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The Mechanism of Amine-Catalyzed Halohydrin Formation from α-Chloro Ketones and Phosphonate Diesters

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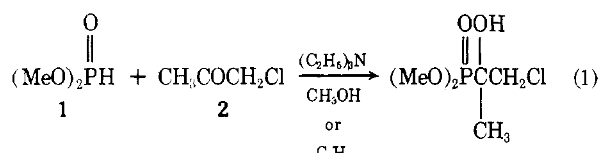
Received November 3, 1975

The formation of halohydrin in the triethylamine-catalyzed reaction of dimethyl phosphonate and chloroacetone was followed by NMR. In benzene the kinetics appear to be complex due to solvent effects and aggregation, and the results cannot be summarized by any simple rate law. The reaction in methanol is approximately first order in phosphonate and first order in triethylamine. The results suggest a rate-determining, tautomeric conversion of the phosphonate to the corresponding phosphite with rate law $v = 1.42 \times 10^{-2}\ M^{-1}\ s^{-1}$ [phosphonate][triethylamine].

The chemistry of bond formation between phosphorus and carbon is a significant problem; it underlies the synthesis of new structures which may be used to extend our knowledge of the chemistry of phosphorus, to furnish useful reagents for new synthetic methods, to investigate biologically important reactions through isosteric similarity to phosphates, and to provide medically useful drugs such as the antibiotic fosfomycin.[1-4] As part of our study on epoxyphosphonate synthesis, we have investigated the kinetics of formation of halohydrin phosphonates which are intermediates in some synthetic sequences.[1,5] The halohydrin **3** is formed by the base-catalyzed reaction of dimethyl phosphonate (**1**) and chloroacetone (**2**). This reaction (eq 1) was studied in methanol and



$$\underset{\mathbf{1}}{(MeO)_2\overset{\overset{O}{\|}}{P}H} + \underset{\mathbf{2}}{CH_3COCH_2Cl} \xrightarrow[\substack{CH_3OH \\ \text{or} \\ C_6H_6}]{(C_2H_5)_3N} \underset{\mathbf{3}}{(MeO)_2\overset{\overset{O\ OH}{\|\ \ |}}{PC}\underset{\underset{CH_3}{|}}{}CH_2Cl} \qquad (1)$$

benzene by observation of the changes in the C–CH_3 signals in ^1H NMR spectra which were taken as the reaction proceeded.

Experimental Section

Kinetics. *In solutions of methanol*, the appropriate concentration of dimethyl phosphonate and chloroacetone was prepared in a 5-ml volumetric flask. A 0.5-ml aliquot was injected into an NMR tube and spun in the probe for 5 min to bring it to constant temperature. To the NMR tube was then added the appropriate amount of triethylamine or buffer stock solution in methanol. The concentrations were corrected for total volume. The reaction was followed by the disappearance of the methyl singlet of chloroacetone, **2**, at τ 7.75 and the appearance of a doublet for the C–CH_3 in **3** (J_{PCCH} = 15 Hz) at τ 8.48.[5] The reaction was followed with a 50 Hz sweep width of the singlet and one peak of the doublet. The area under each peak was determined by multiplying the peak height by the width at half the height. The area of the singlet over the sum of the area of the singlet and two times the area of one doublet peak gives the fraction of chloroacetone remaining at that time.

For experiments in benzene, triethylamine was added neat. The rate was determined by relative *integrations* of the methyl peaks using a Varian A-60A spectrometer. The average result of three integrations was used with the time recorded in the middle of the second integration. For some runs the reaction was also followed by a 50 Hz sweep width and the above described calculation of area. Results from the two methods were in good agreement. All reactions appeared to proceed to completion based on NMR spectra.

Results

Treatment of Rates. Since we followed the concentration of chloroacetone (**2**), it was necessary to express the rate law in terms of **2**. In all reactions the concentration of chloroacetone was less than or equal to that of phosphonate, so the stoichiometry demands that

$$-d[2]/dt = k[2]^a([2] + \Delta)^b[(C_2H_5)_3N]^c \qquad (2)$$

where $\Delta = ([1] - [2])$. The concentration of triethylamine remains constant because it is a catalyst. In methanol as solvent we found that when the rate law was reduced to

$$v = -d[2]/dt = k'([2] + \Delta) \qquad (3)$$

and integrated to give

$$\ln([2] + \Delta) = -k't + \text{constant} \qquad (4)$$

we could fit the observed data and we obtained the first-order rate constants in Table I. Therefore, in methanol the reaction is first order in phosphite and zero order in chloroacetone (Table I). Dividing the k' values in Table I by $[(C_2H_5)_3N]$ gave a constant value for a second-order rate constant (eq 5, 6)

Table I. Kinetics of Phosphonate Halohydrin Formation in Methanol

Reactants, M				
$[(MeO)_2P(O)H]$	$[CH_3COCH_2Cl]$	$[Et_3N]$	$10^4 k'$, s^{-1}	$10^2 k_{\mathrm{I}} = k'/[(C_2H_5)_3N]$, $M^{-1} s^{-1}$
1.28	1.28	2.55×10^{-2}	4.09	1.60
1.27	1.27	3.80×10^{-2}	5.42	1.42
1.28	1.28	5.11×10^{-2}	9.15	1.79
1.27	1.27	7.59×10^{-2}	12.05	1.59
1.28	1.28	2.55×10^{-2}	3.60	1.41
0.64	0.64	2.55×10^{-2}	3.70	1.45
2.56	2.56	2.55×10^{-2}	2.09	0.82
1.28	0.64	2.55×10^{-2}	3.45	1.35
1.28	0.64	2.55×10^{-2}	3.46	1.36
Buffered; $(C_2H_5)_3N/(C_2H_5)_3NH^+ = 1/1$				
1.28	1.28	2.55×10^{-2}	1.38	0.54
1.23	1.23	7.38×10^{-2}	3.83	0.52
1.23	1.23	7.38×10^{-2}	3.83	0.52

Table II. Kinetics of Phosphonate Halohydrin Formation in Benzene

Reactants, M				
$[(MeO)_2P(O)H]$	$[CH_3COCH_2Cl]$	$[Et_3N]$	$10^4 k'$, s^{-1}	$k_{\mathrm{I}} = 10^4 k'/[R_3N]$, $M^{-1} s^{-1}$
1.19	1.19	0.595	3.35	5.6
1.19	1.19	0.595	2.80	4.7
1.10	1.10	1.10	5.12	4.7
2.38	1.19	0.595	3.94	6.6
1.19	0.595	0.595	1.06	1.8
1.19	1.19	0.595	2.23	3.8
1.19	1.19	0.595	2.45	4.1
1.19	1.19	0.595	2.44	4.2
1.19	1.19	0.595	2.29	3.9
1.10	1.10	1.10	4.62	4.2
1.10	1.10	1.10	4.61	4.2
1.10	1.10	1.10	4.57	4.2
2.38	1.19	0.595	3.74	6.3
2.38	1.19	0.595	3.82	6.4
2.38	1.19	0.595	3.67	6.2
2.38	1.19	0.595	3.56	6.0

$$v = k_{\mathrm{I}}[1][(C_2H_5)_3N] \tag{5}$$

$$k_{\mathrm{I}} = k'/[(C_2H_5)_3N] \tag{6}$$

with the exception of one run at high concentrations of phosphite and chloroacetone. The average value of k_{I} is 1.42×10^{-2} M^{-1} sec^{-1}. The deviant value, $k_{\mathrm{I}} \doteq 0.82 \times 10^{-2}$ M^{-1} s^{-1}, is included in this average. Because of the poor temperature control and the speed of these reactions, considerable error is expected in the observed rate constants.

The kinetics in benzene were more complicated and did not appear to be simple first order in phosphite. Therefore, the data were treated without prejudice regarding the order of the reaction. Since $[(C_2H_5)_3N]$ is constant, any individual reaction will show total order = $a + b$ (eq 2). Reactions with $\Delta = 0$ were examined for total order; they plotted best as first order but there was curvature late in the reaction. We also determined $a + b$ directly by fitting [2] to a polynomial dependence on t using a computer program (Figure 1). Since $\Delta = 0$, eq 2 reduces to eq 7 and the log of eq 7 is eq 8.

$$-d[2]/dt = k[2]^{a+b} \tag{7}$$

$$\log(-d[2]/dt) = \log k + (a + b) \log [2] \tag{8}$$

The polynomial fit, [2] vs. t (eq 9), made it possible to evaluate d[2]/dt (eq 10).

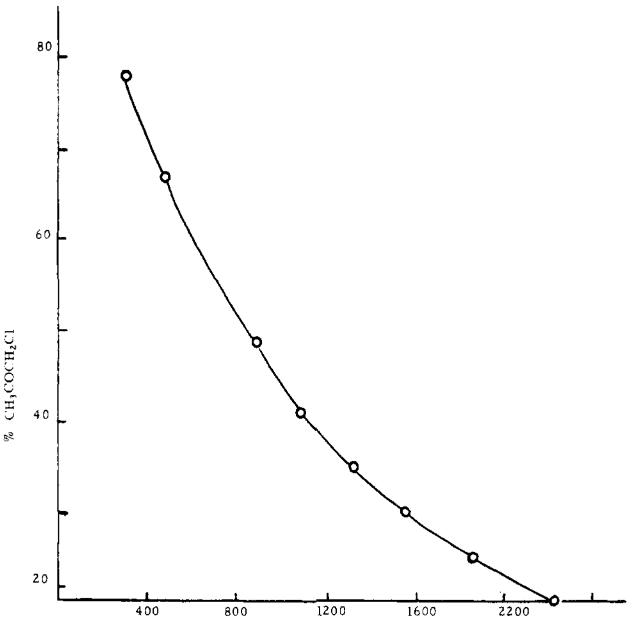


Figure 1. Plot of data for phosphonate halohydrin formation in benzene using a polynomial equation; the date points are circles and the line is the equation of the polynomial (eq 9).

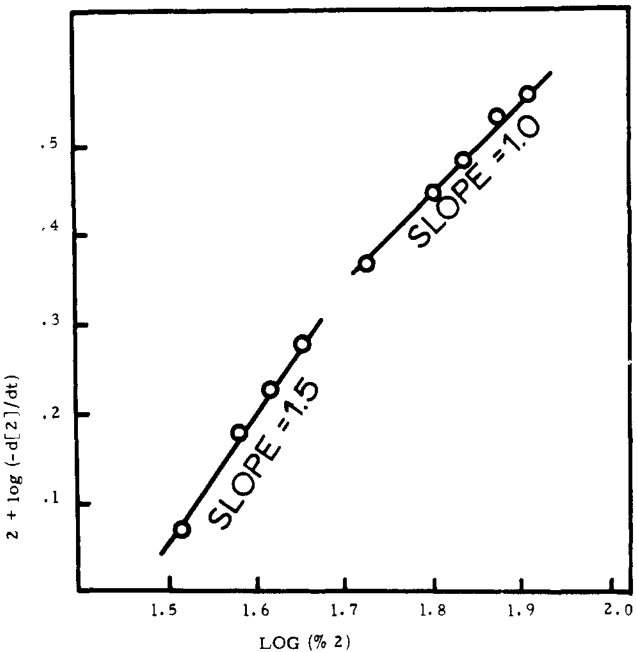


Figure 2. Graphical solution of eq 8.

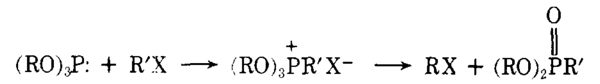
$$[2] = 99.46 - 0.0802t + 0.294 \times 10^{-4} t^2 - 0.426 \times 10^{-8} t^3 \tag{9}$$

$$v = -d[2]/dt = 0.802 - 0.588 \times 10^{-4} t + 1.278 \times 10^{-8} t^2 \tag{10}$$

Graphical solution of eq 8 gives an initial slope (Figure 2) very close to 1.0. The points on Figure 2 were calculated for the times at which [2] was determined in the experiment. However, late in the reaction the order appears to increase. Therefore, in all runs, first-order rate constants were determined (eq 4) and appear in Table II.

Discussion

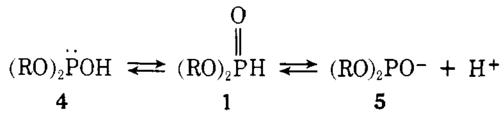
A very common method for synthesis of P–C bonds is nucleophilic attack of a tricoordinated phosphorus compound, such as a phosphine or phosphite, on a reactive carbon compound. This mechanism is the basis of synthesis of phosphonium compounds and is the first step in the Arbuzov reaction in which a trialkyl phosphite is transformed into a dialkyl alkylphosphonate:



$$(RO)_3P\colon + R'X \longrightarrow (RO)_3\overset{+}{P}R'X^- \longrightarrow RX + (RO)_2\overset{O}{\overset{\|}{P}}R' \quad (11)$$

These nucleophilic reactions of trialkyl phosphites have been extensively studied.[2,3] With α-halo ketones, there are three possible products: phosphonate halohydrins, β-ketophosphonates (an Arbuzov reaction), and enolphosphates (the Perkow reaction[4]).

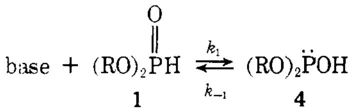
The compounds commonly referred to as dialkyl phosphites exist predominantly as the phosphonate tautomers, **1**; therefore, they are weakly acidic and have much less nucleophilicity than trialkyl phosphites, $(RO)_3P$.[2] In general, one can expect nucleophilic reactions of dialkyl phosphonates to proceed through the phosphite tautomer, **4**, or the phosphonate anion, **5** (eq 12).



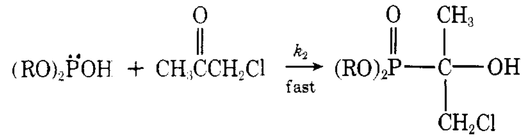
$$\underset{4}{(RO)_2\ddot{P}OH} \rightleftharpoons \underset{1}{(RO)_2\overset{O}{\overset{\|}{P}}H} \rightleftharpoons \underset{5}{(RO)_2PO^-} + H^+ \quad (12)$$

There has been considerable investigation on the reactions of the sodium salts of **5** which are formed by the reaction of sodium with **1**. In the reactions with α-halo ketones, three products are observable: epoxyphosphonates (probably formed through the halohydrin oxy anion[5]), β-ketophosphonates, and enol phosphates.[6]

Kinetics and Mechanism. This chemistry leads one to expect that the mechanism of the reaction we have studied would involve either base-catalyzed tautomerism of **1** into the phosphite tautomer (**4**) or formation of **5** as reactive intermediates. The observed first-order kinetics in [**1**] and the first-order dependence on triethylamine (eq 5, Table I) appear to confirm the scheme below in methanol:



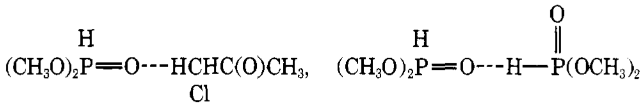
$$\text{base} + \underset{1}{(RO)_2\overset{O}{\overset{\|}{P}}H} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{4}{(RO)_2\ddot{P}OH} \quad (13)$$



$$(RO)_2\ddot{P}OH + CH_3\overset{O}{\overset{\|}{C}}CH_2Cl \underset{\text{fast}}{\xrightarrow{k_2}} (RO)_2\overset{O}{\overset{\|}{P}}-\underset{\underset{CH_2Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}-OH \quad (14)$$

Since k_1 is not lowered by more than a factor of 3 in buffered solutions of triethylamine, the active intermediate cannot be the anion, **5**, the concentration of which would have to be proportional to $[CH_3O^-]$; there should be a large change in $[CH_3O^-]$ between unbuffered and buffered solutions. However, the comparison of k_1 in buffered and unbuffered solutions does indicate that in eq 13 both CH_3O^- and $(C_2H_5)_3N$ contribute to the rate. We expect that the pathway from **1** to **4** involves **5** as an intermediate.

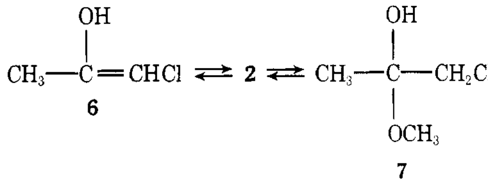
In benzene, there is greater complexity. Increases of concentration of both **1** and **2** give increases in rate constants. Yet the reaction is first order in [**1**]. Two explanations seem possible. (1) Aggregation effects may be important. For example, either of the hydrogen-bonded complexes below might facilitate the reaction by increasing the rate of proton removal from **1**:



$$(CH_3O)_2\overset{H}{P}{=}O\cdots H\underset{Cl}{C}HC(O)CH_3, \quad (CH_3O)_2\overset{H}{P}{=}O\cdots H-\overset{O}{\overset{\|}{P}}(OCH_3)_2$$

(2) The high concentrations of reactants can change the solvent character. Since both **1** and **2** are highly polar, they will contribute to a more polar medium and accelerate the reaction. The values of k_1 in benzene are roughly 1/100 of k_1 in methanol; this demonstrates the effect of solvent on rates and supports this explanation. The low rate constant at 0.595 M chloroacetone (Table II) and the high rate constants at 2.38 M phosphonate indicate that concentrations of both reactants affect the value of the first-order rate constant found in any individual run. The data in Table II support first-order dependence on triethylamine. In summary, we believe that the mechanism in eq 13 and 14 is followed in benzene but the observed rate is highly dependent on concentrations of reactants.

There are a number of other comments which may be relevant in this reaction: (1) The effect of competition between k_2 and k_{-1} on rates may explain some of the dependence of rates on concentration of reactants. (2) There may be other mechanisms for generation of **4** such as proton transfer in a dimer or polymer of **1**. (3) Although we expect this reaction to proceed by reaction with the chloro *ketone*, significant amounts of *enol* (**6**) should be present in both solvents and the keto → enol conversion will be catalyzed by R_3N. (4) In methanol, the chloro ketone will be partially in the form of the hemiketal (**7**) which will be unreactive.



$$\underset{6}{CH_3-\overset{\overset{OH}{|}}{C}{=}CHCl} \rightleftharpoons 2 \rightleftharpoons \underset{7}{CH_3-\underset{\underset{OCH_3}{|}}{\overset{\overset{OH}{|}}{C}}-CH_2Cl}$$

The insights gained from this investigation led us to devise a one-step synthesis of epoxyphosphonates.[1,5]

Acknowledgment. Part of this research was supported by a grant from Merck and Co., Inc. We thank a referee for a valuable, critical reading of an earlier draft.

Registry No.—**1**, 868-85-9; **2**, 78-95-5; **3**, 4185-83-5; Et_3N, 121-44-8.

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