Monomeric Metaphosphate Anion: Reaction with Carbonyl Groups

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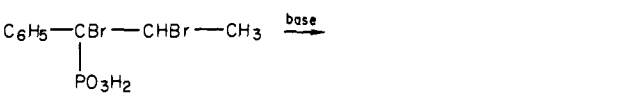
Abstract: The elusive monomeric metaphosphate anion is generated rapidly at room temperature by the fragmentation of *threo*- or *erythro*- (1,2-dibromo-1-phenylpropyl)phosphonate in the presence of a hindered base; it reacts at the carbonyl groups of acetophenone and ethyl acetate. With acetophenone, the product is the enol phosphate. In the presence of aniline and acetophenone, the product is the Schiff base. In the presence of ethyl acetate and aniline, the product is ethyl *N*-phenylacetimidate. These reactions parallel biochemical processes that require ATP and, like those of monomeric methyl metaphosphate that have previously been reported, suggest the possibility that ATP plays a kinetic as well as a thermodynamic role in intermediary metabolism.

Introduction

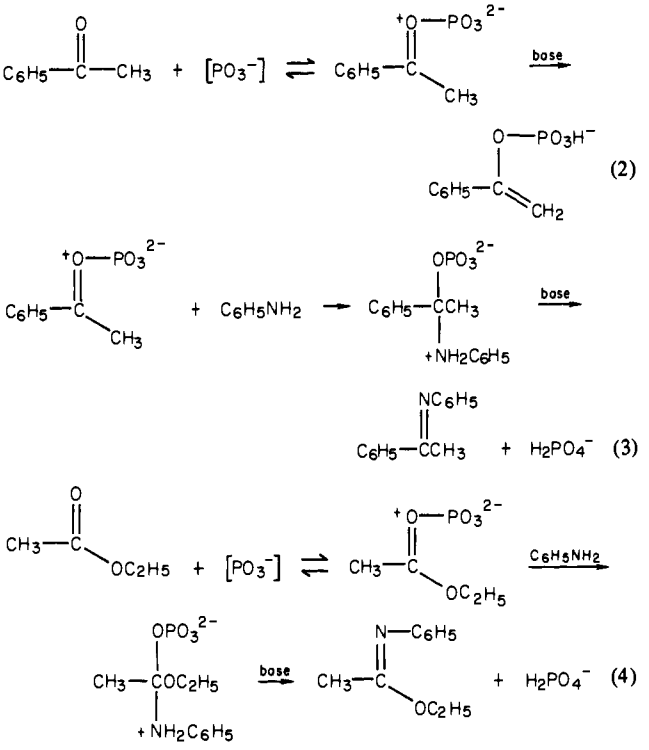
Monomeric metaphosphates have long been postulated as intermediates in phosphorylation reactions. Recently, the chemistry of monomeric methyl metaphosphate,[1] CH_3OPO_2, has been elucidated; the reactive intermediate, generated by Conant–Swan fragmentation,[2] converts acetophenone to the corresponding enol phosphate and in the presence of aniline coverts ethyl benzoate to ethyl *N*-phenylbenzimidate. These latter reactions, which require several days at 70 °C, parallel to some extent some of the biosynthetic phosphorylations that require ATP.[3]

At long last, we are able to report similar but much more rapid phosphorylations with PO_3^-, the monomeric metaphosphate ion itself. This work culminates more than a quarter century of research in this laboratory and many others. The distinction between the monomeric metaphosphate anion and monomeric methyl metaphosphate is an important one. If any of the biochemical phosphorylations carried out by adenosine triphosphate proceeds by way of a monomeric metaphosphate, the effective reagent is, of course, PO_3^-, and not some derivative of it. The chemistry of PO_3^- is also distinctive (see Discussion).

Monomeric metaphosphate anion was generated by the Conant–Swan fragmentation of salts of dihydrogen *threo*- or *erythro*-(1,2-dibromo-1-phenylpropyl)phosphonate[4] (eq 1). The



$$C_6H_5CBr{=}CHCH_3 + [PO_3^-] + Br^- + 2BH^+ \quad (1)$$



(2)

(3)

(4)

fragmentation is essentially instantaneous in alkaline water at room temperature, and preliminary indications suggest that it is also fast in the presence of 2,2,6,6-tetramethylpiperidine in the solvents employed here. When monomeric metaphosphate anion is genrated in acetophenone, it undergoes reaction to yield the corresponding enol phosphate (eq 2). When moderate amounts of aniline are present as well as acetophenone, PO_3^- promotes the formation of Schiff base (eq 3). In ethyl acetate mixed with aniline, PO_3^- promotes amidation (eq 4).

The evidence for these reactions and a discussion of the chemistry involved is presented in the following sections of this paper. Although these studies in no way settle the question of whether the metaphosphate anion is "free" in solution or is solvated,[5] they demonstrate that it is a powerful phosphorylating

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agent capable of chemical transformations which parallel metabolic reactions.

Experimental Section

General Data. Commercial solvents were dried over calcium hydride, distilled, and stored over flame-dried 4-Å sieves. *o*-Trifluoromethylaniline and 2,2,6,6-tetramethylpiperidine were obtained from Aldrich. NMR spectra were obtained as previously described.[1] Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Materials. Dihydrogen *erythro*- and *threo*-(1,2-dibromo-1-phenylpropyl)phosphonates, methyl hydrogen *erythro*-(1,2-dibromophenylpropyl)phosphonate, methyl dihydrogen phosphate, 1-phenylvinyl dimethyl phosphate, dimethyl *N*-phenylphosphoramidate, and **acetophenone anil** were prepared as previously described.[1,4] **2-Bromoethylphosphonic acid** was synthesized according to Kosolapoff;[6] mp 93.5–95 °C (lit. 92.5–94.5 °C).

Ethyl *N*-phenylacetimidate was made according to Taylor and Ehrhart;[7] bp 47 °C (0.43 mm Hg) (lit. bp 71.5–73.5 °C (1.75mm Hg). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3 H), 1.79 (s, 3 H), 4.22 (q, J = 7.1 Hz, 2 H), 6.68–8.23 (br m, 10 H). Commercial 85% phosphoric acid was used; for quantitative comparisons, however, a weighed sample of dihydrogen sodium phosphate was converted to the acid form by passage through Bio-Rad AG 50W-X8 in the protonated form. **Pyrophosphoric acid** and **phenyl phosphoric acid** were prepared by passing commercial salts through Bio-Rad AG 50W-X8 in the protonated form.

Anilinium hydrogen 1-phenylvinyl phosphate was synthesized by allowing a mixture of 1-phenylvinyl dimethyl phosphate[1] (1.0 mL, 5×10^{-3} M) and bromotrimethylsilane[8] (1.3 mL, 1.9 equiv) to stand in a dry, stoppered test tube at room temperature for 4 h. The product mixture was stirred with aniline (0.5 mL, 1 equiv) in 20 mL of ethanol.[9] White plates crystallized within 5 min (60% yield): mp 86.5–87.5 °C. ^{31}P NMR (1 M NaOD): δ −0.20 (s). Anal. Calcd for $C_{14}H_{16}NO_4P$: C, 57.34; H, 5.50; N, 4.78; P, 10.56. Found (hard burning with V_2O_5): C, 57.05; H, 5.58; N, 4.82; P, 10.60. As a crystalline salt, this reportedly unstable compound[9] decomposes only slowly (10% in a month at 4 °C).

Disodium 1-phenylvinyl phosphate was formed by mixing 5 mg of anilinium hydrogen 1-phenylvinyl phosphate with 0.7 mL of 0.1 M NaOH and extracting twice with an equal volume of ether. ^{1}H NMR (D_2O): δ 5.02 (d of d, $J_{HH} \simeq J_{HP} \simeq$ 1.7 Hz, 1 H); 5.15 (d of d, $J_{HH} \simeq J_{HP} \simeq$ 1.7 Hz, 1 H); 7.33–7.79 (br m, 5 H). ^{31}P NMR (0.1 M NaOD): δ 0.20 (s).

Reactions with Carbonyl Compounds. Reactions of dihydrogen *threo*-(1-phenyl-1,2-dibromo)phosphonate (I) with various solvents were carried out in dry, rubber-capped test tubes at room temperature. A premixed reaction solution of solvent, base, and various additives was added to 25 mg of I and vortexed to dissolve the phosphonates (<1 min). Immediately, acetonitrile-d_3–methanol–triethylamine (1.0:1.0:0.3 mL, NMR solution A) was added for ^{31}P NMR spectroscopy. Reactions are complete within the time of vortexing, since methyl phosphate is only formed when methanol is present in the premixed solution and not when it is added with NMR solution A. Products were identified by ^{31}P NMR spectroscopy and yields estimated by integration as previously described.[1] Important products were isolated and identified by ^{1}H NMR spectroscopy as described below.

Enol Phosphate. A premixed solution of acetophenone (3.0 ml) and 2,2,6,6-tetramethylpiperidine (1.0 mL) (here simply called "base") was vortexed with 25 mg of dihydrogen *threo*-(1,2-dibromo-1-phenylpropyl)phosphonate, I. NMR solution A was immediately added for ^{31}P NMR spectroscopy (Figure 1a). The major products are inorganic phosphate (14%, δ −0.63), enol phosphate (18%, δ 3.45), and pyrophosphate (9%, δ 7.11); yields are relative to the initial concentration of I. Additional signals centered at +10 and +25 ppm suggest polymeric material.[10] The same reaction with dihydrogen *erythro*-(1,2-dibromo-1-phenylpropyl)phosphonate gave similar results. Inorganic phosphate and pyrophosphate were identified as products by adding phosphoric acid and pyrophosphoric acid and repeating the spectra. Enol phosphate was identified and quantified by adding an equivalent amount of anilinium

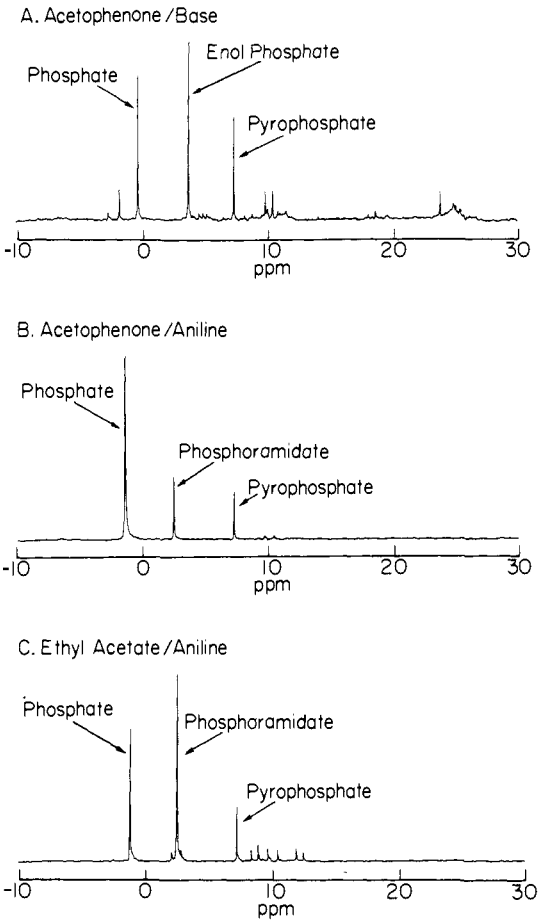

Figure 1. The 40.5-MHz ^{31}P NMR spectra of products formed from the fragmentation of 25 mg of dihydrogen *threo*-(phenyl-1,2-dibromopropyl)phosphonate (I) at room temperature in (A) 3.0 mL of acetophenone mixed with 1.0 mL of 2,2,6,6-tetramethylpiperidine, (B) 3.0 mL of acetophenone mixed with 0.30 mL of aniline and 50 μL of 2,2,6,6-tetramethylpiperidine, and (C) 1.5 mL of ethyl acetate mixed with 50 μL of aniline and 50 μL of 2,2,6,6-tetramethylpiperidine. Chemical shifts are relative to an external standard of 85% phosphoric acid.

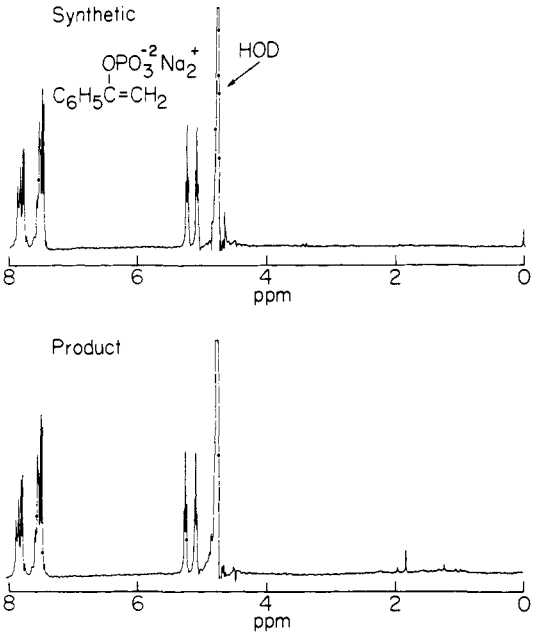

Figure 2. A comparison of the 100-MHz ^{1}H NMR spectra of synthetic disodium 1-phenylvinyl phosphate with that prepared with monomeric metaphosphate anion. Minor impurities between δ 1 and 2 are present in the product. Chemical shifts are in ppm relative to DDS (upper spectrum).

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hydrogen 1-phenylvinyl phosphate and comparing the increase in signal size with that for an added standard of dimethyl *N*-phenylphosphoramidate (5 mg).

1-Phenylvinyl phosphate was isolated by partitioning the product mixture between 10 mL of 0.01 M NaOH and 10 mL of carbon tetrachloride. After a tenfold dilution the aqueous layer was applied to a 2.5 × 2 cm DE52 column (hydroxide form) and the product eluted with 10^{-3} M NaOH–10^{-2} M NaCl in fractions 3–7 (5 mL/fraction). After the chromatographic step was repeated for further purification, the product was identified by comparison of its ^{1}H NMR spectrum with that of synthetic disodium 1-phenylvinyl phosphate (Figure 2).

As a control experiment (see Discussion for rationale), the preparation of enol phosphate was carried out in the presence of 5 mol % (relative to acetophenone) of phenol (0.11 mL) or methanol (0.5 mL). The yield of enol phosphate (25%) showed, if anything, a slight increase in the presence of phenol, although now phenyl phosphate (12%) ws also produced. When methanol was present in the reaction mixture, the yield of enol phosphate was reduced from 18 to 7% and the major product was methyl phosphate (39%). Both phenyl phosphate and methyl phosphate were identified by comparisons of their ^{31}P NMR spectra with those of authentic samples. The yield of enol phosphate is dependent on the concentration of 2,2,6,6-tetramethylpiperidine. When only 50 μL of base is present in the reaction mixture (above), the yield of enol phosphate is ~3% and the complex ^{31}P NMR spectrum of the products suggests largely polymeric material.

Schiff Base. A solution of acetophenone (3.0 mL), aniline (0.3 mL), and 2,2,6,6-tetramethylpiperidine (50 μL) was vortexed with 25 mg of I at room temperature. NMR solution A was added and the ^{31}P NMR spectrum (Figure 2b) obtained. Signals were identified for inorganic phosphate (75%, δ – 1.50), *N*-phenylphosphoramidate (16%, δ 2.39), and pyrophosphate (6%, δ 7.20). Enol phosphate was not a product; when it was added back to the product mixture, it decomposed only slowly. Inorganic phosphate was identified as a product, and its yield confirmed by adding a quantity of phosphoric acid equivalent to that produced in the reaction and using the increase in signal size relative to that for phosphoramidate as a standard. *N*-Phenylphosphoramidate was prepared for this comparison by the reaction of I in aniline. Both *N*-phenylphosphoramidate and pyrophosphoric acid were then identified by adding authentic samples to the product mixture and repeating the spectra.

Acetophenone anil was isolated from the reaction mixture and quantified in the same manner as previously described.[1] The yields of ketimine from three experiments were 53, 64 and 68%. In reconstruction experiments, 73 and 78% of an equivalent amount of acetophenone anil could be recovered from a mixture of it with acetophenone, aniline, and 2,2,6,6-tetramethylpiperidine. The yield of ketimine, corrected for loss during its isolation, is therefore 80 ± 12% and agrees reasonably well with the 75% yield of inorganic phosphate determined by integration. If pyrophosphate is formed by phosphorylation of inorganic phosphate, as seems likely, the true yield of inorganic phosphate is 78%. A control experiment was run to test whether ketimine is formed by the direct attack of aniline on acetophenone under the reaction conditions. 2-(Bromoethyl)phosphonic acid, a model for I, fragments slowly, and in fact no fragmentation could be detected under the reaction conditions for I. When 25 mg of 2-(bromoethyl)phosphonic acid was vortexed with a mixture of acetophenone, aniline, and 2,2,6,6-tetramethylpiperidine (above), no acetophenone anil could be detected as a product. In a further control experiment (see Discussion for rationale), 5 mol % (relative to acetophenone) of *sec*-phenethyl alcohol (0.15 mL) had no observable effect on the yield of ketimine or inorganic phosphate.

Similar experiments to those above were run with *o*-trifluoromethylaniline (0.3 mL) in place of aniline. The products were inorganic phosphate (61%), phosphoramidate (23%), and pyrophosphate (16%). The yield of the trifluoroketimine[1] from one experiment (~75%, corrected for a small loss during workup) is nearly the same as that of inorganic phosphate if loss to pyrophosphate is taken into account.

Imidate. A solution of ethyl acetate (1.5 mL), aniline (50 μL), and 2,2,6,6-tetramethylpiperidine (50 μL) was vortexed with 25 mg of I and NMR solution A added for ^{31}P NMR spectroscopy (Figure 1c). The major products were inorganic phosphate (29%, δ –1.29) *N*-phenylphosphoramidate (47%, δ 2.45), and pyrophosphate (9%, δ 7.16). The products were identified, and the yield of inorganic phosphate was confirmed by comparison with standards as described above. Partition of the reaction mixture between carbon tetrachloride (10 mL) and borate buffer (10 mL) (0.1 M, pH 9.0), followed by rotoevaporation of the organic layer yielded a solution that could be analyzed by ^{1}H NMR. The signals were those for (*Z*)-1-bromo-1-propenylbenzene, 2,2,6,6-tetramethylpiperidine, aniline, and ethyl *N*-phenylacetimidate (II). The presence of acetimidate was confirmed by adding an equivalent amount of synthetic II to the partially purified product and repeating the spectrum. The signals from II, and only those signals, doubled in size. (The aromatic region was obscured by the large excess of aniline present in the mixture.) Addition of ethyl acetate produced clearly different signals. The yield of acetimidate determined by ^{1}H NMR was 24% in each of three experiments. In reconstruction experiments, 76 and 86% of an equivalent amount of acetimidate could be recovered from a mixture of it with ethyl acetate, aniline, and 2,2,6,6-tetramethylpiperidine. The yield of ethyl *N*-phenylacetimidate after correcting for losses during isolation is then 30 ± 5% in agreement with the yield of inorganic phosphate, whether or not pyrophosphate is taken into account. The presence of 5 mol % (relative to aniline) of isopropyl alcohol (2 μL) did not significantly diminish the yield of acetimidate or inorganic phosphate; the only additional product gave a new signal at δ –0.37 (2% yield). An attempt to prepare imidate from ethyl benzoate instead of ethyl acetate was not successful; instead *N*-phenylphosphoramidate (~90% yield) was the major product, and no inorganic phosphate was detected by ^{31}P NMR.

Kinetics. The rates of elimination from methyl hydrogen *erythro*-(1,2-dibromo-1-phenylpropyl)phosphonate (III) (~10^{-4} M) at 25 °C were measured by following the increase in absorbance at 255 nm. First-order rate plots were linear for at least 3–4 halftimes. In aqueous solution at pH 2.0 (hydrochloric acid), $k_{obsd} = 7.1 \times 10^{-4}$ min^{-1} while at pH 9.0 (10^{-2} M borate), $k_{obsd} = 6.8 \times 10^{-4}$ min^{-1}; the rate was considerably slower in 1 M hydrochloric acid (pH 0.05). In acetonitrile mixed with either 0.02 or 0.04 M triethylamine, $k_{obsd} = 8 \times 10^{-3}$ min^{-1}. Fragmentation of dihydrogen *erthyro*- or *threo*-(1,2-dibromo-1-phenylpropyl)phosphonate (~10^{-4} M) in 10^{-2} M borate (pH 9.0) at room temperature was complete in the time of mixing (~3 s); the halftime is <1 s, $k_{obsd} > 40$ min^{-1}. Mixing was carried out with Calbiochem "plumpers".

Results and Discussion

In aqueous solution, monomeric metaphosphate anion is apparently generated from the dianion of (dibromophenylpropyl)-phosphonate in a rapid reaction at room temperature; the halftime is less than 1 s. Elimination of monomeric methyl metaphosphate from III, the analogous monoester monoanion of the bromophosphonate requires days under the same conditions. We had previously[4b] noted that the large increase in rate with increase in negative charge on the starting material is consistent with fragementation (as shown in eq 1) but inconsistent with attack of a nucleophile (e.g., water) on the phosphorus atom of the starting material. The rate of elimination of CH_3OPO_2 from III increases in acetonitrile, but comparable information is not available for the rates of elimination of PO_3^- from I in nonaqueous solvents. Presumably, PO_3^- formation and the multistep processes represented by eq 2–4 are rapid and certainly take place in less than the time that is rquired to obtain a ^{31}P NMR spectrum (several minutes).

The reaction of monomeric metaphosphate anion in acetophenone mixed with 2,2,6,6-tetramethylpiperidine yields enol phosphate as a major product. The reaction almost certainly proceeds by attack of the electrophile on the carbonyl oxygen as shown in eq 2. The ^{1}H NMR spectrum of the isolated product is identical with that for 1-phenylvinyl phosphate. Signals for the vinylic protons show splittings by the phosphorus atom as well as by the geminal proton and are in accord with those for other enol phosphates. Polymeric material is also formed.

A conceivable alternative route to enol phosphate requires reaction of monomeric metaphosphate anion with the minute concentration[11] of enol (≤0.035%) in equilibrium with the ketone. Phenol must have intrinsic reactivity similar to that of an enol and is less sterically hindered. Yet when phenol is present (5 mol %, relative to acetophenone), it has little effect on the yield of enol phosphate. If monomeric metaphosphate anion were reacting with acetophenone enol, it should have reacted preferentially with the much higher concentration of phenol.

The mechanism for the formation of Schiff base is reasonably clear. At room temperature and in the short time required, the direct reaction of aniline with acetophenone does not occur to a detectable extent. The reaction promoted by PO_3^- must therefore proceed as shown in eq 3; attack of PO_3^- on the carbonyl group of the ketone activates it for nucleophilic attack by aniline.[12] As

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required by the stoichiometry of eq 3, the yield of inorganic phosphate equals that of Schiff base. When *o*-trifluoromethylaniline was substituted for aniline, similar reactions were observed. Furthermore, control experiments show that the process does not occur by phosphorylation of carbinolamine or by way of enol phosphate. *sec*-Phenethyl alcohol is a reasonable model for the carbinolamine and should, if anything, be more mucleophilic than the latter. Furthermore, the carbinolamine must be present in solution in only low concentration.[1] Yet, 5 mol % (relative to acetophenone) of *sec*-phenethyl alcohol had no detectable effect on the yield of Schiff base or inorganic phosphate.

Finally, monomeric metaphosphate anion promotes the amidation of ethyl acetate in the presence of aniline to yield ethyl *N*-phenylacetimidate. The reaction presumably occurs as shown in eq 4; the direct reaction between aniline and the ester yields acetanilide. Monomeric metaphosphate anion activates the ester for attack by amine;[12] the tetrahedral intermediate then undergoes elimination. As required by the common intermediate, the yields of inorganic phosphate and imidate are within experimental error. The reaction to produce imidate is unlikely to require phosphorylation of the tetrahedral intermediate that must lie on the pathway to acetanilide. That intermediate is presumably present in solution, but its concentration must be minute[13] relative to that of the isopropyl alcohol added in a control experiment; the alcohol did not appreciably diminish the yield of imidate.

Interestingly, the amidation of ethyl benzoate (which was successeful with monomeric methyl metaphosphate) fails with PO_3^-. Presumably, the ester–PO_3^- adduct formed with ethyl acetate is more efficiently trapped by aniline than is the adduct formed with ethyl benzoate; on both electronic and steric grounds the former adduct is expected to be more highly activated at carbon for reactions with nucleophiles. If the intermediate is not promptly trapped, it probably reacts with aniline to yield the phosphoramidate.

Enzymology. Both formation of enol phosphate and the amidation described above find parallels in enzyme-catalyzed reactions which require adenosine triphosphate (ATP).[3] "High-energy" phosphates including ATP could serve as sources[14] for monomeric metaphosphate anion. Pyruvate kinase catalyzes the reversible formation of phosphoenol pyruvate from pyruvate and ATP, while CTP synthetase promotes ATP-dependent amidation (O^{18} studies[15] demonstrate overall phosphorylation at the oxygen atom of the carbonyl group in the course of this latter reaction). Both of these examples, as well as others, have been discussed previously.[1] Although the chemical reactions reported above provide evidence for a direct reaction of monomeric metaphosphate anion with the carbonyl oxygen group, the enzyme-catalyzed reactions may, but need not necessarily,[16] proceed by attack of ATP on the carbonyl groups of the substrate; furthermore, if they do proceed by phosphorylation of the carbonyl group, the reaction may or may not proceed by way of monomeric metaphosphate. If, however, any of these reactions do proceed by attack of ATP on the carbonyl oxygen atom, with concommitant activation of the carbonyl group, the process would establish that ATP can play a kinetic as well as a thermodynamic role in intermediary metabolism.

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Tetraneopentyltitanium as a Polymerization Catalyst

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Abstract: Tetraneopentyltitanium, $(Neo)_4Ti$, has been investigated as a polymerization catalyst. In the dark, it initiates slow homopolymerizations of styrene and methyl methacrylate, as well as their copolymerization. Reactivity ratios derived from copolymer compositions are in accord with a free radical process. The rates of polymerization of both monomers are greatly enhanced when they are irradiated with $(Neo)_4Ti$. The products in this case have a minor fraction like the polymers obtained in the dark, but in addition a major fraction of much lower molecular weight. Photolysis of $(Neo)_4Ti$ produces trivalent titanium species as shown by EPR studies. However, the photolyzed products behave in the dark similarly to unphotolyzed $(Neo)_4Ti$ in homo- and copolymerizations. $(Neo)_4Ti$ under photolytic conditions also serves as a polymerization catalyst for ethylene and propylene. Mechanisms for these polymerization reactions are discussed.

Introduction

Homoleptic transition-metal σ-hydrocarbyls are often highly unstable; e.g., $TiMe_4$ decomposes readily even at low temperatures.[1] Stability can be enhanced by potential π-acceptor ligands, such as CO, PR_3, or η^5-$C_5H_5^-$. However, transition-metal–carbon σ bonds are not inherently weak; complexes can be made kinetically stable by means of ligands without β hydrogens such as the neopentyl group.[2-5] Even chemical inertness toward oxygen and protic reagents can be achieved with bulky bridgehead ligands such as norbornyl and camphyl,[6] which virtually fill the space

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