Phosphorus Compounds. IV. Tautomerism in Dialkyl Phosphonates[1-3]

WILLIAM J. BAILEY AND ROBERT B. FOX

Department of Chemistry, University of Maryland, College Park, Maryland, and the Naval Research Laboratory, Washington, District of Columbia

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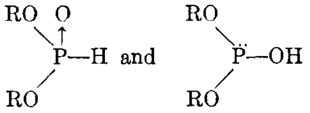
Deuterium exchange between di-*n*-butyl phosphonate and *n*-butyl alcohol-*d* was followed by infrared measurements in the presence of acids or bases as well as in neutral solution. It was shown that a mobile prototropic equilibrium exists between the ester and acidic species present in the reaction mixture. The exchange is both acid and base catalyzed and, in the absence of catalysts, appears to proceed in a manner similar to that found for acetone.

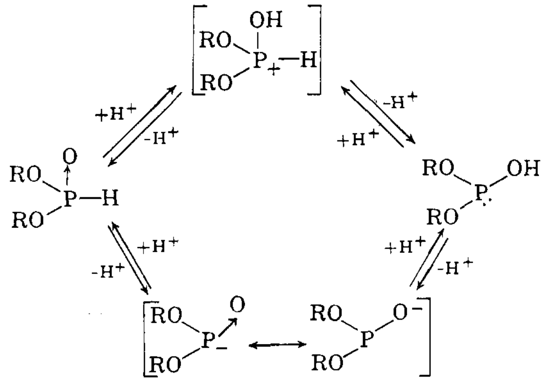
Although more than 200 articles have been published in the last ten years on the base-catalyzed condensation of dialkyl phosphonates with unsaturated compounds, knowledge of the mechanism of such reactions is based almost entirely on analogous reactions among organic compounds. Much of the difficulty in the determination of the structure of the reacting species in the case of substances such as the dialkyl esters of phosphorus acid lies in the fact that a tautomeric pair of structures may be envisioned for them:



Although considerable circumstantial evidence indicating the existence of such tautomers has been reported, very little direct experimental evidence has been produced to show the actual structures of such compounds, either in their chemical reactions or in the pure state.

The evidence adduced for the structure of the dialkyl esters of phosphorous acid might be conveniently divided into three types: (a) reactions diagnostic for one or the other of the possible forms, (b) evidence derived from physical measurements, and (c) kinetic evidence obtained from reactions involving these esters. For example, the fact that many reagents, such as cuprous halides,[4] diazomethane,[5] and phenylazide,[6] appear to react with the trivalent form of these esters was cited as evidence[5] for a tautomeric equilibrium between the trivalent and the pentavalent forms. On the other hand, the consensus of most physical measurements, including Raman,[7] ultraviolet,[8] infrared,[8-10] and n.m.r.[11] spectral data is that the esters exist primarily in the pentavalent or "keto" form. Nylén[12] found that the oxidation of dialkyl esters of phosphorus acid by iodine in aqueous acidic solutions was subject to general acid-base catalysis and proposed that a prototropic rearrangement of P(V) to the P(III) form precedes the attack by triiodide ion.

Since a number of workers[13-15] had shown by deuterium and tritium exchange that phosphorus acid and hypophosphorus acid contain two kinds of hydrogen atoms with respect to exchange, this method seemed ideally suited to follow the possible shift of a hydrogen atom from the phosphorous atom to the oxygen atom in a dialkyl phosphonate if the prototropic shift were either acid or base catalyzed.



For this reason the exchange of hydrogen atoms in dibutyl phosphonate with deuterium atoms in *n*-butyl alcohol-*d* in the presence of acidic or basic catalysts was undertaken.

Experimental

Apparatus.—For all the infrared studies a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics was used. Solid samples were run as potassium bromide pellets while liquids or solutions were run in standard calcium fluoride absorption cells with thicknesses, as determined by measurement of interference fringes in the empty cells, of 0.0982 and 0.1090 mm. Since the 0.0982-mm. cell was used for the compensating solution at all times and the "blank" absorption in the reference cell was always very small, no correction was made for the difference in these path lengths.

Materials.—With the exception of the substances cited, all chemicals were C.P. reagent grade and used as received. *n*-Butyl alcohol and the amines were redistilled before use and then stored under dry nitrogen. Particular care was necessary in the case of the *n*-butyl alcohol, since some lots contained an impurity, not removed by fractionation, which underwent reaction with iodine. Only redistilled alcohol which had no iodine blank was used in this work. Stuart Oxygen Co. 99.8% deuterium oxide was employed in the exchange experiments. The di-*n*-butyl phosphonate

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(1) Previous paper in this series, *J. Org. Chem.*, **27**, 4404 (1962).

(2) Presented before the Division of Organic Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September, 1958.

(3) Abstracted from a thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1959.

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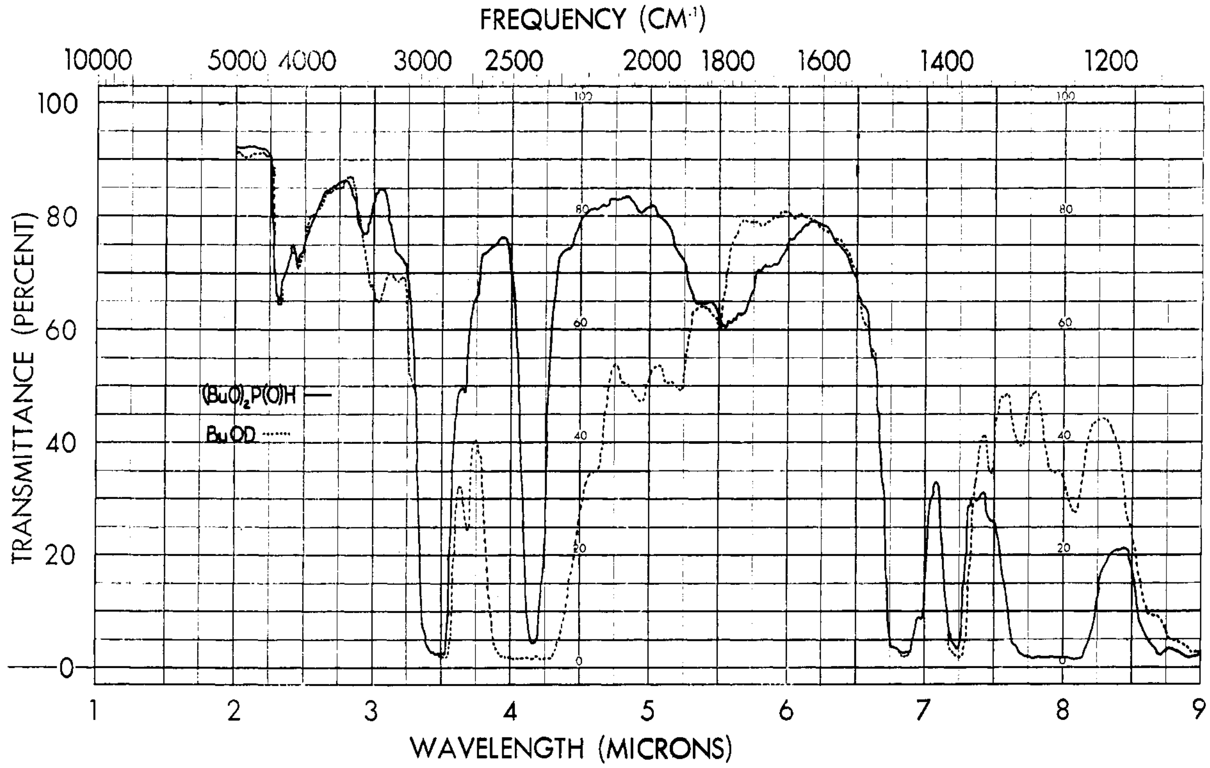


Fig. 1.—Infrared spectrum of di-*n*-butyl phosphonate and *n*-butyl alcohol-*d*.

was from a freshly distilled heart cut, b.p. 92° (2.2 mm.), n^{23}D 1.4231, stored under nitrogen over Drierite.

n*-Butyl alcohol-*d was prepared by successive exchanges between *n*-butyl alcohol and deuterium oxide until the redistilled alcohol in a 0.1-mm. cell showed no absorption at the O—H stretching frequency near 2.9 μ; before use, this material was exchanged twice more with 99.8% deuterium oxide, distilled, and stored over Drierite. Samples of *n*-butyl alcohol-*d* containing small amounts of the undeuterated alcohol were sometimes used if a compensating cell was employed.

Procedure.—Samples for exchange were made by accurately weighing the materials into 1- or 5-ml., glass-stoppered volumetric flasks (volume accuracy to ±0.03 ml.); these samples were held over Drierite at 24° ± 1°. Extreme care was taken to exclude atmospheric moisture which would cause rapid hydrolysis of the ester with the formation of strong acids that would act as catalysts for the exchange reaction.

Preliminary experiments were carried out by observing the infrared spectra of mixtures of the ester and deuterated alcohol. It was found that the P—H stretching vibration of the pure ester has about the same frequency (2400 cm.$^{-1}$) as the O—D stretching vibration of the deuterated alcohol. Unidentified interference is also encountered at 1770 cm.$^{-1}$, the region of P—D absorption; in addition, this band is quite weak. It is, however, apparent that the O—H stretching frequency region at about 2.8 to 3.0 μ is relatively free from interference (Fig. 1), and the work reported was carried out by following the intensity of the band in this region; such a procedure, of course, means that any and all exchange taking place would be recorded, whatever the source.

Direct measurement of the extinction coefficient at 2.92 μ of *n*-butyl alcohol in carbon tetrachloride in a 0.01-mm. cell led to a value of ϵ 12.07 l./mole-mm. Measurement of per cent transmission of known solutions of *n*-butyl alcohol-*d* in a 0.1-mm. cell at the same wave length gave a linear Beer's law plot whose slope led to ϵ 12.11 l./mole-mm.

The exchange experiments were carried out on mixtures of the ester, *n*-butyl alcohol-*d*, catalyst, and *n*-octane (as solvent in specified cases) in known concentrations. Samples were withdrawn at suitable intervals and the spectrum in the 2.9-μ region measured; a matched cell without the catalyst was used in the reference beam for runs with catalysts. Runs without catalysts were carried out against an *n*-butyl alcohol-*d* reference solution containing no ester. A few runs were also made with acetone in place of the ester. Where the exchange was relatively rapid, the extent of reaction was followed on a single sample and reference cell, and a continuous record of the transmittance at 2.9 μ was obtained.

Discussion

Acidic Solutions.—Exchange reactions catalyzed by acid were carried out by adding *p*-toluenesulfonyl chloride to mixtures of the phosphonate and *n*-butyl alcohol-*d* in the concentrations shown in Table I.

$$p\text{-}CH_3C_6H_4SO_2Cl + C_4H_9OD \longrightarrow p\text{-}CH_3C_6H_4SO_2OC_4H_9 + DCl$$

Table I

Acid-catalyzed Di-*n*-butyl Phosphonate–*n*-Butyl Alcohol Exchange

Run	Concentration, moles/l. Ester	C_4H_9OD	Added TsCl	$t_{1/4}$, min.
1	1.05	6.0	0.16	6.8
2	1.00	6.14	0.053	19.8
3	1.04	3.05	0.16	7.0
4	1.07	8.48	0.027	30.0
5	1.20	8.42	0.097	9.0

The absolute acid concentration is unknown, since both the extent of this reaction and the ionization of deuterium chloride in this medium are unknown. The relative values from run to run, however, are of interest, since the qualitative rate dependence on the concentrations of each reactant can still be determined.

These reactions were fairly rapid and were followed in the infrared sample cell itself with the recorder set at 3.000 μ. Some error may be introduced by this procedure, since the frequency of the OH vibration appeared to shift slightly with changing concentration. However, since only a qualitative rather than quantitative picture of the reaction was desired, it was felt that this error would not be unduly great.

Also given in Table I are the times required for one fourth of the initial amount of the phosphonate to undergo exchange based on the assumption that OH arises only from ester hydrogen (PH). These data are plotted in Fig. 2. A comparison of the quarter-times in Table I shows that the rate of exchange is independent of the *n*-butyl alcohol-*d* concentration (runs 1 and 3) and dependent upon the concentration of added *p*-toluenesulfonyl chloride catalyst (runs 1 and 2, 2 and 4, and 4 and 5).

Even though rigorous exclusion of atmospheric moisture and a constant temperature were not maintained in the sample cell during a continuous run, these data do justify the qualitative conclusion that the deuteration of dibutyl phosphonate under these experimental conditions is subject to a rate-controlling prototropic interconversion. It is probable that this preliminary reaction, which is independent of the attacking electrophilic reagent, occurs in two steps analogous to the major process taking place during the oxidation or deuteration of acetone under acid conditions. Further attack by the electrophilic reagent, deuterium ion in the present case, takes place at the free electron pair of the phosphorus atom in the trivalent form. It can be concluded that an acid-catalyzed tautomeric interconversion does take place in the P(O)H diadic system, at least for the phosphonate structure.

Neutral Solutions.—In the absence of added acidic or basic catalysts, the rate of exchange between dibutyl phosphonate and *n*-butyl alcohol-*d* is several orders of magnitude slower than in the presence of such catalysts. In a typical run (see Fig. 3) with about an eightfold excess of the alcohol, the quarter-time for the exchange was approximately 3000 min., which may be compared with the quarter-times of 3 min. or less in the presence of acids or strong bases. (Acetone undergoes one fourth of its theoretical exchange for one hydrogen with a tenfold excess of *n*-butyl alcohol-*d* in about 7500 min.) Even these figures may be too low because, with the small total volumes of solutions involved, a trace of contaminating atmospheric moisture can give rise to a considerable error. On the basis of deuterium exchange, it can only be said that if a tautomeric equilibrium is involved in the exchange reaction, the rate of equilibration is about the same in dibutyl phosphonate as it is in acetone. The latter substance has been shown to contain about 10^{-4} % enol in aqueous solution.[12]

Basic Solutions.—In view of the large number of known base-catalyzed reactions of the dialkyl phosphonates, it is not surprising that the deuterium exchange reaction would also be base catalyzed. A number of runs were carried out with variations in the concentration and base strength (in water) of tertiary amines as catalysts. *n*-Butyl alcohol-*d* again was the source of deuterium, and in many of these runs where the alcohol concentration was relatively low, *n*-octane was added as a solvent. In Table II are given the concentrations and times for 25% of the initial phosphonate to be consumed in each run. The rate data are plotted in Fig. 3. Accuracy of the data did not justify their use in the determination of the order of the reaction.

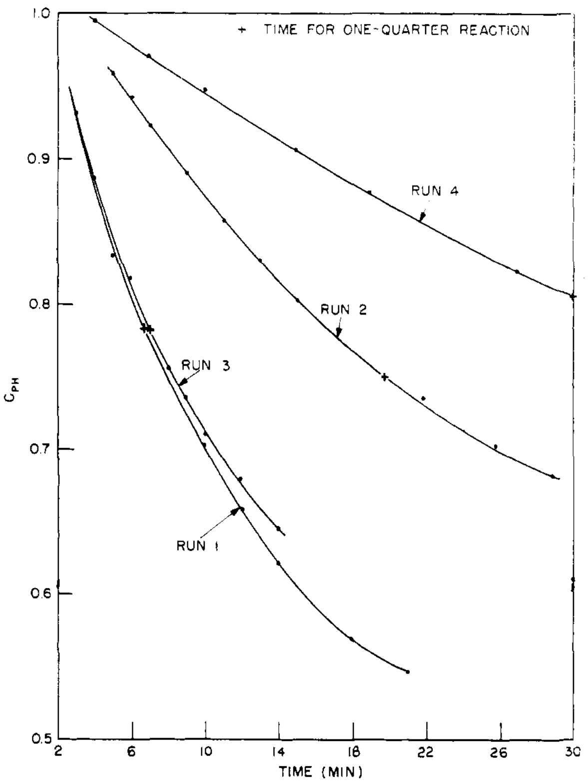


Fig. 2.—Rate of disappearance of $(C_4H_9)_2P(O)H$ in exchange with C_4H_9OD in presence of acid.

TABLE II

BASE-CATALYZED DI-*n*-BUTYL PHOSPHONATE–*n*-BUTYL ALCOHOL EXCHANGE

	Concentration, moles/l.			
Run	Ester	C_4H_9OD	Base[a]	$t_{1/4}$, min.
6	1.00	8.8	0.13	1[b]
7	1.01	8.7	0.14[c]	3.3
8	1.07	7.8	0.75[d]	3360
9[e]	0.98	3.8	0.017	3.9
10[e]	0.95	2.1	0.018	6.8
11[e]	0.98	1.06	0.019	22.5
12[e]	0.99	1.02	0.01	60[f]
13[e]	0.82	2.1	0.01	14.4

[a] Triethylamine, except as noted. [b] Reached equilibrium in less than 3 min. [c] Benzyldimethylamine. [d] Pyridine. [e] *n*-Octane added as solvent. [f] Estimated by extrapolation.

Examination of the rate curves and comparison of the quarter-times for these exchange reactions reveal a dependence of the rate on the concentration of both the *n*-butyl alcohol-*d* and the base and on the relative base strength (in water) of the amine. It should be noted that the quarter-time for exchange in the presence of pyridine, an extremely weak base in water, is about the same as that of the uncatalyzed reaction. Quarter-times in the presence of stronger bases are of the same order of magnitude as those found with the acid catalyst, *p*-toluenesulfonyl chloride, and its acid reaction product with alcohol.

Since the rate of the reaction is dependent on the concentration of both the base and the attacking reagent, it is apparent that removal of a proton in this reaction is not in itself rate controlling. A plausible explanation involves the concept of ionization of the P—H bond in the presence of basic reagents, the activation energy of which should be approximately that for the ionization of *n*-butyl alcohol-*d*. In the presence of base, both reactions might be written

$$X{-}H + B \rightleftharpoons X^- + BH^+$$

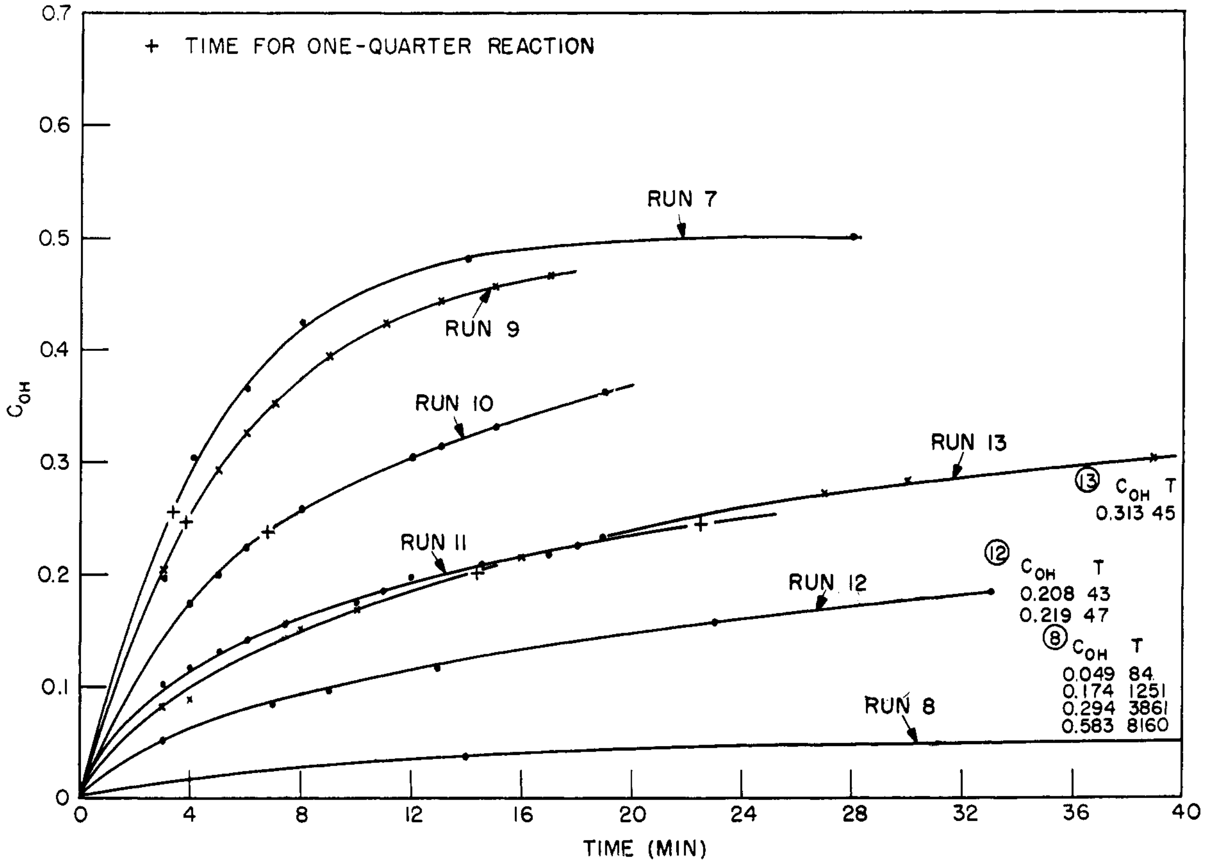
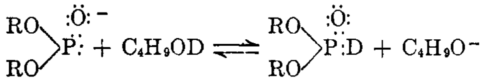
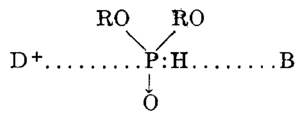


Fig. 3.—Rates of formation of C_4H_9OH in the base-catalyzed $(C_4H_9)_2P(O)H—C_4H_9OD$ exchange.

The anion of the phosphonate is, of course, the strong conjugate base of a weak acid and could enter into reaction with the alcohol.

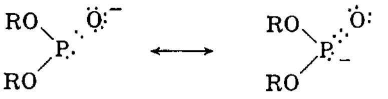


Since the exchange is dependent on both base and deuterium concentrations, it is also possible that a termolecular mechanism may be operating in which the deuterium ion (an electrophilic reagent) attacks the phosphorus simultaneously with the removal of the proton by the base (a nucleophilic reagent):



Such a mechanism corresponds to the termolecular mechanism originally proposed by Lowry[16] and later discussed by Swain[17] in the enolization of ketones and similar substances.

With basic catalysis, whether or not reactions of the phosphonates represent a case of tautomerism may be a question of semantics. Certainly in very strong base the dialkyl phosphonate exists almost exclusively as an anion which is undoubtedly a resonance hybrid. It is, therefore, possible that many base-catalyzed reactions of the phosphonates (including the isotope exchange reaction) proceed directly through this anion without involving tautomerism in the usual sense. Those reactions that can take place only with the uncharged trivalent form, however, would involve base-catalyzed tautomerism in the usual sense.



Since the present work was originally reported,[2] Luz and Silver[18] studied the acid-catalyzed exchange of hydrogen in dialkyl phosphonates in water (deuterium oxide) by nuclear magnetic resonance spectra. They concluded that the rate = k_H [phosphonate] $[H^+]$ + k_w [phosphonate], where k_w is the catalysis constant for the spontaneous acid-independent exchange, in substantial agreement with the portion of our work on the acid side.

Thus we can conclude that, on the basis of deuterium exchange experiments between *n*-butyl alcohol-*d* and di-*n*-butyl phosphonate, it has been shown that a mobile prototropic equilibrium exists between the ester and acidic species present in the reaction mixture. The exchange is both acid and base catalyzed and in the absence of catalysts appears to proceed in a manner similar to that found with acetone.

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