A Mechanistic Study of the Mitsunobu Esterification Reaction

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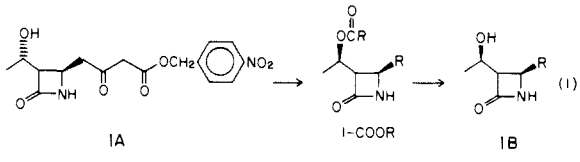
Abstract: The three steps of the Mitsunobu reaction were studied in detail for the esterification, with inversion of configuration, of the 2-(hydroxyethyl)azetidinone **1A**. In all solvents examined, formation of the adduct between DIAD and PPh_3 occurs far more rapidly than the subsequent two steps. For the second step, alcohol activation to form the oxyphosphonium intermediate (**4**), the hydroxyl group must be deprotonated before PPh_3 transfer occurs, and, therefore, the reaction rate is controlled by carboxylate basicity and solvation. Evidence for a 4-coordinate oxyphosphonium intermediate, as opposed to a pentavalent phosphorane, is presented. The final step of the reaction, S_N2 attack of $RCOO^-$ on the oxyphosphonium intermediate, is only slightly sensitive to carboxylate basicity, with a β_{Nu} value of 0.1 being found vs pK_a's in Me_2SO. The competing elimination reaction is reduced by using less basic carboxylate anions or by increasing carboxylate solvation with the conjugate acid of $RCOO^-$. Electron-withdrawing substituents in Ar_3P increased the alcohol activation rate.

The Mitsunobu reaction, pioneered by Mitsunobu and coworkers in 1967 and the ensuing years,[1] has proven useful in a wide variety of synthetic applications involving alcohols. A key step in the synthesis of the new antibiotic thienamycin is the Mitsunobu reaction used to invert the alcohol-bearing carbon of the 2-(hydroxyethyl)azetidinone **1A** (eq 1).[2] The β-lactam is a



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1A **1-COOR** **1B**

delicate compound, and initial work at Merck[3] showed that only under tightly controlled conditions could a good yield of inverted product **1B** be obtained. A search of the literature indicated that the mechanism had been the subject of a few investigations,[4] but no in depth study of the reaction had been made. In order to understand and optimize the reaction, we made a detailed study, the results of which are presented herein.

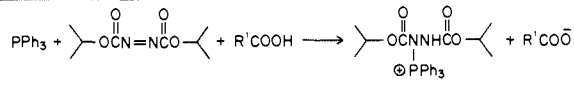
The Mitsunobu reaction takes place in three steps as outlined in Scheme I. The paper is divided into three sections, each devoted to one of the reaction steps.

Results and Discussion

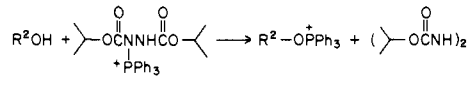
Step 1. Adduct Formation. The general procedure for the Mitsunobu reaction[1] is to add dialkylazodicarboxylate to a solution of the carboxylic acid, the alcohol, and PPh_3. In CH_2Cl_2 or THF solution, formation of the adduct (**2**) between diisopropyl azodicarboxylate (DIAD)[3] and PPh_3 occurs within seconds at −20 °C as evidenced by the decolorization of DIAD upon addition. Previous spectral work (multinuclear NMR and FTIR) has established that the phosphorus is bonded to nitrogen and not oxygen in CH_2Cl_2 solution.[6]

Scheme I

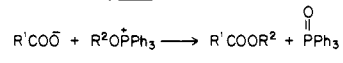
Step 1: Adduct Formation

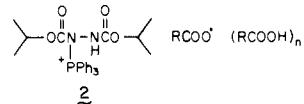


Step 2: Alcohol Activation



Step 3: S_N2 Reaction





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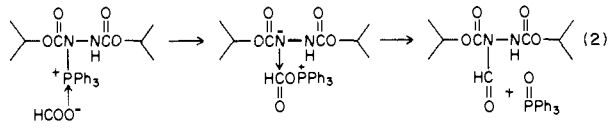
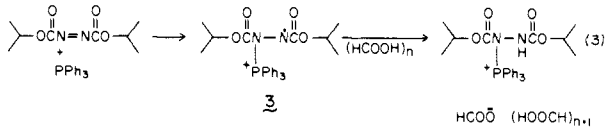
When 1 equiv each of DIAD, PPh_3, and HCOOH (or CH_3COOH) are used in the reaction, rapid N-formylation (or acetylation) of the DIAD adduct occurs (complete reaction in 10 min at ambient temperature), apparently by nucleophilic attack by formate on phosphorus (eq 2). Under these conditions only



(2)

a small amount of esterification of the alcohol takes place. When the amount of HCOOH is increased from 1.0 to 2.0 equiv, the Mitsunobu adduct (**2**) is far more stable, having a half-life of about 15 h at 30 °C. Under these conditions, clean esterification of the alcohol takes place. This difference in reaction pathway can be attributed to the control of $HCOO^-$ reactivity by hydrogen bonding. When only 1 equiv of HCOOH is used in the reaction, all of it is used to protonate the zwitterion (**3**), forming 1 equiv of formate ion (eq 3). When 2 equiv of HCOOH are used, 1



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equiv of $HCOO^-$ is formed and 1 equiv remains unreacted to give

(1) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(2) Thienamycin synthesis using hydroxyl inversion **1A** to **1B**: (a) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. (b) Melillo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913. (c) Shinkai, I.; Liu, T.; Reamer, R. A.; Sletzinger, M. *Tetrahedron Lett.* **1982**, *23*, 4899–4902. (d) Sletzinger, M.; Liu, T.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1980**, *21*, 4221–4224.

(3) The inversion reactions were originally run in these laboratories on a large scale (G. Gal, G. G. Hazen, R. P. Volante) with diisopropyl azodicarboxylate (DIAD) instead of the ethyl ester (DEAD) because the former was considered a safer compound and was more readily available. Thus, our studies centered on the use of DIAD instead of DEAD. Recent work indicates little difference between the two reagents.

(4) (a) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843–1845. (b) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876–6877. (c) Von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557–563. (d) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767–774.

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

(6) Reamer, R. A.; Shinkai, I.; Riseman, S. M.; Hughes, D. L., submitted for publication in *J. Am. Chem. Soc.*

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Table I. Rate of Oxyphosphonium Intermediate (4) Formation with Variable HCOOH/HCOO⁻ Ratios in CH_2Cl_2 Solution

concn of β-lactam 1A, M	concn of DIAD–PPh_3–HCOO⁻ adduct 2, M	concn of HCOOH, M	HCOOH/HCOO⁻	temp, °C	10^4k, M^{-1} s^{-1}	k_{rel} (0 °C)
0.21	0.52	0.52	1.0	−20	3.3	
0.21	0.50	0.50	1.0	0	11.4	
0.23	0.35	0.35	1.0	0	14.4	26
0.16	0.80	0.80	1.0	0	11.7	
0.20	0.54	0.29	0.54	−20	22.5	170
0.20	0.52	1.04	2.0	0	0.47	(1.0)

the strongly hydrogen bonded species, HCOO⁻···HOOCH. This species is apparently orders of magnitude less reactive than the free HCOO⁻. Equilibrium constants for the association of carboxylate ions with their conjugate acids have been measured in CH_3CN by Kolthoff and co-workers.[7] For PhCOOH the equilibrium constant in CH_3CN is 10^4. In the nonpolar solvents such as CH_2Cl_2 and THF used for the Mitsunobu reaction, these constants will likely be far larger. Thus, in the presence of 1.0 equiv of HCOOH, virtually all HCOO⁻ present will be hydrogen bonded.

When the adduct is formed in the presence of the stronger acid, *p*-TsOH, which has a more weakly basic conjugate base, the adduct is more stable and does not decompose even when only 1 equiv of *p*-TsOH is used.

Step 2. Alcohol Activation. The second step of the Mitsunobu reaction is transfer of the PPh_3^+ group from the DIAD–PPh_3 adduct (**2**) to the alcohol (eq 4 and 5). Three factors control the rate of this transfer: (1) the basicity of the counterion generated in formation of the DIAD–PPh_3 adduct, (2) the extent of hydrogen bonding to this counterion, and (3) substituent effects in the triarylphosphine. Before discussing these effects, a note is in order about the structure of the oxyphosphonium intermediate (**4**). Mitsunobu originally hypothesized a phosphonium salt as an intermediate, akin to structure **4**.[1,8] However, several recent papers have presented evidence for a neutral phosphorane structure (**5**) that has 2 mol of alcohol per mole of triphenylphosphine.[4] In all of these papers the purported phosphorane was prepared in the absence of a carboxylic acid.

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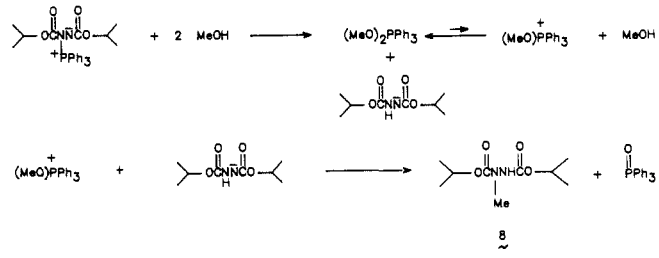
In our work, in the absence of an acid, no phosphorane is formed. Instead, at −20 °C in either CD_2Cl_2 or THF/C_6D_6, the major phosphorus species is $Ph_3P{=}O$ which is completely formed within 10 min of mixing. The fate of the β-lactam **1A** is unknown, but at least three degradation products were observed by ^{13}C NMR. In contrast, in the presence of a carboxylic acid, the stoichiometry and NMR data indicate that the oxyphosphonium intermediate **4** is formed exclusively. Since submission of this paper, Walker and co-workers[5] also found that an oxyphosphonium intermediate was formed in the presence of acid. In contrast to our work, they found that a stable phosphorane was formed in the absence of acid, which reverted to the phosphonium salt upon addition of acid.

To further sort out these findings, we examined reactions of the simple alcohols, MeOH and 2-butanol. In the absence of a carboxylic acid, neither forms observable phosphoranes at room temperature, but the phosphorane of 2-butanol is stable for several hours at −20 °C. The major degradation product from the MeOH reaction was **8** (R = Me), presumably arising as shown in Scheme II. We conclude that phosphoranes of variable stability are formed in the absence of acid. The safest way to run the Mitsunobu reaction is to have carboxylic acid present initially to prevent several undesirable reactions from occurring.

Scheme II



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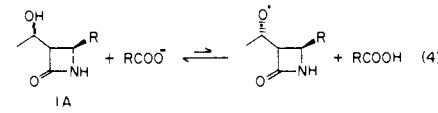
A. Effect of Carboxylate Basicity and Hydrogen Bonding on the Alcohol Activation Step. The rate of transfer of the PPh_3^+ group from the DIAD–PPh_3 adduct (**2**) to the alcohol is highly dependent on the basicity of the counterion generated in forming the DIAD–PPh_3 adduct (**2**) and on the extent of hydrogen bonding to this counterion. This indicates that the role of the counterion in this step is as a base to deprotonate the alcohol, which must occur before PPh_3^+ transfer takes place (eq 4 and 5).



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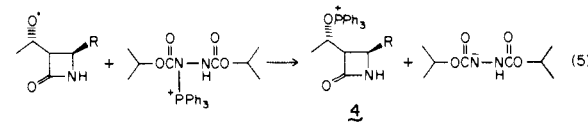

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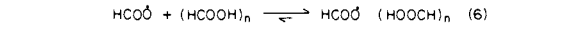
When the DIAD–PPh_3 adduct (**2**) is prepared with *p*-TsOH, no formation of the oxyphosphonium intermediate occurs due to the weak basicity of *p*-TsO⁻, which cannot appreciably deprotonate the alcohol. Use of *p*-TsOH for adduct formation, then adding 2,6-lutidine, also does not initiate formation of **4**, but addition of the stronger base Et_3N does catalyze **4** formation.

When the DIAD–PPh_3 adduct (**2**) is prepared in the presence of a carboxylic acid, the oxyphosphonium intermediate (**4**) forms at a rate that is dependent on the RCOOH/RCOO⁻ ratio and on the basicity of RCOO⁻. Table I shows rates of reaction of the β-lactam (**1**) to form the oxyphosphonium intermediate (**4**) at various ratios of HCOOH/HCOO⁻. The rates were calculated as being first-order in both the β-lactam and in the DIAD–PPh_3 adduct. The reactions were carried out with a β-lactam concentration of about 0.2 M in CH_2Cl_2 solution from 0 to −20 °C. The rates were followed by using normal-phase HPLC by assaying the disappearance of the β-lactam and appearance of the oxyphosphonium intermediate. The Experimental Section contains further details.

The rate is strongly affected by the HCOOH/HCOO⁻ ratio. An increase in this ratio from 0.54 to 2.0 causes a 170-fold decrease in rate. Two factors are responsible for this large rate dependency. From eq 4 the equilibrium will be shifted to the left with added HCOOH, reducing the amount of deprotonated alcohol needed for reaction. This can only account for a small part of the rate decrease. The main cause of the rate diminution is due to solvation of HCOO⁻ by HCOOH, which in effect reduces the basicity of the formate ion (eq 6). The less basic solvated



(6)

(7) (a) Chantooni, M. K., Jr.; Kolthoff, I. M. *J. Am. Chem. Soc.* **1970**, *92*, 7025–7030. (b) Hojo, M.; Imai, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1963–1967.

(8) Oxyphosphonium ions have been isolated and characterized from Mitsunobu reactions: Kunz, H.; Schmidt, P. *Justus Liebigs Ann. Chem.* **1982**, 1245–1260.

Table II. Effect of Carboxylate Basicity on Oxyphosphonium Intermediate (**4**) Formation in CH_2Cl_2 Solution

acid	$pK_a(H_2O)^a$	pK_a-$(Me_2SO)^b$	temp, °C	10^4k, M^{-1} s^{-1}	k_{rel}
CH_3COOH	4.76	12.6	−20	36	20000
HCOOH	3.77	10.6	−20	3.3	
HCOOH	3.77	10.6	0	12.5	1800
$ClCH_2COOH$	2.86	9.0	0	1.5	200
$CNCH_2COOH$	2.43	8.5	0	0.2	30
$Cl_2CHCOOH$	1.29	6.36	40	0.09[c]	(1.0)

[a] Jencks, W. P.; Regensein, J. *Handbook of Biochemistry and Molecular Biology*; Sober, H. A., Ed.; Chemical Rubber Co.: Cleveland, OH, 1968; p J 150. [b] Kolthoff, I. M.; Chantooni, M. K., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 5063–5068. [c] Extrapolated to 0.007 at °C.

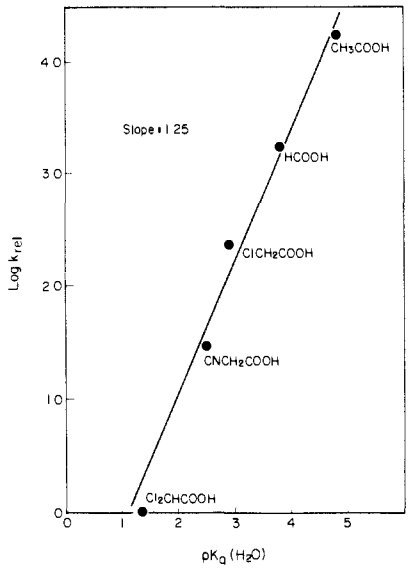


Figure 1. Plot of log k vs $pK_a(H_2O)$ for oxyphosphonium intermediate (**4**) formation in CH_2Cl_2 (eq 4 and 5).

formate ion will deprotonate less alcohol, causing the reduced rate. The situation is similar to the large increase in basicity of alkoxides when transferred from a hydrogen bond donor solvent ($pK_a(H_2O)$ in H_2O is 15.7[9]) to an aprotic solvent such as Me_2SO ($pK_a(H_2O)$ in Me_2SO = 32[10]). Likewise, the basicity of carboxylate ions are 10^7 greater in Me_2SO than in water.[7]

The above argument indicates that the rate of oxyphosphonium intermediate (**4**) formation is controlled by the "effective basicity" of formate ion in the reaction medium. To further test the dependency of this rate on counterion basicity, rates were measured with a series of carboxylate anions. The results are tabulated in Table II. For these reactions the ratio of RCOOH/$RCOO^-$ was 1.0 and the ratio of the DIAD–PPh_3 adduct (**2**) to β-lactam (**1A**) was 2.5. A plot of log k_{rel} vs pK_a(water), shown in Figure 1, has a slope of 1.25, indicating the high sensitivity of the reaction to carboxylate basicity. A similar plot vs pK_a's in Me_2SO, a solvent without hydrogen bond donating abilities and, therefore, somewhat similar to CH_2Cl_2, gives a slope of 0.75. The linearity of these plots and the large slopes suggest that the carboxylate anion is acting as a thermodynamic base, and that the equilibrium concentration of the deprotonated alcohol controls the reaction rate, in accord with the mechanistic picture depicted in eq 4 and 5.

In summary, in CH_2Cl_2 solution the reactivity of $RCOO^-$ as a base and as a nucleophile in the first two steps of the Mitsunobu reaction must be carefully controlled by solvation by RCOOH. With $HCOO^-$ as an example, if there is no solvation with HCOOH, then $HCOO^-$ is a potent nucleophile and reacts with the DIAD–PPh_3 adduct (**2**) (eq 2) competitively with the desired reaction with the β-lactam alcohol (eq 5). However, if too much

(9) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 1st ed.; Harper and Row: New York, 1976; p 153.
(10) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295–3299.

Table III. Rate of Oxyphosphonium Intermediate Formation (Eq 7) at 0 °C with Substituted Triarylphosphines in CH_2Cl_2 Solution

substituent	10^4k, M^{-1} s^{-1}	rel rate
m-Cl	99	6200
p-Cl	57	3600
H	12.5	780
m-Me	4.8	300
p-MeO	0.016	(1.0)

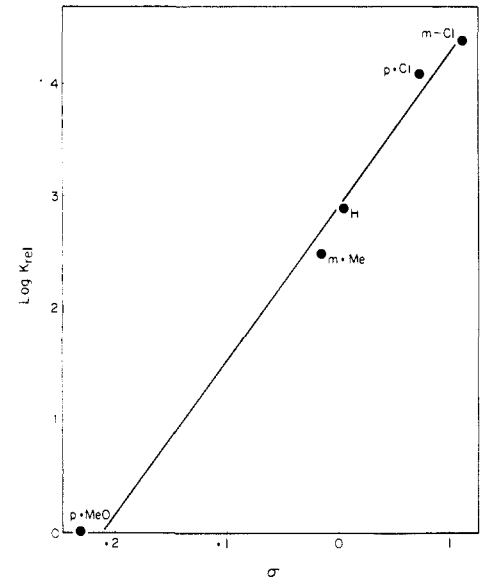
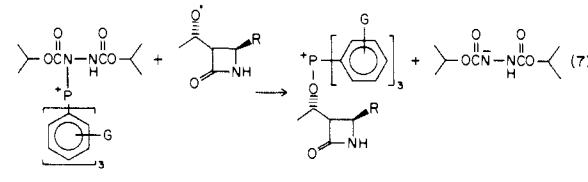


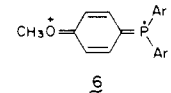
Figure 2. Hammett plot of log k vs δ for reaction shown in eq 7.

HCOOH (2 equiv) is used to reduce $HCOO^-$ nucleophilicity, then the effective basicity of $HCOO^-$ is too low to appreciably deprotonate the β-lactam alcohol, so again little alcohol activation occurs. The optimum ratio for the Mitsunobu reaction in CH_2Cl_2 is 1.0 equiv of HCOOH per 1.0 equiv of $HCOO^-$; under these conditions, alcohol activation proceeds more rapidly than $HCOO^-$ attack at phosporus.

B. Effect of Substitution in the Triarylphosphine on the Rates of Alcohol Activation. Table III lists rates for the alcohol activation reaction (eq 7) using five trisubstituted triphenylphosphines, all measured under the standard conditions of $HCOO^-$ = HCOOH in CH_2Cl_2 solution at 0 °C. Figure 2 shows a Hammett plot for



the reaction with use of standard σ values for *m*-Cl, *p*-Cl, H, and *m*-Me and assuming additivity of the three substituents. The *p*-MeO point would fit near the line if the σ^+ value of −0.78 were used. The slope of the line is 1.5 and is an indication of the sensitivity of the electrophilic nature of phosphorus to electronic effects. As would be expected, the ρ value is positive, indicating that electron-donating substituents diminish the electrophilicity of phosphorus. The strong decelerating effect of the *p*-MeO group suggests that significant $d\pi$–$p\pi$ overlap is occurring between the aryl ring and phosphorus (**6**). From dipole movement mea-



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surements, Goetz et al. have estimated that the resonance form (**6**) contributes 10% to the structure of $(p\text{-}MeOC_6H_4)PPh_2$.[11]

(11) Goetz, H.; Nerdel, F.; Wiechel, K. H. *Justus Liebigs Ann. Chem.* **1963**, *665*, 1.

Scheme III

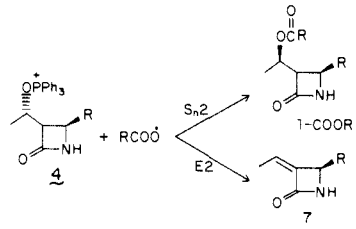

Table IV. Effect of Formic Acid/Formate Ratio on S_N2 and E2 Rates at 30 °C in CH_2Cl_2 Solution

equiv of β-lactam 1A	equiv of $HCOO^-$	equiv of HCOOH	S_N2 rate; 10^5 k, s^{-1}	E2 rate; $10k$, s^{-1}	S_N2/E2 rate ratio
1.0	2.5	1.5	144	13	12
1.0	2.5	2.5	61	3.6	17
1.0	2.5	5.5	12	0.40	30
1.0	2.5	7.5	5.0	0.11	45
1.0	2.5	12.5	0.94	0.014	70

Step 3. S_N2 Reaction. The final step of the Mitsunobu esterification is the S_N2 reaction of the carboxylate anion with the oxyphosphonium intermediate (Scheme III). In CH_2Cl_2 and THF the reaction proceeds with ~200:1 stereochemical inversion, indicating that the S_N1 component, if present, is small. Elimination is a competitive process, accounting for 2–8%, depending on the conditions.[13] With $HCOO^-$ and CH_3COO^-, formation of the oxyphosphonium intermediate (**4**) occurs completely at −20 to 0 °C with only 5–10% formation of the S_N2 product. In other words, build up of **4** occurred because the alcohol activation reaction is faster than the subsequent S_N2 reaction. Therefore, the S_N2 rates were followed by generating **4** at low temperature with HCOOH or CH_3COOH and then appropriately altering conditions as required to study the S_N2 step.

A. Formic Acid/Formate Ratio. The effect of the $HCOOH/HCOO^-$ ratio on the S_N2 and E2 reaction rates is shown in Table IV. The rates are reported as initial first-order rate constants, as the kinetics were roughly first-order in (**4**) and zero-order in $[HCOO^-]$. This unusual rate dependency is due to salt effects, as discussed below. The S_N2 rates were followed by hydrolyzing the resulting ester and measuring the ratio of β-lactam (**1A**) to inverted β-lactam (**1B**) by HPLC.

Inspection of Table IV shows that both the S_N2 and E2 reactions are slowed with increasing amounts of HCOOH, but not to the same extent as the rate of oxyphosphonium intermediate (**4**) formation. Thus, increasing the $HCOOH/HCOO^-$ ratio from one to two reduces the alcohol activation step 25-fold, the E2 reaction 10-fold, and the S_N2 reaction 5-fold.

In summary HCOOH solvation of $HCOO^-$ reduces $HCOO^-$ (1) nucleophilicity toward phosphorus, (2) thermodynamic basicity in the deprotonation of the β-lactam alcohol, (3) kinetic basicity in the E2 reaction, and (4) nucleophilicity toward saturated carbon in the S_N2 reaction.

B. Salt Effects. Kinetic studies indicated that the substitution reaction followed S_N1 kinetics, being first-order in oxyphosphonium salt (**4**) but zero-order in $[HCOO^-]$, although complete stereochemical inversion was occurring as expected for an S_N2 reaction. The apparent zero-order dependence in $HCOO^-$ is due to a salt effect, which can be eliminated by running the reaction in the presence of a swamping electrolyte, n-Bu_4NBF_4. Table V shows a comparison of initial rates measured with and without excess salt at 0 °C in CH_2Cl_2 with $HCOOH/HCOO^-$ = 1.0 and [**1A**] = 0.03 M.

Column 3 of Table V shows how, in the absence of the swamping electrolyte, the rate is not affected by increased formate concentration. Comparison with column 4 shows that the rates

Table V. Salt Effects on Rate of Reaction of Oxyphosphonium Intermediate (**4**) with $HCOO^-$ in CH_2Cl_2 Solution at 0 °C

equiv of 1A	equiv of $HCOO^-$	relative rate constant	
		no added salt	0.5 M n-$Bu_4N^+BF_4^-$
1.0	1.5	10.6	(1.0)
1.0	2.5	11.4	1.5
1.0	5.0	10.6	2.3
1.0	10.0	9.8	5.4

Table VI. Rates of S_N2 Reaction of Oxyphosphonium Intermediate (**4**) with Carboxylate Anions in CH_2Cl_2 at 20 °C

carboxylate anion, (equiv)[a]	pK_a (water)	carboxylic acid (equiv)[a]	10^4k, s^{-1} 30 °C	k_{subst}/k_{elim}
CH_3COO^- (2.5)	4.76	CH_3COOH (2.5)	12	13
$HCOO^-$ (2.5)	3.77	HCOOH (2.5)	6.4	15
$HCOO^-$ (2.5)	3.77	HCOOH (5.0)	1.2	30
$ClCH_2COO^-$ (2.5)	2.86	$ClCH_2COOH$ (2.5)	2.4	18
$ClCH_2COO^-$ (2.5)	2.86	$ClCH_2COOH$ (5.0)	0.9	
Cl_2CHCOO^- (2.5)	1.29	HCOOH (5.0)	0.8	40
CF_3COO^- (2.5)	0	HCOOH (5.0)	0.4	70
p-TsO^- (2.5)	<0	HCOOH (5.0)	0.2	>150

[a] Equivalents of carboxylic acid and anion based on 1.0 equiv of β-lactam **1A** and 2.5 equiv of PPh_3 and DIAD.

are retarded in the presence of the excess salt. For the rates in the presence of n-$Bu_4N^+BF_4^-$, a plot of log k vs log $[HCOO^-]$ has a slope of 0.9, indicating that, when the complications due to salt effects are eliminated, the order in formate is close to unity as expected for an S_N2 reaction.

The reduction in rate upon addition of salt is further evidence for the oxyphosphonium intermediate (**4**) and against the phosphorane intermediate (**5**). For a reaction in which reactants are oppositely charged and products are neutral (as in eq 5), an increase in ionic strength slows the reaction.[12] If the intermediate were a neutral phosphorane, salts would be expected to have little effect on the rate.

C. Effect of Carboxylate Basicity on S_N2 Rates. The rates of reaction of the oxyphosphonium intermediate (**4**) with various carboxylate anions are shown in Table VI. The rates are reported as initial first order rates due to the salt effects noted above. For CF_3COOH, $Cl_2CHCOOH$, and p-TsOH, the S_N2 rates were measured by initially forming the oxyphosphonium intermediate (**4**) at −20 °C with $HCOO^-/HCOOH$ = 1.0 and then adding 1.0 equiv of the strong acid (RCOOH) to form 1.0 equiv of $RCOO^-$ and 2.0 equiv of HCOOH. This was required because with the weaker acid anions, the rate determining step is the alcohol activation, not the S_N2 step.

A Brønsted plot of log k vs pK_a(water) is shown in Figure 3 in comparison with the Brønsted plot for the alcohol activation step. In contrast to the alcohol activation step, there is only a slight dependence of the S_N2 rate on the carboxylate basicity. The slope of the line is 0.15; with the pK_a's in Me_2SO the slope is 0.10. The small β_{Nu} value indicates that the S_N2 transition state is one with much S_N1 characer, having a small amount of bond making and a large amount of bond breaking. This is not unexpected since carboxylates are weak nucleophiles, while triphenylphosphine oxide is an excellent leaving group due to formation of the strong P=O bond.

The large difference in response of the alcohol activation step and the S_N2 step (Figure 3) to carboxylate basicity means that the basicity controls which step is rate determining. With CH_3COO^- and $HCOO^-$, the slow step is the S_N2 reaction, with complete alcohol activation occurring before the S_N2 step. With $ClCH_2COOH$ the rates of alcohol activation and the S_N2 step become comparable.

The recent work of Walker and co-workers[5] can be understood in light of the preceding discussion. They were puzzled that PhCOONa accelerated the Mitsunobu esterification of a steroid alcohol with CF_3COOH without forming a benzoate ester. From Figure 2 we can estimate a difference in reactivity for alcohol activation between $PhCOO^-$ (pK_a = 4.0) and CF_3COO^- (pK_a = 0) to be 5 orders of magnitude. We have measured the solubility

(12) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975; pp 94–105.

(13) Only one isomer is formed, indicating the E2 is the probable mechanism. An E1 mechanism should give a mixture of both geometric isomers. The *Z* stereochemistry was assigned on the basis of long range ^1H–^{13}C coupling constants.

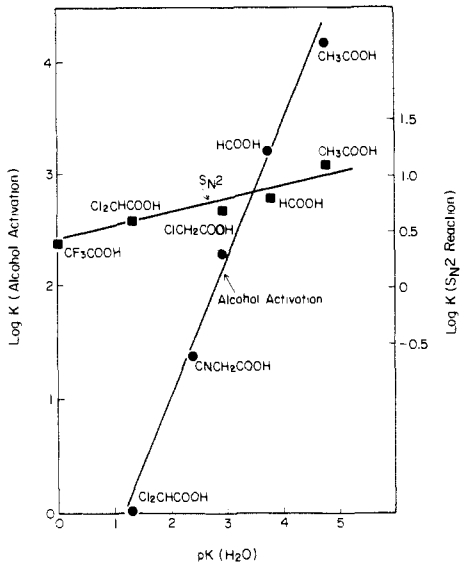

Figure 3. Plots of log k vs pK_a(water) for the alcohol activation step (eq 4 and 5) in comparison with the S_N2 reaction (Scheme III).

of PhCOONa by an HPLC method and found that only 0.03 g/L dissolve in anhydrous THF while 2 g/L dissolve under the actual Mitsunobu reaction conditions of Walker.[5] The latter number is equal to 4 mol %. Since the reactivity of PhCOONa is so high compared to CF_3COO^- and since it will be a true catalyst (it will be regenerated in the reaction sequence), this small solubility will be enough to greatly accelerate the alcohol activation step, yet not enough to generate appreciable amounts of benzoate ester.

Summary

As evidenced by the 400 citations of Mitsunobu's review[1] since 1981, the Mitsunobu reaction has become a valuable tool in the synthetic chemist's repertoire. However, a lack of basic understanding of the reaction has often led to cases where low yields or undesirable side products occur. We have provided a detailed study of the reaction, which should lead to an increased use and control of the reaction. A summary of the key points follows.

(1) As shown in Figure 3, there is a tremendous difference in response of the alcohol activation step and the S_N2 step to carboxylate basicity. When CH_3COO^- and $HCOO^-$ are used, the slow step of the reaction is the S_N2 step, with complete formation of the oxyphosphonium intermediate (**4**) occurring before the S_N2 reaction. With Cl_2CHCOO^-, CF_3COO^-, and p-TsO^-, the slow step is the alcohol activation, and in these cases, no build up of the oxyphosphonium intermediate (**4**) occurs.

(2) The alcohol activation step is also more sensitive than the S_N2 step to solvation of the carboxylate anion by the carboxylic acid. With use of the HCOOH/$HCOO^-$ system as an example, with the HCOOH/$HCOO^-$ ratio ≤ 1, the S_N2 step is the slow step with complete alcohol activation occurring before the S_N2 reaction. At HCOOH/$HCOO^-$ = 2 the rates are comparable and at HCOOH/$HCOO^-$ $\geq$ 3 the alcohol activation step becomes rate determining.

(3) Addition of a swamping salt has little effect on the alcohol activation step but can decrease the S_N2 reaction rate by 10-fold, depending on reactant concentrations. In the absence of swamping salts, the ionic species formed in the first two steps of the reaction cause unusual salt effects on the S_N2 reaction. As the concentrations of reactants are decreased, the concentration of ionic species is also reduced, so the diminution in rate caused by a decrease in concentration is counterbalanced by a comparable rate increase caused by a reduction in ionic strength. Thus, reactant concentrations have a minimal effect on the S_N2 rate, while normal concentration effects are felt by the alcohol activation step.

Experimental Section

General Procedures. NMR spectra were taken on Varian XL-100 and CFT-20, and Bruker WM-250 spectrometers. Diisopropyl azodicarboxylate (96%) was suppled by Muskegon. Formic acid containing 0.8% water was supplied by BASF. Compound **1A** was prepared by methods described in the literature.[9] HPLC conditions for the assay of **1A**, **1B**, and **4** were the following: Whatman PAC 10 column, 25 cm × 4 mm; eluent, 70% CH_2Cl_2, 29% CH_3CN, 0.5% HOAc, and 0.5% water; flow, 1.5 mL/min; ambient temperature; retention times, **4** 6 min, **1A** 9 min, **1B** 11 min. The assay for the formate derivative (1-COOR) was problematic, so the esters were hydrolyzed (2 min at 0 °C in 80% CH_3CN/water) to the hydroxyl compound (**1B**) for assay. The HPLC conditions for measuring the olefin product **7** were the following: Whatman PAC column; eluent, 97% CH_2Cl_2, 2% EtOH, 1% HOAc; flow, 1.5 mL/min; ambient temperature; retention time, 8 min.

Kinetic Measurements. Conditions for three typical kinetic experiments follow.

A. Formation of the Oxyphosphonium Intermediate (1A to 4). The 2-(hydroxyethyl)azetidinone (**1A**) (0.98 g, 2.80 mmol), formic acid (0.68 g, 14.8 mmol), and PPh_3 (1.87 g, 7.14 mmol) were dissolved in 12.4 g of CH_2Cl_2. The mixture was cooled to −20 °C, and diisopropyl azodicarboxylate (DIAD) (1.43 g, 7.08 mmol) was added dropwise over a 0.5-h period. Formation of complex **2** was nearly instantaneous as evidenced by DIAD decolorization on addition. Total volume at this point was 13.6 mL. At the end of the addition, a 0.1-g aliquot was added to a tared 100-mL volumetric flask containing CH_3CN, weighed, and then assayed by HPLC λ 265 nm for **1A** and **4**. Similar aliquots were taken about every 0.5 h (half-life 90 min). The second-order rate constant was determined from data taken over the first 3 half-lives.

B. S_N2 Rate with Trifluoroacetate. 2-(Hydroxyethyl)azetidinone **1A** (0.99 g, 2.83 mmol), formic acid (0.69 g, 15.0 mmol), and PPh_3 (1.88 g, 7.18 mmol) were dissolved in CH_2Cl_2 (12.5 g). Diisopropyl azodicarboxylate (1.43 g, 7.08 mmol) was added at −20 °C over a 0.5-h period, and the mixture was held at −20 °C for 14 h to completely form the oxyphosphonium formate intermediate (**4**). Then CF_3COOH (0.85 g, 7.46 mmoles) was added, and the kinetics was followed by HPLC at 30 °C ($t_{1/2}$ = 7 h). ^{13}C NMR was consistent with formation of the trifluoroacetate ester.

C. S_N2 Rate with Swamping Salt. The 2-(hydroxyethyl)azetidinone **1A** (0.45 g, 1.42 mmol), formic acid (0.34 mmol, 7.4 mmol), and PPh_3 (0.94 g, 3.09 mmol) were dissolved in 5 mL of CH_2Cl_2. Diisopropyl azodicarboxylate (0.71 g, 3.03 mmol) was added over a 0.5-h period at −20 °C and aged there for 15 h to completely form the oxyphosphonium formate intermediate (**4**). The reaction was then diluted to 40 mL with CH_2Cl_2, and 6.58 g of n-Bu_4NBF_4 was added (0.5 M solution), and the kinetics was followed by HPLC at 0 °C. The pseudo-first-order rate constant was calculated from the first 20% of the reaction.

Registry No. **1A**, 84985-43-3; **1B**, 75321-07-2; **1**-COOR (R = H), 84985-45-5; **3**, 86825-70-9; **4**, 115859-53-5; **5** (R = Me), 86825-61-8; **5** (R = 2-Bu), 86825-66-3; **7**, 115859-54-6; **8**, 115859-49-9; DIAD, 2446-83-5; MeOH, 67-56-1; 2-BuOH, 78-92-2; PPh_3, 603-35-0; HCO_2H, 64-18-6; CH_3CO_2H, 64-19-7; i-PrOCON(CHO)NHCOOPr-i, 115859-50-2; p-TsOH, 104-15-4; Et_3N, 121-44-8; PhCOONa, 532-32-1; $ClCH_2CO_2H$, 79-11-8; $CNCH_2CO_2H$, 372-09-8; Cl_2CHCO_2H, 79-43-6; $P(C_6H_4$-m-$Cl)_3$, 29949-85-7; $P(C_6H_4$-p-$Cl)_3$, 1159-54-2; $P(C_6H_4$-m-$Me)_3$, 6224-63-1; $P(C_6H_4$-p-$OMe)_3$, 855-38-9; $HCOO^-$, 71-47-6; CH_3COO^-, 71-50-1; $ClCH_2COO^-$, 14526-03-5; Cl_2CHCOO^-, 13425-80-4; CF_3COO^-, 14477-72-6; p-TsO^-, 16722-51-3; thienamycin, 59995-64-1.