H_2O	170
25% CH_3CN-H_2O	22.9
50% CH_3CN-H_2O	5.15
50% CH_3CN-H_2O[b]	4.81
50% CH_3CN-H_2O[b]	4.81
50% CH_3CN-D_2O	1.73
50% CH_3CN-D_2O[b]	1.53
75% CH_3CN-H_2O	0.78

[a] 26.0 ± 0.1°; unbuffered; ionic strength 0.05 *M* (KCl) unless otherwise stated. [b] No KCl added.

The reactions of **2** with nucleophiles are remarkably different from the reported reactions of **1**,[8] as **2** exhibits no evidence for attack at phosphorus. In part this difference in behavior may reflect the frequently observed differences between five- and six-membered cyclic phosphates.[9] In addition to the difference in ring size, however, **2** is a neutral species, while **1** is present in the anionic form. Nucleophilic attack at the carbonyl of **1** would therefore require the leaving group

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(19) M. L. Bender, E. J. Pollock, and M. C. Neuer, *J. Amer. Chem. Soc.*, **84**, 595 (1962).

(20) T. C. Bruice and W. C. Bradbury, *ibid.*, 87, 4838 (1965).

(21) W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961).

(22) A. R. Butler and V. Gold, *J. Chem. Soc.*, 2305 (1961).

(23) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(24) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

(25) M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Amer. Chem. Soc.*, **85**, 3017 (1963).

(26) A referee has suggested the possibility that the rate-determining step might be the hydrolysis of a new anhydride formed by reaction of **2** with the buffer ions. Although this mechanism should be considered, it is a very unlikely possibility in this case. The rate of hydrolysis of **2** is about 150 times that of acetyl phosphate under similar conditions,[27] and the hydrolysis of acetic anhydride in 50% dioxane proceeds at about $^1/_{25}$ the rate of hydrolysis of **2**.[22] It would appear, then, to be highly unlikely that the similar anhydrides formed by nucleophilic attack of phosphate or acetate on **2** could be intermediates in the hydrolysis.

(27) G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 4400 (1961).

to be a dianion, while nucleophilic attack on **2** displaces a phosphate monoanion. These difference in the leaving group ability may be sufficient to result in the observed differences in behavior. We are currently investigating the reactions of **8** in an effort to assess this possibility.

Experimental Section

Diethyl *trans*-2-carbethoxy-1-phenylvinyl phosphate (4) was obtained by reaction of the sodium enolate of ethyl benzoylacetate with diethyl phosphorochloridate in absolute ethanol. The product had bp 154–157° (0.4 mm) (lit.[12] 151–153° (0.005 mm)). The pmr spectrum of **4** showed it to be exclusively the *trans* isomer, which is characterized by a vinyl hydrogen absorption ($CDCl_3$) at 5.85 ppm (J_{PH} = 2 Hz).[28]

Ethyl *trans*-2-Carbethoxy-1-phenylvinyl Monohydrogen Phosphate (5). A solution containing 78.7 g (0.24 mol) of **4** and 36 g (0.24 mol) of sodium iodide in 500 ml of butanone was heated to reflux for 3 hr. Removal of the solvent *in vacuo* left a viscous residue which was dissolved in 250 ml of water. The aqueous solution was washed with ether to remove unreated **4** (4.0 g), acidified, and extracted with four 100-ml portions of chloroform. The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. Crystallization of the residue from chloroform–petroleum ether afforded 52.8 g (74%) of **5**, mp 62.5–64° dec.

Anal. Calcd for $C_{13}H_{17}O_6P$: C, 52.02; H, 5.77; P, 10.31. Found:[29] C, 51.97; H, 5.80; P, 10.55.

Ethyl Phosphoenol Benzoylacetic Acid (6). The monoacid **5** (48.2 g; 0.16 mol) was added to a solution of 16 g (0.40 mol) of sodium hydroxide in 300 ml of water, and the resulting solution was allowed to stir at room temperature for 16 hr. After acidification with cold HCl, the aqueous solution was extracted with five 100-ml portions of chloroform. Removal of the dried (Na_2SO_4) solvent under reduced pressure left a residue which was crystallized from chloroform–petroleum ether to give 41.0 g (94%) of the diacid, mp 110–112° dec, $\lambda_{max}^{CH_3CN}$ 285 mμ (ε 15,000).

Anal. Calcd for $C_{11}H_{13}O_6P$: C, 48.61; H, 4.82; P, 11.38. Found: C, 48.55; H, 4.95; P, 11.38.

Ethyl β-Hydroxy-*trans*-cinnamic Acid Cyclic Phosphate (2). The diacid **6** (4.90 g; 0.019 mol) was suspended in a solution of 3.70 g (0.019 mol) of N,N′-dicyclohexylcarbodiimide in 100 ml of anhydrous ether. After stirring the mixture at room temperature for 18 hr, the dicyclohexylurea was removed by filtration, and the solvent was removed *in vacuo*. Crystallization of the residue from ether–petroleum ether afforded 3.09 g (68%) of **2**. The analytical sample had mp 57.5–61°.

Anal. Calcd for $C_{11}H_{11}O_5P$: C, 51.97; H, 4.36; P, 12.19. Found: C, 51.76; H, 4.46; P, 12.33.

The infrared spectrum of **2** (Nujol) exhibited a single carbonyl stretching frequency at 1770 cm^{-1}. Additional strong absorptions occurred at 1610, 1300, 1200, 1020, 970, 910, 855, 820, 770, and 680 cm^{-1}. The ultraviolet absorption showed $\lambda_{max}^{CH_3CN}$ 285 mμ (ε 25,000). The nmr spectrum ($CDCl_3$) consisted of a complex aromatic region centered at *ca.* 7.7 ppm (5 protons), a doublet at 6.20 ppm (J_{PH} = 1 Hz; 1 proton), a complex methylene region centered at 4.40 ppm (2 protons), and a methyl triplet at 1.41 ppm (3 protons).

A solution of 0.4271 g of **2** in 8.770 g of benzene, fp 5.40°, exhibited a fp 4.40°, corresponding to a molecular weight of 250 ± 10 (calcd 254).

Hydrolysis of 2. A 418.6 mg sample of **2** was added to 50.0 ml of 0.197 *N* NaOH. After 5 min the excess base was titrated with 0.201 *N* HCl. The resulting titration curve exhibited points of inflection at pH 7.5 (33.2 ml) and at pH 3.8 (41.4 ml) corresponding to an equivalent weight of 128 ± 4 (calcd 127).

In a separate experiment 332 mg (1.31 mmol) of **2** was added to 15 ml of 1 *N* NaOH. After 5 min the solution was acidified and extracted with chloroform. There was obtained 342 mg (93%) of **6**, mp 110–112° dec, identical with previous samples.

Reaction of 2 with *p*-Toluidine. A solution of 515 mg (2.13 mmol) of **2** in 1 ml of dioxane was added to 20 ml of 50% aqueous dioxane containing 500 mg (4.67 mmol) of *p*-toluidine at pH 4.7 (acetate buffer). After 5 min the solution was acidified and extracted with chloroform. Crystallization of the residue remaining after removal of the solvent afforded 694 mg (90%) of amide **2**, mp 133–135°.

Anal. Calcd for $C_{18}H_{19}NO_5P$: C, 60.00; H, 5.31; N, 3.89; P, 8.59. Found: C, 60.08; H, 5.47; N, 3.89; P, 8.63.

Reaction of 2 with Sodium Iodide. A solution of 2.00 g (7.88 mmol) of **2** and 1.20 g (9.00 mmol) of sodium iodide in 30 ml of acetone was heated to reflux for 30 min. The insoluble salt was filtered, washed with acetone, and vacuum dried to give 1.77 g (91%) of **8**. Recrystallization from methanol gave the analytical sample which decomposed at 275°.

Anal. Calcd for $C_9H_6O_5PNa$: C, 43.53; H, 2.44; P, 12.48; equiv wt, 124. Found: C, 43.33; H, 2.45; P, 12.57; equiv wt, 127 ± 5.

The pmr spectrum of **8** (D_2O) exhibited only aromatic and vinyl hydrogens in the expected 5:1 ratio. The carbonyl absorption (Nujol) occurred at 1700 cm^{-1}. Other strong infrared absorptions occurred at 1600, 1570, 1310, 1160, 1050, 975, 810, 765, and 680 cm^{-1}.

Reaction of 6 with Sodium Iodide. A solution of 2.00 g (7.3 mmol) of **6** and 1.08 g (7.3 mmol) of sodium iodide in 30 ml of acetone was heated to reflux for 8 hr. Filtration gave 0.46 g (25%) of **8**, mp 274–276° dec, which was identical with the authentic sample. No additional **8** could be obtained on further heating.

Hydrolysis of 2 in ^{18}O-Enriched Water. A solution of 374 mg of **2** in 1.5 ml of acetonitrile was treated with 1 ml of 2% ^{18}O-enriched water[30] and allowed to stand at room temperature for 45 min. The usual chloroform extraction gave 130 mg of **6**, mp 106–108°, which had an infrared spectrum identical with an authentic sample.

As a control a sample of **6** was treated with ^{18}O-enriched water under identical conditions.

Hydrolysis of 5 in ^{18}O Water. A 0.300 g (1 mmol) sample of **5** was added to a sodium hydroxide solution prepared by dissolving 0.05 g of sodium in 2 ml of 2% ^{18}O water. After stirring at room temperature overnight, dilute hydrochloric acid was used to adjust the solution to pH 5 and the water was removed *in vacuo*. The residue was dissolved in chloroform and separated from sodium chloride by filtration. Crystallization from ether–petroleum ether gave 200 mg (74%) of the diacid **6**, mp 105–107°.

Pyrolysis of 6. A sample of **6** (50–100 mg) was placed in a small flask which was attached to a collecting bottle immersed in liquid nitrogen. The system was evacuated to 0.05 mm, and the sample was pyrolyzed at 200° until decomposition was complete (*ca.* 3 min). The reaction flask was replaced by a second collecting bottle, and the carbon dioxide was purified[31] by several vacuum distillations from a Dry Ice–acetone bath. The purified CO_2 was analyzed on a Varian M-66 medium resolution mass spectrometer.

Kinetic Method. Rates were measured by means of a Cary 14 recording spectrometer equipped with a thermostated cell compartment maintained at 26.0 ± 0.1°. The reactions were initiated by injecting 0.10 ml of a 1.2×10^{-3} *M* solution of **2** in acetonitrile into 2.90 ml of the approprirate buffer.[32] The disappearance of **2** was monitored by following the decrease in optical density (OD) at 285 mμ. Although both **2** and **6** exhibit uv maxima at 285 mμ, the extinction coefficients are sufficiently different to allow use of this technique. First-order rate constants were calculated from the integrated rate expression using graphical methods. Plots of $-\log (OD - OD_\infty)$ *vs.* time were linear for at least 80% of the reaction. All rate constants were made in duplicate, and separate determinations were within 5%.

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(28) The *cis* isomer which may be obtained from the reaction of ethyl α-chlorobenzoylacetate with triethyl phosphite after chromatographic separation on silica gel, exhibits a vinyl hydrogen absorption at 6.09 ppm (J_{PH} = 2 Hz).

(29) Microanalysis by Clark Microanalytical Laboratory, Urbana, Ill.

(30) Fluka A G Chemisches Fabrik, Switzerland.

(31) Other products of the pyrolysis were acetophenone, ethyl benzoylacetate, and a resinous phosphorus-containing residue.

(32) Buffers were prepared as described in "Biochemists Handbook," C. Long, Ed., D. Van Nostrand Co., Princeton, N. J., 1961, pp 22–42.