0.48 g (40%) of **18** as yellow crystals: mp 149–150 °C; IR (KBr) 1710 (C=O), 1300, 1170, 830, 770, 755, 730 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 2.21 (s, 3 H, CH_3), 2.2–2.8 (m, 3 H, aliphatic), 7.4–8.5 (complex, 8 H, aromatic). Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.58; H, 4.29; S, 9.82. Found: C, 62.59; H, 4.60; S, 9.94.

Reaction of 9-Diazothioxanthene 10,10-Dioxide with Benzyne. To a solution of 2.6 g (0.01 mol) of **16** and 1.35 g (0.012 mol) of iosamyl nitrite in 50 mL of methylene chloride heated at reflux was added 1.4 g (0.11 mol) of anthranilic acid in 12 mL of acetone over a period of 1.5 h. The solvent was removed to give 2.87 g of a dark residue. The residue was washed with ethanol and recrystallized from acetonitrile to give 2.85 g (86%) of **19** as orange-red crystals: mp 195–197 °C; IR (KBr) 1600 (w), 1480, 1300, 1170, 750 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 6.8, 7.75, 8.63 (complex aromatic pattern). Anal. Calcd for $C_{19}H_{12}N_2O_2S$: C, 68.67; H, 3.61; N, 8.43; S, 9.64. Found: C, 68.58; H, 3.55; N, 8.50; S, 9.61.

Test for Dark Reactions. Solutions of **8** in tetrahydrofuran and dimethyl fumarate or dimethyl maleate were degassed and allowed to stand in the absence of light. The solutions were monitored by NMR spectroscopy at 5-min intervals for 2 h. No evidence of any reaction was observed.

Acknowledgment. Support from the Research Corporation and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, is greatly appreciated. We thank Dr. W. H. Pirkle for obtaining the 220-MHz NMR data and for helpful comments.

Registry No.—**7**, 66688-04-8; **8**, 23619-77-4; **9**, 27090-16-0; **10**, 492-22-8; **11**, 66688-13-9; **12**, 66688-03-7; **13**, 66688-12-8; **16**, 3166-17-4; **17**, 66688-14-0; **18**, 66719-15-1; **19**, 66688-15-1; cyclohexene, 110-83-8; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6; MVK, 78-94-4; benzyne, 462-80-6.

References and Notes

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(2) Taken in part from the M.S. Thesis of M.A.D., Southern Illinois University, 1976.
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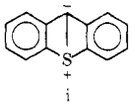

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Reactions of Esters with Phosphorus Ylides. 2.[1] Mechanistic Aspects

Arnold P. Uijttewaal, Froukje L. Jonkers, and Arne van der Gen*

Department of Organic Chemistry, University of Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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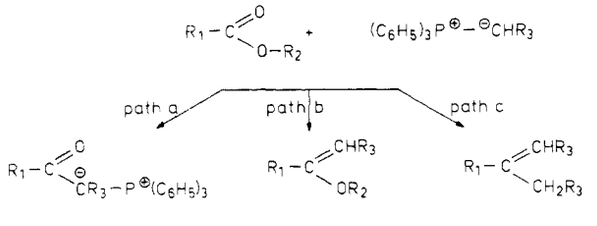
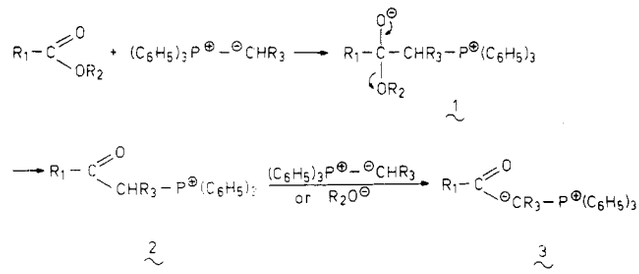
Esters can be directly converted into branched alkenes by reaction with an excess of a nonstabilized phosphorus ylide, $(C_6H_5)_3P^+-{}^-CHR_3$, in polar aprotic solvents or under "salt-free" conditions (Scheme I, reaction path c). On the basis of labeling experiments and the isolation of a reaction intermediate and side products, a mechanism for this conversion is proposed (Scheme II). The rate-determining step appears to be attack of the ylide carbanion on the ester carbonyl to give an alkoxybetaine **22**. This betaine rearranges to a pentacoordinate phosphorus intermediate (**23**) which, after pseudorotation, undergoes attack by a nucleophile, e.g., a second molecule of ylide to form a new phosphonium salt, triphenylphosphine oxide, and an enolate anion. After protonation of this enolate to the corresponding ketone, reaction with a third molecule of ylide provides the final product. The relation of this reaction sequence to the other known reactivities that esters can show toward phosphorus ylides is discussed.

Reaction of esters with phosphorus ylides may result in the formation of several types of products, as depicted in Scheme I. Reaction path a was first discovered by Wittig and Schöllkopf[2] when ethyl benzoate was allowed to react with methylenetriphenylphosphorane, prepared by reacting the corresponding phosphonium bromide with phenyllithium in ether. The reaction sequence can be depicted as shown, starting with nucleophilic attack of the ylide on the ester carbonyl group to form the alkoxybetaine **1**. Loss of alkoxide ion from this betaine leads to the formation of an acylated phosphonium salt **2**. Bestmann and Arnason[3] have shown that this phosphonium salt rapidly loses a proton to a second molecule of ylide or alkoxide ion to form the acylated phosphorane **3**. Several investigators have improved this reaction by using acyl derivatives with a different leaving group (e.g., phenyl esters, phenyl thioesters[3] and imidazolides[4,5]). The phosphoranes **3** can be hydrolyzed to the corresponding ke-

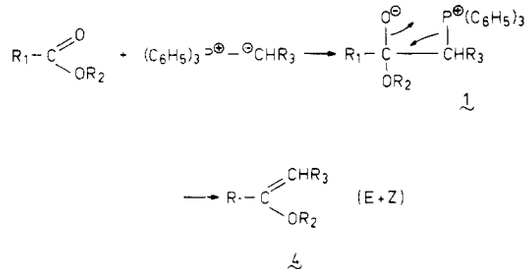
Scheme I. Products from the Reaction of Esters with Phosphorus Ylides





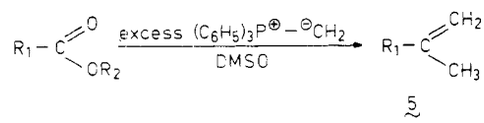
tones by refluxing with potassium hydroxide in aqueous ethanol.[3,6] Although the ylide reactivity in compounds **3** is quite low due to conjugation with the carbonyl group, aromatic aldehydes react with **3** to form the corresponding α,β-unsaturated ketones.[3,6]

When "semi-stabilized" ylides[7] such as benzylidenetriphenylphosphorane are used in conjugation with active esters (formates, oxalates, etc.), a completely different reaction (Scheme I, path b) may be observed, resulting in the formation of enol ethers **4.** The reaction is thought to proceed as a normal



Wittig reaction on the ester carbonyl group. The reaction is usually carried out in solvents of low polarity, e.g., toluene.[8] The alkoxybetaine **1,** which is formed as before by addition of the ylide to the ester carbonyl group, now loses triphenylphosphine oxide to provide a mixture of *E*/*Z* isomers of the enol ethers **4.**[9]

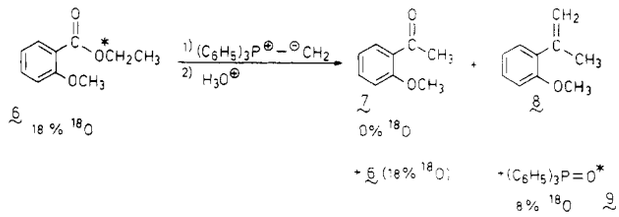
Recently, when performing a Wittig reaction on a hindered γ-keto ester with an excess of methylenetriphenylphosphorane in dimethyl sulfoxide (Me_2SO), a third type of reaction product, the isopropenyl compound **5,** was observed.[1] This



reaction was found to be generally applicable to both aromatic and aliphatic esters.[1] That indeed a different reaction path is followed in this case was shown by the observation that under the reaction conditions used phosphonium salts **2** were instantly converted into phosphoranes **3** and that these phosphoranes as well as the enol ethers **4,** prepared by independent routes, were completely stable and thus can not be intermediates (see Experimental Section). The elucidation of the mechanism which is followed in reaction path c is the subject of the present article. The scope and synthetic applications of this reaction will be published separately.[12]

Results and Discussion

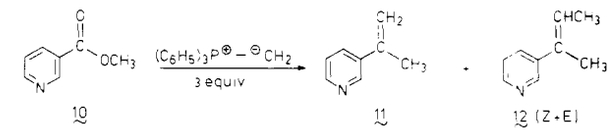
Isolation of a Reaction Intermediate. When the reaction of an aromatic or aliphatic ester with excess methylenetriphenylphosphorane in Me_2SO is followed by GC, no intermediate products can be discovered in most cases. However, when the hindered ester ethyl *o*-methoxybenzoate was reacted in this way, an intermediate was observed. Upon quenching the reaction with water after 9 min at room temperature, the product contained, apart from starting material (52%) and the expected reaction product *o*-isopropenylanisole (**8;** 30%), 17% of a third compound which was identified as *o*-methoxyacetophenone (**7**). This indicated that a methyl ketone and/or its



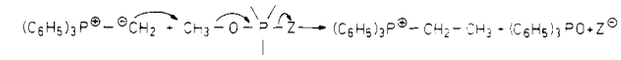
anion are intermediates in this reaction. That no signs of an intermediate methyl ketone are found in most cases is not surprising because ketones react much faster with phosphoranes than esters.[13]

Isolation of the intermediate methyl ketone provides an opportunity to determine, with the aid of labeled ester, which oxygen is the first to leave (note that in reaction path a (Scheme I) the alkoxy oxygen has left, whereas in path b this is the carbonyl oxygen). Mass spectral analysis of the reaction mixture obtained as described above from *o*-methoxy-2-oxabutyrophenone-2-^{18}O (**6**), containing 18% of ^{18}O, revealed that none of this isotope is retained in the methyl ketone. Surprisingly, the ^{18}O was found to end up in the triphenylphosphine oxide (**9**). This implies that the alkoxy alkyl group has become detached from its oxygen atom, a process that can only be envisaged when this oxygen has become part of an efficient nucleofugal group.

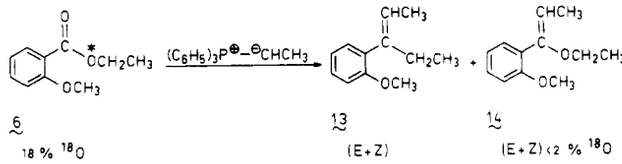
Isolation of Side Products. A clue about the fate of the ester alkyl group was found by studying the reaction of methyl nicotinate (**10**) with the smallest amount (3 equiv) of methy-



lenetriphenylphosphorane that allowed complete conversion of the ester. Two side products were found, which were identified as (*E*)- and (*Z*)-2-(3-pyridyl)-2-butene (**12**). This finding suggests that the intermediate methyl ketone (3-acetylpyridine) has also reacted with ethylidenetriphenylphosphorane. We propose that this reagent is formed in situ by alkylation of methylenetriphenylphosphorane by a process as depicted below, followed by deprotonation.

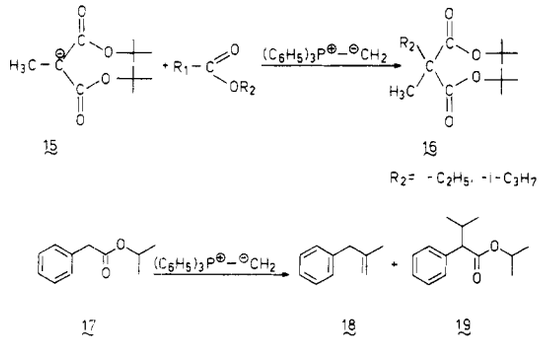


Reacting ethyl *o*-methoxybenzoate with 4 equiv of ethylidenetriphenylphosphorane gave, apart from the expected (*E*)- and (*Z*)-3-(*o*-methoxyphenyl)-2-pentene (**13**), appreciable amounts of (*E*)- and (*Z*)-1-(*o*-methoxyphenyl)-1-ethoxypropene (**14**). To ascertain whether these enol ethers were



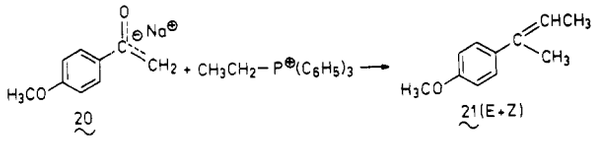
formed by a "Wittig type" reaction on the ester carbonyl (reaction path b, Scheme I), the reaction was repeated with labeled ester **6.** Mass spectral analysis showed that the enol ethers **14** are formed to an extent of at least 90% by alkylation of an intermediate enolate and not by conversion of the ester carbonyl into the ethylidene group.

Confirmation of the Presence of an Alkylating Species. The hypothesis that the ester alkoxy group is converted into an alkylating species was further substantiated by the following two experiments. (i) Addition of 1 equiv of the anion from di-*tert*-butyl α-methylmalonate (**15**) resulted in the formation of the corresponding di-*tert*-butyl α-alkyl-α-



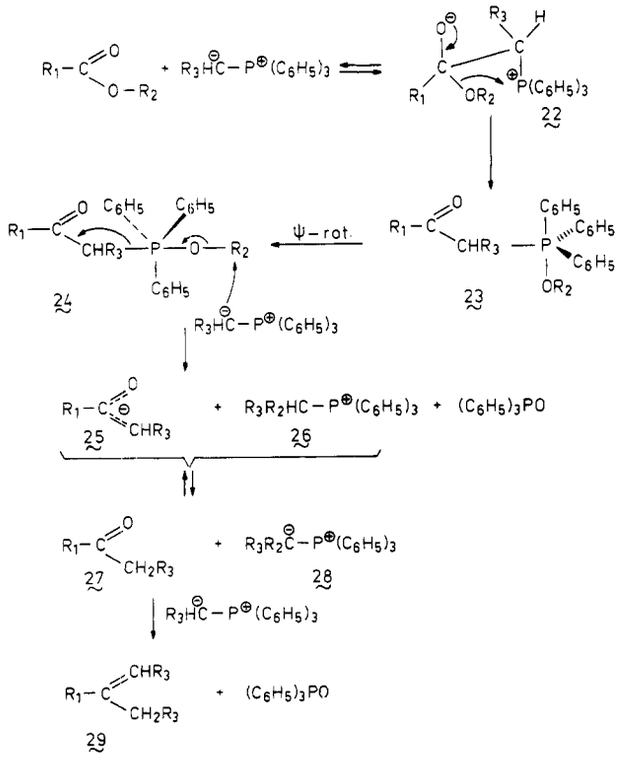
methylmalonate (16). (ii) When isopropyl phenylacetate (17) was allowed to react with 4 equiv of "salt-free" methylenetriphenylphosphorane in benzene, a considerable amount of isopropyl α-isopropylphenylacetate (19) was formed. This sterically hindered ester is apparently stable toward attack by ylide.

Equilibration of Enolate Ions and Phosphonium Salts. Finally, an experiment was carried out to show that enolate ions and alkyltriphenylphosphonium salts are in rapid acid–base equilibrium under the reaction conditions used. Thus, the addition of 1 equiv of ethyltriphenylphosphonium iodide to a solution of the sodium enolate of *p*-methoxyacetophenone (20) in Me_2SO at room temperature resulted in the formation



of the *E* and *Z* isomers of 2-(*p*-methoxyphenyl)-2-butene (21) in the same isomer ratio as in the reaction product obtained from methyl *p*-methoxybenzoate and ethylidenetriphenylphosphorane.[12] Combining the data presented thus far leads to a mechanism for the ester/ylide reaction as depicted in Scheme II. The first step in this process is thought to be attack of the ylide on the ester carbonyl to form the alkoxybetaine

Scheme II. Mechanism of the Ester/Ylide Reaction

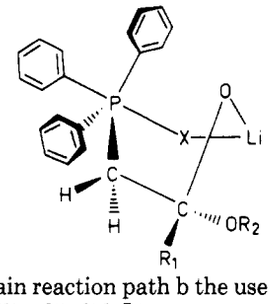


22. This betaine undergoes an intramolecular rearrangement in which the alkoxy group moves to the quaternary phosphorus atom, thus forming a pentacoordinate phosphorus intermediate **23** in which one of the apical positions is initially occupied by a phenyl group. Upon positional isomerization (pseudorotation), the energetically favored **24** is obtained, in which both polar substituents occupy apical positions.[14] The great tendency toward electron displacement in the direction of the apical axis in intermediates such as **24** is well documented.[15] Nucleophilic attack on the alkoxy group in **24** by a second molecule of ylide (or another nucleophile) therefore is likely to proceed as indicated and results in the formation of triphenylphosphine oxide, the new phosphonium salt **26,** and the enolate **25.** Acid–base equilibration between **25** and **26** forms the ketone **27** and the new ylide **28.** Ketone **27** engages in a Wittig reaction with a third molecule of ylide to form the branched alkene **29** as the final product.

To ascertain which step in this reaction sequence is rate determining, the relative rates of a number of *o*-methoxybenzoates were studied. The strong influence of the nature of the $-OR_2$ group on the reaction rate suggests that either the initial step (addition of ylide to the carbonyl group) or the nucleophilic attack on the alkoxy group in intermediate **24** is rate determining. The relative rates observed, methyl (20), ethyl (7), isopropyl (1), neopentyl (3), and *tert*-butyl (0), appear reasonable for nucleophilic addition of ylide to an ester carbonyl group.[16] Nucleophilic substitution in the intermediate **24,** whether S_N2 or S_N1 in character,[17] is expected to show quite different relative rates.[16]

Comparison of the Different Reaction Paths Between Esters and Phosphorus Ylides. Comparing the mechanism of reaction paths a, b, and c makes it clear that the conformation of the initially formed alkoxybetaine is a critical factor in determining the course of the reaction. When a lithium base is used to prepare the ylide, the lithium halide formed must be expected to form a strong complex with the betaine. Schlosser[18] has proposed a twist-boat structure for such a betaine–lithium halide adduct in the Wittig reaction.

If a similar complex is formed in the case of the alkoxybetaines **1,** it is quite reasonable that upon reformation of the carbonyl double bond the alkoxy group is lost, giving rise to the acylated phosphoranes **2** (Scheme I, path a). The low tendency of oxygen, complexed with lithium, to form triphenylphosphine oxide is well documented.[18]



In order to obtain reaction path b the use of another cation and a "semi-stabilized" ylide[7] is necessary. Because solvents of low polarity such as toluene are used,[8] the intermediacy of an alkoxybetaine with a stereostructure as shown is also probable in these cases. The substituent that stabilized the ylide will also stabilize the incipient double bond of the enol ether. Other factors in determining the different outcome of the reaction can be higher reaction temperatures and the less strongly bonded oxygen.

When a strongly solvating aprotic solvent is used, a staggered form as depicted in structure **22** can be expected to predominate. In this situation the alkoxy group is near the quaternary phosphorus atom, a "conditio sine qua non" for the intramolecular rearrangement that is to take place in reaction path c. This strong solvation is only necessary when

alkali halide is present in the reaction mixture. Execution of the reaction under "salt-free" conditions (see Experimental Section) in a variety of solvents has proved to be an excellent way to obtain high yields of branched alkenes according to path c. This is especially beneficial in the case of aliphatic esters, where initially mixtures of products were obtained.[1]

A different improvement of the reaction is possible by adding 1 equiv of the corresponding phosphonium salt to the ylide solution. In the course of the reaction this phosphonium salt is converted into another equivalent of the same ylide so that the formation of side products by reaction with homologous ylide **28** is largely or completely suppressed.

Finally, it is worth noting that no support for the suggestion of Vedejs and Snoble,[19] that the Wittig reaction with ketones and aldehydes occurs via a $_{\pi}2_s + _{\pi}2_a$ cycloaddition mechanism, can be derived from our experiments, which show that even esters react by nucleophilic addition of the ylides to the ester carbonyl group.

Experimental Section

Melting points were taken with a Büchi SMP-20 melting point apparatus and are uncorrected. GC analyses were run on a Hewlett-Packard 402 gas chromatograph equipped with a flame ionization detector using the columns indicated. Preparative GC was carried out using a Varian 920 gas chromatograph equipped with a thermal conductivity detector. Proton magnetic resonance spectra were recorded on a 100-Jeol PFT spectrometer. Chemical shifts are reported in parts per million on a scale relative to tetramethylsilane as an internal standard. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, coupling constants, and interpretation). Mass spectral data were obtained with an AEI-MS 902 apparatus at an ionization potential of 70 eV.

A "dry solvent" refers to solvents distilled from calcium hydride or dried over sodium wire. The term "standard workup conditions", which is used in the following Experimental Section, refers to the following product isolation procedure: pouring the reaction mixture onto a 3-fold quantity of a mixture of crushed ice and pentane; stirring overnight; filtration of the precipitate; separation of the pentane layer and extraction of the water/Me_2SO layer twice with a 0.5-fold quantity of pentane; treatment of the combined pentane layers with anhydrous magnesium sulfate; filtration; solvent removal under reduced pressure; and subjection of the resulting oil to short-path distillation.

Reactivity of Phenacyltriphenylphosphonium Bromide (2; R_1 = Ph, R_3 = H) and Phenacylidenetriphenylphosphorane (3; R_1 = Ph, R_3 = H) toward Methylenetriphenylphosphorane. A dry, nitrogen-purged, 250-mL three-neck round-bottom flask fitted with an addition funnel, magnetic stirrer, and nitrogen system was charged with 2.0 g (0.05 mol) of sodium hydride[20] and 35 mL of dry Me_2SO to prepare a 0.05 M methylsulfinyl carbanion solution.[13a] The flask was cooled to room temperature, and a solution of 20.2 g (0.05 mol) of methyltriphenylphosphonium iodide in 70 mL of dry Me_2SO was added over a 30-min period. Stirring was continued for 30 min. Phenacyltriphenylphosphonium bromide[21] (11.6 g, 0.0025 mol) in 35 mL of dry Me_2SO was added over a 2-h period to the yellow-orange colored ylide solution. Stirring was continued for 3 h at room temperature. The resulting solution was poured into 250 mL of water and stirred for 2 h. The white precipitate was collected on a Büchner filter and dried (reduced pressure, 50 °C, calcium chloride). There was obtained 7.1 g (93%) of phenacylidenetriphenylphosphorane as a white crystalline solid: mp 176–178 °C (lit.[3,21] mp 178–180 °C); NMR ($CDCl_3$) δ 7.99–7.19 (m, 20, arom), 4.39 (d, 1, J = 24 Hz (^1H–^{31}P), =CH).

Reactivity of 1-Ethoxy-1-phenylethene (4; R_1 = Ph, R_2 = C_2H_5, R_3 = H) toward Methylenetriphenylphosphorane. A solution of 1-ethoxy-1-phenylethene (3.0 g, 0.02 mol), prepared as described in the literature,[22] in 10 mL of dry Me_2SO was added over a 30-min period at room temperature to a solution of 0.05 mol of methylenetriphenylphosphorane in 105 mL of dry Me_2SO, prepared as described above using 2.00 g (0.05 mol) of sodium hydride[20] and 20.2 g (0.05 mol) of methyltriphenylphosphonium iodide. Stirring was continued for 1 h at room temperature and for 1 h at 55 °C. After workup under standard conditions, there was obtained 2.8 g (93%) of starting material (**4**): n^{22}_D 1.5304 (lit.[23] $n^{25.5}_D$ 1.5287); NMR ($CDCl_3$) δ 7.54 (m, 2, arom), 7.18 (m, 3, arom), 4.50 (d, 1, J = 2.5 Hz, =CH), 4.04 (d, 1, J = 2.5 Hz, =CH), 3.78 (q, 2, J = 7 Hz, $-OCH_2-$), 1.36 (t, 3, J = 7 Hz, $-CH_3$).

***o*-Methoxy-2-oxabutyrophenone-2-^{18}O (6).** An excess of *o*-methoxybenzoyl chloride in anhydrous diethyl ether was refluxed with absolute ethanol containing 75% ^{18}O.[24] After 1 h unlabeled absolute ethanol was added to obtain equimolarity. After workup under standard conditions, there was obtained 1.6 g (about 100%) of ethyl *o*-methoxybenzoate (**6**), containing 17.69 ± 0.03% of ^{18}O[25] in the ethoxy group: NMR ($CDCl_3$) δ 7.64–6.84 (m, 4, arom), 4.31 (q, 2, J = 7 Hz, $-OCH_2-$), 3.84 (s, 3, $-OCH_3$), 1.36 (t, 3, J = 7 Hz, $-CH_3$).

Isolation of a Reaction Intermediate. Reaction of *o*-Methoxy-2-oxabutyrophenone-2-^{18}O (6) with Methylenetriphenylphosphorane. To a stirred solution of 12.0 mmol of methylenetriphenylphosphorane, prepared as described above using 4.85 g (12.0 mmol) of methyltriphenylphosphonium iodide and 0.48 g (12.0 mmol) of sodium hydride,[20] in 15 mL of dry Me_2SO was added 0.54 g (3.0 mmol) of ester **6** in one portion (the addition funnel was rinsed with an extra 5 mL of dry Me_2SO) at room temperature. After workup under standard conditions, there was obtained 0.27 g of a colorless oil. The collected precipitate was dried (reduced pressure, 50 °C, calcium chloride) and consisted mainly of triphenylphosphine oxide. Preparative GC (6 m, 20% SE-30, Chromosorb W 60–80 mesh) gave three fractions which were analyzed by NMR and mass spectrometry.[25] Analytical GC (2 m, 3% SE-30, Gas Chrom Q 80–100 mesh) showed the following product distributions: 56% of *o*-isopropenylanisole (**8**), containing 0% of ^{18}O [n^{22}_D 1.5330 (lit.[26] n^{29}_D 1.5296); NMR ($CDCl_3$) δ 7.18–6.86 (m, 4, arom), 5.12 (m, 1, =CH), 5.04 (m, 1, =CH), 3.81 (s, 3, $-OCH_3$), 2.15 (s, 3, $-CH_3$)], 12% of *o*-methoxyacetophenone (**7**), containing 0% of ^{18}O [n^{22}_D 1.5386 (lit.[27] n^{20}_D 1.5393); NMR ($CDCl_3$) δ 7.66–6.95 (m, 4, arom), 3.91 (s, 3, $-OCH_3$), 2.63 (s, 3, CH_3)], and 32% of starting ester **6**. The isolated triphenylphosphine oxide (**9**) contained about 8% of ^{18}O[25] (calcd,[28] 9.87%), mp 155–157 °C (lit.[29] mp 159 °C).

Isolation of Side Products. Reaction of Methyl Nicotinate (10) with Methylenetriphenylphosphorane. To a stirred solution of 0.06 mol of methylenetriphenylphosphorane, prepared as described above using 24.4 g (0.06 mol) of methyltriphenylphosphonium iodide and 2.40 g (0.06 mol) of sodium hydride,[20] in 100 mL of dry Me_2SO was added 2.74 g (0.02 mol) of methyl nicotinate (**10**) in 20 mL of dry Me_2SO in one portion. Stirring was continued for 1 h at room temperature and for 1 h at 55 °C. Workup under standard conditions yielded 1.83 g of a colorless oil. Preparative GC (20% SE-30) gave three fractions which were analyzed by NMR and the compositions of which were determined by analytical GC (3% SE-30): 39% of 2-(3-pyridyl)-propene (**11**) [n^{23}_D 1.5418 (lit.[30] n^{20}_D 1.5431); NMR ($CDCl_3$) δ 8.56–7.13 (m, 4, arom), 5.38 (s, 1, =CH), 5.14 (m, 1, =CH), 2.20 (s, 3, $-CH_3$)], 14% of (*Z*)-2-(3-pyridyl)-2-butene [(*Z*)-**12**] [NMR ($CDCl_3$) δ 8.32–7.13 (m, 4, arom), 5.59 (q, 1, J = 7 Hz, =CH), 1.98 (m, 3, $-CH_3$), 1.58 (d of m, 3, J = 7 Hz, $-CH_3$)], and 47% of (*E*)-2-(3-pyridyl)-2-butene [(*E*)-**12**] [NMR ($CDCl_3$) δ 8.42–7.02 (m, 4, arom), 5.80 (q, 1, J = 7 Hz, =CH), 1.97 (s, 3, $-CH_3$), 1.78 (d, J = 7 Hz, $-CH_3$)].

Reaction of *o*-Methoxy-2-oxabutyrophenone-2-^{18}O (6) with Ethylidenetriphenylphosphorane. To a stirred solution of 9.0 mmol of ethylidenetriphenylphosphorane, prepared as described above using 5.0 g (12.0 mmol) of ethyltriphenylphosphonium iodide and 0.36 g (9.0 mmol) of sodium hydride,[20] in 12 mL of dry Me_2SO was added 0.54 g (3.0 mmol) of ester **6** in one portion at room temperature (the addition funnel was rinsed with an extra 5 mL of dry Me_2SO). Stirring was continued for 2.5 h. After workup under standard conditions, there was obtained 0.73 g of a pale yellow oil. Its composition was determined by analytical GC (3% SE-30). Preparative GC (20% SE-30) gave four fractions which were analyzed by mass spectrometry and NMR: 85% of (*Z*)-3-(*o*-methoxyphenyl)-2-pentene [(*Z*)-**13**] [NMR ($CDCl_3$) δ 7.29–6.18 (m, 4, arom), 5.57 (q, 1, J = 7 Hz, =CH), 4.73 (s, 3, $-OCH_3$), 2.33 (q, 2, J = 7 Hz, $-CH_2-$), 1.43 (d, 3, J = 7 Hz, $-CH_3$), 0.93 (t, 3, J = 7 Hz, $-CH_3$)], containing 0% ^{18}O, 6% of (*E*)-3-(*o*-methoxyphenyl)-2-pentene [(*E*)-**13**] [NMR ($CDCl_3$) δ 7.28–6.76 (m, 4, arom), 5.43 (q, 1, J = 7 Hz, =CH), 3.76 (s, 3, $-OCH_3$), 2.48 (q, 2, J = 7 Hz, $-CH_2-$), 1.76 (d, 3, J = 7 Hz, $-CH_3$), 0.86 (t, 3, J = 7 Hz, $-CH_3$)], containing 0% of ^{18}O, 8% of (*E*)-1-(*o*-methoxyphenyl)-1-ethoxypropene [(*E*)-**14**] [NMR ($CDCl_3$) δ 7.46–6.80 (m, 4, arom), 5.10 (q, 1, J = 7 Hz, =CH), 3.78 (s, 3, $-OCH_3$), 3.59 (q, 2, J = 7 Hz, $-OCH_2-$), 1.79 (d, 3, J = 7 Hz, $-CH_3$), 1.28 (t, 3, J = 7 Hz, $-CH_3$)], containing 1.80 ± 0.05% of ^{18}O,[25] and 1% of (*Z*)-1-(*o*-methoxyphenyl)-1-ethoxypropene [(*Z*)-**14**] [NMR ($CDCl_3$) δ 7.46–6.80 (m, 4, arom), 4.87 (q, 1, J = 7 Hz, =CH), 3.81 (s, 3, $-OCH_3$), 2.97 (q, 2, J = 7 Hz, $-OCH_2-$), 1.44 (d, 3, J = 7 Hz, $-CH_3$), 1.20 (t, 3, J = 7 Hz, $-CH_3$)], containing 1.80 ± 0.05% of ^{18}O.[25]

Confirmation of the Presence of an Alkylating Species. Reaction in the Presence of the Anion of Di-*tert*-butyl α-Methylmalonate (15). Di-*tert*-butyl malonate[31] was alkylated in 70% yield (after vacuum distillation) using potassium *tert*-butylate in *tert*-butyl

alcohol and methyl iodide as the alkylating agent: bp 37–39 °C (0.02 mm); $n^{23}D$ 1.4151; NMR ($CDCl_3$) δ 3.27 (q, 1, J = 7.0 Hz, =CH), 1.47 (s, 18, *tert*-butyl CH_3), 1.35 (d, 3, J = 7.0 Hz, $-CH_3$).

A solution of 0.08 mol of methylenetriphenylphosphorane, prepared as described above from 32.3 g (0.08 mol) of methyltriphenylphosphonium iodide and 3.20 g (0.08 mol) of sodium hydride,[20] in 80 mL of dry Me_2SO was added over a 30-min period at room temperature to a stirred solution of 0.02 mol of the appropriate ester (see below) and 0.02 mol of the sodium salt of di-*tert*-butyl α-methylmalonate (**15**) in 20 mL of dry Me_2SO. Stirring was continued at room temperature for the periods of time indicated below. After workup under standard conditions, the following results were obtained.

(A) In the case of ethyl 2-naphthoate (stirring for 2 h), a yield of 6.9 g was obtained. Preparative GC (20% SE-30) gave three fractions which where identified by NMR and analytical GC (3% SE-30): 2-isopropenylnaphthalene (46%) [mp 54–55 °C (lit.[32] mp 54°C); NMR ($CDCl_3$) δ 7.76–7.32 (m, 7, arom), 5.53 (s, 1, =CH), 5.22 (m, 1, =CH), 2.32 (s, 3, $-CH_3$)], di-*tert*-butyl α-methylmalonate (**16**; R_2 = H) (34%), and di-*tert*-butyl α-methyl-α-ethylmalonate (**16**; R_2 = C_2H_5) (20%) [NMR ($CDCl_3$) δ 1.83 (q, 2, J = 7.5 Hz, $-CH_2-$), 1.45 (s, 18, CH_3), 1.29 (s, 3, $-CH_3$), 0.86 (t, 3, J = 7.5 Hz, CH_3)].

(B) In the case of isopropyl benzoate (stirring for 16 h), a yield of 4.1 g was obtained. Preparative GC (20% SE-30) gave three fractions which were identified by analytical GC (3% SE-30) and NMR: isopropenylbenzene (39%) [$n^{22}D$ 1.5400 (lit.[33] $n^{20}D$ 1.5386); NMR ($CDCl_3$) δ 7.52–7.22 (m, 5, arom), 5.35 (s, 1, =CH), 5.06 (m, 1, =CH), 2.16 (s, 3, $-CH_3$)], di-*tert*-butyl α-methylmalonate (**16**; R_2 = H) (43%), and di-*tert*-butyl α-methyl-α-isopropylmalonate (**16**; R_2 = i-C_3H_7) (18%) [NMR ($CDCl_3$) δ 2.40 (m, 1, J = 7.0 Hz, –CH), 1.43 (s, 18, $-CH_3$), 1.22 (s, 3, $-CH_3$), 0.91 (d, 6, J = 7.0 Hz, $-CH_3$)].

Reaction with Isopropyl α-Phenylacetate (17). To a dry, nitrogen-purged, 250-mL one-neck round-bottom flask fitted with a stopper and magnetic stirrer and charged with 11.0 g (0.04 mol) of "salt-free"[34] methylenetriphenylphosphorane in 100 mL of dry benzene was added 1.79 g (0.01 mol) of isopropyl α-phenylacetate in one portion under a nitrogen stream at room temperature. Stirring was continued for 20 h. Workup under standard condtions yielded 1.30 g (75%) of an oil. Preparative GC (20% SE-30) gave two fractions (analyzed by analytical GC (3% SE-30) and NMR): 2-benzylpropene (**18**; 54%) [NMR ($CDCl_3$) δ 7.34–7.10 (m, 5, arom), 4.81 (s, 1, =CH), 4.74 (s, 1, =CH), 3.34 (s, 2, $-CH_2-$), 1.71 (s, 3, $-CH_3$)] and isopropyl α-phenyl-α-isopropylacetate (**19**; 46%) [NMR ($CDCl_3$) δ 7.20 (m, 5, arom), 5.02 (septet, 1, J = 6 Hz, –OCH), 3.15 (d, 1, J = 10.5 Hz, $-CH_3$), 2.40 (d of septets, 1, J = 7 and 10.5 Hz, $-CH(CH_3)_2$), 1.24 (d, 3, J = 6 Hz, $-CH_3$), 1.16 (d, 3, J = 6 Hz, $-CH_3$), 1.08 (d, 3, J = 7 Hz, $-CH_3$), 0.72 (d, 3, J = 7 Hz, $-CH_3$)].

Equilibration of Enolates and Phosphonium Salts. Reaction of the Anion of *p*-Methoxyacetophenone (20) with Ethyltriphenylphosphonium Iodide. A dry, nitrogen-purged, 250-mL three-neck round-bottom flask fitted with a magnetic stirrer and a nitrogen system was charged with 0.80 g (0.02 mol) of sodium hydride,[20] 20 mL of dry Me_2SO, and 3.0 g (0.02 mol) of *p*-methoxyacetophenone. Stirring was continued at room temperature till the evolution of hydrogen had ceased. Ethyltriphenylphosphonium iodide (8.4 g, 0.02 mol) was added in one portion, and stirring was continued for 2 h at room temperature. Workup under standard conditions yielded 2.00 g (62%) of an oil. Preparative GC (20% SE-30) gave three fractions which were analyzed by analytical GC (3% SE-30) and NMR: (*Z*)-2-(*p*-methoxyphenyl)-2-butene [(*Z*)-**21**; 60%] [NMR ($CDCl_3$) δ 7.13 (d, 2, J = 8 Hz, arom), 6.85 (d, 2, J = 8 Hz, arom), 5.52 (q, 1, J = 7 Hz, =CH), 3.81 (s, 3, $-OCH_3$), 2.04 (s, 3, $-CH_3$), 1.64 (d, 3, J = 7 Hz, $-CH_3$)], *p*-methoxyacetophenone (10%) [mp 35–36 °C (lit.[35] mp 37–38 °C); NMR ($CDCl_3$) δ 7.90 (d, 2, J = 8 Hz, arom), 6.90 (d, 2, J = 8 Hz, arom), 3.85 (s, 3, $-OCH_3$), 2.57 (s, 3, $-CH_3$)], and (*E*)-2-(*p*-methoxyphenyl)-2-butene [(*E*)-**21**; 30%] [NMR ($CDCl_3$) δ 7.26 (d, 2, J = 8 Hz, arom), 6.80 (d, 2, J = 8 Hz, arom), 5.76 (q, 1, J = 7 Hz, =CH), 3.80 (s, 3, $-OCH_3$), 2.04 (s, 3, $-CH_3$), 1.81 (d, 3, J = 7 Hz, $-CH_3$)].

Determination of the Relative Rates of Some *o*-Methoxybenzoates in the Ester/Ylide Reaction. To a dry, nitrogen-purged, 250-mL three-neck round-bottom flask fitted with a magnetic stirrer and a nitrogen system and charged with 8.5 g (30.9 mmol) of "salt-free"[34] methylenetriphenylphosphorane in 100 mL of dry Me_2SO was added a mixture of 0.26 g (1.55 mmol) of methyl *o*-methoxybenzoate, 0.28 g (1.55 mmol) of ethyl *o*-methoxybenzoate, 0.30 g (1.55 mmol) of isopropyl *o*-methoxybenzoate, 0.32 g (1.55 mmol) of *tert*-butyl *o*-methoxybenzoate, 0.34 g (1.55 mmol) of neopentyl *o*-methoxybenzoate, and 0.20 g (1.55 mmol) of naphthalene (internal standard) in 20 mL of dry Me_2SO in one portion. Stirring was continued for 100 h at room temperature. The reaction was followed by GC (3% SE-30) by taking small samples from the reaction mixture and adding these to a few drops of water and pentane. After workup of the reaction mixture under standard conditions, 1.05 g (74%) of a colorless oil was obtained consisting of *o*-isopropenylanisole (**8**; 74%), naphthalene (13%), and *tert*-butyl *o*-methoxybenzoate (13%). The approximate relative rates[36] were calculated to be methyl (20), ethyl (7), neopentyl (3), isopropyl (1), and *tert*-butyl esters (0).

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Registry No.—**2** (R_1 = Ph, R_3 = H), 6048-29-9; **3** (R_1 = Ph, R_3 = H) (uncharged form), 859-65-4; **3** (R_1 = Ph, R_3 = H) (charged form), 20913-05-7; **4** (R_1 = Ph, R_2 = Et, R_3 = H), 6230-62-2; **6**, 66702-34-9; **7**, 579-74-8; **8**, 10278-02-1; **9**, 791-28-6; **10**, 93-60-7; **11**, 15825-89-5; (*E*)-**12**, 66702-35-0; (*Z*)-**12**, 66702-36-1; (*E*)-**13**, 66702-37-2; (*Z*)-**13**, 66702-38-3; (*E*)-**14**, 66702-39-4; (*Z*)-**14**, 66702-40-7; **15** Na salt, 66702-41-8; **16** (R_2 = H), 34812-95-8; **16** (R_2 = Et), 66702-42-9; **16** (R_2 = *i*-Pr), 66702-43-0; **17**, 4861-85-2; **18**, 3290-53-7; **19**, 13027-70-8; **20** ketone derivative, 100-06-1; (*E*)-**21**, 38454-63-6; (*Z*)-**21**, 38454-62-5; methylenetriphenylphosphorane, 3487-44-3; *o*-methoxybenzoyl chloride, 21615-34-9; ethanol-^{18}O, 36794-43-1; di-*tert*-butyl malonate, 541-16-2; 2-isopropenylnaphthalene, 3710-23-4; isopropenylbenzene, 98-83-9; ethyltriphenylphosphonium iodide, 4736-60-1; methyl *o*-methoxybenzoate, 606-45-1; ethyl *o*-methoxybenzoate, 7335-26-4; isopropyl *o*-methoxybenzoate, 944-95-6; *tert*-butyl *o*-methoxybenzoate, 16537-20-5; neopentyl *o*-methoxybenzoate, 66702-44-1.

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Reaction of a Mixed Anhydride with Aqueous Hydroxylamine. A Model for the Trapping by Added Nucleophiles of Anhydride Intermediates in Carboxypeptidase A Action

Takuji Sugimoto and E. T. Kaiser*

Department of Chemistry, University of Chicago, Chicago, Illinois 60637

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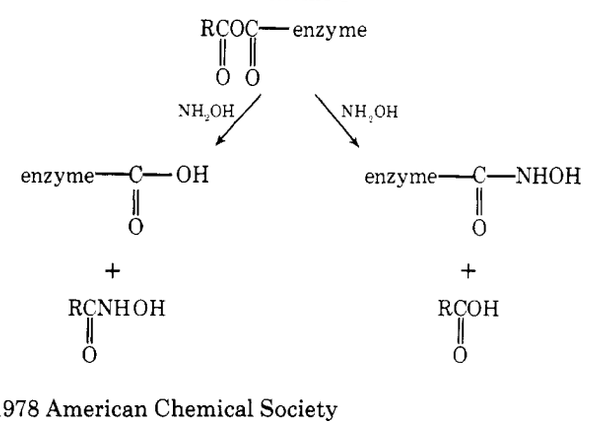
As a model for experiments on the trapping by nucleophiles of acyl-enzyme intermediates formed in the action of carboxypeptidase A, the reaction of *trans-p*-chlorocinnamic propionic anhydride with aqueous hydroxylamine has been examined. Both above and below the pK_a of hydroxylamine, formation of propionohydroxamic acid was found to occur in very high yields. The other dominant product was *trans-p*-chlorocinnamic acid. The pH–rate constant profile for the attack of hydroxylamine on the mixed anhydride was sigmoidal, with an apparent pK_a value of 6.07 ± 0.11 and a limiting second-order rate constant of 2340 M^{-1} s^{-1} calculated in alkaline solution. Within the limits of our measurement, catalysis of anhydride breakdown occurred only with the unprotonated form of hydroxylamine. The results obtained suggest that if the acyl-enzyme intermediate observed in kinetic measurements on the reaction of carboxypeptidase A with *O*-(*trans-p*-chlorocinnamoyl)-L-β-phenyllactate is an anhydride species, nucleophilic trapping with hydroxylamine in the absence of interaction of the active site metal ion with the anhydride may be accomplished in reasonable yields.

The trapping of acyl-enzyme intermediates by the use of potent nucleophiles is a useful mthod which has aided in the elucidation of the structure of reaction intermediates involved in enzymic hydrolysis reactions. Trapping experiments in which hydroxylamine was employed as the nucleophile have been carried out on a variety of peptidases including chymotrypsin,[1] pepsin,[2] and bacterial carboxypeptidase.[3] In many of the trapping experiments performed, hydroxylamine was found to be incorporated into the substrate, giving rise to the formation of a hydroxamic acid derived from the substrate. The enzymes involved have generally been ones which form acyl-enzyme intermediates using serine hydroxyl groups at the active site.

Recently, in a study of the reaction of *O*-(*trans-p*-chlorocinnamoyl)-L-β-phenyllactate with carboxypeptidase A at low temperature in a mixed organic–aqueous solution, kinetic evidence was obtained for the intermediate formation of an acyl-enzyme species.[4] On the grounds that the attacking nucleophile at the enzyme active site was probably the γ-carboxylate group of Glu-270, it was proposed that the acyl-enzyme intermediate had a mixed anhydride structure. In order to test such a hypothesis, nucleophile trapping experiments have been undertaken in our laboratory on the reactions of carboxypeptidase A with ester substrates. Some evidence exists that in cases where zinc ion catalyzes the breakdown of model mixed anhydrides, it is not feasible to use hydroxylamine as a trapping nucleophile,[5] and there are a considerable number of trapping experiments which have been carried out on the native zinc-containing enzyme without any success.[6,7] Therefore, the trapping experiments which we are currently performing on the proposed mixed anhydride species formed at the active site of carboxypeptidase are being done in such a way that the trapping is carried out under conditions where the active site metal ion is coordinated to a strongly bound complexing agent. If the metal ion is prevented from interacting with the mixed anhydride formed at the active site of carboxypeptidase, then a reasonable model for the trapping process in the case of the *trans-p*-chlorocinnamoyl-enzyme should be a study of the reaction of a mixed anhydride such as *trans-p*-chlorocinnamic propionic anhydride (I) with aqueous hydroxylamine. If trapping of the acyl-enzyme with hydroxylamine were successful, then either of the two pathways illustrated in Scheme I might be observed. According to one pathway, hydroxylamine would attack the carbonyl group derived from the active site carboxyl of the enzyme and would result in the formation of an enzyme-bound hydroxamate species. The other pathway would involve attack of the nucleophile on the substrate-derived carbonyl group. Similarly, as illustrated in Scheme II, attack at either the *trans-p*-chlorocinnamoyl group or the propionyl group of I might be observed in the reaction of aqueous hydroxylamine with this model mixed anhydride. In the present article we have described the results we have obtained both on the kinetics of reaction of hydroxylamine with I in aqueous solution and on the product distribution, and we have discussed the

Scheme I



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