Acyl Phosphates from Acyl Phosphonates. A Novel Baeyer–Villiger Rearrangement

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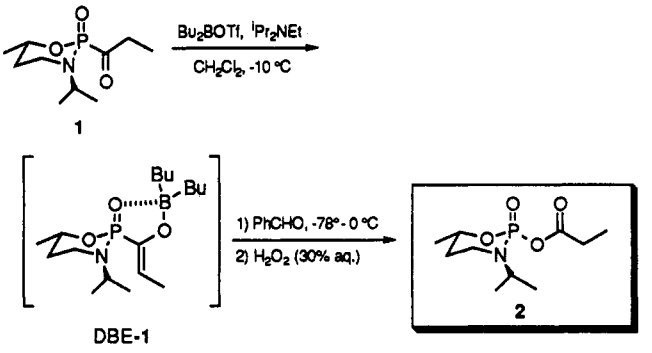
Summary: The mechanism of a novel Baeyer–Villiger rearrangement, characterized by a stereospecific migration of a phosphoryl moiety to a peroxy oxygen, provides an extraordinarily efficient synthetic route to acyl phosphates. The mechanistic subtleties associated with this rearrangement have been explored using ^{17}O-enriched hydrogen peroxide ($H_2{}^*O_2$) as the mechanistic probe with ^{17}O NMR spectroscopy as the analytical tool.

During the course of our research involving the aldol reactions of the metal enolates of α-acyl phosphonates and α-acyl phosphorinanes[1] and benzaldehyde, we discovered that an oxidative workup (*i.e*, aqueous H_2O_2) of the reaction mixture containing the dibutylboron enolate (DBE-1) of α-acyl phosphorinane 1 and benzaldehyde produced acyl phosphate 2 in 75% yield (Scheme I).[2]

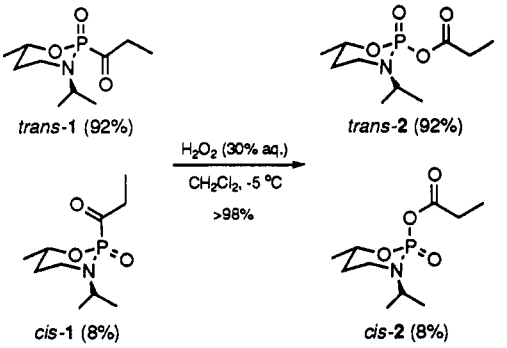
Since direct oxygen transfer from H_2O_2 into DBE-1 to afford 2 seemed implausible, we examined the reaction between H_2O_2 and a 92:8 *trans/cis* diastereomeric mixture of α-acyl phosphorinane 1 (epimeric at the phosphorus atom). At −5 °C (8 h) in an aqueous/dichloromethane medium, a 92:8 *trans/cis* diastereomeric mixture of acyl phosphate 2 was identified from their respective NMR spectral data (Scheme II).[3,4] This result implied that the oxygen insertion was stereospecific and occurred with retention of configuration at the phosphorus atom. The net conversion of 1 → 2 mirrors the Baeyer–Villiger rearrangement[5a,b] where studies detailing the migratory aptitudes of various carbons have been explored inconsiderable detail;[6] however, there are few chemical literature citations that describe the migratory propensity of heteroatoms. To our knowledge, this is the first example of a Baeyer–Villiger rearrangement involving a migrating phosphoryl moiety which promotes the elimination of water from an intermediate α-hydroxyl hydroperoxide. The reaction described here is conceptually similar to the reactions of α-diketones with H_2O_2 which afford anhydrides.[7] The susceptibility of the phosphoryl moiety to facile nucleophilic attack by H_2O_2 appears to be highly favored *only* when the phosphoryl group is integral to a strained ring system.[8] Consequently, it seems highly likely that H_2O_2 attacks the α-carbonyl carbon rather than the phosphoryl phosphorus atom in 1.

In a separate experiment under identical reaction conditions, diethyl propionylphosphonate (3) was oxidized

Scheme I. α-Acyl Oxazaphosphate 2 from α-Acyl Oxazaphosphorinane 1



Scheme II. Stereospecific Baeyer–Villiger Rearrangement



(1) Gordon, N. J.; Evans, S. A., Jr., submitted for publication.

(2) (*S,S*)-2-Oxo-2-(propionyloxy)-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinane (*trans*-2): ^{31}P NMR ($CDCl_3$) δ −6.38 ppm; ^{13}C NMR ($CDCl_3$) δ 8.4 (s, $C(O)CH_2CH_3$), 19.5 (d, $^3J_{PNCC}$ = 2.3 Hz, $NCHCH_3$), 20.5 (d, $^3J_{PNCC}$ = 4.2 Hz, $NCHCH_3$), 21.3 (d, $^3J_{POCC}$ = 5.8 Hz, $OCHCH_3$), 28.6 (d, $^3J_{POCC}$ = 5.7 Hz, $OCHCH_3$), 31.4 (d, $^3J_{POCC}$ = 7.7 Hz, $C(O)CH_2$), 37.0 (d, $^2J_{PNC}$ = 3.7 Hz, $NCH(CH_3)_2$), 46.6 (d, $^2J_{PNC}$ = 4.3 Hz, $PNCH_2$), 76.6 (d, $^2J_{POC}$ = 7.9 Hz, POCH), and 169.4 ppm (d, $^2J_{POC}$ = 10.0 Hz, *C*(O)); ^1H NMR ($CDCl_3$) δ 1.11 (d, $^3J_{HCCH}$ = 6.5 Hz, $NCHCH_3$), 1.13 (t, $^3J_{HCCH}$ = 7.5 Hz, $C(O)CH_2CH_3$), 1.19 (d, $^3J_{HCCH}$ = 6.5 Hz, $NCHCH_3$), 1.37 (dd, $^3J_{HCCH}$ = 6.3 Hz, $^4J_{POCCH}$ = 1.9 Hz, $POCHCH_3$), 1.96 (m, $POCHCH_2$), 2.43 (q, $^3J_{HCCH}$ = 7.5 Hz, $C(O)CH_2$), 3.12 (m, 2H, $NCH(CH_3)_2$) and $PNCH_2$), 4.10 (m, $PNCH_2$) and 4.59 ppm (m, POCH); IR ($CDCl_3$) 1040, 1173, 1260, 1280, 1767, and 2980 cm^{-1}; HRMS calcd for $C_{10}H_{21}NO_4P$ (M + H) 250.1215., found 250.1208.

(3) **Experimental Procedure.** To a stirred solution of 2-oxo-2-propionyl-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinane (100 mg, 0.43 mmol) in dichloromethane (3.00 mL) at 0 °C was added hydrogen peroxide (30% aqueous solution, 5.00 mL) at 0 °C. The biphasic mixture was then stirred for 8 h. The organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to afford 2-oxo-2-(propionyloxy)-3-isopropyl-6-methyl-1,3,2-oxazaphosphorinane (2) as a clear oil in >98% yield. All spectroscopic data were consistent with the assigned structure for 2.[4]

(4) (a) Phosphorinanes 1 are obtained *via* a stereospecific Arbusov reaction involving the corresponding 92:8 *trans/cis* mixture of oxazaphosphites and propionyl chloride. In all cases, the *trans* diastereomer exhibits the higher field ^{31}P NMR chemical shift, a trend that is consistent with other literature data for analogous compounds. In addition, the single-crystal X-ray parameters have been obtained for a derivative of *trans*-phosphorinane 1 which corroborate the structural assignments of 1. (b) Bentrude, W. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 7136.

(5) (a) von Baeyer, A.; Villiger, V. *Ber.* **1899**, *32*, 3625. (b) Koch, S. S. C.; Chamberlain, A. R. *Synth. Commun.* **1989**, *19*, 829.

(6) For reviews see: Lee, J. B.; Uff, B. C. *Q. Rev. Chem. Soc.* **1967**, *21*, 429. Krow, G. R. *Tetrahedron* **1981**, *37*, 2697.

(7) Sawaki, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 6292. It is noteworthy that the Baeyer–Villiger rearrangement involving benzil (2.5 mmol) with hydrogen peroxide (10 mmol) under neutral conditions (95% methanol) occurs slowly (5 days) to afford only 28% methyl benzoate, presumably through methanolic capture of the intermediate anhydride.

(8) Quin, L. D.; Kisalus, J. C.; Mesch, K. A. *J. Org. Chem.* **1983**, *48*, 4466. Nucleophilic attack of water on an α-acyl phosphonate is directed at the carbonyl carbon; *e.g.*, the hydrolysis reaction with ^{17}O labeled water is nicely illustrated in Scheme VI. Finally, diethyl ethylphosphonate is inert to hydrogen peroxide under our reaction conditions. This means that simple phosphonate diesters are resistant to hydrolysis or reaction with hydrogen peroxide under similar reaction conditions.

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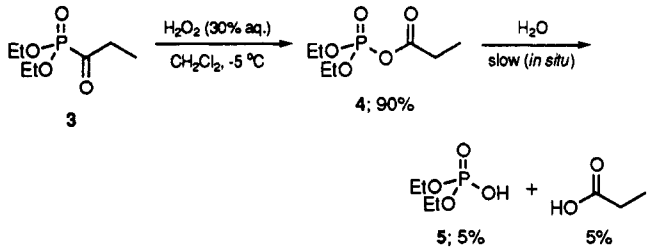
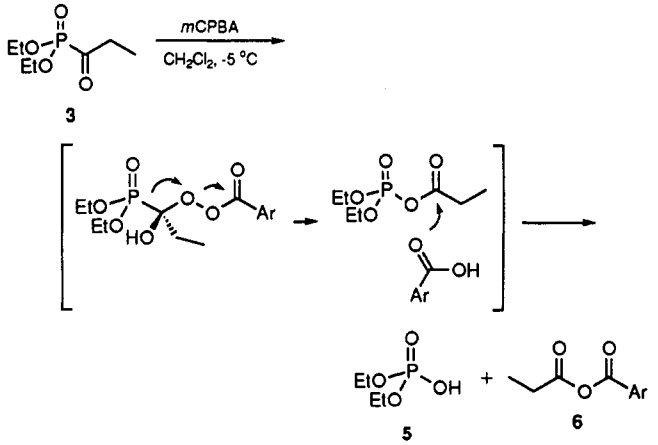
Scheme III. Baeyer–Villiger Rearrangement of Diethyl Propionylphosphonate (3)



Scheme IV. *m*-Chloroperbenzoic Acid Oxidation of Phosphonate 3



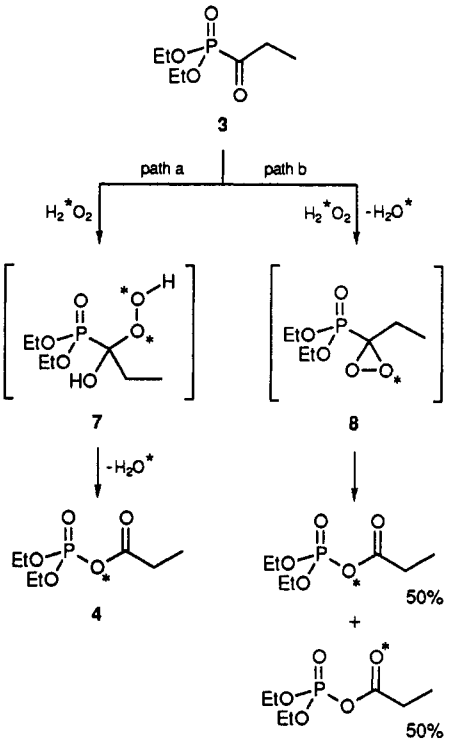
with H_2O_2 to diethyl propionyl phosphate (4; 90%). Presumably, the two other products, diethyl phosphoric acid diester (5; 5%) and propionic acid (5%), resulted from the relatively slow *in situ* hydrolysis of phosphate 4 (Scheme III).

The advantage of a two-phase medium (*e.g*, dichloromethane/water) is that simple hydrolysis of either 1 or 2 is significantly retarded despite the high susceptibility of their respective carbonyls toward attack by water. Finally, oxidation of α-acyl phosphonate 3 to phosphate 4 with *m*-chloroperbenzoic acid (*m*-CPBA) led exclusively to anhydride 6 (>95% yield), apparently formed by (i) rearrangement of a transient "Criegee" intermediate, followed by (ii) propionyl transfer from transient phosphate 4 to *m*-chlorobenzoic acid.

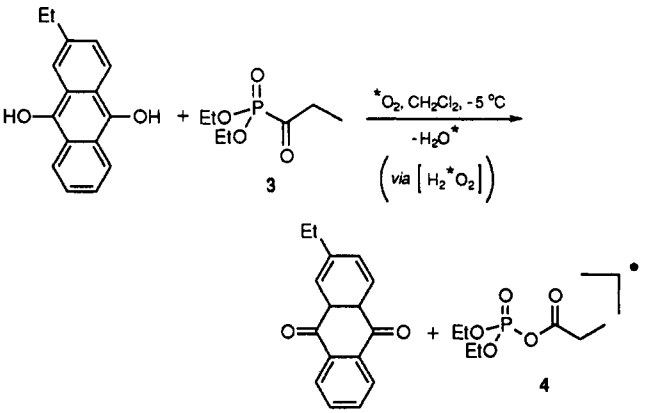
Mechanistic Rationale. We envisioned that the use of ^{17}O-enriched hydrogen peroxide ($H_2{}^*O_2$) employing ^{17}O NMR spectroscopy for product analyses would provide the best opportunities for discerning the importance of two independent pathways for the Baeyer–Villiger rearrangement involving phosphonate 3. The two most reasonable intermediates to emerge are (i) an acyclic "Criegee" intermediate 7, which would be responsible for ^{17}O incorporation into the *ethereal* oxygen of the mixed anhydride linkage (path a), and (ii) a dioxirane intermediate 8 whose decomposition should distribute the ^{17}O label equally between the ethereal and carbonyl oxygens in 4 (path b; Scheme V).[5a,9]

The ^{17}O-enriched hydrogen peroxide was prepared using the IG Farben industrial process which involved the direct oxidation of 2-ethyldihydroanthraquinol with 10 atom %

Scheme V. Mechanistic Proposal for ^{17}O Incorporation into 3



Scheme VI. Oxidation of Phosphonate 3 with $H_2{}^*O_2$



$^{17}O_2$.[10] The Baeyer–Villiger oxidative-rearrangement of propionylphosphonate 3 with $H_2{}^*O_2$ was performed *in situ* to maximize the efficiency of $H_2{}^*O_2$ consumption (Scheme VI). By this method, an efficiency of 75% ^{17}O incorporation was realized, based on the total quantity of available $^{17}O_2$. ^{17}O NMR spectra were recorded in heptane solvent at 90 °C immediately upon completion of the reaction (Figure 1). The natural abundance of ^{17}O nuclei in oxygenated organic molecules does not normally exceed 0.037%; consequently, only the ^{17}O-enriched oxygens are detectable in this NMR experiment. Finally, the ^{17}O NMR line width is directly related to the ^{17}O quadrupolar coupling constant as well as the rotational correlation time, τ_c, for molecular reorientation; therefore, a reduction in τ_c occurs from either a temperature higher than ambient (*e.g.*, 90 °C) and/or a decrease in solution viscosity (*e.g.*, heptane) according to the Stokes–Einstein Debye equation.[11]

(9) (a) Criegee, R. *Ann.* **1948**, *560*, 127. (b) Doering, W. v. E.; Dorfman, E. *J. Am. Chem. Soc.* **1953**, *75*, 5595. (c) Doering, W. v. E.; Speers, L. *J. Am. Chem. Soc.* **1950**, *72*, 5515.

(10) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley and Sons: New York–London, 1988; p 456.

(11) St. Amour, T.; Fiat, D. *Bull. Magn. Reson.* **1980**, *1*, 118.

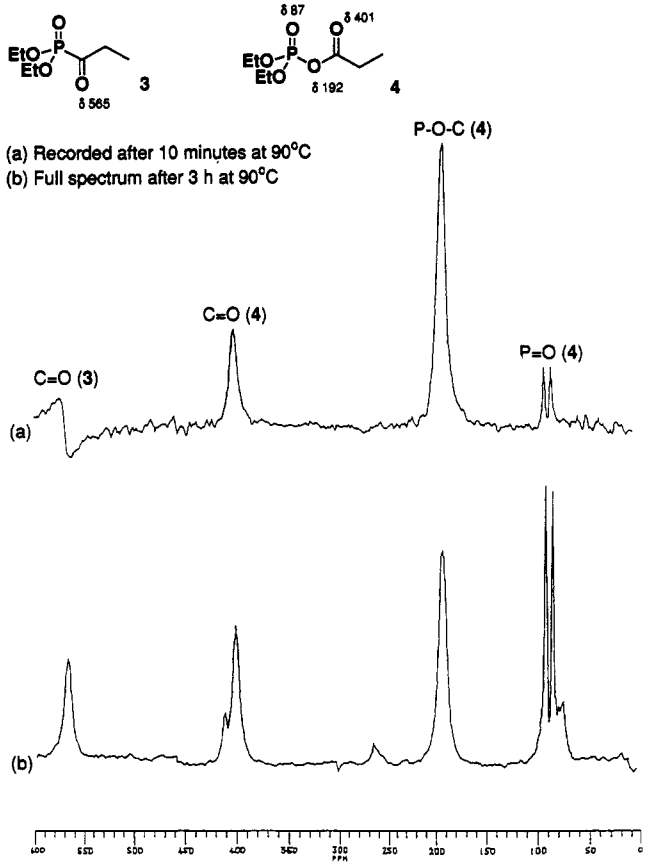
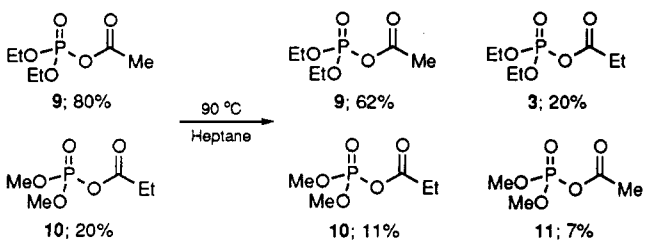


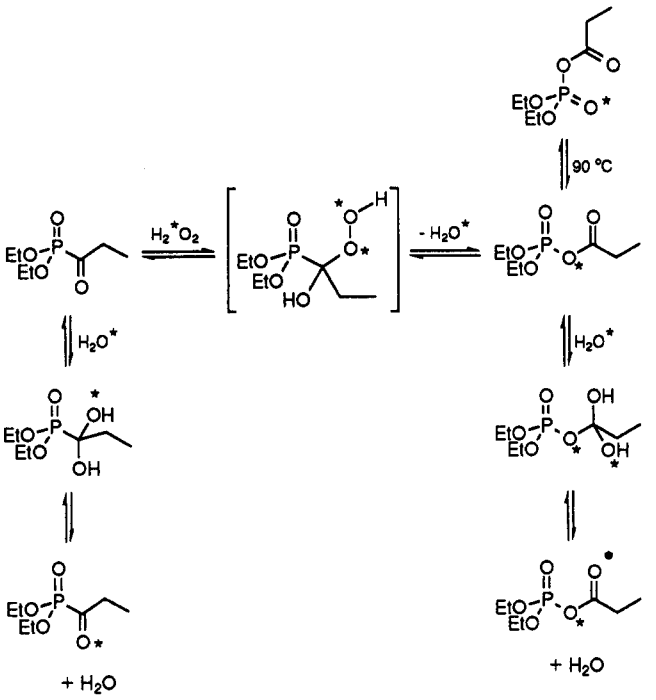
Figure 1. ^{17}O NMR spectra of ^{17}O incorporation in diethyl propionyl phosphate.

Initially, the major ^{17}O NMR resonance appeared at δ 192 ppm, which is consistent with facile formation of phosphate 4 with ^{17}O incorporation into the P–O–C linkage (Figure 1a). ^{17}O-Incorporation was also evident in both the phosphoryl and carbonyl oxygens (δ 87 and 401 ppm, respectively). After *ca.* 90 min at 90 °C, the intensity of the resonance at δ 192 ppm diminished with a corresponding increase in the intensity of the phosphoryl oxygen (δ 87 ppm) until these two absorptions were of equal intensity (Figure 1b). The relative intensities of these two resonances remained unchanged after an additional 12 h. Finally, ^{17}O incorporation into the carbonyl groups of propionyl phosphate 4 (δ 401 ppm) and propionyl phosphonate 3 (δ 565 ppm) also occurred. A mechanistic proposal is described in Scheme VII.

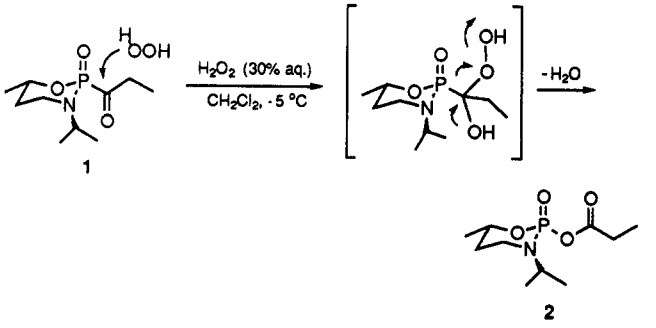
(12) **Crossover Experiment.** Equimolar quantities of diethyl acetyl phosphate (^{31}P NMR δ −8.5 ppm) and dimethyl propionyl phosphate (δ −5.7 ppm) were heated to 90 °C in heptane solvent for 75 min. A ^{31}P NMR spectral investigation of the resultant mixture revealed the presence of diethyl propionyl phosphate (δ −8.3 ppm) and dimethyl acetyl phosphate (δ −5.9 ppm) as well as the original phosphates. The identities of these phosphates were confirmed by comparison of their spectroscopic data with those of the independently synthesized phosphates.



Scheme VII. Pathways for ^{17}O Incorporation



Scheme VIII. Mechanistic Pathway for Baeyer–Villiger Rearrangement of Phosphorinane 1



The apparent "scrambling" of the ^{17}O-label between the ethereal linkage (δ 192 ppm) and the phosphoryl oxygen (δ 87 ppm) in 4 at 90 °C is best rationalized by *propionyl group transfer* between both oxygens to equalize the ^{17}O distribution between these two positions. The results of a thermally-induced (90 °C; heptane solvent; 75 min) crossover experiment[12] between diethyl acetyl phosphate (9) and dimethyl propionyl phosphate (10) to afford diethyl propionylphosphonate (3) and dimethyl acetyl phosphate (11) strongly suggest that propionyl group transfer involving 4 is an *intermolecular* process. ^{17}O-Enrichment occurs in the carbonyl moiety of propionyl phosphate 4 through the reversible addition of $^{17}OH_2$ to the carbonyl group (Scheme VII). Similarly, ^{17}O incorporation into the carbonyl moiety of propionyl phosphonate 3 also occurs via this reversible pathway. Taken together, all of these results support the presence of acyclic intermediate 7, rather than dioxirane intermediate 8.

The appearances of additional ^{17}O NMR resonances in the NMR spectrum over an extended period of time (Figure 1a,b) are attributable to propionyl anhydride (δ 265, 412 ppm) and diethyl phosphate anhydride (δ 75 ppm). Their presence is best rationalized by an *intermolecular* exchange reaction involving two molecules of diethyl propionyl phosphate (4).

In summary, the Baeyer–Villiger rearrangement of phosphorinanes 1 (and propionylphosphonate 3) with hydrogen peroxide is best described in Scheme VIII. In addition, a highly efficient procedure for ^{17}O incorporation into phosphates during hydrogen peroxide oxidations has been described. Finally, the results presented here provide compelling evidence for acyl group exchange in phosphate diesters.

Acknowledgment. We are grateful to the National Science Foundation for support of this research.

Supplementary Material Available: Spectroscopic data for 2 (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.