of these two spectra, also shown in Figure 3) results in a spectrum indistinguishable from the baseline. To further assure meaningful results, a pulse flip angle of ca. 30° was chosen in the integration experiment. As shown by eq 7, the observed intensity is related

$$M_\tau = M_0 \frac{1 - \exp(-\tau/T_1)}{1 - \exp(-\tau/T_1)\cos\alpha} \quad (7)$$

to both the delay time ($\tau$) and the pulse flip angle ($\alpha$), where $M_\tau$ is the measured intensity and $M_0$ is the absolute intensity.[38] Table V (see supplementary material) lists the ratio $M_\tau/M_0$ for delay times of 1–5 $T_1$'s and pulse flip angles of 4–90 s. These experiments indicate that the data reported in Table III are valid.[39] Typically 100 acquisitions were collected for each spectrum, and at least three (averaging nine throughout this work) alkylations were performed for each compound. The deviations were typically less than 10%. $^1H$ and $^{13}C$ NMR spectra were obtained for each alkylation reaction, and excellent correlations were observed for the two methods.

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**Registry No.** 1, 54-11-5; 1 *N*-methyl iodide derivative, 77647-89-3; 1 *cis*-*N'*-methyl iodide derivative, 77647-90-6; 1 *trans*-*N'*-methyl iodide derivative, 77647-91-7; 2, 77698-47-6; 2 *N*-methyliodide derivative, 77629-25-5; 2 *cis*-*N'*-methyl iodide derivative, 77629-26-6; 2 *trans*-*N'*-methyl iodide derivative, 77629-27-7; 3, 13270-57-0; 3 *N*-methyl iodide derivative, 77629-28-8; 3 *cis*-*N'*-methyl iodide derivative, 77629-29-9; 3 *trans*-*N'*-methyl iodide derivative, 77629-30-2; 4, 77629-31-3; 4 *N*-methyl iodide derivative, 77629-32-4; 4 *cis*-*N'*-methyl iodide derivative, 77629-33-5; 4 *trans*-*N'*-methyl iodide derivative, 77629-34-6; 5, 13270-56-9; 5 *N*-methyl iodide derivative, 77629-35-7; 5 *cis*-*N'*-methyl iodide derivative, 77629-36-8; 5 *trans*-*N'*-methyl iodide derivative, 77629-37-9; 6, 77698-94-3; 6 *cis*-*N'*-methyl iodide derivative, 77629-38-0; 6 *trans*-*N'*-methyl iodide derivative, 77629-39-1; 7, 77629-40-4; 7 *N*-methyl iodide derivative, 77629-41-5; 7 *cis*-*N'*-methyl iodide derivative, 77629-42-6; 7 *trans*-*N'*-methyl iodide derivative, 77629-43-7; 8, 77629-44-8; 8 *N*-methyl iodide derivative, 77629-45-9; 8 *cis*-*N'*-methyl iodide derivative, 77629-46-0; 8 *trans*-*N'*-methyl iodide derivative, 77629-47-1; 8 dipicrate, 77629-48-2; methyl 6-methylnicotinate, 5470-70-2; 6-methylnicotinic acid, 3222-47-7; *N*-(trimethylsilyl)pyrrolidinone, 14468-90-7; 6-methylmyosmine, 77629-49-3; 6-methylnornicotine, 77629-50-6; 6-methylnornicotine dipicrate, 77647-92-8; methyl 4-methylnicotinate, 33402-75-4; 5-methylnicotinonitrile, 42885-14-3; methyl 5-methylnicotinate, 29681-45-6; methyl 4,6-dimethylnicotinate, 69971-44-4; 4,6-dimethylnicotinonitrile, 6623-21-8; ethyl β-amino-α-methylcrotonate, 14369-90-5; ethyl 2-methylacetoacetate, 609-14-3; ethyl 2,4-dihydroxy-5,6-dimethylnicotinate, 77629-51-7; diethyl malonate, 105-53-3; ethyl 2,4-dichloro-5,6-dimethylnicotinate, 77629-52-8; ethyl 5,6-dimethylnicotinate, 77629-53-9; ethyl 5,6-dimethylnicotinate picrate, 77629-54-0.

**Supplementary Material Available:** Table V (normalized $^{13}C$ intensity as a function of pulse flip angle and delay time) and Figure 3 ($^{13}C$ NMR spectrum of the reaction mixture of nicotine and 0.75 equiv of $^{13}CH_3I$) (4 pages). Ordering information is given on any current masthead page.

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(39) For a pulse flip angle of 30°, Table V indicates that 97.95% of the intensity of the $^{13}C$ resonance will be measured by using a delay time of $2T_1$. Of course, longer delay times will increase the normalized measured intensity relative to 100%. Preliminary results (obtained with Dr. J. Wooten) indicate that the quaternary pyrrolidine methyl carbon $T_1$'s are ca. 1.5 and the pyridine methiodine methyl carbon $T_1$'s are ca. 4 s. We estimate that our integrations incorporate 98–99.9% of the theoretical areas.

# Rates and Mechanism of the Alkaline Hydrolysis of a Sterically Hindered Phosphinate Ester. Partial Reaction by Nucleophilic Attack at Carbon[1]

Jubrail Rahil and Paul Haake*

*Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457*

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The alkaline hydrolysis of the sterically hindered phosphinate ester, methyl diisopropylphosphinate, has been studied in water. At 100 °C, the rate constant is $5.3 \times 10^{-5}$ $M^{-1}$ $s^{-1}$, $\Delta S^* = -15$ gibbs, and $\Delta H^* = 23.6$ kcal/mol. Mass spectrometric and NMR determination of the point of reaction in oxygen-18 labeled water indicates that there is approximately 75% attack of hydroxide ion at the phosphorus atom, resulting in cleavage of the P–O bond, and 25% attack at the methyl carbon, resulting in cleavage of the C–O bond.

Although dissociative, unimolecular mechanisms have been observed in displacements at phosphorus through metaphosphate intermediates,[2-5] associative reactions are greatly preferred. We observed that phosphinic acids, $R_2PO_2H$, do not form phosphinylium ions, $R_2PO^+$, in sulfuric acid or oleum,[6] conditions under which carboxylic acids form acylium ions.[7] In a solvolytic study of phosphinyl chlorides, $R_2P(O)Cl$, we found clear evidence for associative mechanisms of reaction except for di-*tert*-butylphosphinyl chloride which reacts exceedingly slowly by a unimolecular mechanism;[8] in this case, the associative pathway for reaction appears to be ruled out by the high steric hindrance around the phosphorus atom. The high preference for associative reactions appears to be a result of the weak multiple bonds to phosphorus in a unimo-

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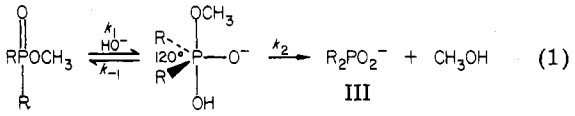
lecular reaction intermediate vs. the high P–O bond energy of the new bond in an associative mechanism.

The isolation of stable pentacoordinate phosphoranes[9] demonstrates that pentacoordinate species might be metastable intermediates in associative pathways of displacement at phosphorus.[10] These phosphoranes frequently have the structural feature of five-membered rings which appear to stabilize the pentacoordinate state.[9] Five-membered rings have been the source of critical experiments which demonstrate the existence of pentacoordinate intermediates in displacement at phosphorus,[11] a mechanism which might be designated $S_N2I(P)$, bimolecular nucleophilic substitution at phosphorus through an intermediate. Angle strain at phosphorus produces rate accelerations[10] because strain is relieved when the ring can span apical and basal positions (90° angle at phosphorus) in a trigonal-bipyramidal intermediate.

Clear evidence for pentacoordinate intermediates has been more difficult to find in acyclic systems. In fact, there is good evidence, from the study of acid-catalyzed hydrolysis of phosphorus amides, that the preferred path of reaction is an $S_N2(P)$ mechanism in which an intermediate does not form.[12] As the structure of the departing amine is changed to give a better leaving group, the mechanism moves toward $S_N1(P)$[13] although it appears that there is participation of nucleophile in the transition state.[14,15] In the acid-catalyzed hydrolysis of phosphorus esters, $^{18}O$ exchange with solvent implicates an intermediate in which the P=O oxygen can become equivalent to the entering oxygen atom of water.[16] The alkaline hydrolysis of phosphinamides also appears to involve $^{18}O$ exchange.[12a]

We raised the question of whether it would be possible to stabilize a pentacoordinate intermediate relative to the ground state by the steric effect[17] of two large R groups in a phosphinate ester (I, eq 1).[18] In the intermediate II



I II III (1)

the C–P–C angle expands to 120° due to the preference of the least electronegative groups for basal positions in the bipyramidal intermediate;[9,11] this angle is larger than the tetrahedral angles in starting material and product, so the pentacoordinate species should be stabilized by relief of nonbonded repulsions between the R groups. Therefore, we suggested that steric effects might lead to an observable concentration of intermediate. In a study of phosphinate esters, we observed an induction period in the alkaline hydrolysis of methyl diisopropyl phosphinate in 1,2-dimethoxyethane–water.[18] We suggested that the induction period was evidence for an intermediate, but subsequently we found this to be an artifact caused by air oxidation of the dimethoxyethane.[1]

Hawes and Trippett reported rates of alkaline hydrolysis of sterically hindered phosphonates and phosphinates.[19] One *tert*-butyl substituent had much less effect on the rate than two *tert*-butyl substituents. This result led them to suggest that a *tert*-butyl group would occupy an apical position in the trigonal-bipyramidal intermediate.

We became concerned that sterically hindered phosphorus esters might react partially by an $S_N2$ reaction at carbon. In this paper we report our investigation of this problem through an $^{18}O$ determination of the pathway of reaction of $HO^-$ with methyl diisopropylphosphinate (I, R = *i*-Pr). We also report our full results on the kinetics of this reaction.[1,18]

## Experimental Section

2-Bromopropane, sulfuryl chloride, and thiophosphoryl chloride were purchased from Aldrich Chemicals, Inc. Dimethoxyethane and deuterated dimethoxyethane (DME-$d_{10}$) were purchased from J. T. Baker and Co. Oxygen-18 $H_2O$ was purchased from Yeda Research and Development Co. Ltd. Water was distilled and freed from $CO_2$ by boiling and cooling under nitrogen. Dimethoxyethane was purified according to standard procedures and used freshly afterwards.[20] Titrations were performed on a Radiometer TTT11 automatic titrator and a Radiometer Model 26 pH meter attached to a Radiometer combination electrode. $^1H$ NMR spectra were taken on a Varian A-60 spectrometer. Chemical shifts are reported with respect to $Me_4Si$ as an internal standard. $^{31}P$ NMR were taken on a Varian XL-200. Mass spectra were performed by using a Hitachi RMU-6L and Hewlett-Packard 5985 GC/MS.

All esters were prepared by reaction of sodium alkoxide with diisopropylphosphinyl chloride which was prepared by treatment of the tetraalkylbiphosphine disulfide with sulfuryl chloride. The tetraisopropylbiphosphine disulfide was prepared from isopropylmagnesium bromide and thiophosphoryl chloride.[21] The phosphinyl chloride was distilled at 50° (0.12 mm) [lit.[21] bp 89–90 °C (12 mm)]. The methyl ester was distilled at 38 °C (0.1 mm),[15] the ethyl ester at 60 °C (0.1 mm), and the isopropyl ester at 36–38 °C (0.01 mm).

Reactions were either carried out in volumetric flasks or in sealed ampules. In the experiments done in volumetric flasks, aliquots were withdrawn at appropriate intervals and titrated as described below. In the sealed-ampule experiments, ampules were taken out of the reaction bath and frozen in dry ice until the experiment was over, at which time all samples were titrated. Aliquots (4 mL) were pipetted and quenched in standard perchloric acid. The solution was then back-titrated to pH 8.45 with standard base by using an automatic titrator. When the base and ester concentration are equal, the rate constant is obtained from the slope of a plot of $(1/(mL_{calcd} - mL_{titr}))$ vs. time (minutes), where $mL_{calcd}$ is the number of milliliters of titrating base necessary to neutralize just the acid used for quenching and $mL_{titr}$ is the amount of base added to back-titrate the acid-quenched aliquot; $k_2$ = slope (milliliters of aliquot/moles per liter of titrant base). When the initial base ($B_0$) and ester ($E_0$) concentrations are not equal, the slope is determined from the plot of log $[(B_0 - x)/(E_0 - x)]$ vs. time where $x$ is the concentration of base remaining at time ($t$). The second order-rate constant $k_2$ ($M^{-1}$ $s^{-1}$) = 2.303 [slope/$(B_0 - E_0)$].

The NMR kinetics were done in sealed NMR tubes. The reaction was monitored by following the collapse of the P–$OCH_3$ doublet ($\delta$ 3.8) as the hydrolysis proceeded.

**Product Identification.** At the end of a hydrolysis reaction, the reaction mixture was acidified to pH 4 and extracted with diethyl ether to remove any unreacted ester. The aqueous layer

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Table I. Results of the Titrimetric Studies in the Reaction of I with Base under Various Conditions

| [E], M | [B], M | solvent | temp, °C | % base consumed | reaction time, h |
|---|---|---|---|---|---|
| 0.1[a] | 0.1 | 60% DME-$H_2O$ | 75 | 75 | 32.5 |
| 0.1[a] | 0.1 | 60% DME-$H_2O$ | 75 | 78 | 32.5 |
| 0.05[a] | 0.1 | 60% DME-$H_2O$ | 75 | 86 | 34 |
| 0.05[a] | 0.21 | 60% DME-$H_2O$ | 75 | 49 | 43 |
| 0.05[a,b] | 0.20 | 60% DME-$H_2O$ | 75 | 0 | 29 |
| 0.020[a] | 0.2 | 30% $CH_3CN$-$H_2O$ | 75 | 0 | 77 |
| 0.05[a] | 0.2 | $H_2O$ | 75 | 0 | 48 |
| 0.05[c] | 0.2 | $H_2O$ | 100.1 | | |
| 0.05 | 0.2 | $H_2O$ | 120.1 | | |

[a] Reactions done in volumetric flasks. [b] Under $N_2$. [c] Reactions done in sealed ampules; $k_2 = 5.32 \times 10^{-5}$ $M^{-1}$ $s^{-1}$ at 100 °C and $2.83 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ at 120 °C.

was further acidified to pH 0 and extracted with diethyl ether to remove diisopropylphosphinic acid. Both compounds were identified by $^1H$ NMR. The acid spectrum in $CDCl_3$ showed the expected peaks at δ 1.2 and 2.0.

**Oxygen-18 Experiments.** The oxygen-18 content of water was determined by measuring the enrichment in methanol resulting from the hydrolysis of methyl *p*-toluenesulfonate (VII) in the $H_2{}^{18}O$. This reaction is known to proceed with nucleophilic attack on the saturated carbon, yielding $CH_3{}^{18}OH$.[22] The methanol product was then distilled carefully through a long fractionating column (1.5 m; bp 68 °C), and it was identified by NMR before being analyzed by mass spectrometry. The hydrolysis of methyl diisopropylphosphinate (I, R = *i*-Pr) was carried out in base at 120 °C for a few hours in sealed ampules. Methanol was distilled as described above. The remaining solution was acidified to pH and extracted with diethyl ether to remove the phosphinic acid. The ether was stripped off and the phosphinic acid distilled; bp 95 °C (0.05 mm) [lit.[23] 84–86 °C (0.02 mm)]. NMR spectra of the phosphinic acid confirmed its identity. There was no unreacted ester in the extract. Control runs in normal distilled water were performed for all the experiments. The atom percent of oxygen-18 excess is $(r_e - r_u)$ 100 where $r_e$ is the ratio of $^{18}O/^{16}O$ in the enriched sample and $r_u$ the ratio in the unenriched sample. The percent enrichment was calculated as in eq 2.

$$Q(\%\ \text{enrichment}) = (\text{atom \% excess in hydrolysis products})100/(\text{atom \% excess in } H_2O) \quad (2)$$

The numerical analysis was done on the Wesleyan University computer system by using a program that performs numerical integration by employing the Runge–Kutta method.[24]

The analogue simulation of kinetics was performed by using a McKee–Pederson system and a circuit which model eq 1.

## Results

In order to check the kinetic interpretation[18,25] of the induction period in the hydrolysis of methyl diisopropylphosphinate (I, R = *i*-Pr), we tried to fit the experimental data to the scheme in eq 1 by using an analogue computer circuit.[1] There was deviation which was greater than experimental error.[1] This led us to the concern that the induction period might be an experimental artifact. By use of numerical integration, it was also impossible to obtain an adequate fit to the experimental data.

NMR spectroscopic observation of the hydrolysis of I was utilized to test the results of titrimetric rates. I has a P–$OCH_3$ doublet and a P–C–$CH_3$ octet. The hydrolysis was followed by monitoring the decrease in the P–$OCH_3$ doublet (δ 4.0) and the appearance of a new singlet due to methanol (δ 3.6). The reaction was first studied at 75 °C in three solvent systems: $D_2O$, 60% dimethoxyethane-$d_{10}$/$D_2O$, and 20% acetonitrile-$d_3$/$D_2O$, at varying concentrations of ester and base. The reaction was carried out over time periods during which $OH^-$ had been consumed (72 h) in previously reported titrimetric experiments (Table I). However, only a small decrease in the P–$OCH_3$ signal or appearance of $CH_3OH$ was observed. At 100 °C in alkaline $D_2O$, the P–$OCH_3$ doublet disappeared, the $CH_3OH$ signal appeared, and the $PCCH_3$ octet collapsed into a quartet, consistent with the hydrolysis reaction giving $[(CH_3)_2CH]_2PO_2^-$. Although the inaccuracy of NMR data led to scatter, we could determine a second-order rate constant for the hydrolysis reaction: $k_{HO^-} = 1.2 \times 10^{-4}$ $M^{-1}$ $s^{-1}$.

**Titrimetric Studies.** In order to investigate the nature of the induction period and the cause of base consumption when the reported hydrolysis of I was carried out in dimethoxyethane–$H_2O$ at 75 °C, further studies were done under similar conditions. Reactions were done in volumetric flasks, and aliquots were pipetted out at intervals. The resulting data from reactions that contained a ratio of ester to base of 1:2 or 1:4 showed that at 75 °C in dimethoxyethane–$H_2O$, base was consumed after induction periods[25] of varying duration (200–800 min, Table I). However, more than 1 equiv of base could be consumed, and the data did not follow second-order kinetics. Furthermore, there was an exponential increase in the rate of base consumption toward the end of the reaction. Such behavior is consistent with a free-radical chain reaction. This assumption was verified by adding catechol (0.01%) to the reaction solution. The solution turned brown, so the catechol was being oxidized, which can be taken as a positive test for the presence of peroxides in the reaction mixture. Under a nitrogen atmosphere (Table I), the above reaction showed no base consumption under otherwise identical conditions. Finally, blank runs that did not include ester I showed base consumption and an induction period. In contrast to the above behavior, the hydrolysis of methyl diisopropylphosphinate was carried out at 100 and 120 °C in pure $H_2O$, and the reaction followed clean second-order kinetics with no induction period (Table I). The rate constants were $2.8 \times 10^{-4}$ and $5.3 \times 10^{-5}$ $M^{-1}$ $s^{-1}$ at 120.1 and 100.1 °C, respectively.

This data enables calculation[26] of the activation parameters for the hydrolysis of I: $\Delta H^{\ddagger} = 23.6$ kcal/mol, $\Delta G^{\ddagger} = 29.3$ kcal/mol, and $\Delta S^{\ddagger} = -15$ eu.

**Oxygen-18 Studies.** These studies were aimed at establishing the position of bond cleavage during the hydrolysis of I (eq 3). The reactions were carried out at 120 °C in $^{18}O$-enriched $H_2O$. Mass spectrometric methods were utilized to follow the $^{18}O$ label by analyzing the reaction

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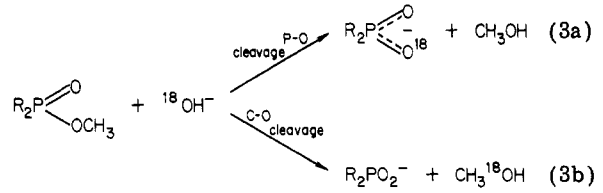


products. Results are shown in Table II. In the last line of the table we report a result for an aryl ester which must give 100% P–O cleavage; C–O cleavage would involve nucleophilic aromatic substitution—a very high-energy reaction for an unsubstituted phenyl. The experimental result suggests that all our analyses of $[(CH_3)_2CH]_2PO_2H$ are low in $^{18}O$. The rough correction factor of 83% can be applied to other results on this product.

The mode of bond cleavage differed slightly upon change in concentraton of reactants. At a 0.6 M concentration of base and ester, the results show 74% P–O and 21% C–O cleavage. At higher ionic strength, 2 M concentration, 69% P–O and 26% C–O cleavage was observed. This change is within experimental error, but its direction is consistent in both products ($R_2PO_2^-$ and MeOH). Finally, neither phosphonic acid nor methanol showed any signs of exchange with the solvent under the reaction conditions.

The $^{18}O$ label was further identified and estimated by $^{31}P$ NMR. The effect of isotopic substitution on the magnetic shielding of nuclei was predicted by Ramsey[27] and has been utilized in mechanistic studies of phosphorus[28] and carbon[29,30] compounds. The heavier isotope shifts the NMR signal of a neighboring nucleus to higher magnetic field. The magnitude of the shift is related to the fractional change in mass and the number of bonds separating the nuclei involved. We found clearly separated $^{31}P$ peaks for isotopic hydrolysis products of I in 30% oxygen-18 enriched $H_2O$. The peak ratio shows 22.5% P–$^{18}O$ in the phosphinic acid. Dividing by the total $^{18}O$ content of the medium gives the percent P–O cleavage: 22.5/30 = 75% P–O cleavage, in good agreement with the mass spectral results.

## Discussion

It is clear from the NMR experiments, which show absence of spectral change at 75 °C in $H_2O$ or in dimethoxyethane–$H_2O$, that the hydrolysis of ester I is very slow under those conditions and could not account for the observed consumption of base reported in our earlier paper.[18] The exponential increase in the rate of base consumption toward the end of the reaction and the disappearance of more than 1 equiv of base (Table I) in the reaction imply the existence of a free-radical chain reaction that involves the solvent.[1,31,32] In order to explain these results, we have suggested a sequence of free-radical reactions of the solvent followed by $HO^-$ cleavage of a peroxyacetal to produce an ester which would be hydrolyzed by base.[1] In summary, the apparent induction period preceding the start of the base consumption is due to oxidation of the solvent, dimethoxyethane, and not to hydrolysis of I.

As suggested by the research of Hawes and Trippett,[19] we then used pure water as the solvent. The alkaline hydrolysis of the ester (I) could be observed at 100.1 °C in pure water. It followed clean second-order kinetics and showed no induction period. The reaction was studied titrimetrically in water and the rate confirmed by NMR. The rate constants were $2.8 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ at 120.1 °C and $5.3 \times 10^{-5}$ $M^{-1}$ $s^{-1}$ at 100.1 °C.

The entropy of activation for the hydrolysis of I is −15 gibbs which is indicative of a bimolecular reaction.[33] This is in agreement with the known chemistry of alkaline substitution at phosphorus esters.[15,34] The enthalpy of activation, $\Delta H^* = 23.6$ kcal/mol, is substantially greater than the values from phosphorus ester hydrolyses that are known to proceed with P–O bond cleavage.[15,34] Although steric inhibition to substitution at phosphorus exerted by the bulky isopropyl groups might be responsible for this activation enthalpy, one could also expect the alkaline hydrolysis of I to proceed in part via the alternative available pathway: nucleophilic substitution at saturated carbon with C–O bond cleavage. The $\Delta H^*$ is in an appropriate range for this process.[35-37] Hawes and Trippett attributed the rate retardation in sterically hindered phosphinates to the energy barrier to forming the preferred pentacoordinate intermediate.[19]

In general, the major factors that decide the position of substitution in the hydrolysis of esters are (a) the strength of the acid resulting from the hydrolysis, (b) the type of the nucleophile, and (c) the steric hindrance to the incoming group.[38] Dostrovsky and co-workers determined the mode of bond fission in the alkaline hydrolysis of a number of esters of organic and inorganic oxy acids.[39] They found that C–O cleavage predominates in esters of very strong acids such as triphenylmethyl perchlorate $[(C_6H_5)_3COClO_3]$, nitrate $[(C_6H_5)_3CONO_2]$, and sulfate $[[(C_6H_5)_3CO]_2SO_2]$. With weaker acids, acyl oxygen cleavage is predominant, e.g., triphenylmethyl acetate $[(C_6H_5)_3COCOCH_3]$ and nitrite $[(C_6H_5)_3CONO]$. Not unexpectedly, a correlation exists between acidity (the ability to donate a proton) and the ease of alkyl oxygen bond fission. In fact, the triphenylmethyl esters of strong acids, triphenylmethyl perchlorate, sulfate, and nitrate, presumably are hydrolyzed by an $S_N1$ mechanism.

In contrast to carboxylic esters, phosphorus esters are relatively strong alkylating agents to nucleophiles with high reactivity toward saturated carbon, e.g., $RS^-$ and $I^-$.[40-42] Even with oxygen nucleophiles, phosphates and phosphonates can give C–O cleavage.[11,43,44] Phosphinates,[15] in agreement with Dostrovsky's findings,[39] show less tendency for C–O cleavage than the phosphate or phosphonate esters; this is consistent with the $pK_a$'s of the acids.[45] P–O cleavage is observed in phosphinates except for the *tert*-butyl ester of diphenylphosphinic acid which gives C–O cleavage presumably via elimination.[15,46] McClelland,

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Table II. Oxygen-18 Content of Compounds Isolated from the Hydrolysis of Methyl Diisopropylphosphinate (I, R = $(CH_3)_2CH^-$)

| compd | $(P + 2)/P$, % | % excess | % enrichment ($Q$) | expt |
|---|---|---|---|---|
| | | Set I[a] | | |
| $H_2{}^{18}O$ | 1.45 | 1.26 | 100 | hydrolysis of MPTS in $^{18}O$-enriched $H_2O$[b] |
| $H_3C^{18}OH$ | 0.52 | 0.33 | 26 | hydrolysis of (I) in $^{18}O$-enriched $H_2O$ |
| $H_3C^{16}OH$ | 0.19 | 0 | 0 | hydrolysis of (I) in $H_2O$ |
| $H_3COH$ | 0.17 | 0 | 0 | exchange in $^{18}O$-enriched $H_2O$ |
| $(i\text{-Pr})_2P(O)^{18}OH$ | 1.15 | 0.718 | 57 (69[c]) | hydrolysis of (I) in $^{18}O$-enriched $H_2O$ |
| $(i\text{-Pr})_2P(^{16}O)H$ | 0.43 | 0 | 0 | hydrolysis of (I) in $H_2O$ |
| $(i\text{-Pr})_2P(O)OH$ | 0.49 | 0.057 | 4.5 | exchange in $^{18}O$-enriched $H_2O$ |
| | | Set II[a] | | |
| $H_2{}^{18}O$ | 1.29 | 1.061 | 100 | hydrolysis of MPTS in $^{18}O$-enriched $H_2O$[b] |
| $H_3C^{18}OH$ | 0.447 | 0.218 | 20.5 | hydrolysis of (I) in $^{18}O$-enriched $H_2O$ |
| $H_3C^{16}OH$ | 0.229 | 0 | 0 | hydrolysis of (I) in $H_2O$ |
| $(i\text{-Pr})_2P(O)^{18}OH$ | 1.10 | 0.655 | 61.7 (74[c]) | hydrolysis of (I) in $^{18}O$-enriched $H_2O$ |
| $(i\text{-Pr})_2P(O)^{16}OH$ | 0.445 | 0 | 0 | hydrolysis of (I) in $H_2O$ |
| $(C_6H_5)_2P(O)^{18}OH$ | 1.33 | 0.885 | 83.4 | hydrolysis of $(C_6H_5)_2POOC_6H_5$ in $^{18}O$-enriched $H_2O$ |

[a] Experiment sets I and II were done at 2 and 0.6 M concentrations of ester and base, respectively. [b] Obtained from mass spectrometric analysis of $H_3C^{18}OH$ produced by the hydrolysis of methyl *p*-toluenesulfonate in $^{18}O$-enriched $H_2O$. [c] Corrected for error in analysis based on the last line of this table for which 100% P–O cleavage must occur; see text.

using isotopic tracers, found 90% P–O cleavage in the acid-catalyzed hydrolysis of methyl methylarylphosphinates.[47]

Methyl diisopropylphosphinate (I, R = *i*-Pr) underwent alkaline hydrolysis with about 25% C–O cleavage (eq 3, Table II), so the $OH^-$ nucleophile attacks both the phosphorus center and the saturated carbon atom in I. The observation of 25% C–O cleavage appears to be the result of steric hindrance to attack of $HO^-$ at phosphorus because it is known that there is a large preference for hydroxide ion to attack the phosphinyl center over the saturated carbon center;[15,48] only in sulfonate esters does $OH^-$ attack the saturated carbon, presumably driven by the high acidity of the outgoing sulfonic acid ($pK_a \simeq 0$).[21,49]

Polar effects are unlikely to be responsible for this C–O cleavage result because of the modest dependence of the reaction on these effects; $\rho^* = 2.1$ and 2.5 for $Ar_2PO_2CH_3$ and $R_2PO_2CH_3$, respectively.[15] These values are comparable to those found in carboxylic esters; $\rho = 1.9$ for $ArCO_2C_2H_5$,[50] and $\rho^* = 2.48$ for $RCO_2C_2H_5$.[17] In addition, the polar substituent effect of the isopropyl group is not especially large ($\rho^* = -0.19$ compared to $\rho^* = 0.00$ for the methyl group).[17]

The steric effect appears more important. Using the Taft equation[17,51] (eq 4), we found that the steric parameter

$$\log (k/k_{CH_3}) = \sigma^*\rho^* + \delta E_s \qquad (4)$$

was 2.6 per phosphinyl substituent for alkaline hydrolysis of $R_2PO_2CH_3$.[15] The comparable value in carboxylic esters ($RCOOC_2H_5$) is $\delta$ 1.0. These values presumably reflect the larger steric compression on addition of $OH^-$ to tetrahedral phosphorus than trigonal carbon.

In phosphinate hydrolysis, existing evidence supports rate-determining breakdown of the intermediate (eq 1). This evidence comes mainly from the very large dependence of the reaction rate on the alkoxy substituent ($\rho^* = 11$ for $(C_6H_5)_2PO_2R$). The rate difference between methyl and ethyl diisopropylphosphinates, $k_{CH_3}/k_{C_2H_5}$, is 5–10.[15,19] In addition to the polar effect, the large dependence of rate on *O*-alkyl substituents can be understood in terms of hindrance to solvation of the pentacoordinate oxyanion and by stereoelectronic control of the orientation of the leaving group.[15,52,53] Such control might be particularly important in a crowded pentacoordinate state.

A similar mechanistic change is likely with ethyl di-*tert*-butylphosphinate which hydrolyzes 500 times slower than ethyl diisopropylphosphinate.[19] The results reported here make it likely that alkyl esters of di-*tert*-butylphosphinic acid hydrolyze by cleavage of the C–O bond. It probably will be necessary to investigate aryl esters in order to determine the steric effect of *tert*-butyl substituents on displacement at phosphorus in esters.

Large steric effects were found in phosphinyl chlorides where the formation of the intermediate is definitely rate determining.[8] The steric effect for di-*tert*-butylphosphinyl chloride is so large that there is a change of mechanism; it hydrolyzes via a dissociative $S_N1(P)$ mechanism passing through the highly unstable phosphinylium intermediate ($R_2P^+{=}O$).

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