General Procedure. TPP (94.4 mg, 0.36 mmol) and neopentyl alcohol (63.5 mg, 0.72 mmol) were dissolved in THF (3 mL) under nitrogen in a 10-mm NMR tube. The solution was cooled to 0 °C, and DIAD (65 μL, 0.33 mmol) was added to the swirled and cooled mixture. The solution was then warmed to room temperature for 2–3 min and then cooled again to 0 °C before adding the benzoic acid (44 mg, 0.36 mmol). The tube was stoppered, sealed with Parafilm, and shaken vigorously for several minutes before the ^{31}P NMR spectrum was recorded. Changing the order of addition of reagents (adding either the DIAD last or the alcohol last) gave identical results. Similarly, the order of addition of reagents made no difference when *p*-nitrobenzoic acid was used instead of benzoic acid.

As diacetone glucose **2** reacted more slowly with the betaine **4**, reactions involving **2** were allowed to stand at room temperature for 15 min before addition of benzoic acid and recording the ^{31}P NMR spectra. The procedure for the mixed alcohol experiments was as follows:

TPP (94.4 mg, 0.36 mmol), neopentyl alcohol (63.5 mg, 0.72 mmol), and diacetone glucose (187 mg, 0.72 mmol) were dissolved in THF (3 mL) under nitrogen in a 10-mm NMR tube. DIAD (65 μL, 0.33 mmol) was added to the cooled (0 °C) solution before warming to room temperature for 15 min. It was then cooled again to 0 °C before adding the benzoic acid (44 mg, 0.36 mmol) and recording the ^{31}P NMR spectrum. If the two phosphoranes **5** and **9** were prepared separately and then mixed before the addition of benzoic acid, the results obtained were identical. Similarly if either phosphorane **5** or **9** was first treated with the benzoic acid before addition of the second alcohol (**1** or **2**, respectively), the same result was again obtained.

In general, the chemical shifts of the phosphoranes were insensitive to concentration changes and were unaffected by various concentrations of diisopropyl hydrazine-1,2-dicarboxylate and of triphenylphosphine oxide (the chemical shift of the latter varied between +24 and +26 ppm; it was therefore useless as an internal standard for comparison of chemical shifts), but were dependent on the solvent to some extent (see Table I). On the other hand, the chemical shifts of the oxyphosphonium carboxylates were sensitive to the solvent and the presence of various concentrations of diisopropyl hydrazine-1,2-dicarboxylate. This sensitivity is discussed in the accompanying paper. Excellent reproducibility (±0.05 ppm) of chemical shift values was obtained by employing a slight excess (5–10%) of TPP (over DIAD) and referencing the chemical shifts to the TPP (set at δP −5.20 ppm) signal as described previously.[6] The results are summarized in Table I.

The reaction of **5** with benzoic acid was also examined by ^{13}C and ^{1}H NMR spectroscopy. Although the ^{13}C NMR spectrum of **5** has been assigned,[11] the reaction mixture consisting of **5**, **6**, triphenylphosphine oxide, and diisopropyl hydrazine-1,2-dicarboxylate in THF, $CDCl_3$, or C_6D_6 gave complex ^{13}C NMR spectra that did not prove useful for the study of this system. ^{1}H NMR spectroscopy was more useful, however, and gave results consistent with the ^{31}P NMR data. Thus, phosphorane **5** in $CDCl_3$ showed neopentyl protons at 0.73 ppm (CH_3) and 2.3 ppm (d, J_{POCH} = 4.2 Hz, CH_2). Addition of 1 equiv of benzoic acid shifted the methylene doublet downfield to 4.0 ppm (d, J_{POCH} = 4.3 Hz) consistent with formation of **6** [lit.[21] for **6** as chloride salt 4.17 ppm, J_{POCH} = 4.3 Hz ($CDCl_3$–CCl_4)]. The methyl protons shifted downfield to 0.95 ppm [lit.[22] for **6** as chloride salt 1.02 ppm (MeCN)]. In C_6D_6, the phosphorane **5** showed neopentyl protons at 0.72 ppm (CH_3) and 2.41 ppm (d, J_{POCH} = 4.3 Hz, CH_2). Addition of 1 equiv of benzoic acid gave rise to four broad peaks at 4.0 (CH_2 of **6**), 3.4 (CH_2 of liberated neopentyl alcohol), 2.4 (CH_2 of **5**), and 0.81 ppm (CH_3 of **5**, **6**, and neopentyl alcohol). Use of 0.5 equiv each of neopentyl alcohol and benzoic acid with the betaine **4** in C_6D_6 gave a broad peak at 3.5 ppm (CH_2 of **6**), a sharp doublet at 2.4 (CH_2 of **5**, J_{POCH} = 4.2 Hz), and a sharp peak at 0.72 (CH_3). Addition of a further 0.5 equiv of benzoic acid caused the peak at 2.4 to disappear and the broad peak at 3.5 to move downfield to 4.1 ppm. Use of THF as solvent and using 2-equiv of neopentyl alcohol and 1 equiv of benzoic acid with **4** gave rise to broad peaks at 4.1 (CH_2 of **6**), 3.1 (CH_2 of **5**), and 0.7 ppm (CH_3 of **5**, **6**, and neopentyl alcohol). The results in THF were not as clear due to the large solvent peaks at 1.7 and 3.6 ppm; however, they do show that the liberated neopentyl alcohol is also exchanging rapidly (on the NMR time scale) with the phosphorane **5** and oxyphosphonium species **6**, as would be expected from the ^{31}P NMR data.

Registry No. **1**, 75-84-3; **2**, 582-52-5; **4**, 86825-70-9; **5**, 105785-75-9; **6**, 120609-90-7; **7**, 120609-91-8; **8**, 120418-15-7; **8** (benzoate), 120418-13-5; **9**, 86825-68-5; **10**, 120609-92-9; **11**, 120609-93-0; **12**, 62785-50-6; **13**, 120609-95-2; **14**, 120609-94-1; DIAD, 2446-83-5; TPP, 603-35-0; $PhCO_2H$, 65-85-0; *p*-$NO_2C_6H_4CO_2H$, 62-23-7.

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(22) Slagle, J. D.; Huang, T. T.-S.; Franzus, B. *J. Org. Chem.* **1981**, *46*, 3526–3530.

Mechanism of the Mitsunobu Esterification Reaction. 2. The Involvement of (Acyloxy)alkoxyphosphoranes

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A ^{31}P NMR examination of the Mitsunobu reaction using triphenylphosphine or diphenyl-2-pyridylphosphine with diisopropyl azodicarboxylate, an alcohol, ROH, and a carboxylic acid, R′COOH, reveals the presence of a dialkoxyphosphorane, $Ar_3P(OR)_2$, in equilibrium with an alkoxyphosphonium carboxylate, Ar_3POR^+ $OCOR'^-$. The ^{31}P NMR chemical shift of the latter species is exquisitely sensitive to the presence of proton sources and the nature of the solvent, varying over a range of more than 100 ppm. The data are interpreted in terms of a rapid equilibrium between an ion pair, Ar_3POR^+ $OCOR'^-$, and the corresponding (acyloxy)alkoxyphosphorane, $Ar_3P(OR)OCOR'$. The role of dialkoxyphosphoranes and of (acyloxy)phosphoranes in the mechanism of the Mitsunobu reaction is discussed.

Introduction

In the previous paper, we showed that both oxyphosphonium salts **6** and phosphoranes **5** (see Scheme 1, preceding paper) are involved as intermediates in the Mitsunobu esterification reaction and that these intermediates are in equilibrium with each other. We also noted that the chemical shift of **6** was extremely sensitive to the presence of excess betaine **4** and to the presence of proton sources. This paper examines that sensitivity and presents data in support of a further (rapid) equilibrium between the oxyphosphonium salt **6** and the corresponding (acyloxy)alkoxyphosphorane **7**. (Acyloxy)alkoxytri-

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Table I. ^{31}P NMR Data for Reaction of Alcohols and Carboxylic Acids with Triphenylphosphine and Diisopropyl Azodicarboxylate

alcohol[a] (equiv)	acid (equiv)	other added reagents (equiv)	solvent	^{31}P NMR shifts[b] (peak width,[c] rel ratio[d])	
1 (2.0)	PhCOOH (1.0)		THF	+59.5 (b, 1)	−57.5 (b, 1)
(2.0)	PhCOOH (0.5)		THF	+55.1 (b, 1)	−57.5 (b, 3)
(2.0)	PhCOOH (1.0)	H_2DIAD (1.0)	THF	+60.2 (b, 3)	−57.5 (b, 2)
(2.0)	PhCOOH (1.0)	H_2DIAD (2.0)	THF	+61.1 (b, 3)	−57.5 (b, 1)
(1.0)	PhCOOH (1.0)		THF	+55.1 (b, 1)	−57.5 (s, 1)
(1.0)	PhCOOH (0.5)		THF	−11.3 (vb, 1)[e]	−57.5 (s, 1)
(0.5)	PhCOOH (0.5)		THF	−27.6 (b, 1)	−57.5 (s, 1)
(0.5)	PhCOOH (0.5)	H_2DIAD (0.5)	THF	−3.0 (b, 1)	−57.5 (s, 1)
(0.5)	PhCOOH (0.5)	H_2DIAD (1.0)	THF	+21.0 (b, 1)	−57.5 (s, 1)
(2.0)	PhCOOH (0.5)	$^{+-}Bu_4NOBz$ (1.0)	THF/C_6H_6	−59.0 (b, 1)	−57.5 (b, 3)
(2.0)	PhCOOH (0.5)	$^{+-}Bu_4NOBz$ (2.0)	THF/C_6H_6	-	−57.4 (s)
(2.0)	PhCOOH (0.5)	pyr·OBz (1.0)	THF	+62.0 (s)	-
(2.0)	PhCOOH (0.5)		C_6H_6	+61.1 (b, 2)	−57.3 (b, 1)
(0.8)	PhCOOH (0.4)		C_6H_6	+39.2 (vb, 1)	−57.3 (s, 1)
(0.5)	PhCOOH (0.5)		C_6H_6	+18.0 (vb, 3)	−57.3 (s, 1)
(0.5)	PhCOOH (0.25)		C_6H_6	+2.1 (vb, 3)	−57.3 (s, 2)
(0.4)	PhCOOH (0.2)		C_6H_6	−11.4 (vb, 2)	−57.3 (s, 1)
(2.0)	PhCOOH (1.0)	$^{+-}Bu_4NOBz$ (1.0)	C_6H_6	+60.3 (b, 1)	−57.3 (b, 1)
(2.0)	PhCOOH (1.0)	$^{+-}Bu_4NOBz$ (2.0)	C_6H_6	+55.9 (b, 1)	−57.3 (b, 10)
(2.0)	PhCOOH (1.0)	Bu_3SnOBz (1.0)	C_6H_6	+62.1 (s)	-
(2.0)	PhCOOH (1.0)	Bu_3SnOBz (2.0)	C_6H_6	+62.1 (s)	-
(2.0)	PhCOOH (1.0)		MeCN	+62.8 (s)	-
(0.5)	PhCOOH (1.0)		MeCN	+62.6 (s, 5)	−56.9 (s, 1)
(0.5)	PhCOOH (1.0)	Bu_3SnOBz (1.0)	$MeCN/C_6H_6$	+62.3 (s)	-
(2.0)	TFA (1.0)		THF	+62.2 (s)	-
(2.0)	TFA (1.0)	$^{+-}Bu_4NOBz$ (1.0)	THF/C_6H_6	+62.0 (b, 5)	−57.5 (b, 1)
(2.0)	pNBA (1.0)		THF	+61.4 (b, 3)	−57.5 (b, 1)
(0.5)	pNBA (0.5)		THF	+58.6 (s, 1)	−57.5 (s, 1)
2 (2.0)	PhCOOH (1.0)		THF	+59.4 (b, 3)	−54.8 (b, 1)
(1.0)	PhCOOH (1.0)		THF	+24.0 (vb, 4)	−54.8 (s, 1)
(0.5)	PhCOOH (0.5)		THF	−42.2 (b, 8)	−54.8 (s, 1)
(2.0)	pNBA (1.0)		THF	+65.2 (s)	-
(1.0)	pNBA (1.0)		THF	+62.6 (s, 10)	−54.8 (s, 1)
(2.0)	PhCOOH (1.0)		C_6H_6	+62.0 (b, 4)	−54.7 (s, 1)
(2.0)	PhCOOH (1.0)	Bu_3SnOBz (1.0)	C_6H_6	+65.7 (s)	-
(2.0)	PhCOOH (1.0)	Bu_3SnOBz (2.0)	C_6H_6	+65.9 (s)	-
(2.0)	PhCOOH (1.0)	pyr·OBz (1.0)	THF	+65.5 (s)	-
(2.0)	PhCOOH (1.0)		MeCN	+66.6 (s)	-
glycolic acid (2.0)			THF		−0.2 (s)
glycolic acid (1.0)			THF		−13.7 (s)[f]
glycolic acid (0.5)			THF		−16.1 (s)
glycolic acid (2.0)			MeCN	+50.7 (s)[b]	
glycolic acid (1.0)			MeCN	+20.0 (s)[g]	
glycolic acid (0.5)			MeCN	+3.2 (s)[b]	

[a] Number of equivalents of alcohol relative to betaine **4**. Solutions approximately 0.1 M (total phosphorus). [b] Peaks due to excess betaine (**4**, +44 ppm), protonated betaine (**8**, +50 ppm), and triphenylphosphine oxide (+25 ppm) are not shown. Spectra recorded at 10 °C unless otherwise stated. [c] s, $W_{1/2} < 0.1$ ppm; b, $W_{1/2} < 1$ ppm; vb, $W_{1/2} > 1$ ppm. [d] Based on peak areas (approximate values only). [e] Recorded at 0 °C. [f] Remained sharp to −90 °C. [g] Broad at −20 °C.

phenylphosphoranes such as **7** have not previously been observed, although they have been proposed as intermediates in Mitsunobu and related reactions.[1]

Results and Discussion

Treatment of equimolar amounts of triphenylphosphine (TPP) and diisopropyl azodicarboxylate (DIAD) in tetrahydrofuran (THF) at 0 °C under nitrogen followed by addition of half an equivalent of neopentyl alcohol, **1**, resulted in the immediate appearance of a single sharp peak at −57.5 ppm in the phosphorane region of the ^{31}P NMR spectrum, corresponding to the formation of **5** as reported in the previous paper. There was also a peak at +44.3 ppm corresponding to the excess betaine **4** [lit.[2] for **4** +43.7 ppm (THF/C_6D_6)] and a minor peak at approximately +25 ppm corresponding to triphenylphosphine oxide as described previously.[3] Addition of half an equivalent of benzoic acid to this solution gave rise to four broad peaks in the approximate ratio of 3:1:1:1, respectively; 2 downfield peaks at +49.5 and +44 ppm corresponding to the protonated betaine **8** [lit.[2] for **8** +51 ppm (as trifluoroacetate salt, THF/C_6D_6)] and the betaine **4**, respectively, an upfield peak at −57.5 ppm corresponding to the original phosphorane **5**, and a new upfield peak at −27.6 ppm. Changing the order of addition of reagents gave the same results (except that addition of half an equivalent of benzoic acid to **4** gave rise to two broad peaks in approximately equal amounts: +49.2 and +44.3 ppm corresponding to **8** and **4**, respectively—use of 1 equiv of acid gave a single sharp peak at +49.9 ppm corresponding to **8** only). The chemical shift of the new upfield peak

(1) See, for example: (a) Pautard, A. M.; Evans, S. A. *J. Org. Chem.* **1988**, *53*, 2300–2303. (b) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843–1845.

(2) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235–4238.

(3) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557–563.

Table II. ^{31}P NMR Data for (Acyloxy)alkoxyphosphorane 7[a]

temp, °C	^{31}P chemical shifts, ppm
0	−11.3 ($W_{1/2}$, 1.3 ppm)
−10	−13.5 ($W_{1/2}$, 0.7 ppm)
−20	−14.7 ($W_{1/2}$, 1.2 ppm)
−30	−14.8 ($W_{1/2}$, 2 ppm)
−40	−15.2 ($W_{1/2}$, 3 ppm)
−50	−14.9 ($W_{1/2}$, 5 ppm)
−60	−15.5 ($W_{1/2}$, 8 ppm)
−70	−15 ($W_{1/2}$, 20 ppm)
−80	−15 ($W_{1/2}$, 30 ppm)
−90	coalescence
−100	+61 ($W_{1/2}$, 8 ppm), −55 ($W_{1/2}$, 10 ppm)
−105	+61 ($W_{1/2}$, 5 ppm), −55 ($W_{1/2}$, 7 ppm)

[a] Prepared by treating neopentyl alcohol with 1 equiv of TPP and 1 equiv of DIAD in THF followed by $^1/_2$ equiv of benzoic acid. Solution approximately 0.1 M (total phosphorus). Peaks due to the phosphorane **5**, betaine **4** and protonated betaine **8** are not shown.

(−27.6 ppm) was very sensitive to the solvent. In benzene for example it shifted downfield to +18.0 ppm, while in acetonitrile it occurred at +62.6 ppm. It was also very sensitive to the presence of proton sources (excess neopentyl alcohol, added benzoic acid, or even added diisopropyl or diethyl hydrazine-1,2-dicarboxylate, H_2DIAD), the presence of which all moved the peak downfield (see Table I). The effect of increasing concentrations of betaine **4** (an efficient scavenger of protons) was studied by adding successive amounts of a solution of betaine **4** in benzene to a mixture of the phosphorane **5** and oxyphosphonium carboxylate **6** prepared in benzene from 1 equiv of betaine **4**, 2 equiv of neopentyl alcohol, and 1 equiv of benzoic acid. Prior to the addition of the excess betaine **4**, the oxyphosphonium salt **6** absorbed at +61.1 ppm. After addition of three successive aliquots of betaine **4**, this peak broadened and moved to +39.2, +2.1, and −11.4 ppm respectively, the final chemical shift corresponding to an approximately 4-fold excess of betaine **4**. This final solution showed peaks at +49.9 (protonated betaine **8**), +44.3 (betaine **4**), −11.4 ("oxyphosphonium salt" **6**), and −57.3 (phosphorane **5**) in the approximate ratio of 1:15:2:1, respectively. It is clear then, that removal of proton sources (addition of betaine **4**) causes the chemical shift of the "oxyphosphonium salt" **6** to move to higher field and to approach the phosphorane region of the ^{31}P NMR spectrum, while addition of proton sources, or use of a polar solvent (acetonitrile), causes the chemical shift to approach a limiting value of approximately +62 ppm, corresponding to a phosphonium species **6** as described in the previous paper. We ascribe this sensitivity to an equilibrium between the oxyphosphonium carboxylate **6** and the corresponding (acyloxy)phosphorane **7**. This equilibrium is fast on the NMR time scale as only a time-averaged, single broad peak is observed, part way between the chemical shift of **6** (+62 ppm) and the expected chemical shift of phosphorane **7** (−50 to −60 ppm by analogy with dialkoxy and bis(aryloxy)triphenylphosphoranes[3-5]).

Confirmation of this equilibrium was obtained by lowering the temperature (Table II). A reaction mixture was chosen where the broad peak to be studied lay toward the mid-point of the expected chemical shifts for **6** and for **7**. As the temperature was lowered, the broad peak became even broader until at −90 °C it could not be seen. At −100 °C, two new broad peaks appeared, a downfield peak at +61 ppm corresponding to **6** and an upfield peak at −55 corresponding to **7** (ratio of **6**:**7** ≈ 5:7). The coalescence temperature for this equilibration was estimated to be about −90 °C corresponding to an activation energy ΔG_c^* of approximately 6.8 kcal/mol.

Further evidence for the equilibrium **6** ⇌ **7** was sought by addition of benzoate ion to the mixture. Sodium benzoate was found to be too insoluble in THF to be useful (no effect was observed); however, tetrabutylammonium benzoate proved effective in shifting the equilibria. Addition of 1 equiv of tetrabutylammonium benzoate to a 1:1 mixture of **5** and **6** (prepared from **4** by addition of 2 equiv of neopentyl alcohol and 1 equiv of benzoic acid), caused a small upfield shift of **6** from +59.5 ppm to +59.0 ppm. However, the dialkoxyphosphorane peak (−57.5 ppm) increased in intensity so that the original 1:1 mixture of **5** and **6** became a 3:1 mixture, respectively. Addition of a further equivalent of tetrabutylammonium benzoate caused the downfield peak to disappear completely, with a resultant increase in the amount of **5** (relative to an internal standard of TPP, −5.2 ppm). It was clear from these experiments that instead of shifting the equilibrium **6** ⇌ **7** toward the (acyloxy)alkoxyphosphorane **7**, the benzoate ion was simply acting as a buffer, effectively reducing the acidity of the benzoic acid and allowing the equilibrium to shift from **6** → **5**. Similar results were observed in benzene (Table I). Interestingly, use of pyridinium benzoate had the opposite effect, the equilibrium shifting from **5** → **6**. It is apparent that in the latter case, pyridinium benzoate is simply acting as a source of protons, favoring formation of the alkoxyphosphonium salt, **6**. Analogous results were obtained with tributyltin benzoate (Table I), which presumably acts as a proton equivalent.

Further support for the equilibrium **6** ⇌ **7** was obtained by replacing the benzoic acid by *p*-nitrobenzoic acid (pNBA). If **7** is involved in the equilibrium, then making the acyloxy ligand a better leaving group (i.e. *p*-nitrobenzoate) should shift the equilibrium further toward the ion pair, i.e. the chemical shift should move to lower field. This was found to be the case. Trifluoroacetate behaved similarly (Table I). This is in accordance with the expectation that phosphoranes with good leaving groups tend to exist as ion pairs.[6] Polar solvents should also favor ion-pair formation, and both pyridine (ϵ 12.3) and acetonitrile (ϵ 38.8) were found to shift the equilibria toward the alkoxyphosphonium salt **6** (at the expense of both phosphoranes **5** and **7**). One apparent anomaly in Table I is that THF (ϵ 7.6) was the solvent that most favored the (acyloxy)phosphorane **7**, even though it is a more polar solvent than benzene (ϵ 2.3). We believe that this is due to the fact that THF is a basic solvent,[7] i.e. in this solvent, any protons are effectively "tied up" by hydrogen bonding to the solvent and are therefore less available to solvate the benzoate ion of **6**, thus favoring formation of the (acyloxy)phosphorane **7**. Apparently pyridine is too polar for this effect to be significant in this solvent.

Analogous results were observed with the secondary alcohol diacetone glucose **2** (Table I). Thus, the alkoxyphosphonium salt **10** exhibited a limiting chemical shift of about +65 ppm in THF, but in the presence of excess (1 equiv) of betaine **4**, the chemical shift moved upfield to −42 ppm, a shift of over 100 ppm. Once again we at-

(4) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1984**, *37*, 2447–2451.
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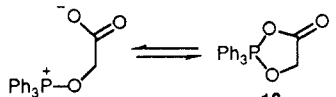
(6) Kosolapoff, G. M.; Maier, L. *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1972; Vol. 3, pp 237–246.
(7) March, J. *Advanced Organic Chemistry*, 2nd ed.; McGraw-Hill: Tokyo, 1977; p 232.

tribute this upfield shift to the equilibrium **10** ⇌ **11**, with the value of −42 ppm clearly favoring the (acyloxy)alkoxyphosphorane **11** in this case. An interesting difference between the secondary alcohol **2** and the primary alcohol **1** is that the secondary alcohol appeared to favor the formation of the (acyloxy)alkoxyphosphorane species (cf. −42 ppm versus −27.6 ppm for reactions carried out under the same conditions). The reason for this difference stems from the higher reactivity of the secondary alcohol derived dialkoxyphosphorane **9** compared to the primary alcohol derived dialkoxyphosphorane **5** toward benzoic acid. Thus, it can be seen (Table I) that whereas treatment of the betaine **4** with 2 equiv of neopentyl alcohol and 1 equiv of benzoic acid gave an approximately 1:1 mixture if alkoxyphosphonium salt **6** and phosphorane **5**, the corresponding reaction with diacetone glucose showed substantially more alkoxyphosphonium salt (**10**:**9** = 3:1). This is not unexpected given the greater steric requirements of the secondary alcohol, i.e. reaction of **9** with acid to give **10** results in a loss of steric strain, so that the equilibrium **9** ⇌ **10** would be expected to be more toward the alkoxyphosphonium salt **10**. Viewed alternatively, reaction of **10** with diacetone glucose to give **9** would be expected to be more difficult than reaction of **6** with neopentyl alcohol to give **5** (by analogy with the corresponding reaction of the respective alcohols with the betaine **4**). This difference affects the stoichiometry of the reaction with the result that the ratio of betaine **4** to protonated betaine **8** is different in the two cases. This was apparent from the ^{31}P NMR data where it was found that the ratio of protonated betaine **8** to betaine **4** was higher in the neopentyl alcohol case. The slightly higher effective concentration of betaine **4** (i.e. higher basicity) in the diacetone glucose case results in a more pronounced upfield shift.

Additional evidence for an equilibrium between oxyphosphonium carboxylate **6** and the corresponding acyloxyalkoxyphosphorane **7** was obtained by employing glycolic acid as the alcohol/carboxylic acid combination. Five-membered rings are well known to stabilize phosphoranes,[8,9] so that treatment of the betaine **4** with glycolic acid should result in an analogous equilibrium **12** ⇌ **13**, but with the equilibrium lying more toward the (acyloxy)phosphorane structure **13**.[10] This was found to be the



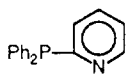
12 **13**

case. Thus, treatment of the betaine **4** with 1 equiv of glycolic acid resulted in a single sharp peak at −13.7 ppm in the ^{31}P NMR spectrum. Use of an excess of glycolic acid resulted in a downfield shift, while an excess of betaine **4** resulted in an upfield shift, in complete agreement with the neopentyl alcohol and diacetone glucose results. Similarly, use of a more polar solvent (acetonitrile) resulted in a large downfield shift (Table I). Phosphoranes containing five-membered rings generally have ^{31}P NMR chemical shifts some 20–40 ppm to lower field than their acyclic analogues.[11] For example, the phosphorane derived from catechol has a ^{31}P NMR chemical shift of −21.1 ppm (see previous paper) whereas the acyclic analogue, diphenoxytriphenylphosphorane, has a chemical shift of −66 ppm in THF.[4,5] Other examples of five-membered ring dioxytriphenylphosphoranes are those derived from ethylene glycol [−36.2 ppm (THF);[12] −35 ppm (CH_2Cl_2)[13]] and adenosine [2′,3′; −26.6 ppm (DMSO)].[14]

By analogy, the chemical shift of **13** would be expected to be about −20 to −30 ppm. The actual chemical shift of −13.7 ppm in THF is therefore consistent with an equilibrium **12** ⇌ **13** lying well toward the (acyloxy)phosphorane **13**. This equilibrium was also very fast on the ^{31}P NMR time scale as the −13.7 peak remained sharp down to −90 °C. Interestingly, the equilibrium appeared to be slower in acetonitrile, peak broadening being observed at −20 °C. This may reflect stronger solvation of **12** by acetonitrile (and therefore a higher activation energy involving desolvation in the equilibrium **12** ⇌ **13**). Unfortunately, it was not possible to study this system at very low temperatures due to the freezing point of acetonitrile (−48 °C).

The recent report by Strijtveen and Kellogg[15] on the thioacetylation of α-hydroxy acids under Mitsunobu conditions suggests that an *O,N*-phosphorane intermediate is involved. The present work with glycolic acid shows clearly that the only stable intermediate formed is the phosphorane **13** (in equilibrium with the oxyphosphonium carboxylate **12**).

Finally, we thought it would be of interest to examine diphenyl-2-pyridylphosphine **14** as an analogue of triphenylphosphine in the Mitsunobu esterification reaction. We have recently shown that **14** can be usefully employed in those Mitsunobu reactions where removal of triphenylphosphine oxide is difficult or troublesome.[16] The oxide of **14** is readily removed by a dilute acid wash.



14

Treatment of **14** with 1 equiv of DIAD in THF at 0 °C under nitrogen gave a clear orange solution, the ^{31}P NMR spectrum of which showed a major peak at +33.0 ppm corresponding to **4′**, the diphenyl-2-pyridyl analogue of the betaine **4**, and a minor peak at +14.7 ppm corresponding to the oxide of **14**. Addition of 2 equiv of **1** resulted in the disappearance of the +33 peak and the immediate appearance of a single sharp peak (−59.3 ppm) corresponding to the formation of **5′**, the diphenyl-2-pyridylphosphine analogue of the phosphorane **5**, a result entirely consistent with previous findings.[3] Addition of 1 equiv of benzoic acid to this solution gave rise to two broad peaks, an upfield peak at −59.3 ppm corresponding to the original phosphorane **5′**, and a downfield peak at +28.5 ppm corresponding to **6′**, the diphenyl-2-pyridylphosphine analogue of the oxyphosphonium salt **6** (in equilibrium with the corresponding **7′**). Once again, the chemical shift of the downfield peak was very sensitive to the presence of proton sources, excess betaine **4′**, and polar solvents. The results are summarized in Table III. An interesting difference between the data for the pyridylphosphine **14** and that for

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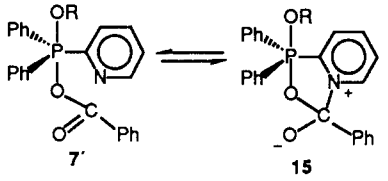
Table III. ^{31}P NMR Data for Reaction of Alcohols and Carboxylic Acids with Diphenyl-2-pyridylphosphine and Diisopropyl Azodicarboxylate

alcohol (equiv)[a]	acid (equiv)	solvent	^{31}P NMR chemical shifts[b] (peak width,[c] rel ratio[d])	
1 (2.0)		THF		-59.3 (s)
(2.0)	PhCOOH (1.0)	THF	+28.5 (vb, 1)	-59.3 (vb, 1)
(2.0)	PhCOOH (2.0)	THF	+46.7 (vb, 3)	-59.3 (vb, 1)
(1.0)	PhCOOH (0.5)	THF	-34.8 (vb, 2)	-59.3 (s, 1)
(0.5)	PhCOOH	THF	-50.1 (b, 3)	-59.3 (s, 1)
(0.5)	CH_3COOH (0.5)	THF	-56.3 (vb, 3)	-59.3 (s, 1)
(0.5)	PhCOOH (0.25)/ CH_3COOH (0.25)	THF	-52.0 (vb, 3)	-59.3 (s, 1)
(0.5)	PhCOOH (0.5)	MeCN	+53.2 (s, 10)	-58.3 (s, 1)
2 (2.0)	-	THF		-59.6 (s)
(2.0)	PhCOOH (1.0)	THF	-7.3 (vb, 3)	-59.6 (vb, 1)

[a] Number of equivalents of alcohol relative to betaine 4′. Solutions approximately 0.1 M (total phosphorus). [b] Peaks due to excess betaine (4′, +33 ppm), protonated betaine (8′, +38 ppm) and diphenyl-2-pyridylphosphine oxide (+14.7 ppm) are not shown. [c] s, $W_{1/2} < 0.1$ ppm; b, $W_{1/2} < 1$ ppm; vb, $W_{1/2} > 1$ ppm. [d] Based on peak areas (approximate values only).

triphenylphosphine (Table I) is that the equilibrium 6′ ⇌ 7′ was shifted further toward the (acyloxy)alkoxyphosphorane structure, i.e. the chemical shift of the "downfield" peak was to higher field in the case of the pyridylphosphine. This was particularly noticeable in the presence of excess betaine 4′, where the chemical shift was -50.1 ppm, highly indicative of a phosphorane structure, not an oxyphosphonium salt. Replacing benzoic acid by the slightly weaker, acetic acid, shifted this peak to -56.3 ppm, almost the same chemical shift as the dialkoxyphosphorane 5′ (-59.3 ppm). Use of an approximately 1:1 mixture of acetic and benzoic acids resulted in a single peak at -52.0 ppm, consistent with rapid carboxylate exchange as indicated by the broad peaks observed (the dialkoxyphosphoranes also exhibit broad peaks and alkoxy group exchange in the presence of excess alcohol).

The reason that 14 stabilizes the (acyloxy)alkoxyphosphorane structure is not just due to the basicity of the pyridine nitrogen, as treatment of the betaine 4 with the alcohol 1 and benzoic acid in the presence of pyridine gave an oxyphosphonium salt (Table I). We suggest, therefore, that the pyridyl nitrogen of 7′ coordinates with the carbonyl carbon, 15, rendering the carboxylate a much poorer leaving group and thereby stabilizing the phosphorane structure.[17]

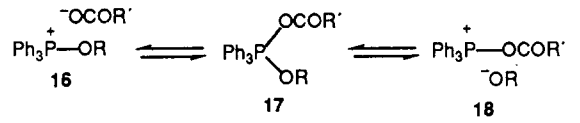


Concluding Remarks

In summary, this paper presents a range of data that support the involvement of (acyloxy)alkoxyphosphoranes 17 as intermediates in the Mitsunobu esterification reaction. These intermediates are clearly important in those reactions where the Michaelis–Arbusov reaction of the alkoxyphosphonium carboxylate (16) is kinetically slow or not possible (i.e. when R is too sterically hindered or when R = aryl). Such intermediates (17) are presumably in

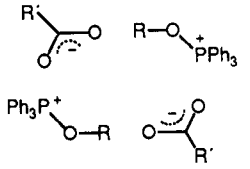
(17) Note that while this structure has a five-membered ring, the ring possesses only one oxygen atom (the downfield chemical shift effect appears to be confined to five-membered ring phosphoranes containing both an apical and an equatorial oxygen. Moreover, the structure is such that π-back-bonding from the pyridyl group to phosphorus d oribtals in the equatorial plane should be facilitated).

Scheme I



equilibrium not only with the corresponding alkoxyphosphonium carboxylate, but also (to at least a minor extent[18]) with the (acyloxy)phosphonium salt 18 (Scheme I), which would lead to acylation of the alcohol with *retention* of configuration. For example, when 10 was heated, the product obtained was 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose,[19] i.e. the configuration of the alcohol was retained. Similarly, in the Mitsunobu esterification of phenols, the "key" intermediate cannot be an oxyphosphonium salt 16 (R = aryl). Nor can it be a diaryloxyphosphorane as claimed by Grochowski and co-workers.[5] We suggest that, once again, esterification takes place via an (acyloxy)phosphonium intermediate 18 (R = aryl). However, it should be noted that in the absence of an alcohol, TPP and DIAD react with benzoic acid to give benzoic anhydride.[20] Thus, an alternative mechanism for the Mitsunobu esterification of phenols involves initial formation of the acid anhydride. It would be expected, however, that the intermediate 18 would be a far better acylating agent than benzoic anhydride.[21]

Whether (acyloxy)alkoxyphosphoranes (or indeed dialkoxyphosphoranes) play a role in "normal" Mitsunobu esterification reactions or whether such species are simply present as "spectator phosphoranes" is less clear. It seems likely that the "key" intermediate, leading to inversion of configuration of the alcohol, is the oxyphosphonium species 16. In nonpolar solvents such as THF, 16 probably exists as a tight ion pair, and subsequent (S_N2) reaction would require the formation of a duplex (such as 19) or of higher ion pair aggregates.[2,22,23]



19

A very recent paper by Hughes et al.[24] concludes that the oxyphosphonium carboxylate 16 is the key intermediate and that the rate of formation of ester is roughly first order in 16 but zero order in [R′COO⁻]. Their paper presents a nice summary of the factors affecting the rate of formation of 16 and of its subsequent breakdown, and

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(19) Kunz, H.; Schmidt, P. *Z. Naturforsch. Teil B* **1978**, *33*, 1009–1011.
(20) Von Itzstein, M. Ph.D. Thesis, Griffith University, 1984, p 152.
(21) The formation of benzoic anhydride from the reaction of 4 with benzoic acid suggests the involvement of an (acyloxy)phosphonium carboxylate intermediate. We have looked for this species by low-temperature ^{31}P NMR but see only protonated betaine 8 and triphenylphosphine oxide. Use of oxalic acid (which could conceivably give a stable diacyloxyphosphorane) gave the same result, even when mixed at -70 °C.
(22) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627–1632. Jones, L. A.; Sumner, C. E.; Franzus, B.; Huang, T. T.-S.; Snyder, E. I. *Ibid.* **1978**, *43*, 2821–2827. Slagle, J. D.; Huang, T. T.-S.; Franzus, B. *Ibid.* **1981**, *46*, 3526–3530.
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(24) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.

the finding that the basicity of $RCOO^-$ and the presence of proton sources (excess RCOOH) can dramatically affect the course of the reaction nicely complements the present study. The zero-order dependence, in [$R'COO^-$] was interpreted in terms of a "salt effect"; however, ion pair aggregate formation seems equally probable.

Any equilibria between **16** and phosphoranes **17** or **5** might be expected to slow down the formation of ion pair aggregates (and possibly the rate of reaction). However, the presence of the dialkoxyphosphorane **5** (Scheme I, preceding paper) means that there must be an excess of carboxylate ion in solution (in the form of **8**). Aggregation of **8** with **6** (to form a complex analogous to **19** for example) might also result in ester formation, i.e. **8** may act as a catalyst for Mitsunobu esterification. There is some evidence for this. Thus, Walker has shown[2] that in the trifluoroacetylation of sterols, addition of triphenylphosphine last gives rise to an alkoxyphosphonium trifluoroacetate, which slowly converts to the steroid trifluoroacetate. However, when the acid is added last (resulting in the formation of equimolar amounts of the alkoxyphosphonium trifluoroacetate, the trifluoroacetate analogue of **8**, and the sterol) significant amounts of the steroid trifluoroacetate are formed immediately. Generation of the alkoxyphosphonium trifluoroacetate in the absence of the trifluoroacetate analogue of **8** resulted in only small amounts of the steroid trifluoroacetate. We suggest, therefore, that dialkoxytriphenylphosphoranes do play a role (albeit an indirect role) in normal Mitsunobu esterification reactions, whereas (acyloxy)alkoxytriphenylphosphoranes are probably only present as "spectator" phosphoranes in most cases. The effect of both types of phosphorane can be minimized by employing an excess of acid (R'COOH) or a more polar solvent.

Experimental Section

The procedures used to obtain the ^{31}P NMR data (Tables I–III) are as described in the preceding paper (Part 1). Tetrabutylammonium benzoate was prepared from tetrabutylammonium hydroxide and benzoic acid and dried by azeotropic removal of water with benzene. Tributyltin benzoate was prepared from bis(tributyltin) oxide and benzoic acid in benzene by azeotropic removal of water. Diphenyl-2-pyridylphosphine was prepared by using the literature procedure.[25]

Acknowledgment. We acknowledge the support of the ARGS and the award of a CPRA (to D.C.). We thank Dr. Keith Walker for useful discussions. The ^{31}P NMR spectra were recorded at the Brisbance NMR Centre, Griffith University, and we thank David Tucker for his assistance in obtaining some of the spectra.

Registry No. **1**, 75-84-3; **2**, 582-52-5; **4**, 86825-70-9; **4'**, 120711-43-5; **5**, 105785-75-9; **5'**, 120711-44-6; **6**, 120609-90-7; **6'**, 120711-46-8; **7**, 120609-91-8; **7'**, 120711-47-9; **8**, 120418-13-5; **10**, 120609-92-9; **11**, 120609-93-0; **12**, 120711-41-3; **13**, 120711-42-4; **14**, 37943-90-1; **14** oxide, 64741-30-6; TFA, 76-05-1; pNBA, 62-23-7; TPP, 603-35-0; DIAD, 2446-83-5; PhCOOH, 65-85-0; CH_3COOH, 64-19-7; glycolic acid, 79-14-1; triphenylphosphine oxide, 791-28-6; 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, 13964-22-2; benzoic anhydride, 93-97-0.

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Mechanism of the Transannular Cyclization of 5-Cyclodecynone

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Acid-catalyzed intramolecular cyclization of 5-cyclodecynone (**1**) under a variety of conditions gives bicyclo[4.4.0]-1(6)-decen-2-one (**8**) as the only product. In earlier reports the reaction was formulated as involving triple-bond participation with a polarized carbonyl group to give a vinyl cation, followed by external attack by a nucleophile. Studies of the rearrangement using Lewis acids in aprotic solvents, taking care to exclude water and moist air during workup, have shown that the oxygen atom in the starting acetylenic ketone **1** is the same as that in the bicyclic product **8**. When the reaction was carried out with HCl in a solvent of methanol–$H_2{}^{18}O$, oxygen-18 incorporation in the final product was not significantly above exchange levels observed when the bicyclic ketone itself was treated with methanol–$H_2{}^{18}O$ under similar conditions. A mechanism that will account for these observations is presented.

It has been clearly established that 5-cyclodecynone (**1**) undergoes transannular cyclization to bicyclo[4.4.0]-1-(6)-decen-2-one (**8**) when treated with HCl in aqueous methanol or with boron trifluoride etherate in aprotic solvents.[1-3] Although bicyclo[5.3.0]decanone (**5**) was shown to be stable to the reaction conditions, its presence could not be detected in any of the reaction products. Similar to 5-cyclodecen-1-yl derivatives[4,5] and to 5-cyclodecyn-1-yl derivatives,[1-3,6] the acetylenic ketone **1** appears to prefer reaction via a six-membered-ring transition state. In earlier reports[1,2] the mechanism outlined in Scheme I was suggested to account for the isomerization of **1** to **8** when treated with HCl in aqueous methanolic solution. This same mechanism has been presumed by others[7] to explain the acid-catalyzed cyclization of 5-cyclononynone to give bicyclo[4.3.0]-1(6)-nonen-2-one as the only product. Such a mechanism is analogous to that postulated by Arens et al.[8] for the reactions of aldehydes and ketones with 1-alkynyl ethers in aqueous solution to give β-hydroxy esters.

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(2) Hanack, M.; Harding, C. E.; Derocque, J. *Chem. Ber.* **1972**, *105*, 421.
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