Samples of both peaks were collected. The proton NMR spectrum of the first peak gave δ 2.0 (m, 6 H), 3.1 (m, 1 H), 3.6 (s, 3 H), 5.8 (s, 2 H), and the compound was assigned structure **7**. The second peak was shown to be a mixture containing methyl benzoate, starting material (**6**), and at least one other compound which was not identified. Qualitatively similar results were obtained on an Alltech CS-8 6 ft × $^1/_8$ in. stainless-steel column (10% cyanosilicone on Chromosorb W-AW, 100/120 mesh).

The flash vacuum pyrolysis of **6** gave a pyrolysate whose proton NMR spectrum could be accommodated solely by the proton signals of methyl benzoate and starting material (**6**).

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Registry No. 1, 22664-28-4; 2, 29569-87-7; 3, epimer 1, 73378-49-1; 3, epimer 2, 73378-50-4; 4a, 30810-15-2; 4b, 40002-24-2; 4c, 54162-19-5; 5, 50983-21-6; 6, 30889-20-4; 7, 25662-37-7.

Methyl Acetyl Phosphate. A Small Anionic Acetylating Agent

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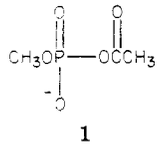
Alkyl monoesters of acetyl phosphate ($ROPO_2(COCH_3)O^-$) are of significant interest for mechanistic studies on the reactivity of carboxylic–phosphoric acid anhydride derivatives. For example, aminoacyl adenylates, the activated derivatives of amino acids which are transient intermediates in the biosynthesis of aminoacyl tRNAs, are elaborate members of this functional classification.[1] On the basis of the known reactivity patterns of such compounds,[2,3] another important potential use would be the acetylation of a nucleophile that is adjacent to a cation in an enzyme. However, to our knowledge, no acceptable synthesis of a simple monoalkyl compound has been reported. Studies of this class of compound, therefore, have invariably involved the easily accessible derivative phenyl acetyl phosphate, prepared from phenyl phosphate and acetic anhydride.[2-6] Extension of this method to the use of ethyl phosphate or methyl phosphate in place of phenyl phosphate gives impure, uncharacterized products.[2,7] Therefore, any preparation of an alkyl monoester of acetyl phosphate requires a different synthetic strategy.

The motivation for our synthesis of methyl acetyl phosphate (**1**) resulted from our work with D-3-hydroxy-



1

butyrate dehydrogenase.[8] This enzyme catalyzes the reduction of acetoacetate and **1** is a functional analogue of this substrate. We believed that **1** would be a good candidate to be an active-site directed acetylating agent of a potentially nucleophilic functional group we proposed to exist on the enzyme[8] adjacent to a cationic binding site. The phenyl ester has an inappropriate functional group for these purposes.

We have developed a simple procedure for the synthesis of **1** based on the conversion of dimethyl acetyl phosphate which itself is readily prepared in an analytically pure condition.[9]

Experimental Section

Dimethyl acetyl phosphate was prepared from a solution of 30 g of acetyl chloride and 70 g of trimethyl phosphate that was refluxed for 12 h.[9,10] Unreacted acetyl chloride was removed under aspirator vacuum. The residue was distilled at 0.01 torr. Fractions boiling between 40 and 55 °C were collected and redistilled on a 10-cm column three times, with the product distilling at 50 °C (lit.[9] bp 51–52 °C (0.05 torr)) to yield 7.5 g of dimethyl acetyl phosphate.

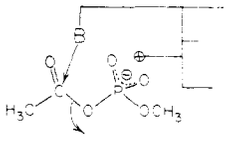
Methyl Acetyl Phosphate (1) Sodium Salt. Dimethyl acetyl phosphate (58 g) was dissolved in 50 mL of acetone which had been dried over magnesium sulfate. To this was added 5.7 g of sodium iodide in 50 mL of dry acetone. The solution was stirred at room temperature in a condenser-equipped flask with a magnetic stirrer. "Drierite" was used to exclude moisture. If heat is used, the reaction causes the product to decompose.[7] After 5 h a large amount of white precipitate had formed. This was collected by filtration and washed with dry acetone. Additional product precipitated from the solution after several hours. The sodium salt of methyl acetyl phosphate was recrystallized from methanol and ether in 70% yield: ^{1}H NMR (D_2O, relative to internal DSS) δ 2.18 (d, $^4J_{PH}$ = 1.4 Hz, 3 H, $CH_3C(O)$), 3.67 (d, $^3J_{PH}$ = 11.6 Hz, 3 H, CH_3O). Anal. (Galbraith Laboratories) $C_3H_6O_5PNa$ (C, H, P).

Kinetics. The rate of hydrolysis of **1** was followed by ^{1}H NMR with 0.05 M substrate and 0.1 M potassium phosphate, pH 7.0 buffer. Cleavage of the anhydride bond produces acetate and methyl phosphate. The concentration of **1** is proportional to the integral of its acetyl proton signal at δ 2.18, whereas the concentration of acetate is proportional to the integral of its proton signal at δ 1.89 (s). The reaction was plotted by first-order methods, yielding a rate constant at pH 7.0, 25 °C, of 1.2×10^{-6} s^{-1}, corresponding to a half-life of 160 h.

Results and Discussion

Methyl acetyl phosphate is relatively stable in solution. The rate of its hydrolysis can be compared to that reported for the phenyl ester by DiSabato and Jencks.[3] Extrapolaring their data at 73, 60, 50, and 37 °C to 25 °C yields a rate constant of 8.2×10^{-7} s^{-1}, which is only slightly less than the rate constant we observe for the hydrolysis of **1**. This suggests that the mechanism involving C–O cleavage of the anhydride found for phenyl acetyl phosphate[2,3] applies to the methyl ester as well.

The stability of methyl acetyl phosphate assures that if it is used as an active-site directed reagent with an enzyme, it will be stable in the absence of nonenzymic nucleophiles. In other words, competing spontaneous reactions are not a problem and acetylation of an enzymic nucleophile may occur specifically if the anionic phosphate group first associates with a cationic binding site. Our



preliminary studies reveal that lactate dehydrogenase, malate dehydrogenase, and alcohol dehydrogenase are all slowly ($t_{1/2}$ ~30 min, 25 mM reagent) inactivated by

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methyl acetyl phosphate. D-3-Hydroxybutyrate dehydrogenase is subject to very rapid ($t_{1/2}$ ~2 min) specific inactivation. We shall report detailed results on this matter elsewhere.

Registry No. 1 sodium salt, 73636-29-0; dimethyl acetyl phosphate, 27744-98-5; acetyl chloride, 75-36-5; trimethyl phosphate, 512-56-1.

Synthesis and Reactivity of Polymer-Supported Reducing Agents with Chemically Modified Surfaces

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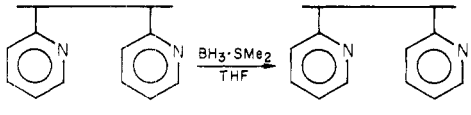
Insoluble polymeric reagents have been developed which oxidize,[1] acylate,[2] epoxidize,[3] halogenate,[4] and hydrogenate[5] to name a few. Their usefulness arises from the simple reaction workup[6] (filtration of the polymer and removal of solvent) and from the ability to recycle spent polymer.[7] Several hydride-delivering polymers are known. One of them, bearing organotin dihydride groups,[8] requires a five-step synthesis and reacts but slowly (24–25 h) with carbonyl compounds. The others are anion-exchange resins having borohydride[9] or cyanoborohydride[10] counterions and a poly(4-vinylpyridine–borane)[11] which gives only low yields of carbonyl reduction in refluxing benzene. We have synthesized solid BH_3 derivatives of poly(2-vinylpyridine) and poly(4-vinylpyridine) which reduce carbonyl groups in high yield at room temperature. In addition, we have studied how partial alkylation of the pyridine nitrogens with ethyl bromide or dodecyl bromide benefits the reducing properties of the polymeric reagents.

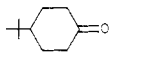
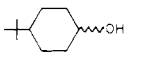
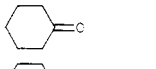
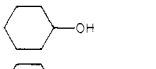
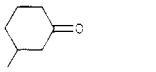
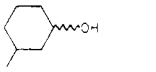
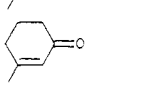
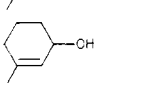
A polymer-supported reducing agent was prepared by treating poly(2-vinylpyridine) with borane–methyl sulfide complex in THF (eq 1). The product precipitates from



(1)

solution. Thus, "reducing beads" can be obtained in a single step starting with commercially available materials. When this polymer was mixed with 6 N HCl (to eventually give a homogeneous solution), the resulting hydrogen evolution corresponded to 77% complexation of the pyridine rings. Not all of this borane is available for reducing carbonyls, however. A heterogeneous reduction of excess octanal in benzene by solid polymer showed that 32% of the boranes fail to react with the aldehyde; presumably, these boranes are buried beneath the polymer surface.

Table I. Heterogeneous Reductions of Aldehydes and Ketones in Benzene at Room Temperature by Solid Poly(2-vinylpyridine)-BH_3 Complex

reactant	reaction time, h	product	yield,[a] %
	3		100[b]
	3		94
	3		93[c]
	3		0[d]
n-$C_7H_{15}CHO$	1	n-$C_7H_{15}CH_2OH$	98 (87[e])
C_6H_5CHO	3	$C_6H_5CH_2OH$	65[e]
$C_6H_5CH_2CHO$	24	$C_6H_5CH_2CH_2OH$	100
$C_6H_5CH{=}CHCHO$	1	$C_6H_5CH{=}CHCH_2OH$	65
C_6H_5COOH[f]	20	$C_6H_5CH_2OH$	11
$C_6H_5COOCH_3$	20	$C_6H_5CH_2OH$	13
C_6H_5COCl	44	$C_6H_5CH_2OH$	44
$C_6H_5COCH_3$	3	$C_6H_5CH(OH)CH_3$	82

[a] Except for two runs, yields were measured by GLC using either 1-phenylhexane, 1-phenyloctane, diphenylmethane, or naphthalene as an internal standard. [b] 41% cis:59% trans. [c] 46% cis:54% trans. [d] Unreacted ketone was observed by GLC. [e] Isolated yield after distillation. [f] Converted into the methyl ester with CH_2N_2 before GLC analysis.

Monomeric pyridine–borane in refluxing benzene reduces aldehydes and ketones in moderate yield.[12] In contrast, our polymeric analogue reduces these carbonyl compounds in high yield at room temperature but only in the presence of $BF_3{\cdot}OEt_2$ (Table I). The role of the additive is not clear; it may facilitate reduction by complexing with the carbonyl oxygen or it may displace borane from the polymer surface. The possibility that the carbonyl reductions are in fact not true surface reactions seems unlikely because polymer washed with hot benzene retains its full reducing capabilities.[13] Furthermore, swelling the polymer in refluxing benzene for 1 h prior to reduction at room temperature greatly facilitates the reaction. Thus, untreated polymer plus octanal gives 39% octanol after 1 h, whereas the yield increases to 98% if the polymer is first exposed to hot benzene. Stirring the polymeric reagent for 12 h in cold benzene likewise improves the reaction time.

In a typical run, 0.25 g of polymer was heated with 3 mL of refluxing benzene for 1 h. When the benzene had cooled, the following were added to the reaction flask: 1 mmol of carbonyl compound, 1 mmol of $BF_3{\cdot}OEt_2$, an internal standard for GLC analyses and 2 mL of benzene. The reaction was allowed to proceed at room temperature after which 0.5 mL of saturated $NaHCO_3$ was added and the solids were removed by filtration. Either the filtrate was assayed by gas chromatography or the product was isolated from the solvent, purified, and weighed. As can be seen from Table I, the reductions proceed in high yield for aliphatic and aromatic aldehydes and ketones but not for acids, esters, acid chlorides, and α,β-unsaturated ke-

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