interpreting the leaving-group, substituent, and solvent effects on the RS^-/RO^- reactivity ratio mentioned above. On the other hand, we cannot utterly exclude it on experimental grounds. Perhaps it will be possible to make a firm decision on the basis of theory. Some many prefer to rely on faith.

Experimental Section

Materials. Most materials were prepared or purified as described in the companion paper.[19] Ethanethiol (Aldrich Chemical Co.) was distilled, and a middle cut (bp 34.5 °C) was taken; its purity was confirmed by GC. *tert*-Butyl ethyl sulfide was prepared, after McAllan et al.,[24] by reaction of the sodium salt of 2-methyl-2-propanethiol with ethyl iodide: ^1H NMR (CCl_4) δ 1.15 (t, 3 H), 1.25 (s, 9 H), 2.40 (q, 2 H).

Instruments and methods were as described in the companion paper.[19]

Kinetics Procedure. The procedure was as described elsewhere.[19] A special feature is that, after ampules had been opened and extractions performed, the aqueous solution for titration with silver nitrate received an addition of 1 mL of aqueous hydrogen peroxide, for the purpose of oxidizing any traces of thiol that may have been present, before titration was performed.

Memorial. This paper was composed in a mood of sadness, for A. J. "Jim" Parker will not be able to read it. He died in 1982, while a strong and vigorous man in what should have been midcareer. Although Jim and I differed in our views on elimination mechanisms, we had much in common scientifically and were personal friends. On our 25th wedding anniversary, my wife and I were guests at a party at his home. The people of Australia and we in the world community of chemists were fortunate to have had Jim Parker among us. (J.F.B.)

Registry No. *t*-BuCl, 507-20-0; EtS^-Na, 811-51-8; MeONa, 124-41-4.

(24) McAllan, D. T.; Cullum, T. V.; Dean, R. A.; Fidler, F. A. *J. Am. Chem. Soc.* **1951**, *73*, 3627.

Mechanism of the Mitsunobu Esterification Reaction. 1. The Involvement of Phosphoranes and Oxyphosphonium Salts

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Received November 28, 1988

In contrast to previous studies, a ^{31}P NMR examination of the Mitsunobu reaction using an unreactive alcohol, ROH, and a carboxylic acid, R'COOH, reveals the presence of *two* intermediates—an alkoxytriphenylphosphonium salt, Ph_3POR^+ $R'COO^-$, in equilibrium with a dialkoxytriphenylphosphorane, $Ph_3P(OR)_2$. The position of the equilibrium depends on the pK_a of the acid and the polarity of the solvent. The alkoxyphosphonium salt is favored in polar solvents or with acids of low pK_a. Where there is a choice between a primary and a secondary alcohol, only the phosphorane and oxyphosphonium salt corresponding to the primary alcohol are observed. The implications of these findings for the regioselectivity and stereoselectivity of the Mitsunobu reaction are discussed.

Introduction

Recent publications by Walker and co-workers[1a] and by Hughes et al.[1b] on the mechanism of the Mitsunobu reaction[2] prompt us to report the results of our work[3] in this area. This study complements the work of Walker and of Hughes, and together with the following paper, provides a clearer understanding of the mechanism of this important synthetic reaction.

Previous work from this laboratory[4-7] and others[8] has shown that treatment of alcohols or phenols with triphenylphosphine (TPP) and diethyl or diisopropyl azodicarboxylate (DEAD or DIAD, respectively) leads to the formation of dioxytriphenylphosphoranes. Such phosphoranes are clearly intermediates in Mitsunobu reactions involving formation of ethers as, for example, in the formation of sucrose 2',3'-epoxide and 3',6'-anhydrosucrose from sucrose,[9] but may not of course be involved in the more common Mitsunobu esterification reaction where a carboxylic acid is present. Indeed, Walker suggests[1a] that a dioxytriphenylphosphorane is only an intermediate in the Mitsunobu reaction in the special case where the acid is added last. In contrast to both Walker's and our own findings, Hughes was unable to observe any phosphoranes, even in the absence of an acid. However, Hughes used an alcohol that is prone to elimination and β-fragmentation.

The experiments to be described below illustrate that the pK_a of the acid and the polarity of the solvent can have a profound effect on the reaction pathway and demonstrate that the true mechanism of the Mitsunobu reaction is more complex than previous studies suggest.

Results and Discussion

For our studies, we employed two alcohols that do not readily undergo elimination or S_N2 attack, the primary

(1) (a) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235–4238. (b) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.
(2) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(3) Presented in part at the 8th National Convention of the Royal Australian Chemical Institute, University of New South Wales, Sydney, August 1987.
(4) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557–563.
(5) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1984**, *37*, 2447–2451.
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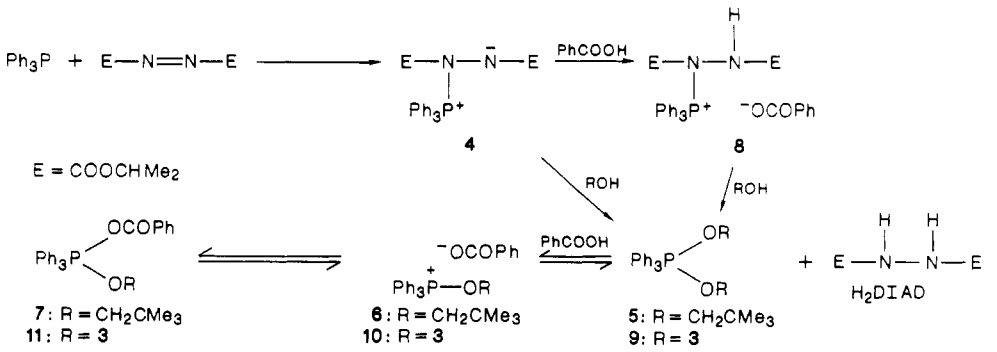
0022-3263/89/1954-3045$01.50/0

Table I. ^{31}P NMR Data for Reaction of Phosphoranes with Carboxylic Acids[a]

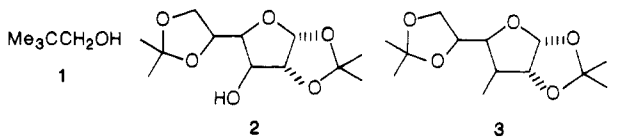
phosphorane	acid (equiv)	solvent	^{31}P chemical shifts	(peak width,[b] rel ratio[c])
5	none	THF		-57.5 (s)
	PhCOOH (0.5)	THF	55.2 (b, 1)	-57.5 (b, 3)
	PhCOOH (1.0)	THF	59.5 (b, 1)	-57.5 (b, 1)
	PhCOOH (2.0)	THF	60.8 (b, 4)	-57.5 (b, 1)
	PhCOOH (3.0)	THF	61.6 (s)	
	PhCOOH (1.0)[d]	THF	62.0 (b, 3)	-57.5 (b, 1)
	PhCOOH (1.0)	C_6H_6	61.1 (b, 2)	-57.3 (b, 1)
	PhCOOH (1.0)	THF (2), $CDCl_3$ (1)	62.2 (b, 5)	-57.6 (b, 1)
	PhCOOH (1.0)	MeCN	62.8 (s)	
	PhCOOH (3.0)	MeCN	62.8 (s)	
	p-$NO_2C_6H_4COOH$ (1.0)	THF	61.4 (b, 3)	-57.5 (b, 1)
	TFA (1.0)	THF	62.2 (s)	
9	PhCOOH (1.0)	THF	59.4 (b, 3)	-54.8 (b, 1)
	PhCOOH (2.0)	THF	63.3 (s)	
	PhCOOH (3.0)	THF	64.4 (s)	
	PhCOOH (1.0)	C_6H_6	62.0 (b, 4)	-54.7 (b, 1)
	PhCOOH (1.0)	MeCN	66.6 (s)	
	PhCOOH (2.0)	MeCN	66.6 (s)	
	PhCOOH (3.0)	MeCN	66.6 (s)	
	p-$NO_2C_6H_4COOH$ (1.0)	THF	65.2 (s)	
9 + 14 + 5	none	THF		-54.8, -55.7, -57.5
	PhCOOH (1.0)	THF	61.0 (s, 5)	-57.5 (s, 1)
	p-$NO_2C_6H_4COOH$ (1.0)	THF	62.5 (s, 20)	-57.5 (s, 1)
	PhCOOH (1.0)	MeCN	62.8 (s)	

[a] Solutions approximately 0.1 M (total phosphorus) unless otherwise stated. [b] s, $W_{1/2} < 0.1$ ppm; b, $W_{1/2} < 1$ ppm; vb, $W_{1/2} > 1$ ppm. [c] Based on peak areas (approximate values only). [d] 1 M concentration.

Scheme I



alcohol 1 (neopentyl alcohol) and the secondary alcohol 2 (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose).

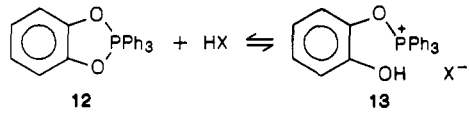


Treatment of equimolar amounts of TPP and DIAD[10] in tetrahydrofuran (THF) at 0 °C under nitrogen, followed by addition of 2 equiv of 1, resulted in the immediate appearance of a single sharp peak (-57.5 ppm) in the phosphorane region of the ^{31}P NMR spectrum, corresponding to the formation of 5 [lit.[11] -58.3 ppm (CH_2Cl_2)]. There was also a minor peak at approximately +25 ppm, corresponding to triphenylphosphine oxide as described previously.[4] Addition of 1 equiv of benzoic acid to this solution gave rise to two broad peaks, an upfield peak at -57.5 ppm corresponding to the original dialkoxyphosphorane 5, and a downfield peak at approximately +60 ppm, corresponding to the alkoxyphosphonium salt 6 (Scheme I). The latter assignment is consistent with the studies of Walker[1a] and Evans[11,12] and our own earlier work employing fluoroboric acid.[13] The broadness of the peaks is due to a typical exchange-broadening phenomenon where the rate of exchange is slow on the NMR time scale. Thus, as the temperature was lowered from 25 °C to -40 °C, both peaks became sharp. Unfortunately, it was not possible to determine the coalescence temperature: when the temperature was gradually raised, the sharp (+25 ppm) triphenylphosphine oxide peak simply increased in intensity until at 60 °C, it was the only peak present.

Changing the order of addition of reagents gave identical results. Thus, addition of benzoic acid (1 equiv) to the betaine 4 (+44 ppm) in THF resulted in the protonated betaine 8 (+50 ppm), in agreement with the studies of Walker[1a] [lit.[1a] for 4 +43.7 ppm (THF/C_6D_6)]. Addition of 1 (2 equiv) gave the same two broad peaks observed above. Interestingly, we did not observe the slow reaction of protonated betaine with alcohol 1 reported by Walker.[1a] We attribute this difference to: (a) the alcohol 1 is primary and therefore more reactive than the secondary (steroid) alcohols employed by Walker and (b) Walker's results suggest that the more acidic the system, the slower the reaction with protonated betaine; the benzoic acid employed here would therefore be expected to result in a faster reaction than when trifluoroacetic acid is employed. Further evidence for the equilibrium 5 ⇌ 6 was obtained

(10) Diethyl azodicarboxylate can also be used but see ref 6.
(11) Kelly, J. W.; Evans, S. A. *J. Org. Chem.* **1986**, *51*, 5492-5494.
(12) Pautaud, A. M.; Evans, S. A. *J. Org. Chem.* **1988**, *53*, 2300-2303.
(13) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767-774.

Scheme II



12 13

by changing the concentration of benzoic acid, changing the pK_a of the acid, and changing the polarity of the solvent. These results are summarized in Table I. It can be seen that in the presence of excess benzoic acid (3 equiv), only the oxyphosphonium salt **6** is observed. Similarly, use of stronger acids (*p*-nitrobenzoic acid or trifluoroacetic acid) favor formation of the oxyphosphonium species at the expense of the dialkoxyphosphorane **5**, as does use of a polar solvent (acetonitrile).

It should be noted that these experiments were carried out with an excess of alcohol (2 equiv instead of 1), whereas under normal "synthesis" conditions, esterification is carried out using a slight excess of the betaine **4**. This was for convenience and simplification of spectral data. Analogous results were obtained when equimolar amounts of benzoic acid and **1** were treated with either an equimolar amount of **4** or an excess of **4**. Under these conditions, additional peaks due to betaine **4** and/or protonated betaine **8** were present, but more importantly, it was found that the chemical shift of the downfield peak (but not the upfield peak) was extremely sensitive to the presence of excess **4** and to proton sources. We tentatively attribute this sensitivity to a (fast) equilibrium between the oxyphosphonium ion pair **6** and the corresponding (acyloxy)alkoxyphosphorane **7**. Data in support of this hypothesis are presented in the accompanying paper. We have also examined the formation of **5** and **6** by ^{13}C and ^{1}H NMR spectroscopy (see the Experimental Section). ^{13}C NMR was not very useful, but the ^{1}H NMR data were consistent with the ^{31}P NMR results.

Analogous results were obtained with the secondary alcohol, diacetone glucose **2**. Diacetone glucose was chosen as it is well known that leaving groups on C3 are extremely difficult to displace for steric and electronic reasons.[14,15] The main difference between **1** and **2** is that the latter reacted more slowly with **4** than did **1** (see below). The data summarized in Table I for phosphorane **9** and the corresponding oxyphosphonium salt **10** were obtained by addition of acid to the preformed phosphorane **9**. The results are analogous to those obtained for the alcohol **1** except that the position of the equilibrium **9** $\rightleftharpoons$ **10** was further toward the oxyphosphonium salt **10** (ratio **10:9** = 3:1 for 1 equiv of benzoic acid, whereas corresponding ratio of **6:5** = 1:1). This is presumably a reflection of the greater steric requirements and/or the higher basicity of the secondary alcohol **2**.

It is apparent from the data in Table I that the chemical shifts of both alkoxyphosphonium carboxylates **6** and **10** approach limiting values of approximately +62 and +65 ppm, respectively, with increasing amounts of benzoic acid, when acids of lower pK_a are used, or with increasing concentrations. The reason for these features appears to be associated with the equilibria **5** $\rightleftharpoons$ **6** and **10** $\rightleftharpoons$ **11** and is discussed in the accompanying paper.

An equilibrium between dioxyphosphorane **12** and oxyphosphonium salt **13** was also observed with the 1,2-diol, catechol (Scheme II), only this time the rate of exchange was fast on the NMR time scale. Thus, treatment of equimolar amounts of TPP, DIAD, and catechol in THF resulted in the immediate appearance of a single sharp peak (−21.1 ppm) in the ^{31}P NMR spectrum corresponding to the formation of **12** [lit.[16] −22.9 ppm ($CDCl_3$)]. Addition of 1 equiv of *p*-nitrobenzoic acid caused a downfield shift of this peak (to −20.6 ppm). Further additions of *p*-nitrobenzoic acid caused further downfield shifts: 2 equiv (−18.0 ppm), 3 equiv (−16.0 ppm), etc. The data are summarized in Table II. The greater relative stability of the phosphorane in this case is not unreasonable, as five-membered rings are well known to result in more stable phosphoranes.[17] Moreover, the lower basicity of the phenolic oxygens would suggest that a stronger acid would be required to give the oxyphosphonium salt **13**. Use of stronger acids (TFA, HBF_4·OEt_2) displaced the equilibrium toward a limiting value of about +65 ppm, corresponding to the oxyphosphonium species **13**. Use of an acid of intermediate pK_a (3,5-dinitrobenzoic acid) resulted in a very broad peak at −1.6 ppm. As the temperature was lowered, this peak broadened further until at −90 °C, it resolved into two peaks at −22 and +65 ppm, corresponding to **12** and **13**, respectively. The coalescence temperature for this equilibration was estimated to be about −75 °C, and the activation energy for the process $\Delta G_c^{\ddagger}$ 7.5 kcal/mol.

Table II. ^{31}P NMR Data for Reaction of Phosphorane 12 with Carboxylic Acids in THF[a]

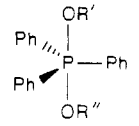
acid (equiv)	temp, °C	^{31}P NMR chemical shifts[b]
–	10	−21.1 (s)
p-$NO_2C_6H_4COOH$ (1.0)	10	−20.6 (s)
p-$NO_2C_6H_4COOH$ (2.0)	10	−18.0 (s)
p-$NO_2C_6H_4COOH$ (3.0)	10	−16.0 (s)
p-$NO_2C_6H_4COOH$ (5.0)	10	−14.3 (b)
TFA (1.0)	10	+60.0 (vb)
TFA (3.0)	10	+67.2 (s)
TFA (5.0)	10	+67.3 (s)
HBF_4·OEt_2 (5.0)	10	+67.5 (s)
3,5-$(NO_2)_2C_6H_3COOH$ (5.0)	10	+62.2 (b)
3,5-$(NO_2)_2C_6H_3COOH$ (3.0)	10	+45.6 (vb)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	10	−1.6 (vb)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	−10	−5.0 ($W_{1/2}$, 5 ppm)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	−30	0 ($W_{1/2}$, 10 ppm)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	−50	+3 ($W_{1/2}$, 20 ppm)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	−70	−12 ($W_{1/2}$, 30 ppm)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	−90	−22 (vb); +65 (vb)
3,5-$(NO_2)_2C_6H_3COOH$ (1.0)	−100	−23 (b, 3); +66 (b, 1)

[a] Solutions approximately 0.1 M in phosphorane **12**. [b] s, $W_{1/2}$ < 0.1 ppm; b, $W^{1/2}$ < 1 ppm; vb, $W_{1/2}$ > 1 ppm.

By use of a mixture of primary and secondary alcohols in excess, it was possible to study the role of phosphorane and oxyphosphonium salt intermediates in determining the regioselectivity of the Mitsunobu esterification reaction. Thus, treatment of an equimolar mixture of **1** and **2** with $^1/_2$ equiv of **4** in THF at 0 °C under nitrogen resulted in the appearance of three sharp phosphorane peaks at −54.8, −55.7, and −57.5 ppm in the ratio of 3:1:7, respectively. The major peaks (−54.8, −57.5 ppm) correspond to the phosphoranes **9** and **5**, respectively, as described in the single alcohol experiments (**9** has been described previously[4]), while the minor peak corresponds to the mixed phosphorane **14**. Analogous mixed phosphoranes have been described previously.[4]

The preferential formation of the phosphorane **5** from the primary alcohol is not unexpected, while the small amount of the mixed phosphorane **14** is further evidence

(14) Kunz, H.; Schmidt, P. *Z. Naturforsch. Teil B.* **1978**, *33*, 1009–1011; *Liebigs Ann. Chem.* **1982**, 1245–60.
(15) Ball, D. H.; Parrish, F. W. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 139–197.
(16) Kosolapoff, G. M.; Maier, L. *Organic Phosphorus Compounds*; Wiley-Interscience: New York, 1972; Vol. 3.
(17) Ramirez, F. *Bull. Soc. Chim. Fr.* **1970**, 3491–3519.

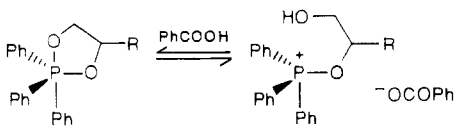


14: R′ = CH_2CMe_3; R″ = 3

that most of the primary alcohol has been consumed before the secondary alcohol reacts. Addition of $^1/_2$ equiv of benzoic acid (i.e. same amount as betaine **4**) resulted in loss of two of the phosphorane peaks (−54.8 and −55.7 ppm) and the appearance of a single oxyphosphonium peak at +61 ppm, i.e. phosphorane and oxyphosphonium peaks corresponding exclusively to the primary alcohol-derived **5** and **6**, respectively, were the only species observed. There was no sign of the secondary alcohol derived **9** or **10**. Changing the order of mixing of the reagents made no difference. Thus, initial formation of **9** and **10** from the secondary alcohol **2**, followed by addition of an equimolar amount of the primary alcohol **1** at 0 °C, resulted in the immediate loss of peaks corresponding to **9** and **10** and the appearance of peaks corresponding to **5** and **6**. Analogous results were obtained with *p*-nitrobenzoic acid (see Table I). The small downfield shifts observed for **6** in the mixed alcohol experiments (from +59.5 to +61.0 ppm in the case of benzoic acid and from +61.4 to +62.5 ppm in the case of *p*-nitrobenzoic acid) are consistent with the increased polarity resulting from the presence of the excess of alcohol **2**. Use of an excess of alcohol **1** caused a similar downfield shift. An alternative interpretation, that the downfield peak is due to **10** or to a rapid equilibration between **6** and **10**, is inconsistent with the presence of only phosphorane **5**. Also, the chemical shift observed in the presence of *p*-nitrobenzoic acid (+62.5 ppm) is much closer to the value observed in the case of the primary alcohol (+61.4 ppm) than in the case of the secondary alcohol (+65.2 ppm).

The results were confirmed by carrying out the experiment in acetonitrile. In this solvent, the phosphorane **9** had a chemical shift of −53.9 ppm. Addition of 1 equiv of benzoic acid gave a single sharp peak at +66.6 ppm, corresponding to the oxyphosphonium salt **10**. Addition of 2 equiv of the primary alcohol **1** to this solution immediately gave a single sharp peak at +62.8 ppm, corresponding to exclusive formation of the oxyphosphonium salt **6**.

From the above ^{31}P NMR results, it is apparent that under normal Mitsunobu esterification conditions, the phosphorane and oxyphosphonium carboxylate intermediates formed are the thermodynamically more stable species derived from the least hindered alcohol. The very recent and only known exceptions to this observed regioselectivity are the benzoylations of 1,2-propanediol and of styrene glycol where the 2-benzoates were the major products obtained.[12] Although this result is at odds with an earlier report,[18] it is conceivable that kinetic protonation of the most stable conformer of a 1,3,2λ⁵-dioxaphospholane intermediate **15** would take place on the apical oxygen followed by ring opening to give the least thermodynamically stable oxyphosphonium benzoate **16**. S_N2 attack by benzoate would then give the kinetic product, the 2-benzoate. The formation of the thermodynamic product in the earlier report may have been due to ester equilibration under the reaction conditions as the betaine **4** (which was present in excess) is known[2] to catalyze transesterification, particularly from more hindered to less hindered alcohols. The concept of kinetic control in the Mitsunobu esterification of 1,2-diols clearly warrants further exploration.



15 16

In those Mitsunobu reactions where no carboxylic acid is present (for example in the formation of epoxides and cyclic ethers[9]), the phosphorane intermediates formed are under kinetic control, and although the phosphorane derived from the (least hindered) primary alcohol is clearly formed faster, phosphoranes derived from the secondary alcohol, together with mixed species, are also formed in appreciable amounts. When such mixtures of phosphoranes are allowed to stand, they do undergo a slow exchange with alcohols and with each other.[4,6,7] Thus, when the reaction mixture containing **9**, **14**, and **5** was allowed to stand overnight at 4 °C, the ratio changed from 3:1:7 to 0:1:16, respectively. That this was an exchange rather than a preferential decomposition of **9** and **14** was shown by the size of the triphenylphosphine oxide peak (+25 ppm), which remained smaller than the mixed phosphorane **14** peak. Tertiary alcohols, such as triphenylmethanol, showed no sign of reaction with the betaine **4** after 1 month at room temperature.

Conclusion

In the Mitsunobu esterification reaction, both oxyphosphonium salts and phosphoranes are involved as intermediates, irrespective of the order of addition of reagents. These intermediates are in equilibrium with each other, the position of the equilibrium depending on the pK_a of the acid and the polarity of the solvent. With acids of low pK_a (such as trifluoroacetic acid), only the oxyphosphonium species is observed. Acids exert a marked catalytic effect on the rate of equilibration of the phosphorane (and oxyphosphonium) intermediates and where there is a choice between a primary and a secondary alcohol only the more thermodynamically stable phosphorane and oxyphosphonium species corresponding to the primary alcohol are observed (except possibly in the case of 1,2-diols at low temperature). This fact, together with the preferential S_N2 displacement at a primary carbon atom, account for the wellknown regioselectivity of the Mitsunobu reaction.[2,19] The role of phosphoranes in the mechanism of the Mitsunobu reaction is discussed in the accompanying paper.

Experimental Section

All reagents and solvents were carefully dried prior to use. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**2**) was prepared according to the literature[20] procedure. NMR spectra were recorded at 10 °C (unless otherwise stated) with either a Bruker CXP-300 or a Bruker WM-250 spectrometer. Spectra recorded on the CXP-300 instrument were acquired by using a 45° flip angle, a 3-s recycle delay, and 0.33-s acquisition time with gated decoupling. Corresponding parameters for the WM-250 instrument were 90°, 5 s, and 0.28 s, respectively. Negative ^{31}P chemical shifts are upfield of external phosphoric acid (85%). ^1H NMR spectra were recorded on the WM-250 instrument at room temperature.

(18) Mitsunobu, O.; Kumura, J.; Iiizumi, K.; Yanagida, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 510–513.

(19) For a recent example, see: Jenkins, I. D.; Goren, M. B. *Chem. Phys. Lipids* **1986**, *41*, 225–235.

(20) Schmidt, O. T. *Methods in Carbohydrate Chemistry*; Whistler, R. L., Wolfram, M. L., Eds.; Academic Press: New York, 1963; Vol. II, pp 321–322.

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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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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