associated data handling system. The number of scans made in each of the three runs was 19 500.

Registry No. 1, 19717-45-4; [^{15}N,^{15}N′]-**1**, 85166-97-8; [$^{13}C_2$]-**1**, 85166-98-9; [^{14}C]-**1**, 85166-99-0; ^{15}N, 14390-96-6; ^{13}C, 14762-74-4; ^{14}C, 14762-75-5; 4-iodo[^{15}N]aniline, 24176-53-2; [^{15}N]aniline, 7022-92-6; 4,4′-diiodo[^{15}N,^{13}N′]azobenzene, 85167-00-6; [1-^{13}C]-4-nitrophenol, 3881-07-0; sodium nitromalonaldehyde, 34461-00-2; [2-^{13}C]propanone, 3881-06-9; [1-^{13}C]-4-aminophenol, 3881-08-1; 1-phenol-5-(4-amino[1-^{13}C]phenoxy)tetrazole, 85167-01-7; 5-chloro-1-phenyltetrazole, 14210-25-4; [4-^{13}C]aniline hydrochloride, 85167-02-8; 4-iodo[4-^{13}C]aniline, 85167-03-9; [4-^{14}C]azobenzene, 81141-91-5; [4-^{14}C]aniline hydrochloride, 85167-04-0; 4-iodo[4-^{14}C]aniline, 85167-05-1; 4-iodoaniline, 540-37-4; 4-iodo[4-^{14}C]acetanilide, 85167-06-2.

Enol Phosphates from the Action of Monomeric Metaphosphate Ion on Ketones

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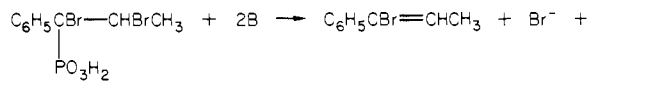
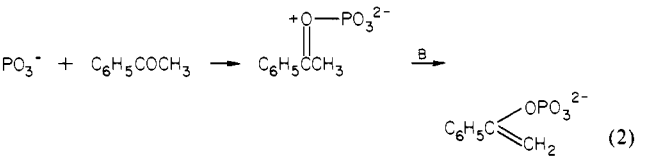
Abstract: Prior research from this laboratory had demonstrated that monomeric metaphosphate ion, generated by fragmentation from β-bromophosphonate dianions, reacts with acetophenone in the presence of excess base to give a modest yield of 1-phenylvinyl phosphate. This paper expands on that finding; it presents studies of the effects of concentration of reagents, of solvents, and of variation in amine structure (i.e., of the base) on the reaction. These studies lead to experimental conditions where the yield of the enol phosphate of acetophenone, based on the β-bromophosphonic acid used, exceeds 80%. Several other ketones can be similarly converted to their enol phosphates, although in inferior yield.

The fragmentation of β-bromophosphonate anions[1-3] presumably yields monomeric metaphosphates[4,5] as unstable electrophilic intermediates that can participate in a number of chemical reactions; for methyl metaphosphate,[6] these include aromatic substitution[7,8] as well as the activation of carbonyl groups. Methyl metaphosphate activates acetophenone both toward Schiff base formation and toward enolization to yield methyl 1-phenylvinyl phosphate; it promotes the reaction of ethyl benzoate with aniline to yield *O*-ethyl *N*-phenylbenzimidate. In 1981, Satterthwait and one of us[9] showed that the monomeric metaphosphate anion, PO_3^-, also activates the carbonyl group of acetophenone toward reaction with aniline to form a Schiff base and reacts with the ketone in the presence of excess 2,2,6,6-tetramethylpiperidine (symbolized by "B" in the equations below) to yield 1-phenylvinyl phosphate.



$$C_6H_5CBr(PO_3H_2)-CHBrCH_3 + 2B \rightarrow C_6H_5CBr{=}CHCH_3 + Br^- + 2BH^+ + PO_3^- \quad (1)$$



$$PO_3^- + C_6H_5COCH_3 \rightarrow C_6H_5C(=O^+-PO_3^{2-})CH_3 \xrightarrow{B} C_6H_5C(OPO_3^{2-})=CH_2 \quad (2)$$

We postulate that the process takes place by the attack of the monomeric metaphosphate on the carbonyl group of the ketone, as shown in eq 2, and competes with polymerization of metaphosphate for the available phosphorus.

Our view of the mechanism of the process has recently been questioned by Ramirez et al.[10] The present paper records our study of the effects of the concentration of reagents (especially of base), of solvents, of the structure of the base, and of the structure of the ketone on the yield of enol phosphates. Questions of mechanisms are then discussed.

Experimental Section

Materials. (1) *erythro*- (I) and *threo*- (II) (1,2-dibromo-1-phenylpropyl)phosphonic acids melted at 188–189 and 181–182 °C, respectively; their spectroscopic properties agreed with those in the literature.[3,8]

(2) (2-Bromo-1,3-diphenyl-3-oxo-1-propyl)phosphonic acid (III) was prepared by the method of Conant and Cook:[2] mp 205–206 °C (lit. mp 196 °C); ^{1}H NMR (CD_3COCD_3) δ 8.28–8.16, 7.70–7.27 (br, m, 10 H), 6.19 (d of d, J_{H-H} = 12 Hz, J_{H-P} = 8.3 Hz, 1 H), 4.31 (d of d, J_{H-H} = 12 Hz, J_{H-P} = 22 Hz, 1 H). Proton decoupled ^{31}P NMR (CD_3COCD_3) δ +17.48 (s). Anal. Calcd for $C_{15}H_{14}BrO_4P$: C, 48.70; H, 3.81; Br, 21.60; P, 8.37. Found: C, 48.82; H, 4.04; Br, 21.46; P, 8.58. The product of the fragmentation of III was identified as *trans*-chalcone by its UV spectrum.[11]

(3) Methyl dihydrogen phosphoric acid showed a proton decoupled ^{31}P NMR peak at δ 1.21 (s). **(4) Anilinium hydrogen 1-phenylvinyl phosphate**[12] melted at 85–86 °C (lit. mp[9] 86.5–87.5 °C). It was converted

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to the corresponding sodium salt as previously described[9] and showed the same ^1H and proton decoupled ^{31}P NMR spectra as those previously reported.

(5) Acetophenone anil melted at 40–41 °C (lit. mp[13] 40–41 °C).

(6) *O*-Ethyl *N*-phenylacetimidate[14] boiled at 46–48 °C/0.5 mm: ^1H NMR ($CDCl_3$) δ 7.35–6.71 (br m, 5 H), 4.22 (q, 2 H), 1.81 (s, 3 H), 1.33 (t, 3 H).

(7) Anilinium hydrogen *N*-phenylphosphoramidate was prepared by allowing I (1.79 g) to react overnight at room temperature with 5 mL of aniline. The white precipitate (0.7 g) melted at 265–267 °C (lit. mp[15] 260–267 °C): proton decoupled ^{31}P NMR (CD_3CN) δ −0.85 (s).

(8) Anilinium hydrogen 1,2-diphenylvinyl phosphate was prepared by a Perkow reaction. A solution of 6.75 g of desylbromide in 10 mL of absolute ethanol and 3 mL of trimethyl phosphite was refluxed for 6 h and subsequently rotoevaporated to a yellow oil, bp 175–179 °C/0.1 mm: ^1H ($CDCl_3$) δ 7.71–7.27 (br m, 10 H), 6.41 (br s, 1 H), 3.53 (d, J_{H-P} = 11 Hz, 6 H). This product (1.16 g of dimethyl 1,2-diphenylvinyl phosphate) was stirred for 4 h with 0.5 mL of trimethylsilyl bromide; the resulting silyl ester was added to 0.38 mL of aniline in 15 mL of absolute ethanol. The white precipitate melted at 125–126 °C. Anal. Calcd for $C_{20}H_{20}NO_4P$: C, 64.89; H, 5.45; N, 3.78; P, 8.37. Found: C, 64.74; H, 5.56; N, 3.89; P, 8.49. It was converted to the sodium salt by the usual procedure:[9] ^1H NMR (D_2O) δ 8.01–7.37 (br m, 10 H), 6.29 (br s, 1 H); proton decoupled ^{31}P NMR (D_2O) δ −0.70 (s).

(9) *N*-*tert*-Butylpiperidine[16] boiled at 48 °C/23 mm: ^1H NMR ($CDCl_3$) δ 2.50 (t, 4 H), 1.76–1.29 (br m, 6 H), 1.05 (s, 9 H).

(10) Dicyclohexylammonium 1-Methylvinyl Phosphate. Dimethyl 1-methyl vinylphosphate[12] (1.5 g) was allowed to react at room temperature for 1 h with trimethylsilyl bromide (2.4 mL). Volatiles were removed by rotoevaporation, and the bis(trimethylsilyl) ester distilled at 53–55 °C/0.1 mm. This ester was cleaved with 1 mL of cyclohexylamine in 15 mL of absolute ethanol. The white solid (1.8 g) formed after 5 min of stirring melted at 221–223 °C with prior softening: ^1H NMR (D_2O) δ 4.56 (d, J = 1.8 Hz, 1 H), 4.31 (br s, 1 H), 3.18 (m, 2 H), 2.20–1.10 (m, 23 H); ^{31}P NMR (D_2O) δ −1.04 (s). Anal. Calcd for $C_{15}H_{33}N_2O_4 \cdot 0.5H_2O$: C, 52.15, H, 9.92; N, 8.11; P, 8.97. Found: C, 52.06; H, 9.70; N, 7.85; P, 9.19. A solution of the disodium salt was prepared by dissolving 10 mg of the dicyclohexylammonium salt in 2 mL of 0.1 N sodium hydroxide and extracting with ether: ^1H NMR (D_2O) δ 4.52 (br s, 1 H), 4.27 (br s, 1 H), 1.83 (br s, 3 H); ^1H decoupled ^{31}P NMR (D_2O) δ −1.04 (s).

(11) Dicyclohexylammonium 1-Furylvinyl Phosphate. 2-(α-Chloroacetyl)furan[17] (5.54 g) was allowed to react overnight at room temperature with trimethyl phosphite (5.21 g) in methanol (50 mL). The product (dimethyl 1-furylvinyl phosphate) boiled at 85–89 °C/0.1 mm. The dimethyl ester was converted to the corresponding bis(trimethylsilyl) ester in the same way as for the 1-methylvinyl analogue; it could not be distilled but was cleaved directly as described above for the 1-methylvinyl compound. The resulting solid was washed with methanol and dried: mp 254–256 °C; ^1H NMR (D_2O) δ 7.59 (br s, 1 H), 6.74–6.58 (m, 2 H), 5.14 (d of d, $J_{H-H} \sim J_{H-P} \simeq$ 1.8 Hz, 1 H), 5.04 (d of d, $J_{H-H} \simeq J_{H-P}$ = 1.6 Hz, 1 H), 3.21 (m, 2 H), 2.19–1.21 (m, 20 H). Anal. Calcd for $C_{18}H_{33}N_2O_5 \cdot H_2O$: C, 55.36; H, 8.40; N, 7.18; P, 7.93. Found: C, 55.07; H, 8.04; N, 7.46; P, 7.77. The corresponding sodium salt, prepared as described above, showed the following: ^1H NMR (D_2O) δ 7.47 (br s, 1 H), 6.62–6.47 (m, 2 H), 5.04 (d of d, 1 H), 4.92 (d of d, 1 H); ^1H decoupled ^{31}P NMR (D_2O) δ −0.39 (s).

(12) Dicyclohexylammonium 1-Cyclohex-1-enyl Phosphate. Trimethylsilyl chloride (16.2 g), triethylamine (15.2 g), and cyclohexanone (12.7 g) were refluxed in 50 mL of dimethyl formamide for 48 h. The resulting silyl enol ester boiled at 60–63 °C/15 mm: ^1H NMR ($CDCl_3$) δ 4.86 (m, 1 H), 2.09–1.44 (m, 8 H), 0.17 (s, 9 H). It (1.43 g) was treated with 1 equiv of *N*-bromosuccinimide in 150 mL of THF for 20 min at 0 °C. Rotoevaporation of solvent left an oil which was dissolved in a solution of trimethyl phosphite (1.04 g) in 10 mL of methanol and allowed to stand at room temperature overnight. The resulting dimethyl 1-cyclohex-1-enyl phosphate boiled at 95–100 °C/0.2 mm: ^1H NMR ($CDCl_3$) δ 5.46 (m, 1 H), 3.80 (d, J_{H-P} = 11.2 Hz, 6 H), 2.25–1.53 (m, 8 H). The dimethyl ester (1 g) was converted to the bis(trimethylsilyl) ester and to the cyclohexylammonium salt as above. The solid (1.2 g) melted at 197–199 °C: ^1H NMR (D_2O) δ 5.26 (m, 1 H), 3.14 (m, 2 H), 2.17–1.07 (m, 28 H). Anal. Calcd for $C_{18}H_{37}N_2O_4P \cdot H_2O$: C 54.80; H, 9.96; N, 7.10; P, 7.86. Found: C, 55.11; H, 9.89; N, 7.29; P, 8.08. The properties of the disodium salt are as follows: ^1H NMR (D_2O) δ 5.27 (m, 1 H), 2.25–1.20 (m, 8 H); ^1H decoupled ^{31}P NMR (D_2O) δ −0.05 (s).

Table I. Effect of Concentration of Base on the Yield of 1-Phenylvinyl Phosphate

vol of base added, mL	yield of enol phosphate, %, based on III
1.00	37
0.70	30
0.30	16
0.10	9
0.05	3

(13) Dihydrogen 2,4-dinitrophenyl phosphate[18] was converted to its monobenzyltrimethylammonium salt by titrating it in methanol solution with Triton B; the salt was dried at 50 °C/0.2 mm overnight.

Other materials were of the highest purity commercially available and were further purified by recrystallization or by distillation from calcium hydride under argon. 2,2,6,6-Tetramethylpiperidine, from Aldrich, boiled at 155–156 °C. Chloroform (alcohol free) and acetonitrile, from Burdock-Jackson, were of high quality and used without further purification. Deuterioacetonitrile, deuteriochloroform, and deuterioacetone were obtained from Merck of Canada.

(14) *O*-Ethyl *N*-Phenylacetimidate. The reaction of 1.5 mL of ethyl acetate and 50 μL of aniline was carried out in the presence of 50 μL of base and 70 μmol of I or III. The yields of HPO_4^{2-}, pyrophosphate, and *N*-phenylphosphorimidate, determined by NMR spectroscopy, agreed with those previously reported.[9] Additionally, the phosphates were separated from the *O*-ethyl *N*-phenylacetimidate by partition between carbon tetrachloride and borate buffer, as described before, but after evaporation of the carbon tetrachloride, the imidate was purified by vacuum sublimation at 38 °C/0.1 mm in an apparatus similar to Ace Glass No. 8021. After the material from the tip of the cold finger had been eluted with $CDCl_3$, it gave a ^1H NMR spectrum identical with that of synthetic material.

Methods. ^{31}P NMR spectra were determined on a Varian-Nicolet XL-100 spectrometer, equipped for Fourier transform and with a phosphorus probe at 40.5 MHz; ^1H NMR spectra were determined on a Varian CFT 20 spectrometer. Analyses were carried out by Galbraith Laboratories, Knoxville, TN.

The standard procedure for phosphorylation was as follows: 60–80 μmol of one of the metaphosphate precursors, I, II, or III, was weighed into a 20-mL test tube, which was then closed with a serum cap that was pierced with an No. 18 syringe needle. The tubes were dried overnight in a vacuum oven at 50 °C. A solution of carbonyl compound (3 mL) and base (usually 1 mL) was then added to the tube by syringe and vortexed until the bromophosphonic acid dissolved (about 1 min). NMR solution A consisting of triethylamine (0.3 mL), methanol (1 mL), and deuterioacetonitrile (1 mL) was then added and the ^{31}P NMR spectrum obtained. The reactions of I and II were complete in the time of mixing; III reacts more slowly. No methyl phosphate was detected in the NMR spectra. No differences have so far been observed between reactions initiated with I, II, or III. The average yields of 1-phenylvinyl phosphate from these three precursors under standard conditions were 40, 40, and 42%, respectively. Major products were identified by their ^{31}P NMR signals and confirmed by adding synthetic material to the NMR tubes and then repeating the spectra.

Yields were estimated from the integrated ^{31}P NMR spectra. Important products were also isolated from the reaction mixtures and then identified by comparing their proton NMR spectra with those of synthetic materials. The procedure for 1-phenylvinyl phosphate was typical. A reaction mixture (without addition of solution A) was partitioned between 10 mL of carbon tetrachloride and 10 mL of 0.1 N sodium hydroxide solution. The aqueous layer was extracted 3 times with 10 mL of ether, and the water removed *in vacuo* to yield a solid residue. The residue was then dissolved in D_2O to observe the ^1H NMR spectrum of the product, or dissolved in H_2O to obtain the UV spectrum, from which the yield of product could be obtained, and compared to that calculated from integration of the ^{31}P NMR spectrum. Control experiments indicated a recovery of about 80% of the enol phosphate from reconstructed reaction mixtures.

1-Phenylvinyl phosphate is stable in the NMR solution A and does not react rapidly with methanol. By way of contrast, the enol phosphate of acetone, in a solution similar to that of the reaction products, disappears with a half-time of a couple of hours; appreciable loss, therefore, occurs

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Table II. Effect of Added Solvent on the Yield of 1-Phenylvinyl Phosphate

solvent added, mL	yield of enol phosphate, %, based on III
none	37
$CHCl_3$ (1 mL)	30
$CHCl_3$ (1.5 mL)	26
$CHCl_3$ (2 mL)	13
CD_3CN (1 mL)	8
dioxane (1 mL)	3

Table III. Effects of Various Bases on the Yield of 1-Phenylvinyl Phosphate

base	pK_a	HPO_4^{2-}, %	$H_2P_2O_7^{2-}$, %	enol phosphate, %
2,2,6,6-tetramethylpiperidine[b]	11.07	4	4	40
diisopropylamine[b]	11.0	14	4	40
Proton Sponge[c]	12.1	7	6	8
2,6-dimethylpyridine[c]	6.75	6	8	8
2,4,6-trimethylpyridine[b]	7.50	6	6	6
diisopropylmethylamine		4	4	3
N-tert-butylpiperidine[d]	11.13	8	5	<2
diisopropylethylamine		4	4	<2
triethylamine[b]	10.7	6	8	<2
diethylamine[b]	11.0	6	6	<2
1,5-diazabicyclo[4.3.0]-non-5-ene		7	4	<2
1,5-diazabicyclo[5.4.0]-undec-5-ene		7	4	<2
2-methylpyridine[b]	5.97	6	6	<2

[a] These experiments were carried out with 3 mL of acetophenone and 1 mL (or gram) of base and 70 μmol of I or III. [b] Reference 27. [c] Reference 28. [d] Reference 29.

Table IV. Yield of Enol Phosphates from Various Ketones

ketone	HPO_4^{2-}, %	$H_2P_2O_7^{2-}$, %	enol phosphate, (av)
acetophenone	4	4	40
acetophenone (dilute)	2	2	82
acetone	5	10	21
2-acetylfuran	8	12	14
cyclohexanone	20	14	8
desoxybenzoin	4	6	2

during the hour required to accumulate NMR data. When only deuterioacetonitrile is added to the solution of reaction products from acetophenone, much polymeric phosphate appears as a precipitate. Addition of methanol dissolves the precipitate but does not cause new peaks to appear; in particular, no peak corresponding to methyl phosphate appears in the hour that is required to obtain an NMR spectrum.

Results

The effect of the concentration of base on the yield of 1-phenylvinyl phosphate from acetophenone is shown in Table I. In these experiments, 3 mL of acetophenone and 70 μmol of III were treated at room temperature with varying amounts of 2,2,6,6-tetramethylpiperidine.

The effect of solvent on the yield is presented in Table II. In these experiments, 30 mg (79 μ mol) of III was allowed to react with acetophenone and 1 mL of 2,2,6,6-tetramethylpiperidine in a total volume of 5 mL.

The results with various bases are shown in Table III.

Experiments were carried out with a number of different ketones, in which 3 mL of ketone, 1 mL of base, and 70 μmol of I or III were used. In order to test the effect of concentration of the bromophosphonate on the yield of enol phosphate, experiments were carried out in which the volume of acetophenone was increased 4-fold to 12 mL and the amount of bromophosphonate was decreased 2.5-fold to 28 μmol, so as to effect a 10-fold dilution of I. The results are presented in Table IV.

When ethyl pyruvate was tried, it underwent rapid base-promoted condensation, as evidenced by an immediate increase in temperature and the formation of a precipitate. The phosphorus-containing product was about 90% inorganic phosphate, presumably as a result of the action of monomeric metaphosphate ion on the water formed in the condensation reaction.

As indicated under Experimental Section, most of the enol phosphates are unstable in the NMR solution A; the yields initially formed must then be somewhat larger than those here reported.

Discussion

The work here reported confirms that previously published from our laboratory[9] but with improved yields and identifications. We had reported the formation of about 16% enol phosphate from acetophenone and PO_3^-. Monomeric metaphosphate ion was prepared by the fragmentation of the dianion of I, and the reaction was complete in a few seconds at room temperature. We proposed the pathway[9] for the reaction that is shown in eq 1 and 2. With more careful drying of apparatus and reagents, the yield of enol phosphate, under the same conditions of time, temperature, concentrations, etc., has been increased to about 40%, regardless of whether the monomeric metaphosphate is prepared from the dianion of I, II, or III. Furthermore, the fragmentations of all of these bromophosphonates in the presence of 2,2,6,6-tetramethylpiperidine are rapid. In the presence of weak bases, however, (those with p*K*'s near 7), the decomposition of III is slowed considerably. The time for reaction of III in the presence of these weak bases was therefore extended to about an hour.

Further, we had previously shown that PO_3^- promotes the reaction of aniline with ethyl acetate to yield *N*-phenyl *O*-ethyl acetimidate. This compound has now been isolated by sublimation from the reaction mixture and its formation confirmed.

The synthesis of enol phosphate requires some base to remove a proton from the methyl group of acetophenone. The yield of enol phosphate depends critically on the concentration of base added, as shown in Table I. This is the expected consequence of competition between the formation of enol phosphate and polymerization of the metaphosphate; base selectively increases the rate of formation of the enol phosphate. In prior work with methyl metaphosphate, a satisfactory yield of methyl 1-phenylvinyl phosphate from acetophenone could be obtained with a 5-fold excess of base over phosphonic acid; with metaphosphate ion, the yield is maximized only in the presence of a 100-fold excess.

The competition between polymerization and formation of enol phosphate mentioned in the introduction is further illustrated by the experiments, recorded in Table IV, where the concentration of the β-bromophosphonate is varied. When the concentration of I in acetophenone is 0.0175 M, the yield of enol phosphate, based on the bromophosphonic acid used, is about 40%. When the concentration of the phosphate is decreased by a factor of 10 to 0.0018 M, the yield of enol phosphate, based on the phosphorus present in solution, exceeds 80%.

Even our lowest concentration of base is, however, 5 times that of the phosphonate. Stoichiometry requires 2 mol of base to neutralize the phosphonic acid and another mole for the formation of enol phosphate, so that this lowest concentration still provides a substantial excess of base. Nevertheless, under these circumstances, our yield of enol phosphate was only 3%. This result is consistent with that of Ramirez et al.,[10] who report a yield of 2% in the presence of only 2 mol of ethyldiisopropylamine/mol of phosphonic acid used. In the light of the data of Table I, it is clear that only in the presence of high concentrations of amine can large yields of enol phosphate be obtained.

In other experiments, Ramirez et al. reported that, with 2 mol of base in acetonitrile as the solvent, they obtained no enol phosphate whatever from acetophenone. We had previously[7] shown that acetonitrile sharply diminishes the yield of the products of electrophilic attack of methyl metaphosphate on the aromatic rings of substituted anilines; the data of Table IV shows that it decreases the yield of enol phosphate. Presumably, both methyl metaphosphate and metaphosphate ion are transferred to aceto-

nitrile to form $CH_3C{\equiv}N^+P(OCH_3)O_2^-$ and $CH_3C{\equiv}N^+PO_3^{2-}$, respectively. Since, with 2 molar equiv of base, the yield of enol phosphate from acetophenone[10] is only 2%, and since acetonitrile would be expected to diminish even that yield, little or no enol phosphate could be anticipated in that solvent.

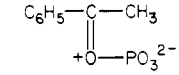
The same yields of 1-phenylvinyl phosphate are obtained with PO_3^- generated from any of our β-bromophosphonic acids I, II, or III. Interestingly, this is not true when 2,4-dinitrophenyl phosphate is used as a source of "monomeric metaphosphate"; with this reagent, no enol phosphate was obtained. The absence of enol phosphate in the reaction of 2,4-dinitrophenyl phosphate with acetophenone had previously been reported by Ramirez et al.[10] Since, however, they carried out the reaction under their experimental conditions—only 2 mol of ethyldiisopropylamine in acetonitrile as the solvent—no enol product could have been expected. But even in acetophenone as the solvent and under conditions of concentration of base and bromophosphonate where I, II, and III yield 40% enol phosphate, dinitrophenyl phosphate yields none. Dinitrophenyl phosphate, however, reacts much more slowly than do the bromophosphonates; it requires 24 h at room temperature for substantially complete decomposition. Whether this difference in rate is in any way responsible for the difference in outcome noted above has not yet been established. The work of Kirby and Varvoglis[18] could perhaps be interpreted in terms of a preassociation mechanism in the sense defined by Jencks;[19] whether such preassociation occurs in the decomposition of 2,4-dinitrophenyl phosphate and not with the β-bromophosphonates, and whether in any event it can explain the differences here noted, remains for further investigation.

After reporting reasonable yields of enol phosphate only from some highly enolized dicarbonyl compounds, Ramirez and his co-workers[10] concluded that monomeric metaphosphate can phosphorylate the enol present in equilibrium with ketones but does not attack the carbonyl group. As pointed out before, and as is inherent in the date of Table I, the low values of enol phosphate that Ramirez et al. obtained arose from their experimental conditions. In our view, our data point strongly to the formation of enol phosphate by the pathway shown in eq 1 and 2.

First and foremost, the quantity of enol in equilibrium with simple ketone is minute. Guthrie[20] estimated that the equilibrium constant for the enolization of acetophenone is 2.5×10^{-7}; only 2.5 parts out of 10000000 of the acetophenone is present as enol. In prior control experiments,[9] the phosphorylation was carried out in the presence of 5% phenol, relative to acetophenone; the phenol was thus present in about 200000-fold excess over the enol. The yield of enol phosphate, under these conditions, was scarcely diminished. In order that the enol of acetophenone could preferentially capture the metaphosphate in the presence of this huge excess of phenol, metaphosphate would have to be highly selective reagent. But considerable evidence[18,21-26] shows that it is particularly nonselective, as would be expected for a strong electrophile.

Other evidence, although much less compelling, is at least consistent with the explanation here offered. The effect of base concentration on the yield of enol phosphate shows that the loss of a proton from the methyl group of acetophenone occurs in the product-determining step. If PO_3^- reacted with an equilibrium concentration of enol, excess base would not affect the yield of product.

The data in Table II accord with, although they do not demand, the scheme of eq 1 and 2. The yield of enol phosphate is somewhat diminished by diluting the acetophenone with chloroform, but it is sharply diminished—almost eliminated—by diluting the reaction mixture with dioxane. Dioxane is a stronger base than acetophenone and when present in substantial amount can compete with it for metaphosphate ion, or capture metaphosphate rapidly from the zwitterionic adduct



postulated in eq 2.

The attack of PO_3^- on carbonyl groups has been established in other instances. The formation of a Schiff base between acetophenone and aniline in seconds at room temperature requires activation of the carbonyl group. The reaction is not one between the enol phosphate and aniline, which do not undergo rapid reaction. The reaction between ethyl acetate and aniline, promoted by metaphosphate, yields *O*-ethyl *N*-phenylacetimidate. This reaction, too, is complete in only a few seconds and must involve the activation of the carbonyl group by the metaphosphate.[9] Analogous reactions have been carried out with methyl metaphosphate.[8] Since metaphosphate attacks the carbonyl group in these instances, the intermediate postulated in eq 2 must necessarily be formed. Once a positive charge has been established on the carbonyl oxygen atom, subsequent enolization in the presence of base becomes highly probable.

The variation in yield of enol phosphate with the structure of the base used, shown in Table III, is complex and not easily understood. The yield is poor with unhindered amines, such as diethyl and triethylamine; presumably these bases capture the monomeric metaphosphate, either directly or in a secondary reaction in which PO_3^- is transferred from the phosphorylated ketone. (The product would be analogous to the zwitterion from quinuclidine and PO_3^- that has been identified by NMR spectroscopy.[24b]) On the other hand, very highly hindered bases, such as diisopropylmethylamine, give poor yields of enol phosphate, presumably because they cannot rapidly catalyze the removal of a proton from the phosphorylated ketone. These relationships require further elucidation.

Formation of enol phosphates, as shown in Table IV, has been observed with a few ketones in addition to acetophenone. In each instance, the identification of the product is secure. The signal from each enol phosphate has been identified in the ^{31}P NMR spectrum of the reaction mixture where the enol phosphate has been formed and confirmed by adding synthetic material directly to the NMR tube. Furthermore, each product has been isolated from the reaction mixture and identified by comparison of its ^1H NMR spectrum to that of synthetic material.

The yields of other enol phosphates, however, have proved poor relative to that from acetophenone. Part of this deficit in yield—but only a part—arises from the instability of the enol phosphates in solution A used for NMR spectroscopy. Presumably the yield is a complicated function of the equilibrium constant for the formation of the zwitterionic intermediate, the rate at which the particular base present can extract a proton from the methyl or methylene group adjacent to the carbonyl group, the rate at which the zwitterionic intermediate can transfer PO_3^- to other nucleophiles present in the solution, and particularly the rate of transfer of PO_3^- to phosphates or phosphonates to form pyro- or polyphosphates or mixed phosphate–phosphonate anhydrides. These factors are not easy to analyze.

Finally, it should be noted that the attempt to phosphorylate ethyl pyruvate in the presence of 2,2,6,6-tetramethylpiperidine failed for an extraneous reason: in the presence of base, ethyl pyruvate undergoes rapid reaction to yield a solid, presumably

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an aldol condensation product. In the presence of phosphorylating system, the phosphorus appears principally as inorganic phosphate, presumably by reaction with the water produced in the self-condensation of pyruvate.

Acknowledgment. We gratefully acknowledge the support of this investigation by the National Science Foundation.

Registry No. I, 10602-62-7; II, 10602-61-6; III, 84959-95-5; disodium 1-phenylvinyl phosphate, 76625-78-0; disodium 1-methylvinyl phosphate, 84959-92-2; disodium 1-furylvinyl phosphate, 84959-93-3; disodium 1-cyclohex-1-enyl phosphate, 84986-91-4; disodium 1,2-diphenylvinyl phosphate, 84959-94-4; acetophenone, 98-86-2; acetone, 67-64-1; 2-acetylfuran, 1192-62-7; cyclohexanone, 108-94-1; desoxybenzoin, 451-40-1; 2,2,6,6-tetramethylpiperidine, 768-66-1; diisopropylamine, 108-18-9; 2,6-dimethylpyridine, 108-48-5; 2,4,6-trimethylpyridine, 108-75-8; diisopropylmethylamine, 10342-97-9; *N*-*tert*-butylpiperidine, 14446-69-6; diisopropylethylamine, 7087-68-5; triethylamine, 121-44-8; diethylamine, 109-89-7; 1,5-diazabicyclo[4.3.0]non-5-ene, 3001-72-7; 1,52-diazabicyclo[5.4.0]undec-5-ene, 41015-70-7; 2-methylpyridine, 109-06-8; trichloromethane, 67-66-3; acetonitrile-d_3, 2206-26-0; dioxane, 123-91-1; *trans*-chalcone, 614-47-1; methyl dihydrogen phosphoric acid, 812-00-0; anilinium hydrogen 1-phenylvinyl phosphate, 70334-78-0; acetophenone anil, 1749-19-5; *O*-ethyl *N*-phenylacetimidate, 19655-72-2; anilinium hydrogen *N*-phenylphosphoramidate, 36097-59-3; anilinium hydrogen 1,2-diphenylvinyl phosphate, 84959-97-7; dimethyl 1,2-diphenylvinyl phosphate, 40731-57-5; dicyclohexylammonium 1-methylvinyl phosphate, 84959-99-9; dimethyl 1-methylvinyl phosphate, 4185-82-4; bis(trimethylsilyl) 1-methylvinyl phosphate, 57222-19-2; dicyclohexylammonium 1-furylvinyl phosphate, 84960-01-0; 2-(α-chloroacetyl)furan, 55984-17-3; dimethyl 1-furylvinyl phosphate, 66602-38-8; dicyclohexylammonium 1-cyclohex-1-enyl phosphate, 84960-03-2; (1-cyclohexen-1-yloxy)trimethylsilane, 6651-36-1; dihydrogen 2,4-dinitrophenyl phosphate, 2566-26-9; dimethyl 1-cyclohex-1-enyl phosphate, 3719-53-7.

Organoaluminum-Promoted Beckmann Rearrangement of Oxime Sulfonates

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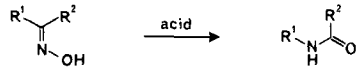
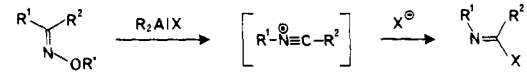
Abstract: The Beckmann rearrangement of oxime sulfonates with simultaneous nucleophilic trapping of the intermediary iminocarbocation by organoaluminum reagents is described. This process provides a new and highly efficient route to imino thioethers, imino selenoethers, imino nitriles, and α-alkylated amines starting from oxime sulfonates by the use of dialkylaluminum thiolates, selenolates, diethylaluminum chloride–trimethylsilyl cyanide, and trialkylaluminum–diisobutylaluminum hydride systems, respectively. The present organoaluminum-promoted Beckmann rearrangement of oxime sulfonates has been successfully applied to the synthesis of naturally occurring alkaloids, pumiliotoxin C and solenopsin A and B, in stereoselective fashion. Moreover, α,α-dialkylation of amines can be realized by the successive treatment of oxime sulfonates with trialkylaluminum followed by allylic or propargylic Grignard reagents in synthetically useful yields.

The Beckmann rearrangement is the skeletal rearrangement of ketoximes in the presence of certain acids, including Lewis acids, to give amides or lactams.[1] Since the first discovery of this



rearrangement by Beckmann in 1886,[2] successive investigations have largely clarified its scope, reaction mechanism, and the stereochemical configurations of the oximes employed. Accordingly, the Beckmann rearrangement has become an increasingly reliable synthetic tool in organic chemistry. The reaction has found broad application as a step in the manufacture of synthetic polyamides.[3] It is a preferred way to incorporate the nitrogen atom efficiently in both acyclic and alicyclic systems, thereby providing a powerful method for a variety of alkaloid syntheses.

The mechanism of the Beckmann rearrangement consists essentially of the formation of an electron-deficient nitrogen atom by the partial ionization of the oxygen–nitrogen bond of the oxime with a simultaneous intramolecular migration of the group anti to the departing hydroxy group, producing the iminocarbocation



which then reacts with water to give the corresponding amide. A careful examination of this reaction mechanism led us to consider that organoaluminum compounds might be employed as amphoteric reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary iminocarbocation by the nucleophile which is originally attached to aluminum.[4] This proved to be the case. In this paper, we wish to disclose the organoaluminum-promoted Beckmann rearrangement of oxime derivatives, from which several new synthetic procedures have been developed as described in the following sections. Moreover, the synthetic utility of these new procedures has been clearly demonstrated by the synthesis of naturally occurring alkaloids, pumiliotoxin C and solenopsin A and B, in stereoselective fashion.

As oxime derivatives, oxime sulfonates can be used preferentially for the following reasons: (1) ready availability from oximes using *p*-toluenesulfonyl chloride or methanesulfonyl chloride in the presence of base in almost quantitative yields; (2) ease of handling because of their fine crystalline properties; (3) high enough reactivity to initiate the rearrangement by organoaluminum reagents.

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