

and 1770 cm^{-1} , from which a maximum isotope effect at 22° may be calculated to be $k^{\text{H}}/k^{\text{D}} = 5.3$. A similar value (5.1 at 25°) also was obtained by Martin¹⁸ for the analogous bond in phosphorous acid. The observed value of $k^{\text{H}}/k^{\text{D}}$ is not far below the calculated maximum value, indicating considerable stretching of the P-H bond in the transition state. It should be noted that the maximum kinetic isotope effect was calculated from the vibration frequencies of the liquid phosphonate and therefore does not apply exactly to the protonated phosphonate in aqueous solution.

The isotope effect for the spontaneous reaction $k_w^{\text{H}}/k_w^{\text{D}}$ is approximately 1.7 and though subject to considerable error, appears to be significantly lower than that for the acid catalyzed reaction. Swain¹⁹ recently has discussed the variation of isotope effect with the strength of the catalyzing acid for some keto-enol isomerizations and postulates that, other things being equal, the kinetic isotope effect increases with acid strength. The lower value of the kinetic isotope effect for the spon-

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taneous reaction, in the present case, possibly is to be explained in a similar manner, assuming water to be the catalyzing acid in the spontaneous reaction.

The effect of solvent D_2O on the oxidation reaction of diethylphosphonate is shown in Table III and Fig. 3. The rates in D_2O are seen to be systematically 15–30% higher than the corresponding runs in H_2O . An increase of this kind has been considered to provide evidence for the existence of a pre-equilibrium protonation.⁶ Long¹² has estimated numerical limits for the expected solvent isotope effects $k^{\text{D}_2\text{O}}/k^{\text{H}_2\text{O}}$ in acid catalysis, giving approximate limits of 1.4 to 3.0 for pre-equilibrium and 0.7 to 1.4 (with less than unity values being more likely), for a slow proton transfer. Although the present studies in D_2O therefore do not exclude the possibility of a slow proton transfer, neither do they rule out the existence of a pre-equilibrium.

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N.m.r. Study of the Exchange of Phosphorus Bonded Hydrogen in Dimethyl- and Diethylphosphonate, Catalyzed by Acetate Ion

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The exchange of the phosphorus-bonded hydrogen with deuterium in D_2O solutions of sodium acetate has been studied for dimethyl- and diethylphosphonate using a nuclear magnetic resonance technique previously described.¹ The exchange was found to be linearly dependent on the acetate ion concentration. From a comparison of the data obtained with those found for the oxidation of the same compounds, it is suggested that the phosphite form of the dialkyl phosphonate serves as a common intermediate for both the exchange and oxidation reactions. The substitution of deuterium for the phosphorus bonded hydrogen in diethylphosphonate had a negligible effect on the oxidation rate. This result is discussed in terms of possible mechanisms for the formation of the phosphite form.

Introduction

The oxidation of dialkyl phosphonates² and the exchange of the phosphorus bonded hydrogen¹ in the same compounds have been found to be acid catalyzed. The mechanisms of both reactions have been interpreted in terms of a tautomeric equilibrium between the normal (phosphonate) form and an active (phosphite) form.^{1–4} The rate determining step in both reactions was shown to be the formation of the phosphite form which serves as a common intermediate for both oxidation and exchange. It is known² that the oxidation of dialkyl phosphonates also is subject to general base catalysis, and it was therefore of interest to determine whether the exchange of the phosphorus bonded hydrogen is similarly catalyzed. That this is in fact the case was determined by preliminary experiments, and a quantitative study of this exchange was performed with the n.m.r. technique previously used¹ in studying the acid cata-

lyzed exchange. The basic catalyst used in the present work was acetate ion, for which comparable data for oxidation are available.² No attempt was made to study hydroxide ion catalysis of exchange since the hydrolysis of dialkyl phosphonates is strongly catalyzed by hydroxide ion. The exchange reaction was studied for dimethyl- and diethylphosphonate. An attempt to study the reaction for di-*n*-propylphosphonate failed since this compound was salted out of solution by the addition of the catalyst.

Experimental

The n.m.r. spectrum of a dialkyl phosphonate includes a doublet due to the phosphorus bonded hydrogen. The rate of exchange of this hydrogen with solvent D_2O may be measured by observing the decrease, with time, of the relative intensity of one component of this doublet (P-H line). The procedure in the present work is identical with that described in reference 1. The reaction solutions contained varying amounts of dialkyl phosphonate, sodium acetate and acetic acid in D_2O . First-order rate constants k for the exchange reaction were evaluated from a plot against time of the logarithm of the relative intensity of a P-H line. Since under the present experimental conditions the hydrolysis of dialkyl phosphonates is negligible,⁵ hydrolysis

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TABLE I
OBSERVED FIRST-ORDER RATE CONSTANT k IN MIN.⁻¹, FOR HYDROGEN EXCHANGE IN 1.7 M SOLUTIONS OF DIETHYLPHOSPHONATE IN ACETATE BUFFERS (TEMP. 21.5 ± 0.5°)

[AcONa], M	0.157	0.240	0.315	0.375	0.522	0.630
	[AcOH]/[AcONa]					
0	1.2 × 10 ⁻²	1.7 × 10 ⁻²	2.6 × 10 ⁻²	2.9 × 10 ⁻²	4.1 × 10 ⁻²	4.6 × 10 ⁻²
1	2.0 × 10 ⁻²	3.3 × 10 ⁻²	4.6 × 10 ⁻²	5.2 × 10 ⁻²
3	3.1 × 10 ⁻²	5.8 × 10 ⁻²

TABLE II
OBSERVED FIRST-ORDER RATE CONSTANTS k IN MIN.⁻¹, FOR HYDROGEN EXCHANGE IN SOLUTIONS CONTAINING VARYING CONCENTRATIONS OF DIMETHYLPHOSPHONATE AND SODIUM ACETATE (TEMP. 21.5 ± 0.5°)

[AcONa], M	0.032	0.048	0.067	0.086	0.105
	[(MeO) ₂ PO-H] (M)				
1.57	2.0 × 10 ⁻²	2.9 × 10 ⁻²	4.3 × 10 ⁻²	5.0 × 10 ⁻²	6.6 × 10 ⁻²
1.05	2.7 × 10 ⁻²	4.0 × 10 ⁻²	6.0 × 10 ⁻²	6.5 × 10 ⁻²
0.52	1.9 × 10 ⁻²	2.8 × 10 ⁻²	4.2 × 10 ⁻²	5.8 × 10 ⁻²

was not taken into account in analyzing the exchange results. Sodium acetate and acetic acid were Analar Reagent Grade. Other materials have been described elsewhere.³

Results

The dependence of the observed first-order rate constant for hydrogen exchange k on total acetate buffer concentration is shown in Tables I and II and the results for diethylphosphonate are plotted in Fig. 1.

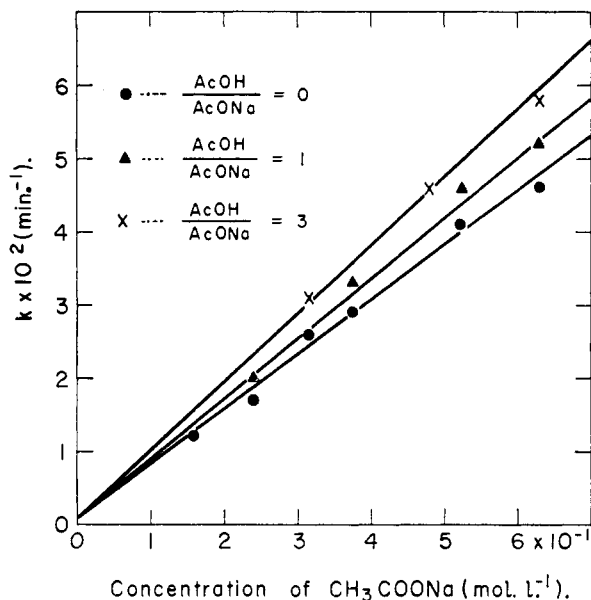


Fig. 1.—Observed first-order rate constants for hydrogen exchange in 1.7 M solutions of diethylphosphonate as a function of sodium acetate concentration for different acetate buffer compositions. (The point for 0.48 mole l.⁻¹ is not given in Table I.)

From the results for diethylphosphonate it may be seen that k shows a linear dependence on both acetate ion and acetic acid concentration. The main part of the exchange rate is due to acetate ion catalysis. The intercept on the vertical axis in Fig. 1 is a measure of the exchange rate due to water and hydroxide ion catalysis, since under the experimental conditions hydrogen ion catalysis is negligible.¹ The magnitude of this intercept ($\sim 1 \times 10^{-3}$ min.⁻¹) is approximately equal to the value found previously for the water catalyzed reaction

of diethylphosphonate¹ ($\sim 2 \times 10^{-3}$ min.⁻¹) and therefore the contribution of hydroxide ion catalysis to the observed rate is not significant under the present conditions. This conclusion also applied to dimethylphosphonate.

It may further be seen, from Table II, that for a given acetate ion concentration the values of k remain practically constant over a three-fold variation in dimethylphosphonate concentration. The exchange reaction is thus first-order with respect to dimethylphosphonate, a result which is presumed to be generally valid for the dialkyl phosphonates.

Discussion

From the results given above the rate law for the exchange reaction in acetate buffer solutions is given by

$$k = \frac{R}{[\text{phosphonate}]} = k_w + k_{\text{AcO}^-} [\text{AcO}^-] + k_{\text{AcOH}} [\text{AcOH}] \quad (1)$$

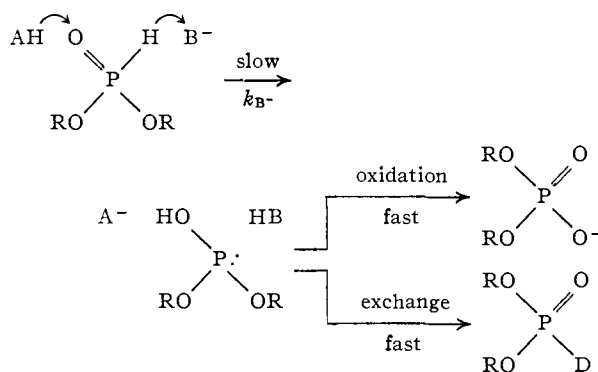
where R is the reaction rate; k_w , k_{AcO^-} and k_{AcOH} are the respective catalytic constants. Values for k_{AcO^-} for dimethyl- and diethylphosphonate may be derived graphically from the results given in Tables I and II and are compared below (Table III) with the corresponding constants obtained by Nylen² for the oxidation reactions of these compounds.

TABLE III
CATALYTIC CONSTANTS k_{AcO^-} IN M⁻¹ MIN.⁻¹ FOR THE ACETATE-ION CATALYZED HYDROGEN EXCHANGE AND OXIDATION OF DIMETHYL- AND DIETHYLPHOSPHONATE

	Exchange ^a	Oxidation ^b
Dimethylphosphonate	0.52	0.32
Diethylphosphonate	7.5 × 10 ⁻²	9.3 × 10 ⁻²

^a From present work, estimated error ± 10%; temp. 21.5 ± 0.5°. ^b From ref. 2, temperature stated 20°.

The rate law for oxidation, observed by Nylen for acetate buffer solutions, is identical with equation 1. This fact and the close correspondence of the catalytic constants suggests that a common rate determining step occurs in both acetate ion catalyzed reactions. The general formula scheme shown is suggested to describe the mechanism of the base catalyzed exchange and oxidation reactions. The first step is the removal by a base of the phosphorus bonded hydrogen, resulting in the formation of the phosphite form. The participation of the



acid HA in this process is indicated for the sake of generality, in principle a proton transfer to the phosphoryl group may occur subsequently to hydrogen removal, or not at all. The phosphite form is extremely reactive, rapidly accepting a hydrogen ion or being oxidized to phosphate in the presence of oxidizing agent, and therefore its formation is the rate determining step in both exchange and oxidation. The rate of both these processes is thus given by the rate of formation of the phosphite form, $d[\text{phosphite}]/dt = k_{B^-}[\text{phosphonate}][B^-][HA]$, in the general case. In the present case the base is acetate ion and the acid presumably water and the rate of phosphite formation is $k_{AcO^-}[\text{phosphonate}][AcO^-][H_2O] = k_{AcO^-}[\text{phosphonate}][AcO^-]$, which is equivalent to the corresponding term in equation 1. It should be noted that an ambiguity exists in the formulation of this term, since it may be written $k'[\text{phosphonate}][AcOH][OH^-]$ corresponding to the attack of hydroxide ion as the base, aided by an acetic acid molecule as the acid. The alternative formulations are kinetically indistinguishable. This does not affect the validity of the present discussion, in which it will be assumed that acetate ion is the attacking base.

TABLE IV

OBSERVED FIRST-ORDER RATE CONSTANTS FOR THE ACETATE-ION CATALYZED OXIDATION OF DIETHYLPHOSPHONATE AND DIETHYLPHOSPHONATE-*d* IN H₂O AND D₂O (COMPOSITIONS OF REACTION MIXTURES ARE GIVEN IN THE TEXT). ESTIMATED ERROR $\pm 4\%$ (TEMP. $20.5 \pm 0.1^\circ$)

	H ₂ O	D ₂ O
(EtO) ₂ PO·H	$10.6 \times 10^{-3} \text{ min.}^{-1}$	$9.7 \times 10^{-3} \text{ min.}^{-1}$
(EtO) ₂ PO·D	$10.1 \times 10^{-3} \text{ min.}^{-1}$	$9.1 \times 10^{-3} \text{ min.}^{-1}$

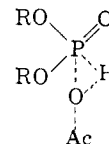
In the acid catalyzed oxidation of diethylphosphonate a kinetic isotope effect (k^H/k^D) of 4 (as compared to a theoretical maximum of 5.3) was observed,³ on substituting deuterium for phosphorus bonded hydrogen. This showed that the rate-determining step in phosphite formation is the fission of the P-H bond. To determine whether a similar effect exists in the acetate-ion catalyzed reaction, some experiments were carried out on the oxidation of diethylphosphonate and diethylphosphonate-*d* in H₂O and D₂O. The reaction mixtures contained 0.0078 *M* diethylphosphonate, 0.14 *M* KI, 0.03 *M* I₂ and 0.1 *M* sodium acetate. Under these conditions the oxidation rate is independent of iodine concentration and the reaction shows first-order kinetics. The reaction was followed by titrating samples of the mixture with sodium thio-

sulfate. The deuteriated compound contained 9% of the normal form of diethylphosphonate, and allowance was made for this in calculating the rate constants for (EtO)₂PO·D. The results are given in Table IV.

From the results it is seen that the normal form reacts only slightly faster than the deuteriated form. This result makes it improbable that the reaction proceeds through a linear transition state

of the type since in this case a large

isotope effect would be expected.⁶ In the acetate ion catalyzed enolization of ketones in which such a linear transition state probably occurs, large kinetic isotope effects are observed.⁶ One alternative mechanism, compatible with both the observed kinetics and a small kinetic isotope effect, involves the nucleophilic attack of the base B⁻ on the phosphorus atom, to give a pentacovalent transition state, which for attack by acetate ion may be written



Simultaneously with, or subsequent to, the attack on the phosphorus atom, the phosphorus bonded hydrogen shifts across to the oxygen of the attacking acetate ion and the transition state breaks up, giving the phosphite form and a molecule of acetic acid. Such a shift is geometrically similar to the so-called hydride shifts for which small isotope effects, compared to the theoretical maximum for the bond, have been observed.⁷ For such "triangular" transition states the stretching of the bond to hydrogen is small, compared with the ground state. The main contribution to the isotope effect comes from differences in the bending frequencies of the bonds to hydrogen and deuterium. Since the bending frequencies of bonds are much lower than their stretching frequencies, only small isotope effects are expected in these cases. The suggestion of attack on the phosphorus atom is further supported by many cases of nucleophilic attack by anions in the bimolecular displacement reactions of numerous organo-phosphorus compounds.⁸ This interpretation, though reasonable, is by no means the only one compatible with the experimental results, the observed isotope effect certainly not being compelling evidence for the suggested transition state.

In principle the phosphorus bonded deuterium may undergo exchange with solvent H₂O at a rate faster or comparable to the rate of oxidation, thus disguising the presence of a large isotope effect. Such behavior would result in a deviation from first-order kinetics for the oxidation, which was not observed. Further evidence against such an exchange is provided by the negligible effect on the oxidation rate of a change in solvent from H₂O to

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D₂O, as seen in Table IV. The small difference observed may be ascribed to a solvent effect between H₂O and D₂O.

In the case of diethylphosphonate k_{AcOH} for the exchange reaction was estimated to be $\sim 6 \times 10^{-3} M^{-1} \text{ min.}^{-1}$, as compared to a value of $0.3 \times 10^{-3} M^{-1} \text{ min.}^{-1}$ obtained by Nylen² for the

oxidation reaction. No explanation is offered for this difference.

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The Hydrolysis of the *d*- and *l*-Forms of H[As(C₆H₄O₂)₃·H₂O] in the Presence of Added Asymmetric Species

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An examination of the rates of hydrolysis of the *d* and the *l* forms of H[As(C₆H₄O₂)₃·H₂O] in the presence of varying concentrations of several added asymmetric species resulted in no differences between enantiomers greater than the estimated experimental error of about 2%. These results indicate that configurational activity effects involving electrolytes in homogeneous solution may be very small in some systems. A discussion of previously reported cases shows that several related aspects of the behavior of solutions in which such phenomena have been reported are only imperfectly known. The problem of the quantitative estimation of configurational activity effects cannot be solved until these related problems are solved.

In 1951, Dwyer, Gyarfás and O'Dwyer^{2,3} reported several lines of evidence that indicated the activities of enantiomeric species, in homogeneous solution, were affected differently upon the addition of a third optically active species. While this type of difference must ultimately be the basis for the formation of diastereoisomers, these had not previously been delineated clearly in homogeneous solution. One of the most interesting aspects of this is the "configurational activity" effect on the rates of racemization of the *d* and *l* forms of [Ni-(*ortho*-phenanthroline)₃]⁺² (hereafter abbreviated Ni(phen)₃⁺²). This results in rates for the *d* and *l* forms which differ by as much as 15% in the presence of an added optically active electrolyte.⁴ The present study was undertaken to delineate the kinetic aspects of configurational activity in greater detail and to establish the nature of the variables governing its magnitude. It was hoped that a quantitative basis for prediction of the magnitude of such effects might be developed.

The system chosen for this work was the arsenic(V)-catechol complex, H[As(C₆H₄O₂)₃·H₂O], whose general kinetic behavior was established in an earlier study.⁵ This system was considered ideal because firstly, the two enantiomeric forms can be obtained easily in a state of high optical purity and secondly, these forms are known to undergo a second order asymmetric transformation very readily in the presence of suitable optically active bases such as quinine, cinchonine, cinchonidine and quinidine.^{6,7} A review of the entire group of phenomena reported as "configurational activity"

has been given by Basolo and Pearson.⁸ The present work is concerned *only* with the kinetic aspects of this phenomenon in *homogeneous solutions of electrolytes*.

Experimental

Apparatus.—A Rudolph Model 62 polarimeter, reading to 0.05°, was used in the kinetic studies on the arsenic complexes. A 4 dm. jacketed polarimeter cell held the sample while water maintained to within $\pm 0.02^\circ$ of the reported temperature by a thermoregulator, was circulated through its jacket. A Schmidt and Haensch polarimeter reading to 0.01° was used in the kinetic studies on the nickel complexes together with a 2 dm. jacketed cell whose temperature was similarly regulated.

Materials.—The resolution of the arsenic complexes was effected by the procedure of Mann and Watson.⁷ The molecular rotations of the complexes used were: Ba[As-(C₆H₄O₂)₃·H₂O]₂, *d* form, $[\alpha]^{25D} +416^\circ$; *l* form, $[\alpha]^{25D} -416^\circ$. The literature values are for the *d* form,⁸ $[\alpha]^{25D} 418.7^\circ$; *l* form, $[\alpha]^{25D} -417.5^\circ$; -438° .⁷ The nickel orthophenanthroline complexes were prepared and resolved using the method given by Dwyer and Gyarfás.⁹

The specific rotations were obtained after storage for ten days in a refrigerator and were: *d* perchlorate, $[\alpha]^{20D} 1381^\circ$; literature⁹ $[\alpha]^{20D} 1463^\circ$; *l* perchlorate, $[\alpha]^{20D} -1390^\circ$; literature⁹, $[\alpha]^{20D} -1463^\circ$. The purity of the samples that were used was thus only 97%, but this seemed to be not detrimental to the reproducibility of the rates.

The buffered solutions were prepared on the basis of the solutions described by Clark and Lubs¹⁰ but also contained added optically active electrolytes. The compositions of these solutions are given in Table I. They were used as solvent solutions in the kinetic runs; the appropriate amount of optically active barium salt was weighed up and dissolved in the buffer solution and then the rate of loss of optical activity was determined for the resulting solution. The amino acids used were "Standardized Amino Acids" obtained from the Nutritional Biochemicals Corp. The ammonium salt of *d*- α -bromocamphor- π -sulfonic acid (abbreviated BCS in the Tables) was obtained from the Aldrich Chemical Co., Milwaukee, Wis. It was found necessary to purify the salt to remove water soluble colored im-

(1) To whom correspondence concerning this paper should be sent.
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