added to a suspension of phenanthrenequinone (10.4 g., 50 mmoles) in dry benzene (100 ml.), under nitrogen with stirring. A clear, red-brown solution was observed after 45 min. at 20° Within 2 hr., the solution was nearly colorless. Removal of the benzene *in vacuo* left a yellow oil which soon became a nearly colorless crystalline mass (16 g.). One recrystallization from hexane gave the colorless **phenanthrenequinone–trimethyl phosphite adduct** (**VII**), m.p. 71–73°, in 90% yield (15 g.). The analytical sample had m.p. 74–75°.

Other trialkyl phosphite adducts were prepared in *ca.* 95% yield by this method. The reaction with aliphatic α-diketones, like biacetyl, is particularly exothermic and must be moderated by external cooling.

(b) **In the Absence of Solvents. Procedure** B.—Trimethyl phosphite (6.82 g., 50 mmoles) was mixed with solid benzil (10.5 g., 50 mmoles) under nitrogen. An exothermic reaction ensued, and a colorless oil resulted within 30 min. The oil was dissolved in hexane (30 ml.) and the solution was cooled at 0°. Colorless crystals of the **benzil–trimethyl phosphite adduct** (**X**), m.p. 47–49° separated within 8–10 hr.; the yield was nearly quantitative.

Biacetyl (74 g.) was added dropwise to trimethyl phosphite (135 g.) under nitrogen, with stirring and external cooling. The mixture was then kept at 60° for 15 min. and submitted to fractional distillation. The **colorless biacetyl–trimethyl phosphite adduct** (**XIII**) was collected at 45–47° (0.5 mm.); the yield was quantitative. The liquid adduct becomes slightly yellow on standing, or in contact with air, even if the latter is dry, since biacetyl is formed by oxidation.

Triphenyl Phosphite Adducts.—A suspension of phenanthrenequinone (2.08 g., 10 mmoles) in triphenyl phosphite (12.4 g., 40 mmoles) was kept 16 hr. at 110°, under nitrogen with stirring. The pale yellow solution was cooled, treated with hexane, and filtered. The colorless insoluble **phenanthrenequinone -triphenyl phosphite adduct** (**IX**) (4.5 g.) had m.p. 143–145°. One recrystallization from benzene–hexane gave material of m.p. 145–147°.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN 11, CONN.]

The Participation of the Amide Group in the Solvolysis of Phosphoric Acid Esters. I. Phosphotriesters in Alkaline Media

BY CHRISTINE ZIOUDROU AND GASTON L. SCHMIR

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Phosphotriesters of type I containing a neighboring amide group have been synthesized. Exposure of such triesters to dilute ethoxide or *t*-butoxide solution at room temperature results in the rapid formation of cyclic structures and expulsion of a phosphodiester fragment. Detailed kinetic data and spectrophotometric evidence support the hypothesis that the rate-limiting step of the reaction consists of intramolecular nucleophilic attack of the amide anion on the alkyl carbon, resulting in carbon–oxygen cleavage. The ability of the phosphodiester anion to act as a leaving group is compared to that of other anions. Quantitative measure of the efficiency of the intramolecular process is provided by comparison to the solvolytic behavior of ethyl diphenyl phosphate.

Introduction

Intramolecular nucleophilic reactions of derivatives of carboxylic acids have received close scrutiny in the past decade because of their possible relevance to the mechanisms of certain enzymatic events.[1] It is less well known that the solvolytic behavior of esters of phosphoric acid is also profoundly influenced by neighboring nucleophilic functions. While there has been sporadic description of phenomena best explained on the basis of intramolecular processes, detailed mechanistic studies have been few and little kinetic information is available. For example, the ease of hydrolysis of *o*-carboxyphenyl dihydrogen phosphate (salicyl phosphate) has been ascribed[2] to participation of the *o*-carboxylate ion. The rapid acid-catalyzed isomerization of phosphomonoesters of 1,2-diols (*e.g.*, α-glycerophosphate) seems to proceed *via* the formation of an intermediate cyclic diester.[3] Numerous investigations[3b,4] have established that the rate and direction of hydrolysis of phosphodiesters is markedly affected by the presence of a vicinal hydroxyl group, whose intervention in the hydrolytic process is responsible, for instance, for the alkaline lability of ribonucleic acids.[5] Alkaline treatment of phosphotriesters derived from ethanolamine[6] or ethylene glycol[7] affords products whose nature suggests the involvement of the neighboring amino or hydroxyl function in the solvolytic reaction. A recent report has demonstrated that the fast rate of hydrolysis of dimethyl phosphoacetoin[8] in weakly basic solution is a consequence of the presence of an adjacent keto group.

It appeared of interest to examine the effects of another nucleophilic entity upon the solvolysis of phosphoric acid esters. To this end, substances incorporating an *amide* grouping appropriately situated *vis-á-vis* a *phosphotriester* function were studied in alkaline media. The intramolecular interaction of the ionized amide group with the phosphotriester moiety is documented in this communication.

Results

In preliminary experiments, phosphotriesters of general structure I were exposed to dilute sodium ethoxide or potassium *t*-butoxide at room temperature. Such treatment resulted in rapid, extensive, and irreversible spectral changes in the ultraviolet region (Fig. 1). Repetition of this procedure on a preparative scale (see Table VI, Experimental) resulted in the isolation of cyclic products II (in yields of 70–95%) and of phosphodiesters (yields of 50–95%). The Δ^2-oxazoline IIa, formed from Ia, Ib, and Id, was shown to be identi-

(1) (a) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); (b) T. C. Bruice, *Brookhaven Symposia in Biology*, **No. 15**, 52 (1962).

(2) (a) J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, **74**, 4347 (1952); (b) F. R. Atherton, Chem. Soc. (London) Spec. Publ. No. 8, 1957, p. 77.

(3) (a) M.-C. Bailly, *Compt. rend.*, **206**, 1902 (1938); **208**, 443 (1939); (b) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 44 (1952).

(4) (a) O. Bailly and J. Gaumé, *Bull. soc. chim. France*, **2**, 354 (1935); (b) E. Baer and M. Kates, *J. Biol. Chem.*, **175**, 79 (1948); **185**, 615 (1950); (c) D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 52 (1952); 2040 (1953); (d) D. M. Brown, D. I. Magrath, and A. R. Todd, *ibid.*, 2708 (1952); (e) D. M. Brown and H. M. Higson, *ibid.*, 2034 (1957); (f) D. M. Brown, G. E. Hall, and H. M. Higson, *ibid.*, 1360 (1958); (g) D. M. Brown, G. E. Hall, and R. Letters, *ibid.*, 3547 (1959).

(5) D. M. Brown and A. R. Todd, in "The Nucleic Acids," Vol. I, E. Chargaff and J. N. Davidson, Ed., Academic Press, Inc., New York, N. Y., 1955, p. 409.

(6) (a) D. M. Brown and G. O. Osborne, *J. Chem. Soc.*, 2590 (1957); (b) G. J. Durant, J. H. Turnbull, and W. Wilson, *Chem. Ind.* (London), 157 (1958).

(7) (a) O. Bailly and J. Gaumé, *Bull. soc. chim. France*, **3**, 1396 (1936); (b) D. M. Brown and N. K. Hamer, *J. Chem. Soc.*, 406 (1960).

(8) F. Ramirez, B. Hansen, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 4588 (1962).

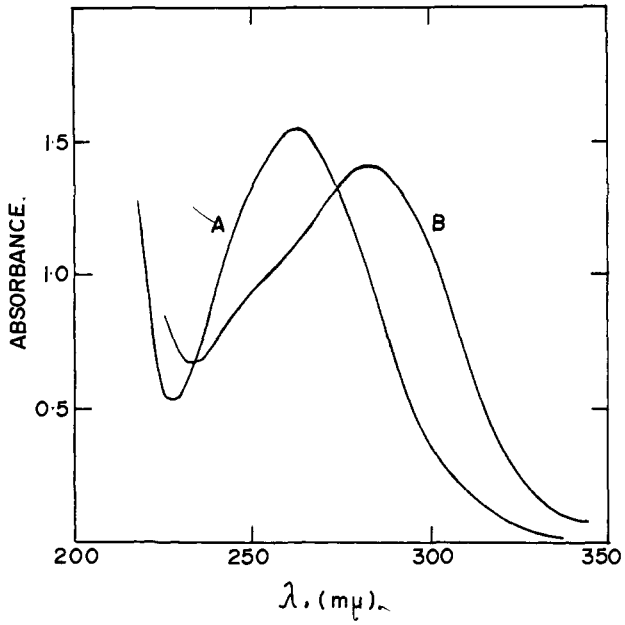
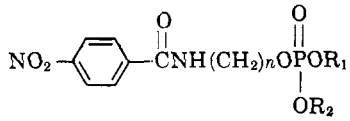
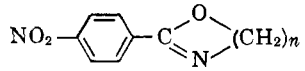


Fig. 1.—Spectral changes in triester Ib on treatment with ethoxide solution: A, Ib at 1.3×10^{-4} M in ethanol; B, after exposure to 0.2 M sodium ethoxide for 20 min. at 30°.

cal in spectral properties and m.p. with the compound prepared by condensation of methyl *p*-nitrobenzimidate and ethanolamine. Similarly, the dihydrooxazine IIb (from Ic) was identified by comparison with a specimen obtained both by the iminoester method and by cyclization of N-(3-hydroxypropyl)-*p*-nitrobenzamide with



Ia, $R_1 = R_2 = C_6H_5$, $n = 2$
b, $R_1 = R_2 = C_6H_5CH_2$, $n = 2$
c, $R_1 = R_2 = C_6H_5$, $n = 3$
d, $R_1 = C_6H_5$, $n = 2$
R_2 = 2-*p*-nitrobenzamidoethyl



IIa, $n = 2$
b, $n = 3$

thionyl chloride. The phosphodiesters were isolated either as the monocyclohexylammonium salt (in the case of diphenyl hydrogen phosphate) or as the free acid. To substantiate the structural assignment of 2-*p*-nitrobenzamidoethyl phenyl hydrogen phosphate (obtained from Id), it was also prepared by phosphorylation of N-(2-hydroxyethyl)-*p*-nitrobenzamide with one equivalent of phenyl phosphorodichloridate followed by hydrolysis. It could be concluded that alkaline treatment of triesters I at spectrophotometric concentrations (*ca.* 10^{-4} M) yields products identical with those isolated since, for example, the ultraviolet spectrum of an equimolar mixture of oxazoline IIa and dibenzyl hydrogen phosphate is the same as that shown by curve B of Fig. 1. During the cyclization of Ia, however, free phenol was formed in the amount of 3–10% (as measured colorimetrically) although, from spectral data, oxazoline formation appeared quantitative.

The significant spectral difference between each triester and its cyclization products was utilized in a detailed study of the kinetics of cyclization in *t*-butoxide and ethoxide solutions. Pseudo-first-order rate constants were obtained in the presence of excess potassium *t*-butoxide from the increase in absorbance at 310 mμ or *the decrease in absorbance at 340 mμ* (see Discussion). The results of these and similar experiments in the presence of excess ethoxide are given in Tables I and II and Fig. 2 and 3.

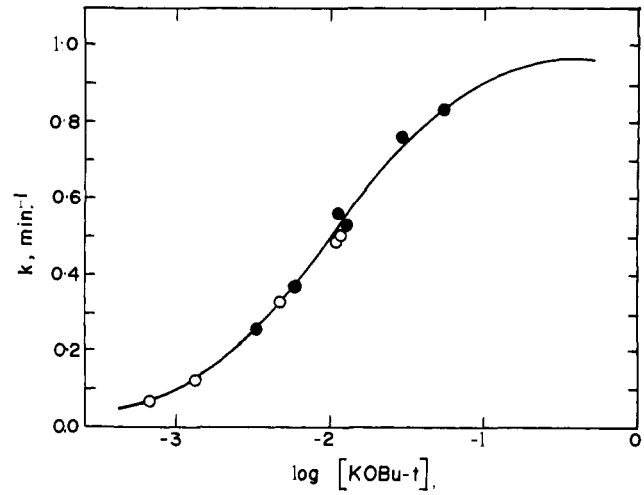


Fig. 2.—Dependence of rate of cyclization at 28° of Ic on *t*-butoxide concentration; triester at 10^{-4} M; ○, rate measured by increase of absorbance at 310 mμ; ●, rate measured by decrease of absorbance at 340 mμ. Solid curve is calculated according to eq. 5, with assumed values of $k_1 = 1$ min.$^{-1}$, $K = 100$ M^{-1}.

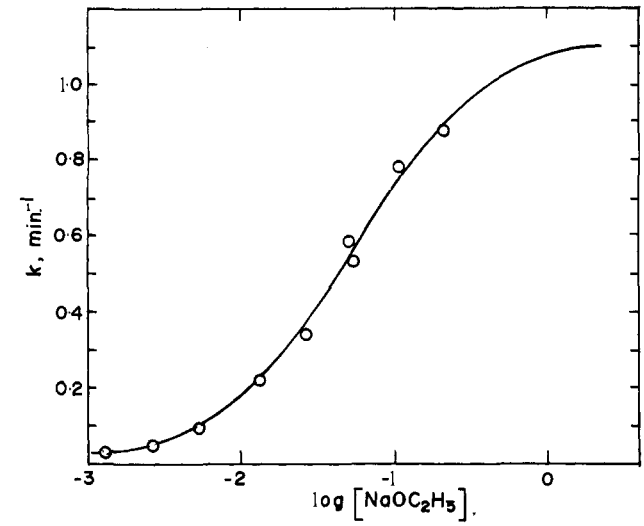


Fig. 3.—Dependence of rate of cyclization at 30° of Ia on ethoxide concentration; triester at 2.5×10^{-4} M. Solid curve is calculated according to eq. 5 with assumed values of $k_1 = 1.13$ min.$^{-1}$, $K = 18.4$ M^{-1}

TABLE I

RATES OF CYCLIZATION OF TRIESTERS IN *t*-BUTOXIDE SOLUTION[a]

Compd.[b]	[KOBu-*t*] × 10³, M	λ,[c] mμ	k, min.$^{-1}$
Ia	0.66	340	9.9
	0.66	340	11.4
	1.3	340	19.3
	3.2	340	21.0
	12.3	340	22.6
Ib	0.66	310	0.72
	0.66	340	0.66
	3.2	310	1.27
	3.2	340	1.20
	28.2	340	1.56
Id	0.66	340	4.6
	1.3	340	7.6
	12.3	340	7.6

[a] In *t*-butyl alcohol at 28°. [b] At 1–2 × 10^{-4} M. [c] Wave length of measurement; rate determined either by increase of absorbance at 310 mμ or decrease of absorbance at 340 mμ.

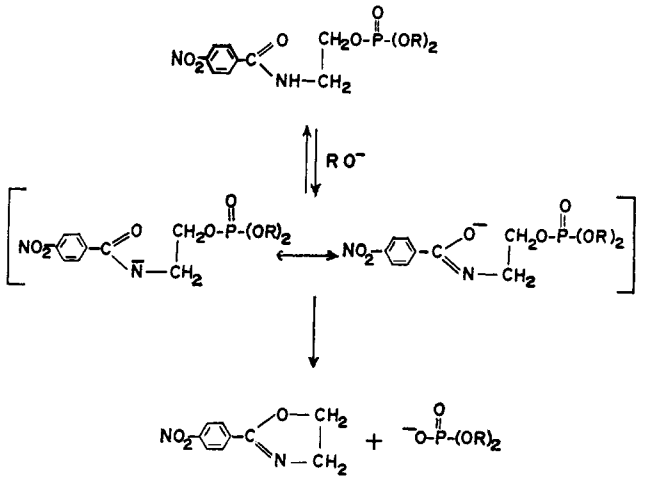


Figure 4.

Cyclization, under basic conditions, of amides of type III to Δ^2-oxazolines has previously been observed.[9] For purposes of comparison to the phosphotriesters of this study, the rates of oxazoline formation from IIIa and IIIb in ethoxide or *t*-butoxide solution were also determined (Table III).

TABLE II

RATE OF CYCLIZATION OF TRIESTERS IN ETHOXIDE SOLUTION[a,b]

$[NaOC_2H_5] \times 10^2$, M	k, min.$^{-1}$	$[NaOC_2H_5] \times 10^2$, M	k, min.$^{-1}$
Compound Ib[c]		Compound Id[c]	
1.4	0.013	0.13	0.021
2.7	.026	.26	.042
5.4	.045	.52	.083
10.9	.082	1.31	.167
16.3	.118	2.66	.318
21.8	.149	5.32	.512
21.8	.155		

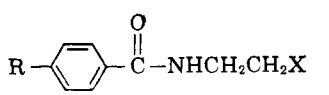
[a] Rates measured by increase in absorbance at 310 mμ. [b] In ethanol at 30°. [c] Ib at 2.6×10^{-4} *M*; Id at 1.5×10^{-4} *M*.

TABLE III

RATES OF CYCLIZATION OF IIIa AND IIIb IN ALKOXIDE SOLUTION

Compd.[a]	$[NaOC_2H_5] \times 10^2$, M[b]	k, min.$^{-1}$	$[KOBu\text{-}t] \times 10^3$, M[c]	k, min.$^{-1}$
IIIa	0.13	0.007	0.7	8.9
	.26	.016	3.2	29.2
	.52	.031	3.2	27.2
	1.31	.072		
	2.62	.125		
	5.24	.215		
	10.5	.368		
	21.0	.539		
IIIb	0.14	2.0		
	.36	3.9		
	.70	7.9		

[a] IIIa at $2.1\text{–}2.4 \times 10^{-4}$ *M*; IIIb at 2×10^{-4} *M*. [b] In ethanol at 30°; rate measured by increase in absorbance at 310 mμ. [c] In *t*-butyl alcohol at 28°; rate measured by decrease in absorbance at 340 mμ.



IIIa, R = $-NO_2$, X = $-Cl$
b, R = $-NO_2$, X = *p*-toluenesulfonyloxy

(9) (a) H. W. Heine, *J. Am. Chem. Soc.*, **78**, 3708 (1956); (b) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

Discussion

Kinetic as well as preparative experiments indicate that alkaline treatment of phosphotriesters I, possessing a neighboring amide function, results in a cyclization reaction accompanied by the expulsion of a phosphodiester fragment. Two conclusions emerge clearly from inspection of the kinetic data presented in Table I and Fig. 2: (a) the cyclization reaction at 28° occurs with exceptional facility in the presence of dilute *t*-butoxide (*e.g.*, $t_{1/2}$ in 0.003 *M* *t*-butoxide varies from 2.9 min. for Ic to *2 sec.* for Ia); (b) the pseudo-first-order rate constant for cyclization increases with, but *is not proportional to*, base concentration. These kinetic observations suggest that the transformation consists of a two-step process (Fig. 4): (a) ionization of the amide group; (b) intramolecular, rate-determining, nucleophilic displacement on *carbon* by the *oxygen* anion.

The mechanism of Fig. 4 is described by eq. 1 and 2, where (AH) and (A^-) represent neutral amide and amide anion, respectively, (RO^-) is *t*-butoxide or ethoxide ion, and (P) stands for the reaction products. The rate of formation of products or the rate of triester disappearance is given by eq. 3 and 4, which are related by the expressions

$$A_t = AH + A^-$$

$$K = [A^-]/[AH][RO^-]$$

$$AH + RO^- \underset{}{\overset{K}{\rightleftharpoons}} A^- \quad (1)$$

$$A^- \xrightarrow{k_1} P \quad (2)$$

$$\frac{d[P]}{dt} = \frac{-d[A_t]}{dt} = k_1[A^-] \quad (3)$$

$$\frac{d[P]}{dt} = \frac{-d[A_t]}{dt} = \frac{[A_t]k_1K[RO^-]}{K[OR^-] + 1} \quad (4)$$

Assumption of the mechanism of eq. 1 and 2 for the cyclization process leads to the predictions that the observed pseudo-first-order rate constant k will vary with base concentration according to eq. 5 and that a plot of k *vs.* log $[RO^-]$ will exhibit a sigmoid shape. At

$$k = \frac{k_1K[RO^-]}{K[RO^-] + 1} \quad (5)$$

high base concentration, the experimental rate constant k reaches the limiting value k_1. The equilibrium constant K for amide ionization is evaluated simply from the inflection point of the sigmoid curve. The data of Fig. 2 indicate close agreement of the experimental values of k for the cyclization of Ic with those calculated from eq. 5, employing values of $k_1 = 1$ min.$^{-1}$ and $K = 100\ M^{-1}$.

Additional support for the existence of the amide anion in these experiments may be derived from the following spectrophotometric observations: (a) the extrapolated zero time absorbance of the triester solution at 310 mμ was noted to increase with increasing base concentration; (b) the progress of the cyclization reaction could be followed by the *decrease in absorbance at 340 mμ*, although the triesters exhibit *lower* light absorption than the products at this wave length *in the absence of added base*. As at 310 mμ, zero time absorbances at 340 mμ increased with base concentration. Presumably, both the instantaneous appearance of strong light absorption at 340 mμ and the increase in zero time absorbance at 310 mμ are due to the presence of the anionic amide species. It should be noted that at *t*-butoxide concentrations greater than *ca.* 0.01 *M*, it was no longer possible to follow accurately oxazoline (or oxazine) formation by the increase in absorbance at 310 mμ, since sufficient amide anion was generated so that its absorbance was similar to that of the reaction products. In these cases, the reaction rate was deter-

mined solely from the decrease at 340 mμ. In several cases (Table I and Fig. 2), rate constants were calculated from measurements both at 310 and 340 mμ and found to be in reasonable agreement.

The proposed mechanism is also supported by the rate measurements carried out in sodium ethoxide solution (Table II and Fig. 3). For Ia, the values of k_1 = 1.13 min.$^{-1}$ and K = 18.4 M^{-1} were chosen to calculate the curve of Fig. 3 according to eq. 5. The rate data obtained for triesters Ib and Id led to the evaluation of k_1 and K for these substances also. In these instances, measurements were carried out over a limited range of alkali concentration, and the derived values of the constants k_1 and K must be considered less reliable. The values of k_1 and K in ethoxide solution calculated from eq. 5 are summarized in Table IV.

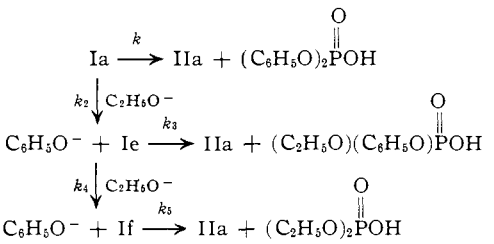
TABLE IV

CALCULATED CONSTANTS FOR CYCLIZATION IN ETHOXIDE SOLUTION[a]

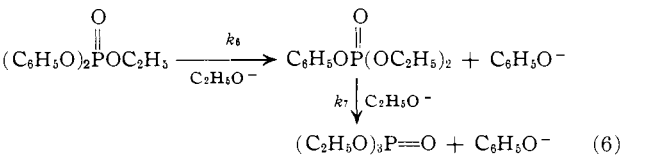
Compd.	k_1, min.$^{-1}$	K, M^{-1}	k_1K, M^{-1} min.$^{-1}$	Relative rates: k_1	Relative rates: k_1K
Ia	1.13	18.4	20.8	1.2	3.65
Ib	0.44	2.25	0.99	0.47	0.17
Id	1.23	13.1	16.1	1.31	2.82
IIIa	0.94	6.1	5.7	1.0	1.0
IIIb			1100		193

[a] Sodium ethoxide in ethanol at 30°.

The observation that 0.03–0.10 mole of phenol is formed per mole of triester Ia during the course of the cyclization process in ethoxide solution leads to a modification of the mechanism of Fig. 4, which accounts also for the fact that conversion of Ia to oxazoline IIa is nevertheless quantitative. According to the annexed scheme,[10] Ia may undergo transformation to triester Ie (I, n = 2, R_1 = C_6H_5, R_2 = C_2H_5) *via* a transesterification[7b,11] reaction which results in the release of phenoxide ion. Similarly, triester Ie may be further converted to triester If (I, n = 2, R_1 = R_2 = C_2H_5). The three triesters (Ia, Ie, and If) may be expected to yield oxazoline IIa, although possibly at different rates. As is discussed below, the pathway involving If need not be considered further. Whether the rate of formation of oxazoline IIa will approximate pseudo-first-order kinetics with respect to Ia will be largely determined by the ratio k/k_2. If $k \gg k_2$, deviation from the first-order rate law will be negligible. When k and k_2 are of similar magnitude, the ratio k/k_3 becomes the significant factor, since the closer this ratio is to unity, the smaller will be the deviation from first-order kinetics.



To obtain an estimate of the magnitude of the transesterification rate constants k_2 and k_4, the rates of solvolysis in ethoxide solution of the model triester ethyl diphenyl phosphate were measured.[12] Equation 6 formulates the two consecutive transesterification reactions of this substance. In the range of ethoxide concentrations of 0.015–0.18 M, k_6 varied from 0.01–0.13 min.$^{-1}$, and k_7 from 0.0006–0.009 min.$^{-1}$. From these values and the rate data for Ia (Fig. 3), it is seen that k/k_6 varies from 24–7 and k/k_7 from 400–95 in the same alkali range. A comparison of the rates of cyclization of Ia and Id (Table II) suggests that k_3 is not much smaller than k. Assuming that $k_4 \simeq k_7$, it follows that $k \gg k_4$ and that consequently $k_3 \gg k_4$. It may be concluded then that the species If is formed to a negligible extent. If it is assumed that the release of the first mole of phenol from ethyl diphenyl phosphate occurs at about the same rate as from Ia (*i.e.*, $k_6 \simeq k_2$), then k/k_2 is of the order of 25–10, and the pathway Ia → Ie → IIa is at best a minor one. Oxazoline formation from Ia was found to obey first-order kinetics to at least 60% of completion. In view of the estimated relative magnitudes of k, k_2, and k_3, the rate constant derived from the initial rates of oxazoline appearance is approximately equal to k. In addition, the amount of free phenol (3–10%) found at the end of the reactions is consistent with the k/k_2 ratio estimated above.



(6)

For a given triester, the observed rate constant k approaches the limiting value k_1 at high alkali concentration. At low alkali concentration ($[RO^-] \ll 1/K$), k is directly proportional to $[RO^-]$ (see eq. 7). The second-order rate constant k_1K is listed in Table IV for triesters Ia, Ib, and Id. It is apparent that relative rates of oxazoline formation in a series of triesters will vary between two limiting values: at high $[RO^-]$, cyclization rates will be in the same proportion as the corresponding k_1 values; at low $[RO^-]$, the relative rates will be given by the ratios of the k_1K values for the series.

$$k = k_1K[RO^-] \quad (7)$$

Mechanisms analogous to that of Fig. 4 have been proposed[9] for base-catalyzed displacements by amide groups of halide and arylsulfonate ions in substances of type III. To place the reactivity of phosphotriesters I in the proper perspective *vis-à-vis* related compounds, the rates of oxazoline formation in ethoxide solution from the chloride IIIa and the *p*-toluenesulfonate IIIb were established (Table III). The dependence of cyclization rate for IIIa on ethoxide ion concentration agreed with eq. 5, allowing computation of k_1 and K for this compound (Table IV). The rapidity of the cyclization of IIIb permitted measurements to be made only at relatively low ethoxide concentration, where k was still proportional to $[RO^-]$. For this substance, therefore, no estimate of K could be made and only the second-order term k_1K is recorded in Table IV.

The relative rates of cyclization for the five compounds studied in ethoxide solution are listed in the last two columns of Table IV, with reference to the chloride IIIa. The leaving tendencies of the three phosphodiester anions and of chloride ion appear to be fairly similar (*cf.* relative k_1 values), although it is also possible that the nature of the leaving group affects somewhat the nucleophilicity of the attacking oxygen anion. When the ionization constant K becomes kinetically significant (at low $[RO^-]$), rate differences become more pronounced (*cf.* relative k_1K values). The strikingly greater reactivity of the toluenesulfonate IIIb may be

(10) The terms k, k_2, k_3, etc., in the scheme represent pseudo-first-order rate constants for the transformations shown, at a fixed ethoxide ion concentration.

(11) (a) H. D. Orloff, C. J. Worrel, and F. X. Markley, *J. Am. Chem. Soc.*, **80**, 727 (1958); (b) H. A. C. Montgomery, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4603 (1956).

(12) Rates were determined spectrophotometrically at 30° by appearance of phenoxide ion at 290 mμ; see Table VII, Experimental.

TABLE V

Compd.	Yield, %	M.p., °C.	Solvent of recrystn.	Empirical formula	Calculated C	Calculated H	Calculated N	Calculated P	Found C	Found H	Found N	Found P	Molar extinction in ethanol: ϵ_{310} mμ	Molar extinction in ethanol: ϵ_{max} at 262 mμ
Ia	96	110	$CHCl_3$–*n*-heptane	$C_{21}H_{19}N_2O_7P$	57.06	4.32	6.34	7.02	56.27	4.32	6.63	6.90	1750	13,000
Ib	70	93–95	$CHCl_3$–*n*-heptane	$C_{23}H_{23}N_2O_7P$	58.70	4.93	5.95	6.60	58.52	5.13	6.23	6.46	1400	12,000
Ic	98	63–65	Ethanol–water	$C_{22}H_{21}N_2O_7P$	57.90	4.64	6.14	6.80	57.77	4.51	6.12	6.58	1740	12,500
Id	68	132	$CHCl_3$–*n*-heptane	$C_{24}H_{23}N_4O_{10}P$	51.66	4.15	10.04	5.56	51.58	4.39	10.08	5.40	2700	20,400

largely attributed to the stability of the anion formed. In intramolecular reactions of the type considered here, the leaving group influences reaction rate because of at least three factors: (a) intrinsic stability of the expelled anion; (b) inductive effect on K; (c) inductive effect on the nucleophilicity of the attacking group. At present, it is premature to attempt to separate these closely interrelated factors.

The unusual facility of the intramolecular process directs the solvolysis in ethoxide solution predominantly toward cyclization (intramolecular attack on *carbon*) rather than toward transesterification (intermolecular attack on *phosphorus*). As discussed above, the rate ratio for these two paths is of the order of 10–25 for Ia. Variation in the nature of the alkoxide ion may considerably alter this ratio: in the presence of *t*-butoxide ion in *t*-butyl alcohol (strong base, but extremely poor nucleophile), cyclization alone takes place. On the other hand, the use of methoxide ion (weaker base than ethoxide[13] but strongly nucleophilic toward phosphorus) leads to the release of considerable phenol, subsequently followed by cyclization.[14]

It is of interest to compare the relative rates of *intramolecular attack on carbon* by the oxygen anion to *intermolecular attack on the same carbon atom* by ethoxide ion. The studies of Orloff, *et al.*,[11a] on the solvolyses of trimethyl and dimethyl phenyl phosphate in methoxide solution indicate that methoxide ion attack on phosphorus occurs *ca.* 200 times faster than on carbon. Consequently, it may be estimated that nucleophilic attack by ethoxide ion on the alkyl carbon of Ia takes place at a rate no greater than one-two thousandth that of the intramolecular process.

The amide anion may be considered to possess two nucleophilic centers: the oxygen atom, as reported in this study and earlier,[9] and the nitrogen atom.[15] It was anticipated, therefore, that an alternate intramolecular reaction, the nucleophilic attack of the nitrogen atom of the amide group upon the phosphorus atom of I, might take place. No evidence for such a reaction has been found in the course of this work. That phosphotriesters may undergo intramolecular displacement both on carbon and on phosphorus has been shown[7b] for the neighboring oxide anion. Similar conclusions have been drawn[6] for the neighboring amino group, although the available evidence is less compelling in this case.

Experimental[16]

N-(2-Hydroxyethyl)-*p*-nitrobenzamide.—An ice-cold solution of 2 ml. (28 mmoles) of ethanolamine (Matheson Coleman and Bell) in 50 ml. of aqueous 2 *M* potassium hydrogen carbonate was treated with 4.62 g. (25 mmoles) of powdered *p*-nitrobenzoyl chloride. The mixture was stirred magnetically at room temperature for 5 hr. The crystalline precipitate was collected by filtration, washed with water, and air dried. It was recrystallized twice from hot ethyl acetate and melted at 132–134° (lit.[17] 132–133°); yield 86%, ϵ_{max} at 262 mμ 11,500 (ethanol).

N-(3-Hydroxypropyl)-*p*-nitrobenzamide.—A solution of 18.8 g. (0.1 mole) of *p*-nitrobenzoyl chloride in 100 ml. of anhydrous tetrahydrofuran was treated at 0° with 25 ml. of 3-amino-1-propanol (Aldrich). After 2 hr. the solution was evaporated to dryness *in vacuo* and the oily residue crystallized by the addition of chloroform and petroleum ether. After recrystallization from toluene, it melted at 97° (lit.[18] 102.5–103.5°).

Synthesis of Phosphotriesters Ia–Ic. General Method.—N-(2-Hydroxyethyl)- or N-(3-hydroxypropyl)-*p*-nitrobenzamide (10 mmoles) was dissolved in 10–15 ml. of anhydrous pyridine and treated at −10° to −5° with 11 mmoles of diphenyl phosphorochloridate (Aldrich) or dibenzyl phosphorochloridate.[19] Optimal yields were obtained with a reaction time of 1 hr. in the cold followed by an additional hour at room temperature. The solution was then poured into 200 ml. of ice-water and crystallization was initiated by scratching. When crystallization was complete, the supernatant liquid was decanted and the crystalline material triturated twice with ice-cold water, collected by filtration, washed thoroughly with water, and dried over P_2O_5 *in vacuo*. Triesters Ia–Ic can be purified by recrystallization at room temperature or in the cold from any of the solvents: acetone–water, methanol–water, chloroform–*n*-heptane, or methylene chloride–*n*-heptane. Analytical data are recorded in Table V. Triesters Ia–Ic were also prepared in an anhydrous, inert solvent such as tetrahydrofuran at −5° in the presence of one equivalent of triethylamine. The yields under those conditions were lower.

Di-(2-*p*-nitrobenzamidoethyl) Phenyl Phosphate (Id).—Phenyl phosphorodichloridate (1.2 ml., 5 mmoles) was added to a solution of 2.10 g. (10 mmoles) of N-(2-hydroxyethyl)-*p*-nitrobenzamide in 10 ml. of anhydrous pyridine at −10°. After 1.5 hr. in the cold and an equal length of time at room temperature the solution was poured in 200 ml. of ice-water. The crystalline product was collected by filtration, washed with water, dried over P_2O_5, and recrystallized from chloroform–*n*-heptane (analytical data in Table V).

Preparation of Phosphodiesters. A. 2-*p*-Nitrobenzamidoethyl Phenyl Hydrogen Phosphate.—To an ice-cold solution of 2.10 g. (10 mmoles) of N-(2-hydroxyethyl)-*p*-nitrobenzamide in 30 ml. of anhydrous tetrahydrofuran was added 2.5 g. (11.1 mmoles) of phenyl phosphorodichloridate, followed by 1.5 ml. (10 mmoles) of anhydrous triethylamine. The reaction mixture was shaken at 0° for 40 min. and stirred at room temperature for 2 hr. longer. Triethylamine hydrochloride (1.35 g.) was removed by filtration and the filtrate evaporated to dryness *in vacuo* at 30°. The resulting sirup (2-*p*-nitrobenzamidoethyl phenyl phosphorochloridate) was hydrolyzed at 0° with 28 ml. of aqueous 1 *N* NaOH for 1.5 hr. Traces of insoluble material were removed by filtration and the filtrate acidified at 0° with concentrated HCl to strong congo reaction until permanent turbidity. The resulting suspension was extracted with 5 × 25 ml. of ethyl acetate, the extracts washed with water, dried over $MgSO_4$, and the solvent removed *in vacuo*. The product which crystallized from acetone–ether melted at 133–136°. It was recrystallized from chloroform–petroleum ether and melted at 135–136°; yield 2.8 g., 76.5%; ϵ_{max} at 262 mμ, 10,500; ϵ_{310} mμ 1070 (ethanol); neut. equiv., 363. *Anal.* Calcd. for $C_{15}H_{15}N_2PO_7$ (366.27): C, 49.2; H, 4.13; N, 7.65; P, 8.48. Found: C, 48.80; H, 4.19; N, 7.52; P, 8.38.

During the course of this preparation attempts were made to isolate in pure state the sirupy 2-*p*-nitrobenzamidoethyl phenyl phosphorochloridate by treatment with chloroform and petroleum ether. After 2 weeks in the ice chest, a 95% yield (based on the amount of sirup used) of N-(2-chloroethyl)-*p*-nitrobenzamide melting at 118–120° was isolated. After recrystallization from methylene chloride–*n*-heptane, it melted at 119–120°. Mixture m.p. with authentic chloride IIIa showed no depression, and infrared spectra ($CHCl_3$) were identical; ϵ_{max} at 262 mμ 11,300 (ethanol). *Anal.* Calcd. for $C_9H_9N_2ClO_3$ (228.66): C, 47.20; H, 3.96; N, 12.23; Cl, 15.48. Found: C, 47.10; H, 3.96; N, 12.00; Cl, 15.70.

B. **Diphenyl hydrogen phosphate** (Aldrich) was purified by recrystallization from chloroform–petroleum ether and converted to its cyclohexylammonium salt by addition of one equivalent of

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(14) Unpublished experiments in this Laboratory.

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(16) All m.p.'s are uncorrected. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology. Ultraviolet spectra were determined by means of a Perkin–Elmer Model 350 recording spectrophotometer.

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(18) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 422 (1915).

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cyclohexylamine to an ethanolic solution of the acid, followed by precipitation with ether; m.p. 198° (lit.[20] m.p. 198°).

C. Dibenzyl hydrogen phosphate was prepared from dibenzyl phosphite (Aldrich) by the method of Clark and Todd[21]; m.p. 79–80° (lit.[22] 78°).

Ethyl diphenyl phosphate was prepared by reaction in the cold of diphenyl phosphorochloridate with sodium ethoxide in ethanol at equimolar concentrations. The sodium chloride was removed by filtration and the ethanolic filtrate evaporated to dryness *in vacuo*. The oily residue was subsequently distilled at 2.1 mm. The fraction of b.p. 188–192° was collected (lit.[23] b.p. 181–185° (2 mm.)); ϵ at 261 mμ 700, at 267 mμ 540 (ethanol).

N-(2-Chloroethyl)-*p*-nitrobenzamide (IIIa).—A suspension of 1.68 g. (8 mmoles) of N-(2-hydroxyethyl)-*p*-nitrobenzamide in 10 ml. of thionyl chloride was maintained at 30° for 30 min., while gradual solution occurred. The homogeneous mixture was placed in a bath at 60° for 2 min., cooled to room temperature, and the solvent removed *in vacuo*. The crystalline residue was triturated with cold water, collected by filtration, and dried *in vacuo* over P_2O_5 and KOH pellets; yield 1.73 g. (95%), m.p. 122–123° (lit.[24] 124–125°). After recrystallization from chloroform–*n*-heptane at room temperature, the m.p. was unchanged; ϵ_{310} mμ 1270; ϵ_{max} at 262 mμ 11,300 (ethanol). *Anal.* Calcd. for $C_9H_9N_2ClO_3$ (228.66): Cl, 15.48; Found: Cl, 15.02.

2-*p*-Nitrobenzamidoethyl *p*-Toluenesulfonate (IIIb).—A solution of 1.05 g. (5 mmoles) of N-(2-hydroxyethyl)-*p*-nitrobenzamide in 10 ml. of anhydrous pyridine was treated at −20° with a solution of 1.4 g. (7.5 mmoles) of *p*-toluenesulfonyl chloride in 5 ml. of pyridine. The mixture was maintained at −20° for 15 min. and for 30 min. at room temperature. It was then poured into a large excess of ice–water. The crystalline precipitate was collected, washed with cold water and dried over P_2O_5; yield 1.33 g. (73%). It melted at 108–110° with immediate resolidification and subsequent melting at 160–164°.[25] It was recrystallized at room temperature from methylene chloride–cyclohexane, cooled quickly in ice to induce crystallization, and the purified material was immediately collected by filtration; ϵ_{max} at 264 mμ 12,100 (ethanol). *Anal.* Calcd. for $C_{16}H_{16}N_2O_6S$ (364.37): C, 52.74; H, 4.43; S, 8.80. Found: C, 53.39; H, 4.79; S, 8.64.

2-*p*-Nitrophenyl-Δ^2-oxazoline (IIa).[26]—To a solution of 1.8 g. (10 mmoles) of methyl *p*-nitrobenzimidate[27] (m.p. 94–95°) in 7 ml. of methanol, a solution of 0.975 g. (10 mmoles) of ethanolamine hydrochloride (m.p. 82–83°[28]) in an equal volume of methanol was added and the reaction mixture kept overnight at room temperature. The flask was chilled briefly to complete crystallization and the crystalline deposit collected (0.97 g., 50% yield, m.p. 172–176°). It was recrystallized from boiling 95% ethanol and melted at 177–179° (lit.[29] m.p. 178–179°); ϵ_{310} mμ 5050 and ϵ_{max} at 282 mμ 10,900 (ethanol). *Anal.* Calcd. for $C_9H_8N_2O_3$ (192.17): C, 56.20; H, 4.20; N, 14.55. Found: C, 56.10; H, 4.98; N, 14.39.

2-*p*-Nitrophenyl oxazoline was found to be photosensitive, acquiring a yellow to pink color on standing.

2-*p*-Nitrophenyl-5,6-dihydro-1,3-oxazine (IIb). A. Thionyl Chloride Method.[30]—One gram (4.47 mmoles) of N-(3-hydroxypropyl)-*p*-nitrobenzamide was added in small portions to 4 ml. of thionyl chloride kept at 0°. After 2 hr. in the ice bath, the excess thionyl chloride was evaporated *in vacuo*. The solid residue was triturated with cold water, an insoluble substance immediately removed by filtration, and to the cold filtrate was added 20 ml. of cold 5% aqueous $NaHCO_3$. The precipitated oxazine was collected and washed with cold water; yield 680 mg. (74%), m.p. 145–146° (lit.[31] 145°). The product was purified by recrystallization from hot 95% ethanol, m.p. unchanged. *Anal.* Calcd. for $C_{10}H_{10}N_2O_3$ (206.20): N, 13.59. Found: N, 13.25.

The water-insoluble material (103 mg., m.p. 100–102°) was recrystallized in long needles of m.p. 100–102° from chloroform–*n*-heptane. Its elementary analysis and infrared spectrum in chloroform are consistent with the suggestion that this by-product (yield 9.5%) is N-(3-chloropropyl)-*p*-nitrobenzamide. *Anal.* Calcd. for $C_{10}H_{11}ClN_2O_3$ (242.68): C, 49.49; H, 4.57; Cl, 14.63. Found: C, 49.35; H, 4.64; Cl, 14.48.

B. **Iminoester Method.**—To a solution of 2.16 g. (10 mmoles) of methyl *p*-nitrobenzimidate hydrochloride[27] in 7 ml. of methanol was added a solution of 785 mg. (10.5 mmoles) of 3-amino-1-propanol in 6 ml. of methanol. After 30 hr. at room temperature, the solvent was removed *in vacuo* and the residue taken up in water, yielding 350 mg. of oxazine, m.p. 144–145°. To the filtrate was added 20 ml. of 5% aqueous $NaHCO_3$ and the mixture was kept at room temperature for 6 days, during which slow deposition of crystalline oxazine occurred, yielding 1.20 g. of product, m.p. 143–145°. The combined products (1.55 g., 75%) were recrystallized from 95% alcohol, with the m.p. increasing to 145–146°. The mixture m.p. with the oxazine obtained by method A showed no depression.

Isolation and Characterization of Cyclization Products.—The following general procedure was employed for the cyclization of triesters Ia–d and of IIIa.

To a solution of 1–2 mmoles of triester in 10–20 ml. of anhydrous ethanol was added 2 equiv. of sodium ethoxide in 10–20 ml. of ethanol. The mixture was maintained at 30° for periods of time varying from 15–180 min. (Table VI). Neutralization of excess alkali with a few drops of glacial acetic acid was followed by evaporation of the solvent *in vacuo*. The solid residue was triturated with 10–20 ml. of cold water and the crystalline oxazoline or oxazine collected by filtration, dried, and recrystallized from 95% ethanol.

TABLE VI

CYCLIZATION REACTIONS

Compd.	Solvent[a]	Reacn. time, min.[b]	Products, % yield— Cyclic product[c]	Phosphodiester[d]
Ia	E	40	73	52
Ia	B	5	71	56
Ib	E	180	69	94
Ib	B	12	94	91
Ic	B	40	74	72
Id	E	15	81	76
IIIa	E	45	90	

[a] E = sodium ethoxide in ethanol, B = potassium *t*-butoxide in *t*-butyl alcohol. [b] At 30°. [c] Oxazoline IIa obtained from Ia, Ib, Id, and IIIa; oxazine IIb obtained from Ic. [d] Diphenyl hydrogen phosphate cyclohexylammonium salt obtained from Ia and Ic, dibenzyl hydrogen phosphate obtained from Ib, 2-*p*-nitrobenzamidoethyl phenyl hydrogen phosphate from Id.

The crystalline phosphodiesters derived from Ib and Id were isolated as the free acids after acidification of the aqueous filtrate with 6 *N* HCl, followed by chilling and seeding.

In the case of Ia and Ic, the acidified aqueous filtrate was extracted with several portions of chloroform and the organic phase dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded an oily residue which was dissolved in absolute ethanol, then treated with a solution of 2 equiv. of cyclohexylamine in absolute ethanol. Upon slow addition of anhydrous ether, diphenyl hydrogen phosphate cyclohexylammonium salt crystallized in long, silky needles.

Yields of products are detailed in Table VI. The identity of all products was verified by comparison of m.p., mixture m.p., and infrared and ultraviolet spectra to authentic samples.

The cyclization reactions in the presence of potassium *t*-butoxide in *t*-butyl alcohol were performed as described above for the ethoxide–ethanol procedure.

Kinetics in Sodium Ethoxide.—Solutions of triesters Ia, Ib, Id and of compounds IIIa and IIIb in anhydrous ethanol and solutions of sodium ethoxide (0.02–0.3 *M*) were equilibrated in a constant temperature bath at 30°. The appropriate solutions were mixed and transferred immediately into a rectangular 4-ml. Beckman cuvette inserted in a water-jacketed cuvette holder maintained at 30° by means of a circulating bath. The spectrophotometer (Beckman Model DU) had been nulled in advance against the corresponding sodium ethoxide solution. The cell was stoppered quickly and the increase in absorbance at 310 mμ resulting from the formation of IIa was recorded at appropriate times. The pseudo-first-order rate constants were calculated using the expression

$$k = \frac{2.303}{t} \log \frac{D_i - D_f}{D_t - D_f}$$

where D_f = optical density at infinite time, D_i = initial optical density, and D_t = optical density at time t. All reactions were followed to completion and the values of the final optical densities as well as complete spectral profiles were compared to those of the products at the same concentrations. The sodium eth-

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(23) M. Halmann and S. Pinchas, *ibid.*, 626 (1953).
(24) D. Ben-Ishai, *J. Am. Chem. Soc.*, **78**, 4962 (1956).
(25) When a slow rate of heating was used, only the m.p. at 160–164° was observed. Presumably IIIb is converted to the corresponding oxazolinium *p*-toluenesulfonate on heating. An authentic sample of the oxazolinium salt, prepared from IIa and *p*-toluenesulfonic acid in ethanol–ether, was found to melt at 169–171°.
(26) The iminoester method has found previous use; *cf.* D. F. Elliott, *J. Chem. Soc.*, 589 (1949).
(27) W. Hilpert, *Am. Chem. J.*, **40**, 150 (1908).
(28) J. H. Jones, *J. Assoc. Official Agr. Chem.*, **27**, 467 (1944).
(29) E. M. Fry, *J. Org. Chem.*, **15**, 802 (1950).
(30) For another example of the use of this method in the preparation of a 5,6-dihydro-1,3-oxazine, *cf.* J. Sicher, *et al.*, *Coll. Czech. Chem. Comm.*, **24**, 2727 (1959).
(31) A. Novelli and R. Adams, *J. Am. Chem. Soc.*, **59**, 2259 (1937).

oxide solutions used were prepared by dissolving sodium metal (thoroughly washed with anhydrous ethanol) in an appropriate volume of ethanol. Aliquots were removed, diluted 1:3 with water, and titrated with standardized HCl using bromothymol blue as indicator.

Determination of Phenol.—When the reactions of triesters Ia and Id had reached completion, 2–3-ml. aliquots containing 0.2–0.4 μmole of products were evaporated to dryness. The residue was dissolved in water and free phenol was estimated colorimetrically at 650 mμ by the Folin–Ciocalteu[32] method using a standard curve for phenol.

Kinetics in Potassium *t*-Butoxide.—*t*-Butyl alcohol (Eastman) was purified by refluxing overnight over exsiccated barium oxide and distilling twice from sodium through a 30-cm. Vigreux column. Repeated distillation did not completely free the *t*-butyl alcohol of an impurity absorbing between 240 and 260 mμ.

Potassium *t*-butoxide was prepared by dissolving potassium metal (prewashed with anhydrous *t*-butyl alcohol) in the purified *t*-butyl alcohol and was titrated as described for the ethoxide solutions. The Beckman Model DU spectrophotometer used for the kinetic measurements was converted to a linear direct reading instrument by a Gilford Model 220 optical density converter. The absorbances were recorded continuously by means of a Honeywell Brown electronic recorder. The reaction mixture was kept at 28° using Beckman thermospacers maintained at constant temperature by means of a circulating bath. The temperature of the reaction solutions in the cuvette was checked occasionally with a microprobe connected to a Thermistor thermometer. Solutions ($1–2 \times 10^{-4}$ *M*) of compounds Ia–Id and IIIa in anhydrous *t*-butyl alcohol were equilibrated in a 28° constant temperature bath. For each kinetic run, the solution of the compound was transferred into a 4-ml. Beckman cell using a 3-ml. volumetric pipet calibrated for *t*-butyl alcohol. The appropriate amount of potassium *t*-butoxide (5–1000 μl.) was added rapidly using a Carlsberg pipet followed by immediate manual mixing with a glass–stainless steel Hershberg-type microstirrer. The cell was stoppered and the increase in absorbance at 310 mμ or the decrease in absorbance at 340 mμ was recorded. The instrument was nulled against the appropriate *t*-butoxide solution. At the end of the reaction, a sample was removed by means of a 2-ml. calibrated pipet. These samples, after addition of 4 ml. of water, were titrated with standard 0.1 *N* HCl to the yellow color of bromothymol blue using an Agla microburet. The *t*-butoxide concentrations ($2–50 \times 10^{-3} M$) determined by titration were in close agreement with the expected values calculated from the dilution of the *t*-butoxide stock solution. Concentrations of *t*-butoxide lower than 2×10^{-3} *M* were calculated from the appropriate dilution factor. Pseudo-first-order rate constants were calculated either from the integrated first-order rate equation or by the Guggenheim method.[33] In the latter case, Δt was chosen to be over 2.5 half-lives. The wave length selected (310 or 340 mμ) was the one where the value $(D_f - D_i)$ was the larger.

Solvolysis of Ethyl Diphenyl Phosphate.—The procedure described above for the kinetics of cyclization in sodium ethoxide was employed here. Appearance of phenoxide ion was followed by measuring the increase in absorbance at 290 mμ. The pseudo-first-order rate constant k_6 was estimated by plotting the rate data obtained in the initial portion of the reaction (*ca.* 0–20% completion) according to the integrated first-order rate equation. The rate constant k_7 was similarly estimated by using the data obtained at 60–100% completion of reaction (at which time release of the first mole of phenol was more than 99% complete). The results of these experiments are summarized in Table VII.

TABLE VII

SOLVOLYSIS OF ETHYL DIPHENYL PHOSPHATE[a]

$[NaOC_2H_5]$, *M*[b]	$k_6 \times 10^2$, min.$^{-1}$	$k_7 \times 10^2$, min.$^{-1}$
0.180	12.90	0.90
.075	5.25	.37
.030	2.08	.14
.015	1.03	.06
.0075	0.50	

[a] In ethanol at 30°; ethyl diphenyl phosphate at 2.5×10^{-4} *M*. [b] All reaction mixtures made up to 0.36 ionic strength with $LiClO_4$.

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Acid-Catalyzed Hydrolysis of Carboxylic Acid Orthoesters

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Several empirical mechanistic criteria indicate that hydrogen ion-catalyzed aliphatic orthoester hydrolysis occurs by a unimolecular (A-1) mechanism, involving formation of resonance-stabilized carboxonium ion intermediates. In view of this, it is suprising that the influence of acyl substituents on the reactivity of orthoesters toward hydrogen ion-catalyzed hydrolysis depends almost entirely on their inductive effects. Substituents, such as phenyl and ethoxy, which should increase the stability of the carboxonium ion intermediate actually decrease the reactivity of the orthoester. This fact, together with a recent suggestion that methyl orthobenzoates hydrolyze by a bimolecular (A-2) mechanism, prompted a study of the energies and entropies of activation for hydrogen ion-catalyzed hydrolysis of ethyl orthoformate, ethyl orthoacetate, and ethyl orthobenzoate in aqueous dioxane acetate buffers. These data, as well as the deuterium solvent isotope effect on ethyl orthobenzoate hydrolysis, support the A-1 mechanism for hydrolysis of all three of these orthoesters. The apparently anomalous substituent effects are rationalized by assuming that, owing to the greater stability of carboxonium ions than carbonium ions, the acyl carbon atom is so far from attaining a trigonal configuration in the transition state that resonance stabilization of the transition state by acyl substituents is not a significant factor in determining reactivity. The data on general acid-catalyzed orthoester hydrolysis are consistent with a mechanism involving rate-determining dissociation of a hydrogen-bonded complex of the ester and acetic acid into a carboxonium ion, ethanol, and acetate ion.

Kinetic studies of the hydrolysis of aliphatic orthoesters played an important role in the development of modern theories of acid catalysis. The first examples of general acid catalysis to be discovered were hydrolysis reactions of ethyl orthoacetate, ethyl orthopropionate, and ethyl orthocarbonate.[2]

The most extensively studied orthoester hydrolysis reaction is that of triethyl orthoformate

$$HC(OC_2H_5)_3 + H_2O \longrightarrow HCO_2C_2H_5 + 2C_2H_5OH \quad (1)$$

This reaction is specific acid-catalyzed in aqueous buffer solutions.[3–9] The hydrogen ion catalytic coefficient for ethyl orthoformate hydrolysis is more than twice as large in deuterium oxide buffer solutions than in protium oxide buffers,[6–9] and the hydrogen ion-catalyzed reaction has a small positive entropy of activa-

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