# Phosphoric–Carbonic Anhydrides.[1] The Hydrolysis of Dibenzyl p-Nitrocarbobenzoxy Phosphate

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Triesters (III) of phosphoric–carbonic anhydride were prepared by reaction of silver dibenzyl phosphate with an alkyl chloroformate. The anhydrides were readily hydrolyzed to dialkyl phosphate, carbon dioxide, and the corresponding alcohol. Hydrolysis in ^{18}O-enriched water indicated carbon–oxygen fission. The hydrolysis is subject to general base catalysis and to catalysis by certain metal ions.

Previous reports from these laboratories have described the control of carboxylation–decarboxylation equilibria through chelation with metal ions.[3] For example, the carboxylation of nitroalkanes with magnesium methyl carbonate was shown to rest upon the stability of complexes between the nitro acid and magnesium ion[3a] (I).

I
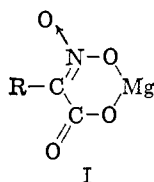
We became interested in the possibility that chelation with metal ions might serve to stabilize various carboxylate species $(X\!-\!CO_2^-)$ which otherwise would be unstable with respect to X^- and carbon dioxide. One such structure of interest is the hypothetical anhydride of phosphoric and carbonic acids (II). This structure, as the free acid, is a formal addition product of phosphoric acid and carbon dioxide, and could hardly be expected to be stable relative to these substances. However, anions derived from II, by formal analogy with pyrophosphate,[4] might well form stable complexes with appropriate metal ions.


II
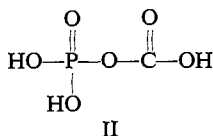
The aims of the present work were the synthesis of derivatives of the anhydride II and an investigation of their behavior under a variety of conditions, par-

ticularly toward metal ions. Coordination complexes of such species (including those derived from phosphate monoesters) would be of interest not only because of their possible role in influencing equilibria between phosphate and carbonate species but because of the possibility that they would represent potential reagents for effecting carboxylation or phosphorylation of other substrates. Indeed, phosphoric–carbonic anhydrides have been discussed as possible intermediates in the enzymatic carboxylation of coenzyme A esters[5] and in the phosphorylation of fluoride[6] and hydroxylamine[7] by adenosine triphosphate in reactions catalyzed by pyruvic kinase.

Initial attempts to observe metal–ion promoted additions to carbon dioxide of various phosphate species were unsuccessful,[8] and we turned our attention to the preparation of triesters (III) of phosphoric–carbonic anhydride, in the hope that selective dealkylation of the triester would lead to the desired compounds.

This paper describes a method for the preparation of triesters of phosphoric–carbonic anhydride (III) and a kinetic study of the hydrolysis of a representative compound, dibenzyl p-nitrocarbobenzoxy phosphate (IIIb). The effect of added metal ions on the rate of hydrolysis was studied in an effort to evaluate the coordinating ability of the mixed anhydrides.[9]

Synthesis of Mixed Phosphoric–Carbonic Anhydrides. The pyridine-catalyzed reactions of silver dibenzyl phosphate with benzyl or p-nitrobenzyl chloroformate (eq. 1) proceeded smoothly in ether solution at 0°. Both the tribenzyl derivative IIIa, which did not crystallize, and the p-nitro compound IIIb, m.p. 67–69°, gave elemental analyses and infrared spectra consistent with the expected structures. Basic hydrolysis of
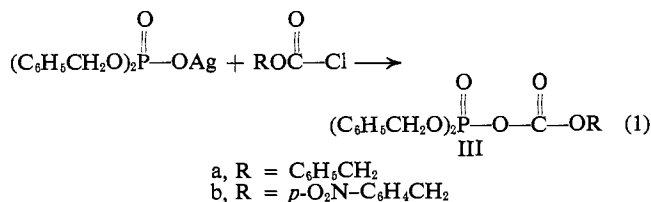
either IIIa or IIIb produced equivalent quantities of dibenzyl phosphate and carbon dioxide. A satis-

(1) (a) Taken largely from the Ph.D. Thesis of D. L. G., University of Michigan, 1964. (b) This research was supported in part by the National Science Foundation, Grant 11395. (c) A portion of this work was presented to the Division of Biological Chemistry, the 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1960, Abstracts, p. 7C.

(2) (a) National Science Foundation Cooperative Fellow, 1962–1964. (b) Fellow of the Alfred P. Sloan Foundation.

(3) (a) H. L. Finkbeiner and M. Stiles, *J. Am. Chem. Soc.*, 85, 616 (1963); (b) M. Stiles, *Ann. N. Y. Acad. Sci.*, 88, 332 (1960); (c) M. Stiles, *J. Am. Chem. Soc.*, 81, 2598 (1959); (d) M. Stiles and H. L. Finkbeiner, *ibid.*, 81, 505 (1959).

(4) J. R. Van Wazer, "Phosphorus and Its Compounds," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1958, p. 630.

(5) Y. Kaziro, E. F. Hass, P. D. Boyer, and S. Ochoa, *J. Biol. Chem.*, 237, 1460 (1962).

(6) M. Flavin, H. Castro-Mendozz, and S. Ochoa, *ibid.*, 229, 981 (1957).

(7) B. K. Bachhawat and M. J. Coon, *J. Am. Chem. Soc.*, 79, 1505 (1957); *J. Biol. Chem.*, 231, 625 (1958); F. P. Kupiecki and M. J. Coon, *ibid.*, 234, 2428 (1959).

(8) M. D. Buckmaster, unpublished results.
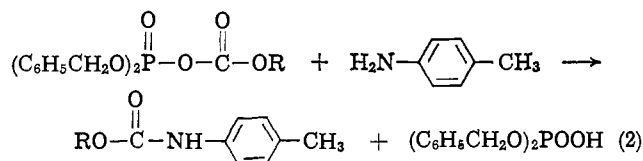
(9) The influence of metal ions on the rate of solvolysis reactions has previously been taken as an indication of the complexing ability of the related compounds, tetrabenzyl pyrophosphate[10] and acetyl phosphate.[11]

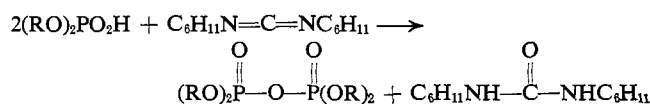(10) F. H. Westheimer, Special Publication No. 8, The Chemical Society, London, 1957, p. 1 ff.

(11) D. E. Koshland, Jr., *J. Am. Chem. Soc.*, 74, 2286 (1952).

factory value for the saponification equivalent in each case was obtained from titration of either the strong acid or the weak acid produced. When the anhydrides (III) were allowed to react with excess p-toluidine, it was possible to isolate both dibenzyl monohydrogen phosphate and the corresponding benzyl p-tolylcarbamate in excess of 90% of the theoretical yields (eq. 2).

$$\underset{\substack{\text{O}\\\shortparallel}}{(C_6H_5CH_2O)_2P}-O-\underset{\substack{\text{O}\\\shortparallel}}{C}-OR \; + \; H_2N-\!\!\left\langle\!\!\bigcirc\!\!\right\rangle\!\!-CH_3 \; \longrightarrow$$

$$RO-\underset{\substack{\text{O}\\\shortparallel}}{C}-NH-\!\!\left\langle\!\!\bigcirc\!\!\right\rangle\!\!-CH_3 \; + \; (C_6H_5CH_2O)_2POOH \quad (2)$$

Since no other reasonable structure can account for the products of hydrolysis and of the reaction with p-toluidine, it is clear that the product of reaction 1 is the phosphoric–carbonic anhydride of structure III.[12]

Position of Bond Rupture in the Hydrolysis of IIIb. Since the hydrolysis of IIIb might involve rupture of either the phosphorus–oxygen or the carbon–oxygen bond, a sample of the anhydride was hydrolyzed in water containing 1.56 atom % ^{18}O. Phosphorus–oxygen cleavage would lead to dibenzyl hydrogen phosphate containing labeled oxygen in the POOH group at a level of enrichment one-half that in the water. The product was isolated and allowed to react with dicyclohexylcarbodiimide.[13,14]

$$2(RO)_2PO_2H \; + \; C_6H_{11}N=C=NC_6H_{11} \; \longrightarrow$$

$$\underset{\substack{\text{O}\\\shortparallel}}{(RO)_2P}-O-\underset{\substack{\text{O}\\\shortparallel}}{P}(OR)_2 \; + \; C_6H_{11}NH-\underset{\substack{\text{O}\\\shortparallel}}{C}-NHC_6H_{11}$$

Examination of the mass spectrum of ordinary dicyclohexylurea revealed a strong parent peak at m/e 224, in addition to strong peaks at 143, 99, and 56. No fragments in the range m/e 143 to 224 were detected. The m/e ratio of 226/224 was determined with the results reported in Table I. It is clear that no significant phosphorus–oxygen cleavage occurred in the hydrolysis of IIIb.

Table I. ^{18}O Content of Dicyclohexylurea (DCU)

Sample of DCU[f]	$R(226/224)$
Natural abundance[a]	0.0141 ± 0.0002
^{18}O enriched[b]	0.0358 ± 0.0002
Sample 1[c]	0.0143 ± 0.0002
Sample 2[c]	0.0142 ± 0.0002

[a] Prepared by hydrolysis of dicyclohexylcarbodiimide with ordinary distilled water. [b] Prepared by hydrolysis of dicylohexylcarbodiimide with 1.56 atom % ^{18}O water. [c] Samples derived from dibenzyl hydrogen phosphate produced by the hydrolysis of IIIb in 1.56 atom % ^{18}O water.

Base Catalysis in the Hydrolysis of IIIb. The rate of hydrolysis of dibenzyl p-nitrocarbobenzoxy phos-

(12) A. Lapidot and M. Halmann, *J. Org. Chem.*, **28**, 1394 (1963), prepared a triester of phosphoric carbonic anhydride by essentially the same technique as that described here and in ref. 1c.
(13) H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, 2257 (1953).
(14) Use of this reaction in determining the ^{18}O enrichment in the POOH group of diethyl hydrogen phosphate has been described previously.[15] It was clear from the earlier work[15a] that a dialkyl hydrogen phosphate does not exchange oxygen with solvent water under the conditions of our experiments.
(15) (a) I. Dostrovsky and M. Halmann, *J. Chem. Soc.*, 1004 (1956); (b) M. Halmann, *ibid.*, 305 (1959); (c) A. Lapidot, S. Pinchas, and D. Samuel, *Proc. Chem. Soc.*, 109 (1962); *J. Chem. Soc.*, 1128 (1963).

Figure 1. pH–rate profile for the hydrolysis of dibenzyl p-nitrocarbobenzoxy phosphate (IIIb).

phate was measured in a series of buffers which varied from pH 1.05 to 8.95. Table II and Figure 1 show that below pH 7 the rate of hydrolysis is independent of the acid concentration, while above pH 7 increasing the pH rapidly increases the rate of hydrolysis. This behavior is characteristic of a reaction which is catalyzed by base, has a significant uncatalyzed term, but is not measurably catalyzed by acid. In 0.64 M perchloric acid the rate was the same, within the experimental error, as in 0.64 M sodium perchlorate.
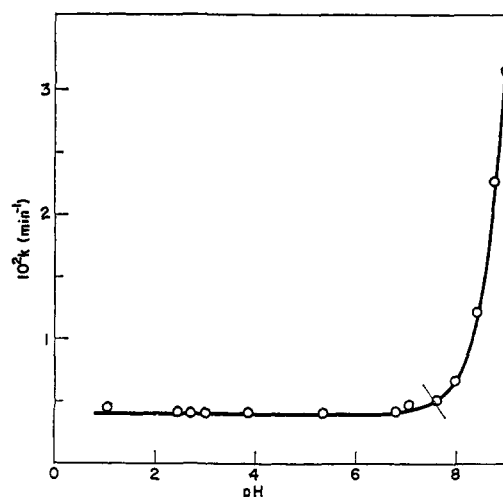
Table II. The Effect of pH on the Rate of Hydrolysis of IIIb[a]

pH[b]	10^3k, min.$^{-1}$[c]
1.05[d]	4.58
2.45[e]	4.17
2.70[f]	4.04
3.00[f]	4.01
3.85[e]	4.15
5.35[g]	4.02
6.80[e]	4.20
7.05[e]	4.73
7.60[e]	5.12
7.95[e]	6.70
8.40[e]	12.2
8.75[e]	22.7
8.95[e]	31.5

[a] $18.0 \pm 0.1°$; ionic strength 0.100 M (KCl); 40% dioxane (v./v.). [b] Observed with Leeds and Northrup pH indicator (7664), standardized with Beckman buffer solutions. [c] Values of k were extrapolated to zero buffer concentration. [d] 0.100 M hydrochloric acid. [e] Phosphate buffer. [f] Dibenzyl phosphate buffers. [g] Acetate buffer.

The concentration of each buffer solution was varied, while holding constant the ratio of buffer components, and the rate was found to depend linearly on the buffer concentration as described by the usual equation (3) for general base catalysis

$$k \; = \; k_0 \; + \; \Sigma k_b(B^-) \quad (3)$$

where the observed first-order rate constant k is the sum of an uncatalyzed term k_0 and a term due to catalysis by the basic components (B$^-$) of the buffer. Table III summarizes the data.
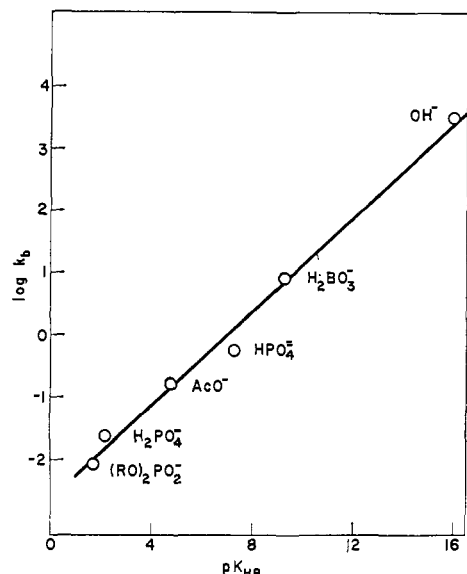
Figure 2. Brønsted plot of catalytic constants for the hydrolysis of dibenzyl p-nitrocarbobenzoxy phosphate (IIIb).

Table III. Catalysis by General Bases in the Hydrolysis of IIIb[a]

Base	Concn. of base, M	10^3k, min.$^{-1}$	k_b, l. mole^{-1} min.$^{-1}$
Water		4.03 (k_0)	
Dibenzyl phosphate[b]	0.0300	4.30	0.00902
	0.0600	4.53	0.00833
	0.0900	4.78	0.00833
			Av. 0.00856 ± 0.00040
Dihydrogen phosphate[c]	0.0090	4.37	0.0244
	0.0180	4.57	0.0233
	0.0270	4.83	0.0252
	0.0450	5.25	0.0244
			Av. 0.0244 ± 0.0008
Acetate[d]	0.0040	4.65	0.165
	0.0080	5.35	0.170
	0.0120	5.93	0.162
	0.0200	7.32	0.167
Acetate[e]	0.0040	4.67	0.170
Acetate[f]	0.0200	7.34	0.167
Acetate[g]	0.0200	7.42	0.171
			Av. 0.166 ± 0.003
Borate[h]	0.00125	17.6	8.65
	0.00250	27.1	8.12
	0.00375	38.9	8.55
			Av. 8.44 ± 0.26
Monohydrogen phosphate[i]			0.844
Hydroxide[i]			3.11 × 10³

[a] 18.0°; ionic strength 0.100 M (KCl); 40% dioxane (v./v). [b] pH 2.85. [c] pH 3.85. [d] pH 5.35. [e] pH 4.90. [f] pH 5.60. [g] pH 5.65. [h] pH 8.60. [i] Determined by successive approximation so as to give the best fit of data obtained in phosphate buffer at pH values above 6.

A comparison of the catalytic effect of the bases with their basic strength (Figure 2) indicates a very good agreement with the Brønsted catalysis law,[16] in which the value of β is 0.40.

$$\log k_b = \beta pK_{HB} + \log G \qquad (4)$$

The Deuterium Oxide Solvent Isotope Effect. The magnitude of the deuterium oxide solvent isotope effect in hydrolysis reactions has been demonstrated to correlate rather well with other criteria for distinguishing between general base catalysis and nucleophilic catalysis.[17] Isotope effects of 2–3 are characteristic of hydrolysis reactions proceeding with general base catalysis,[17] while a much smaller effect is generally observed in reactions proceeding by nucleophilic catalysis. Hydrolysis of IIIb in deuterium oxide containing 60% (v./v.) dioxane indicated an isotope effect of $k(H_2O)/k(D_2O) = 2.2$, a value very similar to that (2.3) observed in the hydrolysis of acetic anhydride in a dioxane–water mixture of nearly the same composition.[18]

The Kinetics of the Reaction of p-Bromoaniline with IIIb. Although the rate of the reaction of dibenzyl p-nitrocarbobenzoxy phosphate with aniline or p-toluidine (eq. 2) was too fast to measure by our analytical method, it was possible to determine the rate of the reaction with p-bromoaniline in slightly acidic solutions. The results of several measurements are summarized in Table IV. In these experiments the total amine concentration was more than five times that of the initial concentration of IIIb, so that pseudo-first-order rate constants (k_{obsd}) were measured to good precision. The data indicate that the reaction is first order both in anhydride and in p-bromoaniline. Furthermore, no catalysis either by hydronium ion, phosphoric acid, or acetic acid is observable.

Metal Ion Catalysis. The rate of the hydrolysis of IIIb was enhanced markedly by addition of certain

(16) J. N. Brønsted, *Chem. Rev.*, **5**, 231 (1928).
(17) M. L. Bender, E. J. Pollock, and M. C. Neuer, *J. Am. Chem. Soc.*, **84**, 595 (1962).
(18) A. R. Butler and V. Gold, *Chem. Ind.* (London), 1218 (1960).

salts. The data in Table V refer to a series of experiments in which each salt was added at three different concentrations, the ionic strength being held 0.10 M with the requisite amount of potassium chloride. The data fit the expression $k_{obsd} = k_u + k_c(\text{salt})$ with good precision, where k_u represents the rate in 0.10 M potassium chloride alone (and includes a contribution from acetate ion in those cases where a buffer was present), and k_c was determined from a plot of k_{obsd} vs. (salt).

The metal ion catalyzed hydrolyses are clearly first order in metal ion in the concentration range studied. The observed rate enhancement cannot be due to a change in pH resulting from hydrolysis of the salts, since the measured reaction is pH independent in this acidity range (Figure 1). The zinc and aluminum salts were used in unbuffered solutions, and the uncatalyzed rate (k_u) obtained by extrapolation to zero concentration of zinc or aluminum was in excellent agreement with the rate measured in potassium chloride alone. The other three salts were measured in acetate buffer. Extrapolation to zero concentration of manganese and cobalt chlorides gave values for 10^3k_u (5.38 and 5.2, respectively) in fair agreement with the rate of hydrolysis in acetate buffer containing only potassium chloride. Similar extrapolation of the data for magnesium chloride yields a value (4.76 × 10³) which is distinctly lower than this. It appears probable that the catalytic activity of acetate is reduced somewhat by complexation with magnesium ions. To the extent that this complexation equilibrium is important the linear relationship between rate and magnesium concentration should not be observed. It

Table IV. Kinetics of the Reaction of IIIb with p-Bromoaniline[a,b]

$10^3 \times$ (RNH$_2$)	pH	Buffer	Concn. of buffer, M	k_{obsd}, min.$^{-1}$	k_{hydr}, min.$^{-1}$	k_2, l. mole^{-1} min.$^{-1}$
4.65[c]	4.00	Phosphate	0.002	0.155	0.005	32.3
6.26[c]	4.00	Phosphate	0.002	0.208	0.005	32.4
3.00[d]	5.60	Acetate	0.010	0.104	0.006	32.7
3.00[d]	5.60	Acetate	0.030	0.106	0.009	32.3
3.00[d]	5.60	Acetate	0.050	0.107	0.012	31.7

[a] 18.0°; ionic strength 0.100 M (KCl); 40% dioxane (v./v.); the pK_a of p-bromoaniline in this solvent was found to be 3.00. [b] $k_2 = (k_{obsd} - k_{hydr})/(p\text{-bromoaniline})$. [c] (IIIb)$_0$ = 1.00 × 10^{-3} M. [d] (IIIb)$_0$ = 5.00 × 10^{-4} M.

would appear prudent to place less reliance on the value of the catalytic constant for magnesium ion than the other catalytic constants, considering the possibility that the apparent linearity is fortuitous.

Table V. Catalytic Effect of Metal Ions in the Hydrolysis of IIIb[a]

Salt	Concn., M	$10^3 k_{obsd}$, min.$^{-1}$	k_c, l. mole^{-1} min.$^{-1}$
KCl	0.100	4.03	...
ZnCl$_2$[b]	0.010	4.22	19
	0.020	4.38	
	0.033	4.63	
AlCl$_3$[b]	0.005	4.35	60
	0.010	4.65	
	0.015	4.95	
MgCl$_2$[c]	0.005	5.02	53
	0.010	5.30	
	0.020	5.82	
MnCl$_2$[c]	0.005	5.66	55
	0.010	5.97	
	0.020	6.50	
CoCl$_2$[c]	0.005	5.24	
	0.010	5.18	$\sim$0
	0.020	5.20	

[a] At 18.0°; 40% dioxane (v./v.); ionic strength maintained at 0.10 M with KCl. [b] Unbuffered. [c] In 0.01 M acetate buffer, pH 5.5.

Discussion

Catalysis of a hydrolytic reaction by species such as those listed in Table III can often be attributed either to general base catalysis or to nucleophilic catalysis.[19] The former term designates mechanisms in which the catalyst functions as a proton acceptor in the measured process. The latter term describes mechanisms in which the catalyst performs a nucleophilic displacement to form an intermediate which is more reactive than the substrate.

The catalytic effect of the anions listed in Table III on the hydrolysis of dibenzyl p-nitrocarbobenzoxy phosphate (IIIb) can be ascribed to the former mechanism on the following grounds. (a) There is a satisfactory correlation between catalytic activity and the basicity of the anions (Figure 2). (b) The hydrolysis is slower by a factor of 2.2 when solvent water is replaced by deuterium oxide. (c) Dibenzyl phosphate ion is a catalyst for the reaction, and its catalytic constant falls on the Brønsted plot (Figure 2). The catalysis by dibenzyl phosphate is perhaps the most convincing evidence since nucleophilic attack by this species at the carbonyl group could only regenerate starting material.[20] Attack of dibenzyl phos-

(19) M. L. Bender, Chem. Rev., 60, 91 (1960).

phate ion on the phosphorus of IIIb would have produced tetrabenzyl pyrophosphate, which is less readily hydrolyzed than IIIb.

Of the various detailed mechanisms which have been envisaged[19] to account for general base catalysis of the hydrolysis of carboxylic acid derivatives, the one represented by V is unique in that it does not involve
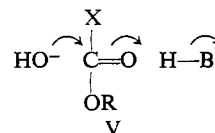
catalysis by B$^-$ but by the combination of hydroxide ion and HB. According to this mechanism the observed first-order rate constant would be described by eq. 5

$$k = k_0 + (\text{OH}^-)\Sigma k_b'(\text{HB}) \qquad (5)$$

which cannot be distinguished from eq. 3, since

$$k_b' = k_b(\text{B}^-)/(\text{OH}^-)(\text{HB}) = k_b K_{HB}/K_w. \qquad (6)$$

This mechanism requires that the stronger acids (HB) should have the greater catalytic constants (k_b'). Unfortunately, this requirement does not constitute a criterion for mechanism V, since eq. 3 and 6 imply eq. 7. Thus a Brønsted relation between k_b and K_{HB} necessarily leads to the required order in catalytic con-

$$k_b' = K_{HB}^{1-\beta}\left(\frac{G}{K_w}\right) \qquad (7)$$

stants (k_b') when the alternative formulation is used, provided only that β is less than unity.

The mechanism V appears very unlikely in the present case when one examines the kinetics of reaction between IIIb and p-bromoaniline. The amine reacts as a nucleophile toward the mixed anhydride, forming the corresponding carbamate nearly quantitatively. Second-order rate constants for this reaction are affected neither by changes in pH nor by changes in concentration of acetate or phosphate buffer (Table IV). The absence of acid catalysis in this reaction, which involves a nucleophile of reactivity comparable to hydroxide ion,[21] and the failure to observe an acid-catalyzed term in the hydrolysis reaction (Figure 1) both argue strongly against this mechanism.

There remains as the most likely mechanism the one (eq. 8) in which the nucleophilic attack of a water
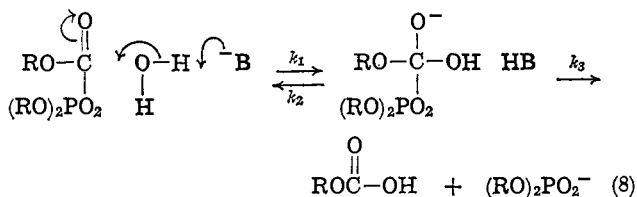
(20) A. R. Butler and V. Gold, Proc. Chem. Soc., 15 (1960), have utilized this criterion for general base catalysis by acetate ion in the hydrolysis of acetic anhydride.
(21) Toward benzoyl chloride, aniline is a slightly better nucleophile than hydroxide ion,[22] but the p-bromo group reduces the nucleophilic reactivity somewhat.[23]
(22) C. G. Swain and C. B. Scott, J. Am. Chem. Soc., 75, 141 (1953).
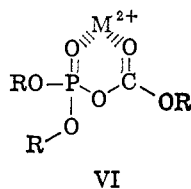(23) H. Jaffe, Chem. Rev., 53, 191 (1953).

molecule is assisted by the removal of a proton by the basic catalyst. Studies of the general base catalyzed hydrolysis of ethyl dichloroacetate[24] and of intramolec-

$$
\begin{array}{c}
\underset{\substack{\text{RO}-\text{C}\\|\\(\text{RO})_2\text{PO}_2}}{\overset{\overset{\text{O}}{\|}}{}} \quad \text{O} - \text{H} \quad \text{B} \quad \underset{k_2}{\overset{k_1}{\rightleftarrows}} \quad \underset{\substack{\text{RO}-\text{C}-\text{OH}\\|\\(\text{RO})_2\text{PO}_2}}{} \quad \text{HB} \quad \xrightarrow{k_3}
\end{array}
$$

$$
\underset{}{\overset{\overset{\text{O}}{\|}}{\text{RO}\text{C}-\text{OH}}} \quad + \quad (\text{RO})_2\text{PO}_2^- \quad (8)
$$

ular catalysis in the hydrolysis of p-nitrophenyl salicylate[25] have led previous workers to postulate such a role for the catalyst.

A further point in connection with this hydrolysis mechanism should be mentioned. The structure of the tetrahedral intermediate is such that k_3/k_2 would be expected to be very large in this case, reflecting the ease of elimination of dibenzyl phosphate anion compared to hydroxide ion. It seems unreasonable to postulate that the observed basic catalysis is associated with the collapse of the tetrahedral intermediate. Indeed, it may be that the phosphoric–carbonic anhydride IIIb represents a substrate the hydrolysis of which is adequately described as a one-step displacement reaction. The tetrahedral structure may appear so close to the energy maximum as to be indistinguishable from the transition state for a direct displacement process.

Catalysis by Metal Ions. The effectiveness of certain metal ions in the hydrolysis of IIIb is such that addition of 0.1 *M* aluminum, magnesium, or manganous chloride more than doubles the rate of the hydrolysis. The lack of acid catalysis, even in 0.6 *M* perchloric acid, argues against a simple electrophilic catalysis by the metal ions. Chelate complexes such as VI, similar

$$
\begin{array}{c}
\overset{\text{M}^{2+}}{\underset{\substack{\text{RO}-\text{P}\\|\\\text{R}}}{\overset{\text{O}\quad\quad\text{O}}{\|\quad\quad\|}}}\\
\text{O}\quad\quad\text{C}\\
\text{O}\quad\quad\text{OR}\\
\text{O}
\end{array}
$$

VI

to that postulated by Koshland[11] to explain magnesium ion catalysis in the hydrolysis of acetyl phosphate, are presumed to be involved. The catalytic constants in Table V are similar in magnitude to that found by Koshland, but with the important distinction that only the *anion* of acetyl phosphate is affected, the magnesium ion catalysis being negligible in acid solutions where acetyl phosphate is present as the free acid. In the present case the complexation must involve uncharged substrate. The difference may be owing as much to the difference in solvent as to the variation in complexing ability of the two substrates.

The substantial catalysis by metal ions in the hydrolysis of IIIb may be taken as an indication that these triesters exhibit coordinating properties toward certain metal ions. Anions derived from less completely alkylated derivatives of the parent substance (II) would be expected to possess these properties in still greater degree. It is concluded that further attempts to synthesize coordination complexes of phosphoric–carbonic anhydride are warranted.

(24) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 83, 1743 (1961).
(25) M. L. Bender, F. J. Kézdy, and B. Zerner, *ibid.*, 85, 3017 (1963).

Experimental[26]

Dibenzyl p-Nitrocarbobenzoxy Phosphate (IIIb). A suspension of 20.0 g. (0.052 mole) of silver dibenzyl phosphate[27] in 500 ml. of anhydrous ether was cooled to 0° and 10.8 g. (0.050 mole) of p-nitrobenzyl chloroformate was added. The reaction was initiated by the addition of 0.5 ml. of pyridine, and the mixture was allowed to stir for 5 hr. at 0°. The silver chloride was removed by filtration and washed with about 100 ml. of methylene chloride. The clear solution was then washed with cold, dilute hydrochloric acid and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a pale yellow oil which was dissolved in a small volume (*ca.* 20 ml.) of methylene chloride. The addition of petroleum ether (b.p. 30–60°) resulted in crystallization of 17.8 g. (78%) of the colorless product, m.p. 67–69°. Strong infrared absorptions occurred at 5.62, 6.60, 7.45, 7.80, 7.95, 8.10, and 9.85 μ (chloroform).

Anal. Calcd. for $C_{22}H_{20}NO_8P$: C, 57.77; H, 4.41; N, 3.06; P, 6.77. Found: C, 58.01; H, 4.40; N, 3.30; P, 6.50.

Hydrolysis of Dibenzyl p-Nitrocarbobenzoxy Phosphate. The anhydride IIIb (462 mg.) was dissolved in 25 ml. of dioxane and 25 ml. of 0.100 *N* sodium hydroxide. After 24 hr., the excess base was back-titrated with 0.100 *N* sulfuric acid. A plot of the pH as a function of the added acid showed breaks at pH 9.50 and 5.50, requiring 5.15 and 15.10 ml. of acid, respectively. These data indicate that 0.990 mmole of strong acid and 0.995 mmole of weak acid are formed during hydrolysis. The assumption that 1 mole of each acid is formed for each mole of anhydride gives an observed molecular weight of 466 (calcd. 457).

After the titration was completed, extraction and purification of the products gave 132 mg. (85%) of p-nitrobenzyl alcohol, m.p. 92–93° (lit.[28] 93°), and 225 mg. (80%) of dibenzyl monohydrogen phosphate, m.p. 78–80° (lit.[29] 78–80°).

Reaction of Dibenzyl p-Nitrocarbobenzoxy Phosphate with p-Toluidine. A solution of 250 mg. (2.34 mmoles) of p-toluidine in 10 ml. of dioxane was added to 457 mg. (1.00 mmole) of IIIb in 10 ml. of dioxane. After standing at room temperature for 30 min., water (*ca.* 100 ml.) was added and the resulting mixture was extracted with ether. The ethereal solution was then extracted with 5% hydrochloric acid and dried over anhydrous sodium sulfate. Removal of the solvent and crystallization from ether–petroleum ether resulted in the isolation of 280 mg. (98%) of brilliant yellow crystals, m.p. 135–136°, of p-nitrobenzyl N-p-tolylcarbamate.

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.91; H, 4.93; N, 9.78. Found: C, 63.04; H, 4.99; N, 9.75.

The aqueous solution remaining after the ether extraction was acidified, and extraction resulted in the isolation of 258 mg. (93%) of dibenzyl monohydrogen phosphate, m.p. 78–80°.

(26) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(27) F. Lynen, *Ber.*, 73, 367 (1940).
(28) "Dictionary of Organic Compounds," Vol. 3, I. Heilbron, Ed., Oxford University Press, New York, N. Y., 1953, p. 645.
(29) V. M. Clark and A. R. Todd, *J. Chem. Soc.*, 2023 (1950).

Dibenzyl carbobenzoxy phosphate (IIIa) was prepared in 80% yield from silver dibenzyl phosphate and benzyl chloroformate.[30] The product was a pale yellow oil having strong infrared absorptions at 5.62, 7.78, 7.95, 8.13, and 9.88 μ (chloroform).

Anal. Calcd. for $C_{22}H_{21}O_6P$: C, 64.05; H, 5.13; P, 7.51. Found: C, 63.71; H, 5.14; P, 7.32.

Hydrolysis of Dibenzyl Carbobenzoxy Phosphate. The anhydride IIIa (636 mg.) was hydrolyzed in 25 ml. of dioxane and 25 ml. of 0.100 N sodium hydroxide. Back titration of the excess base gave breaks at pH 9.75 and 5.55. The amounts of acid required corresponded to 1.49 mmoles of strong acid and 1.50 mmoles of weak acid produced in hydrolysis, giving an observed molecular weight of 424 (calcd. 412).

Reaction of Dibenzyl Carbobenzoxy Phosphate with p-Toluidine. From 412 mg. (1.00 mmole) of IIIa and 250 mg. (2.24 mmoles) of p-toluidine there were obtained 236 mg. (98%) of benzyl N-p-tolylcarbamate, m.p. 82–83° (lit.[31] 83°), and 264 mg. (95%) of dibenzyl monohydrogen phosphate, m.p. 78–80°.

Reaction of Dibenzyl p-Nitrocarbobenzoxy Phosphate with p-Bromoaniline in Aqueous Solution. A sample of the anhydride IIIb (100 mg., 0.22 mmole) in 1 ml. of dioxane was added to 100 ml. of a solution containing 150 mg. (0.87 mmole) of p-bromoaniline and 50 ml. of dioxane and buffered at pH 7.5. After 30 min., the solution was extracted with ether, washed with dilute acid, and dried over anhydrous sodium sulfate. Removal of the solvent and recrystallization of the residue from ether–petroleum ether resulted in the isolation of 75 mg. (97%) of p-nitrobenzyl N-p-bromophenylcarbamate, m.p. 171–172°.

Anal. Calcd. for $C_{14}H_{11}BrN_2O_4$: C, 47.88; H, 3.16; N, 7.98; Br, 22.75. Found: C, 47.87; H, 3.23; N, 8.02; Br, 22.84.

Determination of the Percentage of Phosphorus–Oxygen Cleavage in the Hydrolysis of Dibenzyl p-Nitrocarbobenzoxy Phosphate. The anhydride IIIb (200 mg., 0.44 mmole) was dissolved in 10 ml. of dioxane and 10 ml. of 1.56 atom % ^{18}O-enriched deuterium oxide was added. After 10 days, the solution was made basic and extracted with chloroform. The remaining aqueous solution was acidified and extracted with five 30-ml. portions of chloroform. Removal of the solvent and recrystallization of the residue from ether–petroleum ether gave 74 mg. (61%) of dibenzyl monohydrogen phosphate, m.p. 79–80°.

The dibenzyl monohydrogen phosphate was added to a solution prepared by dissolving 28 mg. (0.133 mmole) of freshly distilled dicyclohexylcarbodiimide

in 10 ml. of absolute ether. After 12 hr., the product was removed by centrifugation and recrystallized from anhydrous methanol to give 20 mg. (68%) of dicyclohexylurea, m.p. 231.0–231.5° (lit.[13] 233°).

The ratio of the peaks of mass 224 to mass 226 was determined by means of an Atlas MAT mass spectrometer, Model CH 4.[32]

Kinetic Methods. A. Hydrolysis Reactions. Solutions were prepared containing 40 ml. of dioxane, the appropriate buffer, and sufficient added salt to give a constant ionic strength of 0.100 M, and diluted to 100 ml. with distilled water. After equilibration at 18.0 ± 0.1° for several hours, the reaction was initiated by the addition of 1.00 ml. of 0.100 M anhydride in dioxane. At intervals, 1.00-ml. samples were removed and injected into 1.00 ml. of 0.025 M p-toluidine in dioxane. Upon completion of a kinetic run, the samples were diluted to 50 ml. with 0.1 N hydrochloric acid and the optical density was measured at 245 mμ. A plot of $-\log(O.D. - O.D._\infty)$ *vs.* time gave a linear dependence for at least 75% of the reaction, and the first-order rate constant could be determined from the slope of that line.

B. Reaction with p-Bromoaniline. A solution containing 40 ml. of dioxane, the appropriate buffer and salt, and the p-bromoaniline was prepared as before. After equilibration, the reaction was again initiated by the addition of 1.00 ml. of anhydride in dioxane, and 1.00-ml. samples were removed at intervals and injected into a mixture of 10 ml. of 1 M hydrochloric acid and 10 ml. of methanol. At the completion of a run, the solutions were diluted to 50 ml. with water and the optical density was determined at 245 mμ. The slope of a plot of $-\log(O.D._\infty - O.D.)$ gave the pseudo-first-order rate constant. Second-order rate constants were calculated using the known value of the rate of hydrolysis by means of the equation

$$k_2 = (k_{\text{obsd}} - k_{\text{hydr}})/(p\text{-bromoaniline})$$

and were found to be independent of the concentration of the p-bromoaniline used.

Hydrolysis of the Anhydride IIIb in Perchloric Acid. In four experiments, the rate of hydrolysis was measured at 18° in 40% (v./v.) dioxane containing perchloric acid at concentrations of 0, 0.32, 0.48, and 0.64 M, with sufficient sodium perchlorate to maintain the ionic strength at 0.64 M. The observed first-order rate constants ($\times 10^3$) were 4.60, 4.70, 4.76, and 4.80 (min.$^{-1}$), respectively. Although the variation is in the direction expected for acid catalysis, the total variation ($<5\%$) is too small to warrant the conclusion that the reaction is acid catalyzed.

(30) H. E. Carter, R. L. Frank, and H. W. Johnson, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 167.

(31) N. C. Bergstrom and A. E. Martell, *J. Am. Chem. Soc.*, 67, 494 (1945).