Solvolysis of Tetrabenzyl Pyrophosphate. Catalysis by Imidazole[1]

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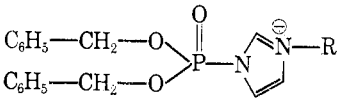
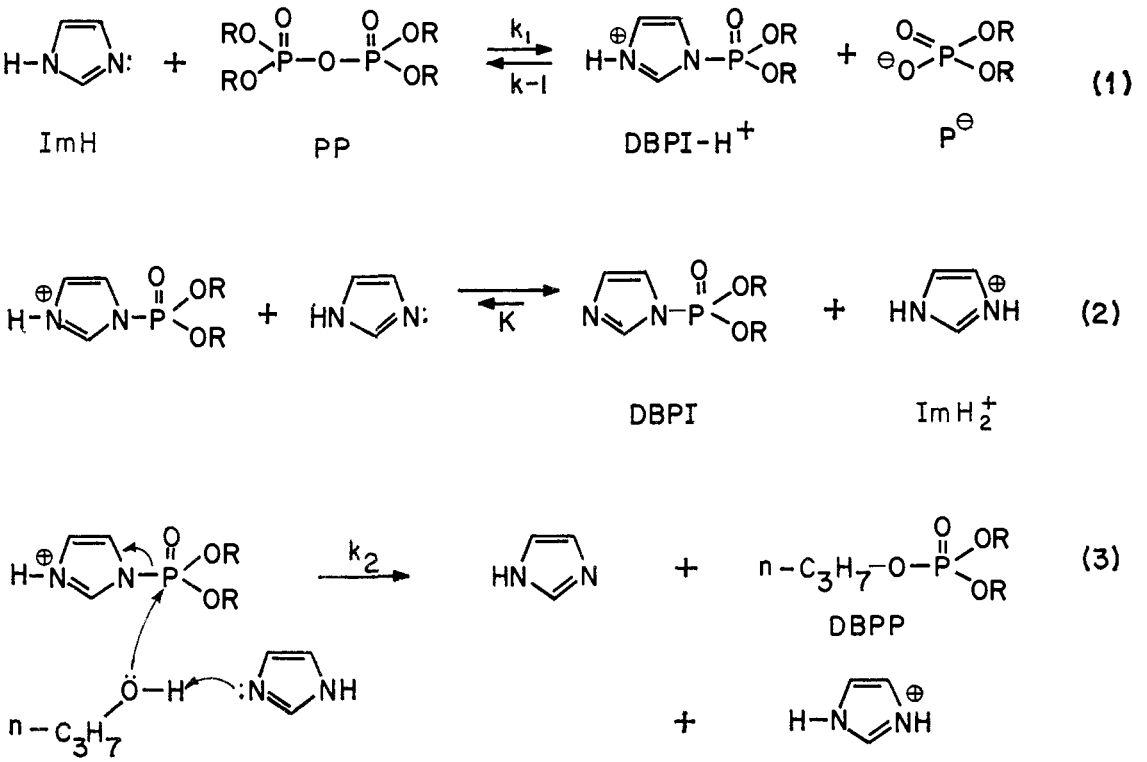
Abstract: The solvolysis of tetrabenzyl pyrophosphate in 1-propanol is catalyzed by imidazole and by N-methylimidazole. The catalysis results from nucleophilic attack by the amine on phosphorus, forming N-(dibenzylphosphoryl)imidazolium ion (I, R = hydrogen or methyl), and displacing dibenzyl phosphate ion. When R is methyl,



I

I is present at low, steady-state concentrations. When R is hydrogen, I is in equilibrium with N-(dibenzylphosphoryl)-imidazole. The latter has been synthesized, and its rates of reaction have been measured. The kinetics of the overall process have been shown to be in accord with, and to demand, this intermediate. The results fit into a general pattern for amine catalysis in the solvolysis of phosphates.

The solvolysis of tetrabenzyl pyrophosphate in propanol yields dibenzyl propyl phosphate and dibenzylphosphoric acid (or its salts). 2,6-Lutidine accelerates the reaction by general base catalysis, with attack of the amine at the ionizable proton of propanol.[2] Pyridine, by contrast, attacks at carbon; the products are the N-benzylpyridinium ion and tribenzyl pyrophosphate ion.[3] In this paper, we show that imidazole catalyzes the solvolysis of tetrabenzyl pyrophosphate by nucleophilic attack at phosphorus according to eq. 1–3.



Catalysis by N-methylimidazole follows an analogous scheme, through N-(dibenzylphosphoryl)-N′-methylimidazole as intermediate; of course, the equilibrium of eq. 2 has no analog in the N-methyl series. The conclusion that this scheme is correct depends on a detailed kinetic analysis of the reactions, and on the successful synthesis of N-(dibenzylphosphoryl)imidazole.

This compound is hereafter frequently referred to simply as dibenzylphosphorylimidazole, and abbreviated as DBPI. Solutions of this compound in chloroform have been prepared previously[4,5] from the reac-

(1) Preliminary communication: 18th National Organic Symposium of the American Chemical Society, Columbus, Ohio, June 1963.

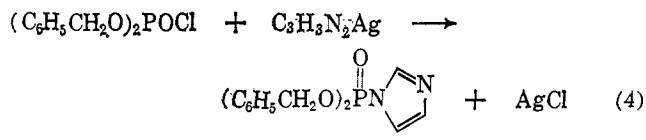
(2) G. O. Dudek and F. H. Westheimer, *J. Am. Chem. Soc.*, 81, 2641 (1959).

(3) G. O. Dudek, Thesis, Harvard University, 1959.

(4) J. Baddiley, J. G. Buchanan, and R. Letters, *J. Chem. Soc.*, 2812 (1956).

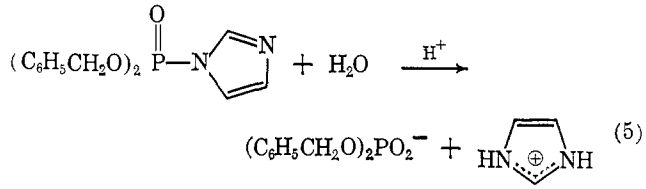
(5) H. Hellman, F. Lingens, and H. Burkhardt, *Chem. Ber.*, 91, 2290 (1958).

tion of dibenzylphosphoryl chloride with imidazole, but the substance was not obtained pure, and the unstable solutions had to be used immediately. We now report a synthesis by way of the silver salt of imidazole which gives a product stable for weeks at $-10°$, and which shows the correct analysis by precision mass



spectrometry. (The synthesis and some chemistry of N-(diisopropylphosphoryl)imidazole,[6] N-(diphenylphosphoryl)imidazole,[7] and N-(di-*p*-nitrobenzylphosphoryl)imidazole[8] have been reported previously.)

The presence of dibenzylphosphorylimidazole in solution during the catalyzed solvolysis of tetrabenzyl pyrophosphate was inferred from the results of two titration procedures, one to an acidic and one to a basic end point. Imidazole has a pK of 6.8; therefore, free imidazole can be estimated by titration to a pH around 4.7, whereas imidazolium ion can be determined by titration to a pH around 9.7. Control experiments have shown that dibenzylphosphorylimidazole is relatively stable in neutral or basic solutions, so that titration of reaction mixtures to a basic end point measures only the amount of imidazolium ion formed by reactions 1–3. However, in aqueous acid, DBPI is rapidly hydrolyzed according to eq. 5. Therefore, a titration



to an acidic end point will measure only the amount of free imidazole present; DBPI will completely hydrolyze to form imidazolium ion, which is not measured by titration to pH 4.7. Neither titration (to the acidic or to the basic end point) measures dibenzylphosphorylimidazole, which then can be estimated from the difference between the two titers. These titrations are subject to some errors, discussed in the paper, but they are approximately valid.

Of course, the presence of dibenzylphosphorylimidazole in solution does not prove that it is an intermediate; it could have been formed in a steady state in a bypass to the main mechanistic pathway, and therefore be irrelevant to the mechanism. The kinetic studies show that this possibility must be discarded, and that dibenzylphosphorylimidazole is a true intermediate in the imidazole catalyzed solvolysis of tetrabenzyl pyrophosphate in propanol.

Experimental Section

Materials. Tetrabenzyl pyrophosphate, m.p. 61.3–62.4°, was synthesized by the method of Khorana and Todd.[9] Dibenzylphosphoric acid, m.p. 80.0–80.8°, was prepared by the method of Clark and Todd.[10] Dibenzylphosphite, purchased from Aldrich, was treated with ammonia and distilled at high vacuum[11]; it melted at about 17°. Dibenzylphosphoryl chloride was prepared according to Atherton, Howard, and Todd.[11] Imidazole (Aldrich), after three recrystallizations from benzene, melted at 89.5–90.0°.

Guanidinium dibenzyl phosphate[12] was prepared by adding 2.70 g. of recrystallized guanidinium carbonate to a suspension of 8.35 g. of dibenzylphosphoric acid in 18 ml. of warm methanol. After three crystallizations from methanol, the salt (4.4 g., 43% of theory) melted at 154–156°. *Anal.* Calcd. for $C_{15}H_{20}N_3O_4P$: C, 53.41; H, 5.98; N, 12.46; P, 9.18. Found: C, 53.29; H, 6.04; N, 12.54; P, 9.20 (Scandanavian Microanalytical Laboratory). Guanidinium perchlorate, m.p. 249.7–250.2°, was prepared[13] from guanidinium carbonate and 70% perchloric acid. Imidazolium perchlorate was prepared by adding 1.73 ml. of 70% perchloric acid to a solution of 1.36 g. of imidazole in 3 ml. of methanol. After three crystallizations, the salt melted at 302.5–307.5° dec. A sample which had been precipitated from methanol–ether four times was submitted for analysis. *Anal.* Calcd. for $C_3H_5ClN_2O_4$: C, 21.38; H, 2.99; Cl, 21.04; N, 16.62. Found: C, 21.32; H, 3.04; Cl, 21.13; N, 16.77. N-Methylimidazolium perchlorate was prepared in a manner analogous to that used for imidazolium perchlorate, but proved too hygroscopic to obtain in analytical purity. Tetra-*n*-butylammonium perchlorate, m.p. 211.2–211.8°, was prepared as before.[2] All the perchlorates were handled with the care appropriate to explosives.

N-Methylimidazole was synthesized from imidazole, methyl iodide, and alkali,[14] purified by distillation from sodium, and redistilled through a 1.5 × 13 cm. column filled with Helipak. It boiled[15] at 195–197° (760 mm.). 1-Propanol was dried over calcium hydride and purified by distillation through a 0.8 × 60 cm. vacuum jacketed Helipak column at a 10:1 reflux ratio; this procedure was repeated three times, and the center cut, boiling at 97.1–97.2° (760 mm.), was stored in Pyrex with all-glass syphon and inlet for dry nitrogen. Propanol-OD had been prepared by Dudek.[2] Carbon tetrachloride was dried over P_2O_5; spectral grade acetonitrile, dried over P_2O_5, was distilled as for the propanol, b.p. 81.6–81.7° (760 mm.).

Dibenzylphosphorylimidazole. Two procedures were used to prepare this material.

(a) A solution of 20 g. of imidazole in 20 ml. of water was added to a solution of 50 g. of silver nitrate in 100 ml. of water and 40 ml. of concentrated ammonia. The precipitated silver salt of imidazole was stirred in the suspension for 20 min., filtered, washed, and dried *in vacuo* in the dark.

A 100-ml., three-necked flask was equipped with a vibromixer, nitrogen inlet, and dropping funnel. A solution of 6.5 g. of dibenzylphosphite in 50 ml. of carbon tetrachloride was cooled in ice, and 2.05 ml. of sulfuryl chloride in 20 ml. of carbon tetrachloride was added over a 30-min. period. The reaction mixture was stirred for 1 hr. before the silver salt of imidazole was added in three 5-g. portions over 0.25 hr. After 2 hr., the colorless solution was filtered once through Whatman No. 1 filter paper and twice through Whatman No. 50 filter paper, with minimum exposure to the atmosphere. The solution then was concentrated on a rotary evaporator without heating. The resulting colorless syrup, obtained in 55–60% yield, is essentially pure dibenzylphosphorylimidazole.

The compound was analyzed for phosphate[16] and for imidazole (by titration). A 1.15×10^{-3} M solution (by weight) in acetonitrile was found to be 1.21×10^{-3} M in phosphate and 1.17×10^{-3} M in imidazole. The mass spectrum of the colorless syrup was determined with an Associated Electric Industries MS-9 spectrometer, using a direct insert probe at an ion chamber temperature of about 100°. High resolution of the parent peak showed the mass of this fragment to be 328.0989 ± 0.0017. *Anal.* Calcd. for $C_{17}H_{17}N_2O_3P$: 328.0977. No other molecular formula fits within the precision of this analysis. Furthermore, the spectrum is a particularly clean one; the only other major high-mass peaks are at 158 (N-benzylimidazole) and at 91 (benzyl cation). The mass spectrum then showed no indication of major impurities in

(6) T. Wagner-Jauregg and B. E. Hackley, Jr., *J. Am. Chem. Soc.*, **75**, 2125 (1953); B. Atkinson and A. L. Green, *Trans. Faraday Soc.*, **53**, 1334 (1957).
(7) F. Cramer, H. Schaller, and H. Staab, *Chem. Ber.*, **94**, 1612 (1961).
(8) D. Theodoropoulos, J. Gazopoulos, and I. Souchleris, *J. Chem. Soc.*, 5257 (1960).
(9) H. G. Khorana and A. R. Todd, *ibid.*, 2257 (1953).
(10) V. M. Clark and A. R. Todd, *ibid.*, 2023 (1950).
(11) F. R. Atherton, H. T. Howard, and A. R. Todd, *ibid.*, 1106 (1948).
(12) G. W. Kirby, Thesis, Cambridge University, 1958.
(13) G. Williams and M. L. Hardy, *J. Chem. Soc.*, 2560 (1953).
(14) M. Häring, *Helv. Chim. Acta*, **42**, 1845 (1959).
(15) J. Sarasan, *ibid.*, **6**, 370 (1923).
(16) R. Allen, *Biochem. J.*, **34**, 858 (1940).

the sample. The unstable compound was stored in solution in acetonitrile or carbon tetrachloride at −20°.

The infrared spectrum of dibenzylphosphorylimidazole is characterized by absorptions at 6.62, 6.80, 7.70 (sharp, strong), 8.45 (sharp, strong), and a broad, strong band centered about 9.8 μ. The n.m.r. spectrum of dibenzylphosphorylimidazole in carbon tetrachloride shows a doublet (J = 9 c.p.s.) in the benzyl methylene region 5 p.p.m. downfield from tetramethylsilane. Each of the components of the doublet is further split (J = 2 c.p.s.). In acetonitrile, the major splitting is 8.8 c.p.s., and the minor splitting disappears. The differences may be due to changes in conformation of the benzyl group.[17]

(b) A solution of dibenzylphosphorylimidazole used early in this work was obtained by allowing tetrabenzyl pyrophosphate to react with a threefold excess of guanidinium perchlorate and imidazole in acetonitrile.[18] The guanidinium dibenzyl phosphate which formed was removed by centrifugation. The supernatant was used in kinetic studies. This method of synthesis was less desirable than (a) because of the excess imidazole and guanidinium perchlorate, and because of incomplete reaction.

Products. A solution of 0.02 M tetrabenzyl pyrophosphate and 0.04 M N-methylimidazole plus 0.03 M guanidinium perchlorate in 1-propanol was allowed to stand for 32 hr. at 10°. After the propanol was removed by evaporation, the product was taken up in toluene and extracted successively with acid and bicarbonate. Evaporation of the toluene gave 1.23 g. (95% of theory) of dibenzyl propyl phosphate, identified as to purity through its n.m.r. and infrared spectra.[2,3] In an analogous preparation, a propanol solution 0.034 M in tetrabenzyl pyrophosphate and 0.086 M in imidazole was heated for 3.5 hr. at 50°. After a similar work-up,[3] dibenzyl propyl phosphate (87% yield) and dibenzyl hydrogen phosphate (65% yield after one recrystallization) were obtained. Dibenzyl propyl phosphate has also been formed by shaking 0.62 mmole of dibenzylphosphorylimidazole in 10 ml. of carbon tetrachloride with 0.4 ml. of 1-propanol and 1 mmole of imidazolium perchlorate for 24 hr. at room temperature. The reaction mixture was extracted with water; after drying and evaporating the carbon tetrachloride, 202 mg. (102%) of dibenzyl propyl phosphate, identified by n.m.r., was isolated.

Dibenzylphosphorylimidazole (0.31 mmole) in 10 ml. of carbon tetrachloride reacted with 2.07 mmoles of guanidinium dibenzyl phosphate and 1 mmole of imidazolium perchlorate on shaking for 22 hr. at room temperature. The solution was extracted with water and bicarbonate, dried, and concentrated by evaporation. When the carbon tetrachloride had been removed, 111 mg. (65% of theory) of a pale yellow syrup remained, which was identified as tetrabenzyl pyrophosphate by its n.m.r. spectrum. The product was crystallized from carbon tetrachloride and hexane (yield, 54 mg.).

Tetrabenzyl pyrosphosphate also was isolated from the aqueous propanol solutions which were obtained in the titration procedures outlined below. These solutions were extracted with carbon tetrachloride, and the washed and dried extracts examined by n.m.r.

Methods. (a) Titrimetric Procedure. Kinetic experiments were started by mixing a small weighted quantity of imidazole or N-methylimidazole into a propanol solution of tetrabenzyl pyrophosphate and salts, thermostated at 10° (or other temperature). At predetermined times, 3.00 ml. of the reaction mixture was transferred to 15 ml. of ice-cold water or standard acid. The solutions were titrated rapidly at 10° with a Beckman Model G pH meter equipped with a general-purpose glass electrode (Beckman 40498) and a fiber-type calomel reference electrode. An Aminco Meniscomatic 3-ml. buret was used for the titrations. The equivalence points for the titration of imidazole in acid and base varied a little with the concentrations used. Control experiments showed that, at an imidazole concentration of 0.025 M, the two end points are at pH 4.83 and 9.66, whereas at 0.06 M they are at pH 4.64 and 9.90. The corresponding end points for 0.04 M N-methylimidazole are at pH 4.65 and 9.75. These values are those read from the pH meter without correction for the junction potential between water and 17% propanol.

In order to evaluate the accuracy of the titration procedures, a solution of dibenzylphosphorylimidazole (0.169 M) in 0.2 ml. of acetonitrile was introduced into 18 ml. of a 17% aqueous propanol solution containing imidazolium perchlorate (1.67×10^{-3} M), guanidinium dibenzyl phosphate (1.67×10^{-3} M), imidazole (3.34×10^{-3} M), and guanidinium perchlorate (3.34×10^{-3} M). The quantities of dibenzylphosphorylimidazole and other components were chosen as approximately equal to the maximum present during a kinetic experiment. If dibenzylphosphorylimidazole were stable in base and quantitatively hydrolyzed in acid according to eq. 5, the introduction of this material would not affect the titrations for imidazolium ion and imidazole, respectively. In fact, a solution which contained 0.0337 mmole of DBPI required 0.0022 mmole, or 7%, more alkali to reach the end point at pH 9.7 in a rapid titration, and a similar sample dissolved in acid and back titrated to the end point at pH 4.7 required 0.0070 mmole, or 21%, less base than expected. (This deficiency is consistent with the formation of some tetrabenzyl pyrophosphate during acid titration; see the section on Products.) In order to obtain approximately correct results from the titrations, the values of x_a (titer to the acid end point "normalized" by dividing by the initial concentration of tetrabenzyl pyrophosphate) and x_b (titer to the basic end point, similarly normalized) were corrected for the known titration errors cited above. The concentration of dibenzylphosphorylimidazole is given to a first approximation by $x_a - x_b$, so that a first approximation to the amount of the unstable intermediate can be found; the final values of x_a and x_b are obtained by successive approximations. The resulting values of x_b are obviously crude but valid within a few per cent; the values of x_a and of the concentration of the intermediate, DBPI, are considerably less precise.

(b) Spectrophotometric Method. The extinction coefficients of the various starting materials and products are listed in Table I. Although the absorption is in every case that of a phenyl ring insulated from its chemical environment by a methylene group, the differences in extinction coefficients are nevertheless large enough to allow the rates to be determined spectrophotometrically.

Table I. Extinction Coefficients at 2638 Å. in Propanol

Compd.	Ext. coefficient
Tetrabenzyl pyrophosphate	874 ± 4
Dibenzylphosphorylimidazole	481 ± 4
Guanidinium dibenzyl phosphate	303 ± 2
Dibenzyl propyl phosphate	381 ± 4

The progress of the reactions was followed using a Cary 14 spectrophotometer equipped with a 0–0.1 slide wire. The stability of the hydrogen lamp was checked before and after each experiment by measuring the absorbance of a standard potassium chromate solution. In general, the absorbance of the solutions was in the range of 0.5–1.5, and the change in absorbance during an experiment about 0.1 to 0.2 absorbance unit. In actual measurements, the reference compartment contained a 3-ml. Teflon-stoppered cuvette with neutral density screens necessary to place the recorder on the proper scale. The width of the pen trace, with the pen damper set at a 5-sec. response time, was about 0.002 absorbance unit. Earlier experiments without damping were slightly less precise.

Results

Solvolysis of Dibenzylphosphorylimidazole Catalyzed by Imidazolium Ion. The solvolysis of dibenzylphosphorylimidazole in propanol was followed spectrophotometrically. The data were analyzed by the Guggenheim method,[19] so as to avoid excessive dependence on the initial and final readings. The individual rate constants were obtained with a precision of ±2%. Some of the data are shown in Figure 1. The observed first-order rate constant for the solvolysis is linear in imidazolium ion, and the data extrapolate to zero rate at zero buffer concentration; *i.e.*, the uncatalyzed reaction and that catalyzed by hydrogen ion can be neglected in comparison with the process catalyzed by imidazolium ion.

(17) G. Whitesides, J. Grocki, D. Holtz, H. Steinberg, and J. D. Roberts, *J. Am. Chem. Soc.*, 87, 1058 (1965).

(18) R. Blakeley, Thesis, Harvard University, 1964.

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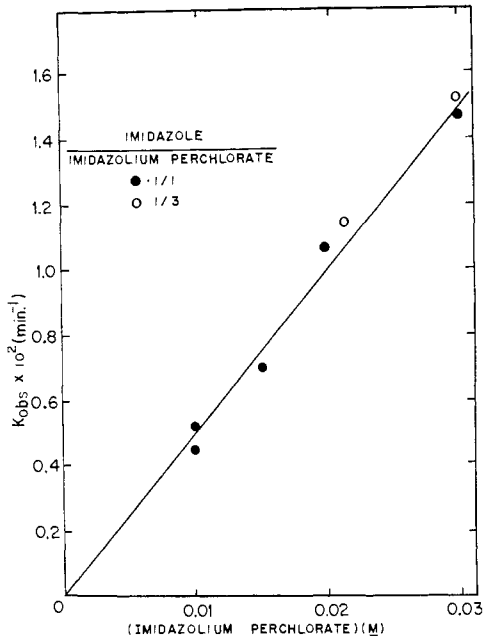

Figure 1. Solvolysis of N-(dibenzylphosphoryl)imidazole catalyzed by imidazole at 10° in propanol (3.2% in acetonitrile).

Incidentally, water reacts readily with dibenzylphosphorylimidazole in propanol solution. The data in Figure 1 for 1:1 buffer ratio were obtained with propanol which had been carefully dried according to the methods presented in the Experimental Section. The data for the 3:1 buffers were obtained with somewhat less carefully purified propanol; when propanol which had not been dried well was used, the data did not extrapolate to the origin; *i.e.*, the rate at zero buffer concentration was not negligible. Data similar to those shown in Figure 1 were also obtained at 25° and are presented in Table II. The solution of dibenzylphosphorylimidazole used for the experiments at 25° was prepared by method (b) discussed in the Experimental Section, but gave substantially the same results as those obtained with dibenzylphosphorylimidazole prepared according to method (a) recorded in the Experimental Section. These data require that the solvolysis of dibenzylphosphorylimidazole (DBPI) at 10° proceeds according to the equation

$$-\mathrm{d(DBPI)}/\mathrm{d}t = 0.50(\mathrm{DBPI})(\mathrm{ImH_2^+}) \qquad (6)$$

where the rate constant is quoted in liters per mole per minute, and ImH_2^+ represents imidazolium ion.

Table II. Solvolysis[a] of Dibenzylphosphorylimidazole at 25° in Imidazole–Imidazolium Perchlorate Buffers

Buffer ratio, (ImH)/(ImH_2^+)	(ImH_2^+), *M*	$k_{obsd} \times 10^2$, min.$^{-1}$
0.99	0.00984	1.63 ± 0.05
±0.01		1.57 ± 0.05
	0.0195	2.99 ± 0.01
	0.0289	4.21 ± 0.12
		4.36 ± 0.06
2.00	0.00976	1.70 ± 0.025
		1.62 ± 0.05
	0.0194	3.29 ± 0.06
		3.19 ± 0.07
	0.0292	4.72 ± 0.07
		4.76 ± 0.1

[a] $(DBPI)_0 = 0.0015$ *M*. Solvent: 3.2% acetonitrile in *n*-propyl alcohol. Sufficient guanidinium perchlorate was included in each buffer to make the total salt concentration 0.039 *M*. Rates were measured spectrophotometrically.

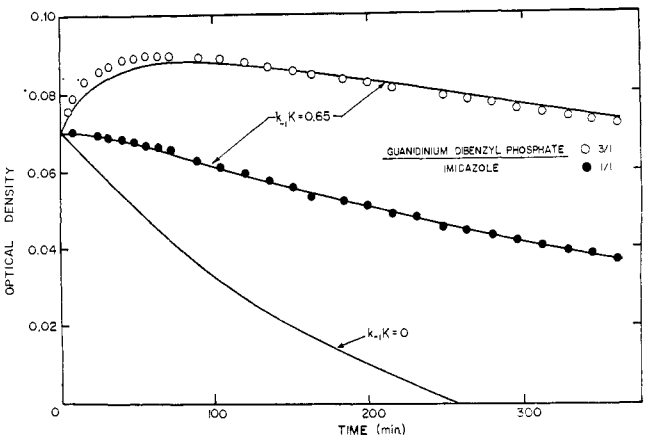

Figure 2. Change in optical density on solvolysis of N-dibenzylphosphorylimidazole (9.54×10^{-4} *M*) in propanol at 10°. The solid lines were computed for $k_1 = 0.70$, $k_{-1}K = 0.65$ and $k_2K = 0.50$ M^{-1} min.$^{-1}$: ○, guanidinium dibenzyl phosphate (0.003 *M*) and imidazole (0.001 *M*); ●, guanidinium dibenzyl phosphate (0.0020 *M*) and imidazole (0.0023 *M*). The concentration of imidazolium ion was 0.02 *M* in both experiments, and the total salt concentration was maintained at 0.04 *M* with guanidinium perchlorate.

"Back Reaction" from Dibenzylphosphorylimidazole. When dibenzylphosphorylimidazole is allowed to react with dibenzyl phosphate ion in propanol, tetrabenzyl pyrophosphate is formed according to the "back reaction" of eq. 1. Since the rate of solvolysis of dibenzylphosphorylimidazole is known, the rate of the competing reaction can be determined. Inspection of the extinction coefficients in Table I shows that the solvolysis of DBPI results in a decrease in extinction coefficient from 784 (for dibenzylphosphorylimidazole plus dibenzylphosphate ion) to 684 (for dibenzyl propyl phosphate plus dibenzyl phosphate ion), whereas the back reaction causes an increase in extinction coefficient to 874 (for tetrabenzyl pyrophosphate). Ideally, experimental conditions could be arranged where the back reaction dominates; actually, the best experimental conditions here achieved were those where the back reaction proceeds a few times faster than solvolysis. The data for two experiments are shown in Figure 2. The experimental points are compared with the values for the absorbance calculated from an IBM 1620 computer program (see the Appendix) with the initial rate constant, k_1, equal to 0.70 l. mole^{-1} min.$^{-1}$, that for solvolysis of DBPI, k_2K, equal to 0.50 l. mole^{-1} min.$^{-1}$, and that for the back reaction equal to 0.65 l. mole^{-1} min.$^{-1}$ These values are appropriate to the 0.04 *M* salt concentration used. The change in absorption which would have occurred with the rate constant for the reverse reaction equal to zero has been appended. These data provide therefore a complete set of rate constants for the over-all reaction.[20]

(20) The observed rate constant for the solvolysis of dibenzylphosphorylimidazole is k_2K, and that for the reverse reaction is $k_{-1}K$, provided only that *K* (defined for the reverse of eq. 2) is small. The derivations of the rate equations and the evidence supporting the assumption concerning the equilibrium constant *K* are presented in the Appendix.

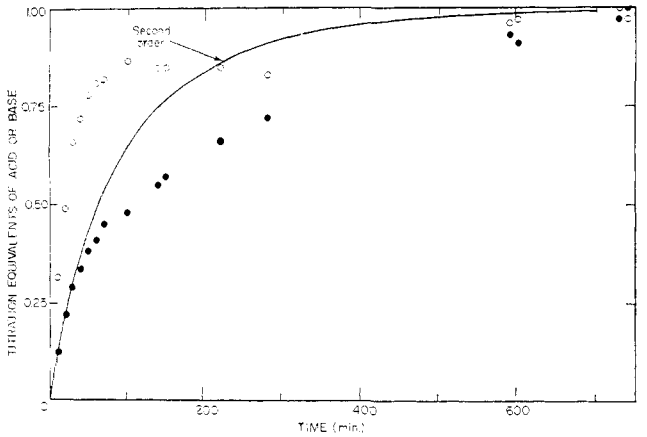

Figure 3. Solvolysis of tetrabenzyl pyrophosphate (0.02 M) in the presence of imidazole (0.04 M) at 10°. The solid line represents a simple second-order curve: O, x_a, the concentration of imidazole reacted divided by the initial tetrabenzyl pyrophosphate concentration; ●, x_b, the concentration of imidazolium ion divided by the initial tetrabenzyl pyrophosphate concentration.

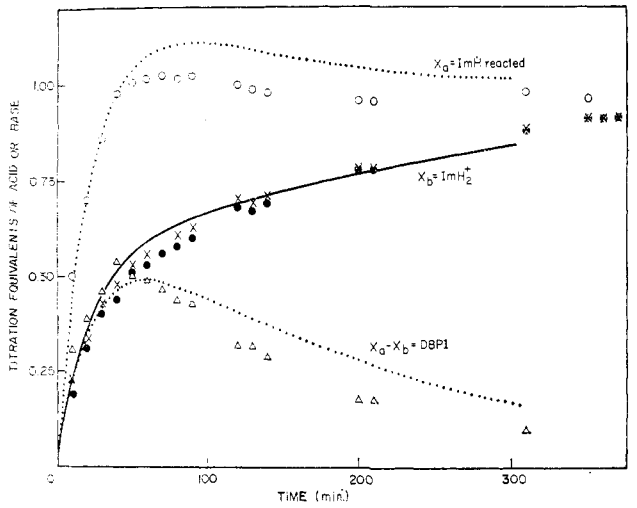

Figure 4. Solvolysis of tetrabenzyl pyrophosphate (0.02 M) in the presence of imidazole (0.04 M) with added guanidinium perchlorate (0.03 M) in propanol at 10°. O, ●, and △ represent corrected experimental points for x_a, x_b, and [DBPI], respectively; x = uncorrected x_b values. Dotted and solid lines were computed with $k_1 = 0.70$, $k_{-1}K = 0.65$, and $k_2K = 0.50$, M^{-1} min.$^{-1}$.

Solvolysis of Tetrabenzyl Pyrophosphate Catalyzed by Imidazole. Figure 3 shows the titration results (corrected as explained in the Experimental Section) for the solvolysis of 0.020 M tetrabenzyl pyrophosphate in the presence of 0.040 M imidazole at 10°. In the figure, x_b (titration to the basic end point) measures the concentration of imidazolium ion, and x_a (titration to the acid end point, with concommitant hydrolysis of dibenzylphosphorylimidazole) measures the difference between the initial concentration of free imidazole and that present at any particular time. A simple, second-order curve is also shown in Figure 3 to demonstrate that the data cannot be correlated by this equation. However, the initial rate and the initial second-order rate constant, k_1, can be determined from the data for the first 35% of the reaction. In this way, the constant of 0.39 l. mole^{-1} min.$^{-1}$ was established from this and similar experiments. Data showing the values of k_1 with various salt concentrations are given in Table III.

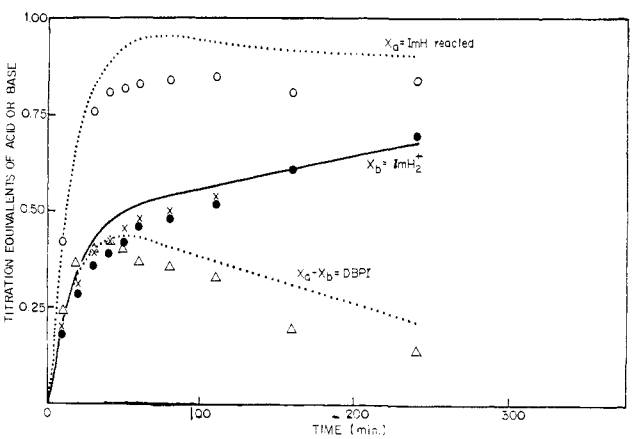

Figure 5. Effect of added guanidinium dibenzyl phosphate (0.03 M) on the solvolysis of tetrabenzyl pyrophosphate (0.02 M) in propanol at 10°; imidazole, 0.04 M. O, ●, and △ represent corrected experimental points for x_a, x_b, and [DBPI], respectively; x = uncorrected x_b values. Dotted and solid lines were computed with $k_1 = 0.70$, $k_{-1}K = 0.65$, and $k_2K = 0.50$ M^{-1} min.$^{-1}$.

The proper kinetic analysis for the solvolysis of tetrabenzyl pyrophosphate in the presence of imidazole is presented graphically in Figures 4 and 5. The rate constants are those determined by the various independent schemes given above, and the theoretical curves calculated from a computer program (see Appendix).

Table III. Initial Rate Constants in the Presence of Added Salts in the Solvolysis of Tetrabenzyl Pyrophosphate at 10° Catalyzed by Imidazole[a]

Salt concn., M	k_1, M^{-1} min.$^{-1}$
No added salt	0.39 ± 0.02[b]
0.01 M $ImH_2^+P^-$	0.42
0.03 M $Bu_4N^+ClO_4^-$	0.38
0.03 M $GH^+ClO_4^-$	0.64
0.03 M GH^+P^-	0.59
0.05 M GH^+ ClO_4^-	0.78
0.03 M $GH^+ClO_4^-$ }	0.75
0.02 M GH^+P^- }	

[a] (Tetrabenzyl pyrophosphate)$_0$ = 0.02 M; (imidazole)$_0$ = 0.04 M. [b] Error given indicates maximum deviation. GH^+ = guanidinium ion.

The decrease in rate and in the concentration of dibenzylphosphorylimidazole in the presence of dibenzyl phosphate ion are especially significant for the mechanism. The computed curves utilize the three rate constants (k_1, $k_{-1}K$, and k_2K) derived from independent experiments, and do not contain arbitrary parameters fitted to the individual rate experiments. The calculated and observed curves are in good agreement for x_b, where the corrections to the titrations (shown in the figures) are small. The agreement is satisfactory but much less exact for x_a, where the corrections to the experimental titration values are large and uncertain, and similarly the agreement between calculated and observed curves is satisfactory but only approximate for the concentration of dibenzylphosphorylimidazole (DBPI), where the observed points depend critically on the precision with which x_a is known.

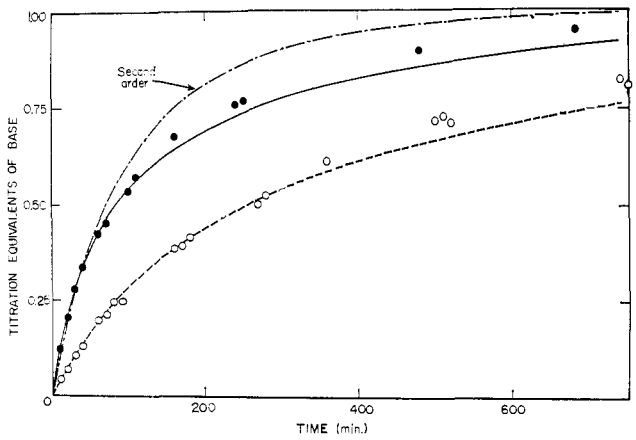

Figure 6. Solvolysis of tetrabenzyl pyrophosphate (0.02 M) in the presence of N-methylimidazole (0.04 M) at 10°. The solid line is the computed curve and the filled circles (●) the experimental points for x_b with guanidinium perchlorate (0.03 M). The broken line is the computed curve and the open circles (○) the experimental points for x_b with guanidinium dibenzyl phosphate (0.03 M). The second-order curve was plotted with a rate constant 0.3 M^{-1} min.$^{-1}$.

Solvolysis of Tetrabenzyl Pyrophosphate in the Presence of N-Methylimidazole. The solvolysis of tetrabenzyl pyrophosphate in the presence of N-methylimidazole has been followed both by titration and by spectrophotometry. The titration experiments with added guanidinium perchlorate and added guanidinium dibenzyl phosphate are illustrated by Figure 6. The data have been fitted with curves obtained by analog computer techniques with the initial rate constant, k_1, equal to 0.42 l. mole^{-1} min.$^{-1}$, and the ratio for the solvolysis to the back reaction, k_2/k_{-1}, is equal to 0.25. The reactions obviously do not follow a second-order equation, but are fitted by a mechanism based on eq. 1 and 3.

A series of experiments was carried out spectrophotometrically with different concentrations of N-methylimidazole; these data are presented in Figure 7. The observed rate constants are first order in N-methylimidazole, and the reaction proceeds at the same rate in 1-propanol as in a solvent where the ionizable hydrogen atom had been replaced by deuterium, but is slower in the presence of dibenzyl phosphate ion.

The salt effect on the reaction rate is marked as shown in Figure 8. Although tetrabutylammonium perchlorate does not have a large effect on the reaction rate, guanidinium salts cause a marked acceleration; 0.08 M salt increases the rate more than threefold. Presumably salt effects are equally pronounced in the solvolysis catalyzed by imidazole itself, and may account for some of the minor discrepancies between runs at different concentrations.

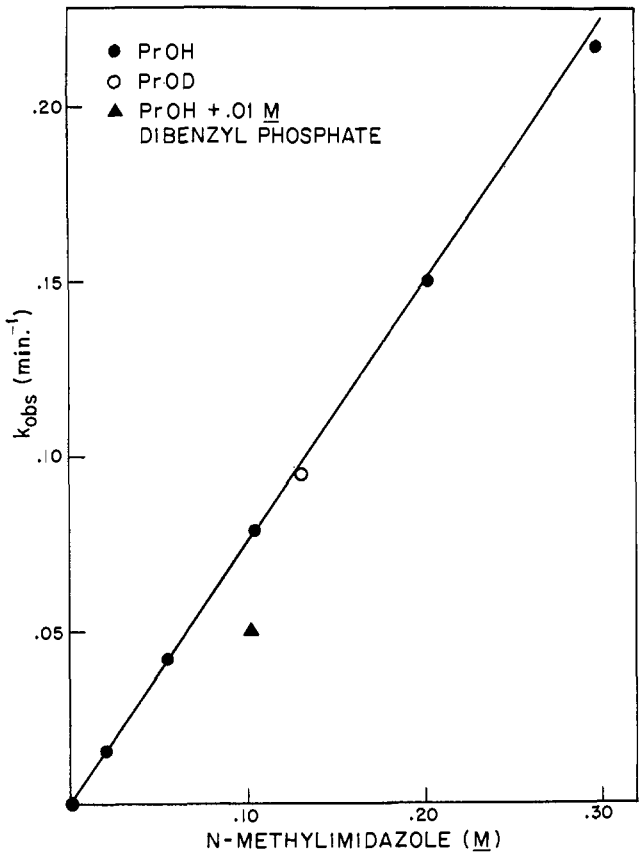

Figure 7. Solvent deuterium isotope effect in the solvolysis of tetrabenzyl pyrophosphate (4 × 10^{-4} M) catalyzed by N-methylimidazole at 25°.

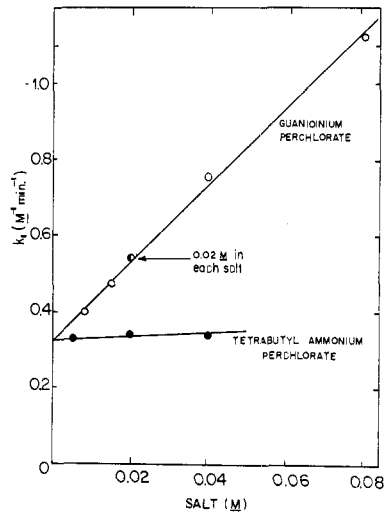

Figure 8. The effect of salts on the solvolysis of tetrabenzyl pyrophosphate (4 × 10^{-4} M) catalyzed by N-methylimidazole at 25°.

Discussion

The results presented for the solvolysis of tetrabenzyl pyrophosphate in the presence of imidazole are consistent with nucleophilic attack of the base on the pyrophosphate in a reversible reaction to produce the intermediate I followed by a general base catalyzed reaction between the solvent and I, as shown in eq. 1–3. The data for N-methylimidazole are similarly consistent with a scheme involving equations analogous to 1 and 3. For N-methylimidazole, the mechanism is less complicated than for imidazole, because the equilibrium (eq. 2) for proton transfer from I is impossible, and the solvolysis must necessarily proceed by way of the cationic species. The general base catalyzed alcoholysis of I for imidazole is kinetically equivalent to the experimentally observed facts, which may also be described as general acid catalysis of the alcoholysis of dibenzylphosphorylimidazole, *i.e.*

$$k_2(\text{DBPIH}^+)(\text{ImH}) = k_2K(\text{DBPI})(\text{ImH}_2^+) = k_{\text{obsd}}(\text{DBPI}) \quad (7)$$

However, mechanistically the first of these processes is preferred, since then the reaction should parallel that catalyzed by N-methylimidazole, and is then consistent with the interpretations previously offered for other acid-catalyzed solvolyses of acyl derivatives of imidazole.[21]

The synthesis of dibenzylphosphorylimidazole has permitted the separate measurements of the rates of the reactions postulated for this compound in eq. 1 and 3; the isolation of products has shown that the over-all chemistry is correct. The reaction forming the intermediate is demonstrated by the titrimetric experiments. The over-all titrimetric experiments are fitted in an approximate fashion by the rate constants and equations here presented; an exact fit could hardly have been expected in consideration of the known errors of the basic and acidic titrations. Similarly, the data for the reaction catalyzed by N-methylimidazole can be fitted by the kinetic equations here presented. The data for N-methylimidazole can, however, be fitted by a range of kinetic constants, so that the possible error in the assigned values is large (perhaps as great as 50%).

The data are all fitted on the assumption that dibenzylphosphorylimidazole is a true kinetic intermediate in the solvolysis. We necessarily considered the possibility that this material is merely present in steady state with the reactants, but that an alternative pathway accounts for the major portion of the reaction from tetrabenzyl pyrophosphate to the products. This possibility must be rejected for the following reasons. (1) The rate of the solvolysis of DBPI has been measured independently, and is so fast as to compete favorably with the back reaction. (2) The over-all rate of disappearance of tetrabenzyl pyrophosphate is diminished by the addition of dibenzyl phosphate ion. Now, if dibenzylphosphorylimidazole were not a true intermediate (*i.e.*, if the reaction proceeded by some other path from tetrabenzyl pyrophosphate), then the addition of dibenzyl phosphate ion would increase and not decrease the rate. When the back reaction is favored, the concentration of dibenzylphosphorylimidazole is decreased, but that of tetrabenzyl pyrophosphate is increased. Therefore, only a reaction which proceeds by way of the dibenzylphosphorylimidazole as an intermediate will show a decrease in rate with added dibenzyl phosphate ion.

Further evidence as to the mechanism of the reaction comes from the experiment with N-methylimidazole in deuterated propanol as solvent. The rate is indistinguishable from that in ordinary propanol. This result is consistent with a mechanism for the reaction which involves nucleophilic attack of the base on the pyrophosphate, but would be hard to reconcile with general base catalysis in the initial rate-limiting step. If the base operated by attack on the hydroxyl group of the alcohol to form an incipient alkoxide ion, the rate of reaction should be considerably slower when deuterium rather than hydrogen is removed from the alcohol. This theoretical expectation is strongly reinforced by the observation[2] that the catalysis of the solvolysis by 2,6-lutidine is in fact 3.4 times as fast with propanol as with propanol-OD. The deuterium experiment is quite clean-cut with N-methylimidazole, where the intermediate, I, cannot accumulate, and where the first attack by the base on tetrabenzyl pyrophosphate is rate limiting.

These results together with those previously[2,3] published show that tetrabenzyl pyrophosphate is attacked in three different ways by bases: 2,6-lutidine with general base catalysis, pyridine with attack at carbon, and imidazole and N-methylimidazole with attack at phosphorus. Why? The reactions of 2,6-lutidine are subject to strong steric hindrance.[22] Such steric hindrance is especially marked at phosphorus[23] and therefore nucleophilic attack by this reagent is prevented. With 2,6-lutidine, then, a pathway is preferred which is not strongly subject to steric effects.[24] But what causes attack at carbon with pyridine and attack at phosphorus with imidazole? Perhaps the transition state for attack by imidazole at a phosphorus atom is stabilized by d–π, p–π overlap. An unshared pair of electrons is more available in imidazole than in pyridine, and so can favor attack by this reagent at phosphorus.

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Appendix

The kinetic equations for various mechanistic schemes, and in particular for that represented by eq. 1–3, are too complicated for integration in closed form. Before any attempt at solution, they were simplified by the assumption that the equilibrium constant, K, defined by eq. 8, is small; *i.e.*, that the reaction 2 as written proceeds largely from left to right, and that imidazole is a strong base relative to dibenzylphosphorylimidazole. This assumption is electronically reasonable and is supported experimentally by the following observations. The hydrolysis of dibenzylphosphorylimidazole in the presence of guanidinium dibenzyl phosphate and imidazole was followed at pH 4.6 using a Radiometer pH-Stat to maintain the acidity and to measure the amount of imidazole produced by the formation of tetrabenzyl pyrophosphate as a function of time. The half-time for the formation of tetrabenzyl pyrophosphate at 10° was about 1 min. with the following initial concentrations: dibenzylphosphorylimidazole, 8.6×10^{-3} M; guanidinium dibenzyl phosphate, 1×10^{-2} M; imidazole, 2×10^{-2} M. Little or no acid had to be added to maintain pH 4.6 at the instant dibenzylphosphorylimidazole was injected into the solution. Unless the pK of dibenzylphosphorylimidazole[25] was below 4.6, acid would have to be added instantaneously to maintain the pH.

(21) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1280 (1959).

(22) A. R. Butler and V. Gold, *J. Chem. Soc.*, 4362 (1961); V. Gold and E. G. Jefferson, *ibid.*, 1409 (1953); H. C. Brown, H. I. Schlesinger, and S. Z. Cardon, *J. Am. Chem. Soc.*, **64**, 325 (1942).

(23) P. S. Traylor and F. H. Westheimer, *ibid.*, **87**, 553 (1965); D. M. Brown and N. K. Hamer, *J. Chem. Soc.*, 1155 (1960).

(24) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963); J. A. Feather and V. Gold, *J. Chem. Soc.*, 1752 (1965).

(25) B. Atkinson and A. L. Green, *Trans. Faraday Soc.*, **53**, 1334 (1957), report that the pK of N-(diisopropylphosphoryl)imidazole is 6.9 at 0°, as determined "by potentiometric titration with sodium hydroxide." In view of our experiments, this value seems to us extraordinarily high, and surprisingly close to that of imidazole.

Assuming that the equilibrium constant, K, is small, the concentration of $DBPIH^+$ (*i.e.*, of intermediate I, with R = H) may be written as

$$(DBPIH^+) = K(DBPI)(ImH_2^+)/(ImH) \quad (8)$$

When the reaction is begun with a solution of pure dibenzylphosphorylimidazole (with no added dibenzyl phosphate ion), the stoichiometry is that shown in eq. 3, and the kinetic equation simply

$$-d(DBPI)/dt = k_2K(DBPI)(ImH_2^+) = k_{obsd}(DBPI)$$

where k_{obsd} is a first-order rate constant. The solvolysis proceeds with the net formation of dibenzyl propyl phosphate and imidazole. Since the reaction does not affect the concentration of imidazolium ion, the reaction remains first order thoughout. To be sure, the fraction of protonated intermediate, $DBPIH^+$, decreases as the reaction proceeds, but the concentration of imidazole increases, and the product of these concentrations changes exactly as does the product of the concentrations of DBPI and ImH_2^+. The value of k_2K can then be determined spectrophotometrically.

When the solvolysis of dibenzylphosphoryl imidazole is carried out in the presence of guanidinium dibenzyl phosphate, the appropriate kinetic equations are those (9–12) given below.

$$-d(PP)/dt = k_1(PP)(ImH) - k_{-1}K(P^-)(DBPI)(ImH_2^+)/(ImH) = d(ImH_2^+)/dt = d(P^-)dt \quad (9)$$

$$d(DBPI)/dt = k_1(PP)(ImH) - k_{-1}K(P^-)(DBPI)(ImH_2^+)/(ImH) - k_2K(DBPI)(ImH_2^+) \quad (10)$$

$$-d(ImH)/dt = 2k_1(PP)(ImH) - 2k_{-1}K(P^-)(DBPI)(ImH_2^+)/(ImH) - k_2K(DBPI)(ImH_2^+) \quad (11)$$

$$d(DBPP)/dt = k_2K(DBPI)(ImH_2^+) \quad (12)$$

where $DBPIH^+$ and DBPI represent protonated and neutral dibenzylphosphorylimidazole, ImH_2^+ and ImH represent protonated and unprotonated imidazole, PP represents tetrabenzyl pyrophosphate, P^- represents the dibenzyl phosphate anion, and DBPP represents dibenzyl propyl phosphate.

These equations involve nine variables or unknowns: (PP), (P^-), (DBPI), (DBPP), (ImH), (ImH_2^+), k_1, $k_{-1}K$, and k_2K. The assumption that K is small means that the concentrations of $DBPIH^+$ may be neglected, so that neither k_{-1} nor k_2 can be determined from the kinetic scheme, but only $k_{-1}K$, k_2K, and the k_{-1}/k_2 ratio. The nine variables are connected by four stoichiometric equations (13–16)

$$(PP)_0 = (PP) + (P^-) \quad (13)$$

$$(P^-) = (ImH_2^+) = (DBPI) + (DBPP) \quad (14, 15)$$

$$(ImH)_0 = (ImH) + (ImH_2^+) + (DBPI) \quad (16)$$

Further, two of the four differential equations given above (*e.g.*, 9 and 11) are independent. Both k_1 and k_2K have been found independently by the methods already noted. Eight relationships are at hand; only one more is therefore needed to determine the values of all nine of the variables, and to achieve a solution (in principle) for the kinetic equations. This additional relationship is supplied by the measurement of the optical density of the system as a function of time, *i.e.*

$$\text{O.D. (obsd.)} = \epsilon_{PP}(PP) + \epsilon_{DBPI}(DBPI) + \epsilon_{P^-}(P^-) + \epsilon_{DBPP}(DBPP) \quad (17)$$

All the extinction coefficients have been measured (Table I) at 2638 Å.; at this wave length, imidazole and imidazolium ion are transparent.

When the solvolysis of tetrabenzyl pyrophosphate is followed by titration, the appropriate kinetic equations are again 9–12. Here, however, the system is actually completely determined. The nine variables and ununknowns are fixed by the four stoichiometric equations, two differential equations, and prior determinations of k_1, k_2K, and $k_{-1}K$. Therefore, the values of x_b (imidazolium ion, determined by titration) and x_a (imidazole concentration) can in principle be calculated, and the calculated values can be compared with experimental ones.

The kinetic equations, as stated above, cannot be solved in closed form, but the system can be worked out with the aid of computers. The equations controlling the titrimetric data for the solvolysis of tetrabenzyl pyrophosphate in the presence of imidazole and the spectrophotometric data for the solvolysis of tetrabenzyl pyrophosphate in the presence of N-methylimidazole were solved[18] with a PACE 16-31R Analog computer (Electronics Associates) which was made available to us through the courtesy of Dr. A. E. Pandiscio of the Department of Physics, Harvard University.

More recently, the system of differential equations has been approximated by a set of difference equations,[26] and programmed for an IBM 1620 electronic digital computer, and in Dynamo Language for an IBM 7090 computer, which was made available to us through the courtesy of the computer center at Massachusetts Institute of Technology. For the reaction of dibenzylphosphorylimidazole with guanidinium dibenzyl phosphate in propanol, all the constants are known but one ($k_{-1}K$), and this was determined by trial and error. The computer was programmed to plot the data on an X–Y recorder, and the value of $k_{-1}K$ was systematically varied to produce the best fit to the experimental points. The computation for the titrimetric data involves no unknown constants, and the (approximate) fit to the experimental data was computed with rate constants previously determined.

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