Amide–Phosphate Interactions: Acid Catalysis in Amide-Assisted Hydrolysis of Phosphonate Esters[1]

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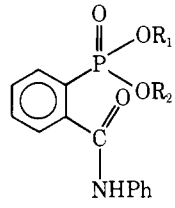
Abstract: Nucleophilic catalysis of the hydrolysis of phosphonate esters by an adjacent amide moiety has been used as a probe of covalent interactions between amides and phosphates. The ester hydrolysis of diethyl 2′-phosphonobenzanilide (**1**) is rapid in acidic solutions, whereas that of diethyl 4′-phosphonobenzanilide is undetectable under comparable conditions. The hydrolysis of **1** is subject to acid catalysis, paralleling with unit slope a newly measured set of H_0 and D_0 values for 50:50 acetone–water. Analysis of the hydrolysis and transesterification reactions of **1** relative to its para analogue and hydrolysis of a more highly substituted ester suggest a mechanism involving acid catalysis of intramolecular nucleophilic catalysis. It is suggested that phosphorylation of amides may also occur in biochemical reactions.

Our interest in reactive intermediates, which may result from covalent interactions of biochemically important molecules, led us to investigate a reaction proceeding via attack of an amide at a phosphate center.[4] Since phosphonate esters are normally highly resistant to hydrolysis,[5] amide–phosphate interactions are "reported" by acceleration of ester hydrolysis in the presence of a neighboring amide.[4,6] In this work we have studied the hydrolysis of ortho-substituted phosphonate esters (**1–5**) and a para-substituted analogue in acidic solutions. By



1, $R_1 = R_2 = Et$
2, $R_1 = Et$; $R_2 = H$
3, $R_1 = R_2 = H$
4, $R_1 = R_2 = Me$
5, $R_1 = R_2 = i\text{-Pr}$

determination of an acidity function for the reaction medium, variation of the steric bulk of the leaving group, and monitoring of a transesterification reaction, we have been able to specify characteristics of this reaction which we felt were likely, but were unproven in preliminary reports,[4,6] and have gained further insights into the mechanism of the reaction.

Experimental Section

Materials. The structures of all compounds synthesized were consistent with ir (Beckman IR7), NMR (Varian A-60, HA-100), uv (Unicam SP 1800), and MS (AEI MS9) spectra. All melting points reported were measured using capillary tubes exposed to atmosphere in a Büchi apparatus. All new compounds were analyzed by Galbraith Laboratories and gave results within ±0.3% (C, H, P, N).

Diethyl 2′-Phosphonobenzanilide (1). The procedure[4] is similar to that described by Plumb and Griffin.[8] Powdered *o*-iodobenzanilide[7] (100 g) and 500 ml of triethyl phosphite (Aldrich) were placed inside a double-jacketed silica reaction vessel cooled by chilled water. The mixture was stirred continuously and maintained under a nitrogen atmosphere. The suspension was irradiated with a quartz-jacketed high-pressure uv lamp for 2 days. During the first day, all solid dissolved. Slightly yellow crystals of the product began to deposit on the inner wall of the reaction vessel the following day. After the reaction was complete (3 days), the solution was filtered and the crude product was recrystallized twice in acetone–water. The yield was usually about 35%. The pure sample exists as colorless needles, mp 145 °C: ir (KBr) 1670 (C=O), 1240 cm^{-1} (P=O); NMR ($CDCl_3$) δ 1.3 (t, 6, J = 8 Hz, CH_3), 4.2 (quin, 4, J = 8 Hz, CH_2), 7–8 (m, 9, Ar).

Similar procedures were used to synthesize phosphonic esters with other alkoxy groups by using the corresponding trialkyl phosphite and *o*- or *p*-iodobenzanilide.

Dimethyl 2′-phosphonobenzanilide (4), mp 131 °C: ir (KBr) 1680 (C=O), 1250 cm^{-1} (P=O); NMR (acetone-d_6) δ 3.58 (d, 6, J = 10.5 Hz, CH_3), 6.8–7.7 (m, 9, ar).

Diisopropyl 2′-phosphonobenzanilide (5); mp 136 °C: ir (KBr) 1670 (C=O), 1245 cm^{-1} (P=O); NMR ($CDCl_3$) δ 1.28 (d, 12, J = 6 Hz, CH_3), 4.7 (m, 2, CH), 7–8 (m, 9, ar).

Triethyl 4′-phosphonobenzoate: ir (KBr) 1715 (C=O), 1255 cm^{-1} (P=O); NMR ($CDCl_3$) δ 1.4 (t, 3, J = 6 Hz, $COCCH_3$), 1.33 (t, 6, J = 7 Hz, $POCCH_3$), 4.4 (q, 2, J = 8 Hz, CH_2), 4.15 (quin, 4, J = 7 Hz), 7.5–8.5 (m, 4, ar).

Diethyl 4′-Phosphonobenzanilide. Methylmagnesium chloride (11 ml) in tetrahydrofuran (Fisher, titer = 3.1 mol/l.) was placed in a 100-ml round-bottomed flask cooled with a water bath. Redistilled dry aniline (3.2 ml) in 10 ml of dry ether was added dropwise into the methyl magnesium chloride solution with stirring. When the reaction had subsided, 4.74 g of triethyl 4′-phosphonobenzoate in 10 ml of dry ether was added to the reaction mixture dropwise and the whole mixture was refluxed for 2 h. Water was added to the cooled reaction mixture along with sufficient 2 M hydrochloric acid to dissolve the precipitate in the mixture. The organic layer was separated, dried, and evaporated to give the crude product. Pure sample was obtained in 50% overall yield by recrystallization in ethyl acetate–hexane solution (mp 107 °C): ir (KBr) 1670 (C=O), 1220 cm^{-1} (P=O); NMR (acetone-d_6) δ 1.3 (t, 6, J = 7 Hz, CH_3), 4.13 (quin, 4, J = 7 Hz, CH_2), 7–8.2 (m, 9, ar).

Monolithium Salt of Ethyl 2′-Phosphonobenzanilide (2). Diethyl 2′-phosphonobenzanilide (2.1 g) was mixed with 0.25 g of lithium hydroxide ($LiOH \cdot H_2O$) in 50 ml of 50% (v/v) solution of acetone and water. The solution was refluxed overnight. After the solution was evaporated to dryness under vacuum, the residue was dissolved in excess water and centrifuged. The water solution was separated. Further vacuum evaporation of the water solution gave the slightly yellow crude product. Since the product is hygroscopic, from this step on all operations were done under a nitrogen atmosphere. The crude product was reprecipitated from methanol–water and then from ethyl acetate–hexane solution. The pure sample is a white solid (70% yield): ir (KBr) 1645 (C=O), 1195 cm^{-1} (P=O); NMR (D_2O) δ 1.13 (t, 3, J = 7 Hz, CH_3), 3.83 (quin, 2, J = 7 Hz, CH_2), 7–8 (m, 9, ar).

2′-Phosphonobenzanilide (3). Diethyl 2′-phosphonobenzanilide (5 g) was dissolved in 25 ml of acetone. Hydrochloric acid (20 ml) was added slowly. Acetone was added to redissolve any precipitate. After 24 h, the solution was evaporated in vacuum and the residue was washed with acetone and then with water. The dried solid was reprecipitated twice from hot absolute ethanol in over 98% overall quantitative yield. The pure sample has a melting point of 213–214 °C: ir (KBr) 1600 (C=O), 1160 cm^{-1} (P=O); NMR (Me_2SO-d_6) δ 7–8.9 (m, ar).

Kinetics. All reagents which had been obtained commercially, unless otherwise stated, were purified by recrystallization or redistillation.

Acid Hydrolysis of Diethyl 2′-Phosphonobenzanilide. NMR Method.

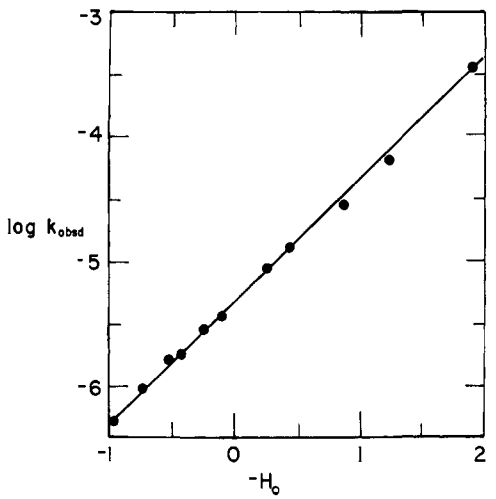


Figure 1. The observed first-order rate constant (s^{-1}) for the hydrolysis of **1** to **3** in 1:1 acetone:water-HCl or acetone-d_6:deuterium oxide-DCl at 30° as a function of solvent acidity, based on the indicator *p*-nitroaniline.

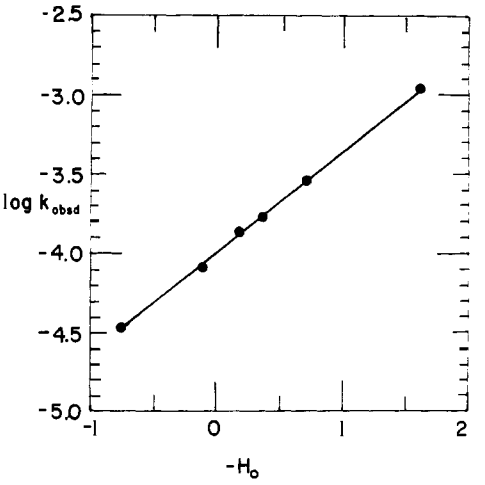


Figure 2. The observed first-order rate constant (s^{-1}) for the hydrolysis of **2** to **3** in 1:1 acetone:water-HCl or acetone-d_6:deuterium oxide-DCl at 30° as a function of solvent acidity, based on the indicator *p*-nitroaniline.

Table I. Acidity Functions (H_0 in H_2O, D_0 in D_2O) in 50% (v/v) Acetone-HCl (H_2O) or Acetone-d_6-D_2O Using *p*-Nitroaniline as Indicator ($pK_a = -0.2$)

[HCl], M	H_0	DCl	D_0
0.15	0.77	0.01	1.95
0.49	0.11	0.06	1.22
0.98	−0.34	0.08	1.03
1.43	−0.63	0.11	0.92
2.04	−1.00	0.17	0.70
2.04	−1.36	0.56	0.042
2.45	−1.74	1.11	−0.45
		1.41	−0.74
		2.02	−1.11
		2.42	−1.39

Diethyl 2′-phosphonobenzanilide (0.02 g) was dissolved in 0.18 ml of acetone-d_6 (Bio-Rad Laboratories) in a NMR tube. After the sample was completely dissolved, 0.18 ml of deuterated hydrochloric acid in deuterated water solution was added and immediately mixed thoroughly. Both the acetone-d_6 and the deuterated hydrochloric acid solution were preequilibrated at 30 °C. The NMR tube with the mixed solution was maintained at 30° in a water bath. The deuterated hydrochloric acid solution was prepared by diluting a 38% solution of deuterium chloride in deuterium oxide (purchased from Merck Sharp and Dohme of Canada, Ltd.). The concentration of the acid was determined by titration against 0.1 M sodium hydroxide using a Radiometer automatic titrator, TTT11.

A Varian A-60 NMR spectrometer was used to follow the hydrolysis of **1**. The initial NMR spectrum consists of two closely overlapping quartets due to the splitting of the methylene proton signal of the ethoxy groups by the phosphorus atom. The spectrum appears as a quintet which is centered at δ 4.5. This is due to the close values of the coupling constants: J_{POCH} = 10 Hz and J_{CHCH} = 8 Hz. During the hydrolysis a quartet centered at δ 4 appears, which is due to the absorption of the methylene protons of the product ethanol. The relative proportion of the starting material and the product was determined by integrating the original quintet and the newly formed quartet. At least three integrations were taken at each interval. When all the settings of the NMR machine were ready, each reading could be finished within 20 s. The procedure was repeated until the integral of the starting material was no longer large compared to noise. Reproducibility of integrations was about ±10%. The reaction was followed for 3–4 half-times. Plots gave straight lines of about ±5% uncertainty. The concentration of deuterated hydrochloric acid in the reaction mixture was calculated, taking into account the dilution by the added acetone. Any change in volume due to mixing was neglected. The same procedure was applied to follow the hydrolysis of dimethyl 2′-phosphonobenzanilide, diisopropyl 2′-phosphonobenzanilide, and the ethyl 2′-phosphonobenzanilide. Since total product and starting material were always observable, accurate "infinity" values were obtained at each point.

Determination of H_0. Since H_0 and D_0 had not been previously determined for the solvent-acid system we used, we evaluated these functions with *p*-nitroaniline indicator by standard procedures.[9]

Transesterification. Samples of **1** were dissolved in CH_3OH-HCl-H_2O solution and proton NMR spectroscopy was used to observe the fate of alkyl ester groups. The quintet of the ethyl group decreased as a higher field methoxyl doublet (due to phosphorus) appeared. Heteronuclear decoupling[10] confirmed the assignment of the doublet.

Results

Diester **1** hydrolyzes readily in acidic solution to yield the amide acid **3** and 2 equiv of ethanol. For example, at 30° the half-time for hydrolysis in 1 M acid is about 1 h.[4] By comparison, a 1 M aid solution of the para-substituted analogue is not detectably changed (NMR detection of 5% as limit) in 1 month. This suggests that the apparent "concentration" of the amide in **1** is $>10^3$ M if **1** hydrolyzes with internal participation of the amide at phosphorus. Since facile hydrolysis of **1** requires the addition of acid to the solution, the dependence of the observed first-order rate constant for the hydrolysis of **1** on the acidity of the solution was determined.

The reaction rate constant does not yield a straight line when plotted as a function of acid concentration[4] above about 0.5 M (DCl in 50:50 (v/v) acetone-d_6-D_2O). However, when we determined D_0 for this solvent-acid system (Table I), we found that a straight line with unit slope relates the observed rate constant to D_0 (Figure 1). A plot similar to that in Figure 1 for the hydrolysis of monoester **2** (Figure 2) is also a straight line, but with a slope of 0.6. The monoester **2** is hydrolyzed more rapidly than is the diester **1** under the conditions of our study, indicating that if hydrolysis of **1** is stepwise, the loss of the second ester is not likely to be rate determining overall.

Therefore, for the diester (using symbols for nondeuterated solutions):

$$v = k_{obsd}[\text{ester}] \quad (1)$$

$$\log k_{obsd} = \log k' - H_0 \quad (2)$$

This implies that the most straightforward and least controversial application of the Hammett-Zucker hypothesis[11,12] can be made. For a reaction involving a transition state which differs from the starting material by addition of a proton, with no major changes in solvation in the rate-determining step, the Bronsted rate expression[13] can be applied:

Table II. Rate of Hydrolysis of 2′-Dialkylphosphonobenzanilides in 50% (v/v) Acetone-d_6–DCl (D_2O) as Observed by NMR (see Experimental Section)

Compd	Temp, °C	[DCl], M	k_{obsd}, $s^{-1} \times 10^7$
1	30	3.48	2750
		2.32	778
		1.74	297
		1.16	133
		0.87	80.5
		0.48	36.1
		0.39	30.5
		0.29	19.4
		0.24	16.7
		0.15	8.33
		0.10	5.55
	40	0.48	105
		0.29	61.1
		0.16	27.8
	45	0.48	125
		0.29	86.1
		0.16	50.0
4	30	0.966	336
		0.773	236
		0.483	119
	36	3.03	8250
		2.54	4500
		2.06	2540
		1.67	1280
		1.13	664
	44	2.52	7940
		2.04	6080
		1.52	2800
		1.03	1430
5	30	3.03	360
		2.54	103
		2.06	94.4
		1.67	47.2
		1.13	25.0
		0.53	8.33
	36	3.00	1050
		2.52	536
		2.04	333
		1.52	180
		1.03	66.7
	44	3.00	2210
		2.52	1150
		2.04	622
		1.52	308
		1.03	197

$$k_{obsd} = k_0(\gamma_s/\gamma_\pm)a_{H^+} \quad (3)$$

$$k_{obsd} = k_0(h) \quad (4)$$

since $h = (\gamma_B/\gamma_{BH^+})a_{H^+}$ if $(\gamma_B/\gamma_{BH^+}) = (\gamma_s/\gamma_\pm)$. This implies that the hydrolysis reaction of the diester **1** obeys a kinetic form, which is reducible to:

$$H^+ + S \overset{K}{\rightleftharpoons} (HS')^+ \overset{k}{\rightarrow} \text{products} \quad (5)$$

$S'H^+$ may simply be S plus a proton or a protonated cyclized compound.

Since Figure 2 indicates that the hydrolysis of **2** depends on H_0 with a slope of 0.6 rather than of 1.0 as does the hydrolysis of **1**, the acidity function is probably inappropriate. However, the amide-based acidity function H_A[14] bears approximately the same relationship to the aniline-based acidity function H_0 as the dependence of the observed rate constant for the hydrolysis of **2** does to the acidity function (H_0) followed by **1**.

Table III. Activation Parameters for Acid-Catalyzed Hydrolysis of *o*-Dialkylphosphonobenzanilides in 50% (v/v) Acetone-d_6–DCl (D_2O) Solution

Compd	$\Delta E^\ddagger$, kcal/mol	$\Delta H^\ddagger$, kcal/mol	$\Delta G^\ddagger$, kcal/mol	$\Delta S^\ddagger$, eu
4	12.4	11.8	24.4	−41.6
1	21.5	20.9	25.1	−14
5	25.8	25.2	26.2	−3.2

Therefore, an equation similar to (5) holds for the monoester as well.

Steric Effects. Rate constants for the hydrolysis of dimethyl, diethyl, and diisopropyl esters of **3** are summarized in Table II. Activation parameters are summarized in Table III. The steric effects indicate that there is a reduction in rate with increasing ester size, but the increase is not nearly as large as would arise if displacement at carbon occurred. We present this as evidence that the reaction occurs at the phosphorus center.[15]

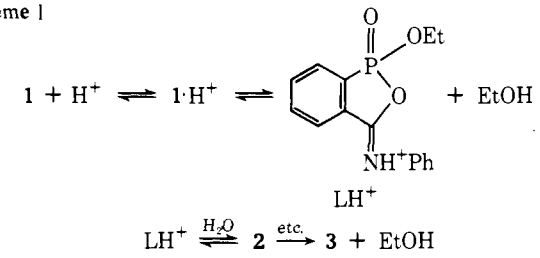
Transesterification. Conversion of the diethyl ester (**1**) to the dimethyl ester was readily accomplished in the presence of acid, as monitored by NMR spectroscopy. When **1** was incubated in acidic methanol, a doublet (J = 11.5 Hz) appeared 0.4 ppm upfield of the ethoxyl quintet of compound **1**. Both the ethoxyl signal and methoxyl signal were decoupled at the same phosphorus frequency on the HA-100 (40.48 MHz, nominal), indicating that either the dimethyl ester with a phosphorus chemical shift nearly the same as that of the diethyl ester had formed or a mixed methyl-ethyl ester had formed (1 M HCl in CH_3OH). When the reaction was carried out in acetone-d_6 containing equimolar quantities of water and methanol (2.5 M HCl), the methoxyl doublet appeared rapidly (reaching a steady state after ~0.5 h at 35°), maintained a constant level, and then decreased after several days. This indicates that transesterification compares favorably with hydrolysis, but that the hydrolysis products are favored at equilibrium. The occurrence of the two reactions at comparable rates indicates that cleavage of the phosphorus–oxygen bond of the ester occurs.

Discussion

General Observations. We have observed that **1** undergoes facile ester hydrolysis in acidic solution, whereas the corresponding para-substituted compound and unsubstituted phosphonate are highly resistant to hydrolysis.[4] The large enhancement of the reactivity of **1** is attributable to the presence of the amide functionality in the ortho position with respect to the phosphonate ester group. The large enhancement is characteristic of intramolecular nucleophilic catalysis.[16,17] The requirement for acid and the unitary dependence of observed rate constant on the acidity function we have measured for the reaction medium is consistent with the acid functioning in a pre-equilibrium step. The acid may function by (1) protonating the starting material to promote cyclization to form a reactive intermediate, (2) protonating the leaving group to facilitate breakdown of an intermediate in the direction of products, or (3) a combination of (1) and (2). Overall, acceleration must arise from a lower free-energy barrier existing by a path involving participation of the amide on a protonated derivative of the substrate, since both acid and adjacent amide are necessary in our case (Scheme I).

We have shown that **2** is hydrolyzed more readily than **1** under the conditions of our study and that **2** does not accumulate. Therefore, the step leading to initial cleavage of the first ester is rate-determining overall. In more concentrated acid, extrapolation of the data in Figures 1 and 2 suggests that

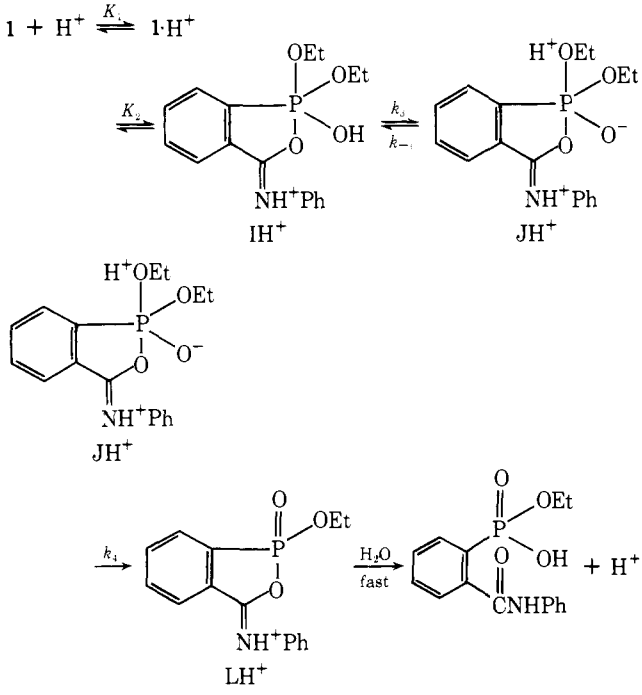
Scheme I



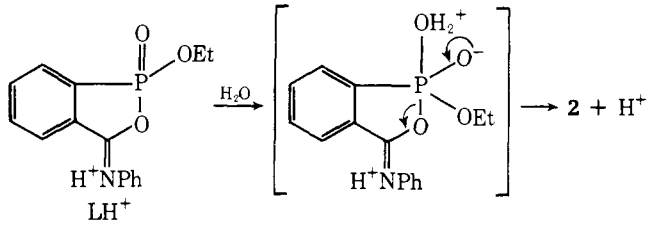
this situation might change to a biphasic situation. In all cases, the amide was recovered intact so that hydrolysis of the ester is not likely to involve addition of water to the protonated amide, since some amide hydrolysis could be expected. A complete study of the hydrolysis of amide **3** has been performed and it is clear that the ester hydrolysis of **1** is at least two orders of magnitude faster under the conditions of the present study than is the amide hydrolysis.[18]

Nature of Intermediates. Distinct requirements on the structure of intermediates can be implied from what is known about structural energetics of other cyclic organophosphorus compounds.[19] Attack of the amide at phosphorus (presumably via the oxygen part of the functional group, as is normal for nucleophilic reactions of un-ionized amides) will place the amide in the apical position of a trigonal-bipyramidal transition state, which might lead to formation of a pentacovalent intermediate or to direct expulsion of ethoxide (or ethanol if the leaving group is protonated). Pseudorotation of the intermediate is unnecessary and electronic requirements of pentacovalent phosphorus compounds are fulfilled by the arrangement of ligands leading directly to intermediate tetracoordinate products. A proton transfer converts IH^+ to JH^+. Alternatively, direct protonation of the alkoxyl is possible (either before or after cyclization). We favor a mechanism involving protonation followed by cyclization and proton transfer (Scheme II), since this would explain why Steinberg et al.[6] did

Scheme II



not observe participation by anilides in neutral solution with related compounds containing a *p*-nitrophenoxide leaving group that does not require protonation. The proton transfer step (k_3) to form JH^+ may be rate determining. Intermediate LH^+ should be extremely reactive toward water at phosphorus.[19] Geometric and electronic requirements of a pentacovalent transition state force the alkoxyl group to occupy an equatorial position with a high barrier to pseudorotation.[19,20] In addition, the ring can open without requirement for a proton transfer, since the nitrogen is likely to be protonated.[21] Thus, a stable intermediate need not even exist. Therefore, compound **2** should be an obligatory intermediate in the hydrolysis of **1**.



Intermediate LH^+ should also react rapidly with methanol to give the mixed methyl-ethyl ester, which after recyclization could produce dimethyl ester **4**. This would provide a consistent mechanism incorporating our observation of facile transesterification of **1**.

Kinetic Equations. According to Scheme II, either k_3 or k_4 is associated with the rate-determining step. Preequilibria involve protonation and cyclization of the starting material. Until further evidence is available, we can state that Scheme II is consistent with our observed kinetics, with either k_3 or k_4 being rate determining. For a first trial, we assume k_4 is rate determining and k_3/k_{-3} is an equilibrium equal to K_3. Then:

$$v = k_{obsd}(\mathbf{1}) = k_4(JH^+) \tag{6}$$

and since

$$K_1 = (\mathbf{1})(a_h{}^+)/(\mathbf{1}\cdot H^+);\ K_2 = \frac{(IH^+)}{(\mathbf{1}\cdot H^+)};\ K_3 = \left(\frac{JH^+}{IH^+}\right) \tag{7}$$

$$v = k_4(K_2K_3/K_1)(a_h{}^+)(\mathbf{1}) \tag{8}$$

$$k_{obsd} = (K_2K_3k_4/K_1)(a_h{}^+) \tag{9}$$

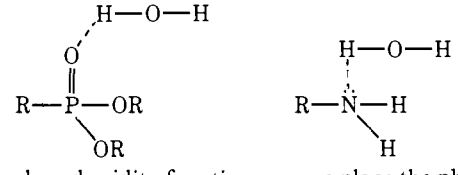
From eq 4,

$$\log k_0 = \log\frac{K_2K_3K_4}{K_1} + \log a_{H^+} + H_0 = \log\frac{K_2K_3}{K_1}\frac{\gamma\mathbf{1}\cdot H^+}{\gamma\mathbf{1}} \tag{10}$$

If k_3 is rate determining, a similar expression (without K_3 and with k_3 in place of k_4) results.

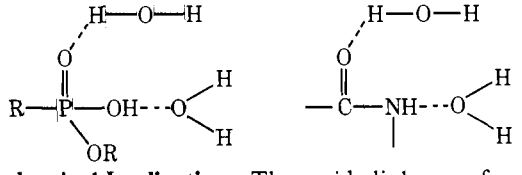
Acidity Function Dependence and Solvation. The hydrolysis of **1** gives a straight line, unit slope relationship for log k_{obsd} vs. H_0 or D_0, whereas the hydrolysis of **2** gives a straight line with a slope of 0.6. These results indicate that nitroaniline is solvated and protonated similarly to **1** (or the intermediate derived from **1**). The dependence of **2** differs in a manner much like that observed for amides compared to aniline. This is suggested by the fact that the amide-based acidity function H_A differs from H_0 by having a similarly less steep slope.

If we assume the "three variable" hypothesis,[11,22] then the differing behavior of **1** and **2** can be accounted for on the basis of solvation effects. The diester **1** has one major hydrogen bond-accepting position, the oxygen of the phosphoryl group. The monoacid monoester **2** differs by having in addition a hydrogen bond-donating site, the acid proton. We can see a parallel to amines and amides in these differences. If **1** follows



the amine-based acidity function, we can place the phosphoryl in a position analogous to the amine nitrogen.

The monoacid and amide can also be solvated in parallel fashion, as shown below. These hypotheses have not been tested further in our case, but they do provide an explanation based on the assumption used in employing acidity functions.



Biochemical Implications. The amide linkages of proteins and peptides are widely distributed in organisms. These often exist in proximity to phosphate bonds of nucleotides. It is usually assumed that covalent interactions between the two types of functional groups do not occur. This assumption is obviously a necessary one and no experimental evidence to the contrary exists. However, our interest in the possibility of covalent interactions is related to the formation of transient "high-energy" intermediates in reactions involving formation or breakage of interphosphate bonds. Since it is unlikely that these can be observed directly, information on the facility of their occurrence and methods for trapping them need to be obtained. We have previously suggested[4] that conformational changes of proteins could be used to generate an interphosphate bond, if the change led to a situation which caused the peptide bond to become a reactive electrophile toward a phosphate, forming a phosphorylated peptide intermediate (analogous to that proposed in DCC-catalyzed dehydration), which would then transfer phosphate to form a new interphosphate bond. This can provide a chemical mechanism for oxidative phosphorylation via conformational coupling. In addition, other phosphate transfers could occur via this type of reactive intermediate.

References and Notes

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(2) Author to whom inquiries should be addressed.
(3) Fellow of the Alfred P. Sloan Foundation.
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Hydroboration. 42. Cyclic Hydroboration of Representative Acyclic α,ω-Dienes with Monochloroborane Etherate

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Abstract: Hydroboration of representative acyclic α,ω-dienes, such as 1,4-pentadiene, 1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, 1,6-heptadiene, 1,7-octadiene, and 1,13-tetradecadiene, with monochloroborane etherate has been examined in order to establish the utility of this reagent for cyclic hydroboration and to attain an understanding of the reaction processes involved in such cyclic hydroborations. The initial hydroboration product is partially polymeric in the case of 1,4-pentadiene and 1,5-hexadiene and essentially polymeric in the case of higher dienes. The polymeric products could be depolymerized in many cases by careful distillation and the desired cyclic *B*-chloroboracycloalkanes isolated in excellent yields. No extensive isomerization of the ring moiety was observed for products derived from C_5–C_7 dienes. Pure *B*-chloroborinane, *B*-chloroborepane, and *B*-chloro-3,6-dimethylborepane were readily isolated. A 75:10:15 mixture of *B*-chloroborocane, *B*-chloro-2-methylborepane, and *B*-chloro-2-ethylborinane was obtained from 1,6-heptadiene. Distillation of the *B*-chloroorganoboranes from 1,7-octadiene was accompanied by extensive isomerization leading to a mixture of substituted *B*-chloroborocane, *B*-chloroborepanes, and *B*-chloroborinanes. The *B*-chloroboracycloalkanes were transformed into *B*-methoxyboracycloalkanes which were in turn converted into cyclic ketones via the DCME reaction. Pure cycloheptanone, 3,6-dimethylcycloheptanone, and cyclooctanone were isolated from the reaction products derived from 1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, and 1,6-heptadiene, respectively. Hydroboration of 1,7-octadiene under high dilution conditions followed by methanolysis and the DCME reaction gave 1,10-cyclooctadecanedione in 6% yield. Under the same conditions, 1,13-tetradecadiene produced cyclopentadecanone in 7% yield.

In recent years cyclic hydroboration of dienes has been actively investigated.[2-7] The conversion of the boron heterocycles thus produced into cyclic carbon structures by the carbonylation reaction opened promising new synthetic possibilities.[8-10] However, relatively few hydroborating agents have been explored for this reaction. Monosubstituted borane derivatives would appear to be best suited for the cyclic hydroboration of dienes. One such reagent, thexylborane, has proved to possess valuable characteristics in this area.[11] The low aptitude of the thexyl group for migration in carbonylation reaction made possible the syntheses of various cyclic and bicyclic ketones.[8]