J. Am. Chem. Soc. **1993,** *115,* 7823–7832

Carbon versus Phosphorus Site Selectivity in the Gas-Phase Anion–Molecule Reactions of Dimethyl Methylphosphonate

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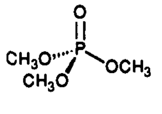
Received October 5, 1992

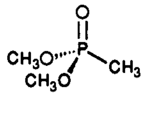
Abstract: The reactions of dimethyl methylphosphonate and its conjugate base with a variety of anions and neutral substrates, respectively, have been examined with use of the thermally equilibrated conditions (298 K) of the flowing afterglow. The conjugate base of dimethyl methylphosphonate reacts readily with alcohols and carbonyl compounds; its reaction with alcohols yields products from proton transfer, proton transfer followed by substitution at carbon, and proton transfer followed by substitution at phosphorus, while its reaction with carbonyl compounds generates products from proton transfer, Horner–Emmons–Wadsworth reaction, addition/elimination, and adduct formation. Dimethyl methylphosphonate undergoes facile reaction with a diverse set of anions ranging in base strength from amide to hydrogen sulfide and in structure from localized heteroatomic bases and localized carbon bases to delocalized carbanions. Four reaction pathways account for the interaction of anions with dimethyl methylphosphonate: proton transfer, nucleophilic substitution at carbon, reductive elimination, and nucleophilic substitution at phosphorus. Proton transfer and nucleophilic substitution at carbon dominate all reactions, while reductive elimination is observed only for the strongest base examined, amide. Methoxide and fluoride are the only anions that react at phosphorus. A reaction coordinate diagram is used to interpret the reactions of dimethyl methylphosphonate and its conjugate base. The acidity of dimethyl methylphosphonate was bracketed to be $\Delta H^\circ_{\mathrm{acid}}[(CH_3O)_2(CH_3)PO] = 373 \pm 3$ kcal mol^{-1}.

Phosphate esters are important biological species since they are the backbone of DNA, ATP, and various pesticides;[1] their reactivity has been studied extensively, particularly in relation to enzymatic reactions that bring about cleavage of the P–O bond.[2] In phosphate compounds used as models for the enzymatic process, reaction at both carbon and phosphorus sites occurs; the preferred site of reactivity is controlled by the size of the attacking nucleophile.[3] Phosphonate esters are closely related structurally to phosphate esters and are also widely employed in biological chemistry. In the condensed phase, these two classes of compounds share much in the way of reaction mechanisms. For example, Hudson and Keay[4] have measured the rate of alkaline hydrolysis for dimethyl methylphosphonate (I), a prototypical phosphonate, while Westheimer and co-workers[5] have measured that for trimethyl phosphate (II), a prototypical phosphate. The results from the two groups indicate that both hydrolysis reactions occur with cleavage of the P–O bond; dimethyl methylphosphonate hydrolyzes to methyl methylphosphonic acid, while trimethyl phosphate hydrolyzes to dimethyl phosphate. The rate coefficient for dimethyl methylphosphonate hydrolysis is an order of magnitude faster than that for trimethyl phosphate.

We have previously examined the reaction of anions with trimethyl phosphate[6] in the gas phase and found that there are essentially two chemical processes that account for all observations: (i) reductive elimination across a carbon–oxygen bond, which is the major pathway for RHN^- ions and which is not found for ions less basic than hydroxide, and (ii) nucleophilic substitution at carbon, which is observed to some extent for every anion and is the exclusive pathway for ions less basic than hydroxide. Only methoxide and ethoxide were found to give products arising from attack at phosphorus, and then only in trace (<2%) yield. To a first approximation, it is expected that in the gas phase, these same preferences will be followed when anions are allowed to react with dimethyl methylphosphonate. For dimethyl methylphosphonate, an additional factor must also be considered. In the gas phase, proton transfers are often found to be kinetically facile and usually outcompete all other reaction pathways.[7] Thus, given that dimethyl methylphosphonate has a relatively acidic proton compared to trimethyl phosphate, many of the nucleophiles used for gas-phase studies may also react by a proton transfer pathway. However, gas-phase proton transfer reactions are simply controlled by exothermicity, thus if one examines a series of nucleophiles of decreasing base strength, at some point the proton transfer pathway will become endothermic and no longer viable. Once the proton transfer is made thermochemically impossible, other reaction channels such as nucleophilic substitution at carbon or substitution at phosphorus should become kinetically viable and can then be studied.



I



II

In the liquid phase, synthetic chemists have taken advantage of the acidic site in phosphonates and extensively used phosphonate-stabilized carbanions to carry out regiospecific methylene transfers on carbonyl compounds.[8] These phosphonate carbanions, however, must be additionally stabilized by electron withdrawing groups in order for the reaction to proceed.[9]

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Phosphonates are preferred to the phosphoranes normally used in the Wittig reaction because the phosphonates are more reactive and it is easier to recover the olefin from the reaction mixture.[10]

We chose to study the factors that control the gas-phase reactions of dimethyl methylphosphonate using the room temperature conditions readily obtained with the flowing afterglow as part of our development of a comprehensive understanding of the intrinsic reactivity of anions with prototypical organic esters. Previously, we have extensively studied methyl acetate,[11] methyl pyruvate,[12] dimethyl sulfite,[13] and trimethyl phosphate[6] as well as related molecules such as dimethyl disulfide.[14] In this work, we report the products observed and our mechanistic interpretations of the reactions of dimethyl methylphosphonate with a diverse set of anions (varying both in structure and basicity) as well as the reactions of its conjugate base with a variety of neutral substrates in the gas phase. We are interested in what determines the outcome of the intramolecular competition between reaction sites or specific reaction types when a bare ion collides with a single molecule of dimethyl methylphosphonate or when its anionic conjugate base encounters a reactive neutral molecule in the gas phase, where there are no solvent molecules, counterions, or aggregates present to modify the intrinsic reactivity of the partners.

Experimental Section

The experiments reported herein were carried out at ambient temperature (298 K) and in 0.3 Torr of helium buffer gas in a flowing afterglow[15,16] which has been previously described.[17] Amide, the atomic oxygen radical anion, methoxide and fluoride were generated by dissociative electron attachment to ammonia, nitrous oxide, methanol, and nitrogen trifluoride, respectively (e.g., eq 1a). When methoxide or fluoride is used as a reagent ion, 3 mTorr of argon is added to the flow tube 15 cm downstream from the ion source (where CH_3OH or NF_3 is added) to quench any metastable helium atoms before dimethyl methylphosphonate is added. Hydroxide was generated by allowing the atomic oxygen radical anion to abstract a hydrogen atom from methane (eq 1b).[18] HS^- was formed by allowing HO^- to react with carbon disulfide (eq 2).[19] Ethoxide and *tert*-butoxide[20] were generated by allowing amide to react with diethyl ether and di-*tert*-butyl peroxide, respectively. All other reactant anions used in this work were synthesized in the flow tube by exothermic proton transfers from an appropriate neutral to amide anion (e.g. $C_6H_5^-$ from C_6H_6). {Note that in eq 1b, "+5.9 kcal mol^{-1}" indicates that the reaction is 5.9 kcal mol^{-1} exothermic (i.e., ΔH°_{rxn}[eq 1b] = -5.9 kcal mol^{-1}) and the bimolecular rate coefficient shown above the arrow is in units of cm^3 molecule^{-1} s^{-1} (k_{obs}[eq 1b] = 1×10^{-10} cm^3 molecule^{-1} s^{-1}); these conventions are used throughout this paper.}

$$N_2O \xrightarrow{e^-} O^{\bullet -} + N_2 \qquad (1a)$$

$$O^{\bullet -} + CH_4 \xrightarrow{1\times 10^{-10}} HO^- + CH_3^{\bullet} + 5.9\ \text{kcal mol}^{-1} \qquad (1b)$$

$$HO^- + CS_2 \xrightarrow{1.5\times 10^{-9}} HS^- + OCS + 48.7\ \text{kcal mol}^{-1} \qquad (2)$$

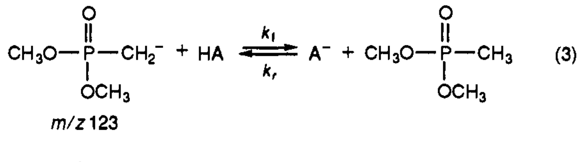
Dimethyl methylphosphonate (Aldrich, 97% pure) was vacuum distilled before use. The ^{1}H NMR and ^{31}P NMR spectra of the distilled sample in $CDCl_3$ revealed that there is a 2.5% impurity of either trimethyl phosphate or methyl phosphonic acid in the sample. A ^{1}H NMR spectrum of the distilled dimethyl methylphosphonate that had been further treated with $NaHCO_3$ revealed no changes in the amount of the impurity present; the impurity is therefore considered to be trimethyl phosphate. The positive and negative ion chemical ionization mass spectra ($CH_5^+/C_2H_5^+$ and Cl^-, respectively) of the distilled dimethyl methylphosphonate confirmed that the impurity was trimethyl phosphate. CD_3OH was prepared by taking a 1:1 (by volume) mixture of CD_3OD and H_2O and distilling the mixture once and the distillate three more times. Negative ion chemical ionization of CD_3OH in the flowing afterglow with Cl^- showed no trace ($\leq$0.5%) of methanol-d_4. Propylamine was distilled before use. All other reagents were obtained from standard commercial suppliers and used as received. Before use, each liquid sample was subjected to several freeze–pump–thaw cycles to remove dissolved gases.

Because dimethyl methylphosphonate is a relatively nonvolatile liquid (bp$^{760\text{mm}}$ 181 °C), a low flow of "sweep" gas (helium, first passed through a molecular sieve trap immersed in liquid nitrogen) was gently bubbled through the dimethyl methylphosphonate and used to carry it into the flow tube at higher flows than can be achieved by the direct distillation method. The ^{1}H NMR spectrum, the positive and negative ion chemical ionization mass spectra ($CH_5^+/C_2H_5^+$ and Cl^-, respectively) of the sample of dimethyl methylphosphonate after it had been used with the flowing afterglow, showed that no decomposition or introduction of additional impurities occurred as a result of the sweep gas.

Reactions of interest were examined in one or more of several different ways: by qualitative experiments to identify all reaction products, by kinetic experiments to measure total reaction rate coefficients, and by branching ratio experiments to quantitate the yields of the various product ions. The qualitative experiments entailed taking a complete mass spectrum at each of several times during the course of a reaction. Rate coefficients were obtained by monitoring the disappearance of the reactant ion as a function of time (distance), under pseudo-first-order conditions (i.e., constant flow of the neutral reactant was maintained).[21] The absolute accuracy of our rate coefficients is ±20%. Collision rate coefficients (k_{coll}) were calculated according to the variational transition state theory of Su and Chesnavich.[22] Reaction efficiencies, the probability of chemical reaction per collision, are determined as the ratio of the observed rate coefficient to the collision rate coefficient (EFF = k_{obs}/k_{coll}). Branching ratios were obtained by monitoring the reactant and product ion intensities of a given reaction at a fixed concentration of neutral reagent, under pseudo-first-order conditions, as a function of the time (distance).[13,14] The precision of our branching ratios is shown in Table IV; we estimate that the absolute error in accuracy is a few percent or less.

Results

In order to bracket the acidity of dimethyl methylphosphonate between Brönsted acids of known acidity, we have examined the proton abstraction reactions of $(CH_3O)_2P(O)CH_2^-$ (m/z 123, produced via the reaction of HO^- with $(CH_3O)_2(CH_3)PO$ vide infra) with a series of well-characterized acids (k_f, eq 3) *and* the



$$CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}-CH_2^- + HA \underset{k_r}{\overset{k_f}{\rightleftharpoons}} A^- + CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}-CH_3 \qquad (3)$$

reactions of dimethyl methylphosphonate with a series of well-characterized anionic bases (k_r, eq 3); the results of these studies are collected in Table I. The structure of m/z 123, the conjugate base of dimethyl methylphosphonate, was probed by allowing it

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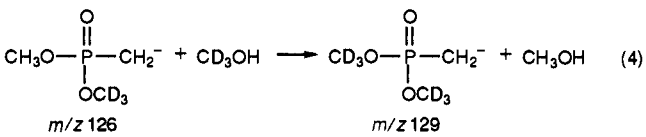
Table I. Summary of Results Concerning the Gas-Phase Acidity of Dimethyl Methylphosphonate at 298 K

AH	$\Delta G°_{acid}$[a] (kcal mol^{-1})	$\Delta H°_{acid}$[a] (kcal mol^{-1})	is proton transfer obsd in eq 3 for ...?[b] k_f	k_r
NH_3	396.1 ± 0.7	403.6 ± 0.8	–	yes
C_6H_6	390.9 ± 2.0	400.7 ± 2.5	–	yes
$CH_3CH_2CH_2NH_2$	391.0 ± 3.0	398.4 ± 3.9	–	yes
H_2O	384.1 ± 0.2	390.8 ± 0.1	no	yes
$H_2C{=}CHCH_3$	384.1 ± 2.0	390.8 ± 2.4	–	yes
C_6H_5F	378.9 ± 2.0	387.2 ± 2.5	no	yes
CD_3OH	374.5 ± 2.0[c]	382.0 ± 0.7[c]	no	yes
$C_6H_5CH_3$	373.7 ± 2.0	380.8 ± 2.4	–	yes
CH_3CH_2OH	370.8 ± 2.0	377.4 ± 2.3	no	–
$(CH_3)_2CHOH$	368.8 ± 2.0	375.4 ± 2.3	no	–
$HC{\equiv}CH$	368.5 ± 2.0	376.7 ± 2.3	no	yes
$(CH_3)_3COH$	368.0 ± 2.0	374.6 ± 2.2	–	yes
CH_2Cl_2	366.8 ± 3.0	374.6 ± 3.9	trace	yes
$CH_3OCH_2CH_2OH$	366.8 ± 2.0	373.8 ± 2.8	trace	–
$(CH_3)_3CCH_2OH$	366.0 ± 2.0	372.6 ± 2.8	trace	–
CH_3CN	365.2 ± 2.0	372.9 ± 2.6	yes	yes
HF	365.2 ± 0.4	371.0 ± 0.3	–	no
$CH_3CO_2CH_3$	365.1 ± 2.0	371.9 ± 2.3	yes	no
FCH_2CH_2OH	363.5 ± 3.5	370.1 ± 3.9	yes	no
CH_3COCH_3	361.9 ± 2.0	369.1 ± 2.6	yes	no
CH_3CHO	359.0 ± 2.0	365.8 ± 2.9	yes	no
$CH_3COCOCH_3$	351 ± 3[d]		yes	–
H_2S	344.8 ± 2.0	351.2 ± 2.1	–	no

[a] Acidities, unless otherwise noted, were obtained from ref 23. [b] A dash in the k_f or the k_r columns indicates that the reaction was not examined. [c] Reference 24. [d] Reference 25.

to react with D_2O, CD_3OD, and CD_3CD_2OD; all these reactions showed two fast H/D exchanges, yielding $(CH_3O)_2P(O)CD_2^-$.

The results found for the reactions of the conjugate base of dimethyl methylphosphonate with a variety of alcohols are summarized in Table II; most of these reactions were examined only by the qualitative type of experiments described above. A representative branching ratio plot for the reaction of $(CH_3O)_2P(O)CH_2^-$ and CD_3OH is shown in Figure 1. The data in Figure 1 indicate that the m/z 126 product ion, $(CH_3O)(CD_3O)P(O)CH_2^-$, reacts rapidly with a second molecule of methanol-d_3 to give a product ion at m/z 129, $(CD_3O)_2P(O)CH_2^-$; this reaction is shown in eq 4.



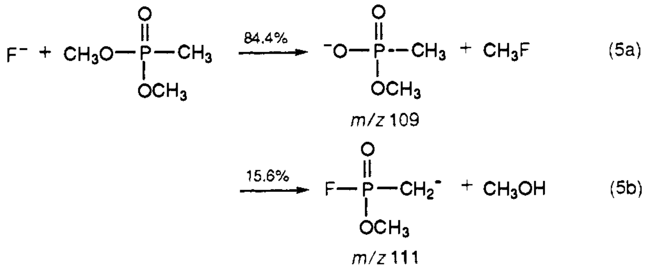
$$CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCD_3}{|}}{P}}-CH_2^- + CD_3OH \longrightarrow CD_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCD_3}{|}}{P}}-CH_2^- + CH_3OH \qquad (4)$$

m/z 126 $\qquad$ m/z 129

The results found for the reactions of the conjugate base of dimethyl methylphosphonate with a variety of carbonyl compounds are collected in Table III. In order to determine whether the termolecular reaction product ion, formed by the association of the conjugate base of dimethyl methylphosphonate and the carbonyl compound and stabilized by collisions with helium, is either a covalently bound adduct (i.e., a tetrahedral intermediate) or a loosely coordinated cluster (i.e., $(CH_3O)_2P(O)CH_2^-\cdots R_2C{=}O)$), solvent switching experiments were carried out. Both acetone and acetaldehyde were allowed to react with the adduct/cluster from the reaction of the conjugate base of dimethyl methylphosphonate with acrolein. No solvent switching was observed; i.e., no association products between the conjugate base of dimethyl methylphosphonate and acetone or acetaldehyde were found.

The quantitative branching ratios for the thermally equilibrated reactions of a variety of anions with dimethyl methylphosphonate in 0.3 Torr of helium are summarized in Table IV. Column three shows the m/z value for the most abundant isotopic peak for each unique product ion; these are the ions actually monitored during an experiment (amounts observed are in column four). Column six contains the molecular formula that we have assigned to each product ion. The last column contains the best experimental product yields for these reactions calculated from the "observed amounts" and "isotope factors" as described in footnote *d* to Table IV. Comparing the "observed amounts" and the "product yields" in Table IV shows that the correction for naturally occurring isotopes is small and of approximately the same magnitude as the error in the measurement.

In the reactant ion spectra for nucleophiles studied that are stronger bases than hydroxide, a minor hydroxide contaminant, formed from the reaction of the nucleophile with "adventitious water", is usually present. We always correct the branching ratios observed for the strongly basic reactant ions (i.e., those more basic than HO^-) to remove any contributions due to the reaction of the contaminating hydroxide signal. For amide and propyl amide, the hydroxide contaminant was 11.3% and 4.8% of the reactant ion signal, respectively. The correction was done by first obtaining the branching ratio for hydroxide and then correcting the amide or propyl amide data on a point by point basis as previously described.[13,27] Since we have previously[6] noted that amide, propyl amide, and hydroxide display rapid reaction with trimethyl phosphate, the branching ratio data for these anions were corrected for the reaction of the 2.5% trimethyl phosphate impurity.[28] A branching ratio plot representative of all those used to define the data in Table IV is shown in Figure 2 for the reaction of fluoride and dimethyl methylphosphonate. The data in Figure 2, which show that the reaction was followed to greater than 95% completion, averaged with a second measurement (data not shown) and corrected as described above, yield the results in eq 5. In this plot, the product ion yields track linearly with the extent of reaction indicating that there are no fast secondary reactions occurring. A secondary reaction is defined as the reaction between a first formed product ion and a second equivalent of the neutral reactant (i.e., dimethyl methylphosphonate). Note also that an ion at m/z 97 (i.e., $(F)(CH_3)PO_2^-$) was carefully searched for, but not found, indicating that if formed, it is less than a 0.2% product.



$$F^- + CH_3O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}-CH_3 \xrightarrow{84.4\%} {}^-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}-CH_3 + CH_3F \qquad (5a)$$

m/z 109

$$\xrightarrow{15.6\%} F-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OCH_3}{|}}{P}}-CH_2^- + CH_3OH \qquad (5b)$$

m/z 111

In addition to those anions listed in Table IV, the reactions of several other nucleophiles with dimethyl methylphosphonate were examined qualitatively; the observations for these reactions are included in Table V. The reactions of phenide, acetylide, *tert*-butoxide, and the conjugate base of methylene chloride yield a major amount of m/z 123 and a minor amount of m/z 109. For the enolate of methyl acetate and 2-fluoroethoxide, the reactions produce a major amount of m/z 109 and a minor or trace amount of the adduct/cluster, respectively. Exclusive adduct/cluster formation was found for the reaction of the enolates of acetaldehyde and acetone, while a major amount of the adduct/cluster and a minor amount of m/z 109 was found for the reaction of HS^-.

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[27] When the competing hydroxide reaction is ignored, the branching ratio obtained for the reaction of amide (average of two measurements) yielded 2.9 ± 1.1% m/z 93, 3.0 ± 0.6% m/z 109, and 93.7 ± 0% m/z 123. Comparison of this "uncorrected" branching ratio to the best value which is listed in Table IV for the amide–dimethyl methylphosphonate reaction shows that the overall correction is small, but none the less significant.

[28] When the competing trimethyl phosphate reaction is ignored, the branching ratio obtained for the reaction of amide (average of two measurments) yielded 3.5 ± 0.8% m/z 93, 5.5 ± 0.8% m/z 109, and 91.0 ± 1.5% m/z 123. Comparison of this "uncorrected" branching ratio to the best value which is listed in Table IV for the amide–dimethyl methylphosphonate reaction shows that the overall correction is small, but none the less significant.

Table II. Observed Products for the Gas-Phase Reactions of the Conjugate Base of Dimethyl Methylphosphonate with Alcohols at 298 K[a]

ROH	## IIa ##	## IIb ##	## IIc ##	adduct[b]	RO^-
CD_3OH[c]	8.6%	1.9%	89.5%		
CH_3CH_2OH[d]	~50%		~50%		
$(CH_3)_2CHOH$	major		minor	trace	
$CH_3OCH_2CH_2OH$	major		trace	minor	minor
$(CH_3)_3CCH_2OH$	major		trace	minor	minor
FCH_2CH_2OH	major		trace	minor	minor
$HOCH_2CH_2OH$	minor			minor	major

[a] A blank indicates that this product was not observed (≤0.6% of the reaction). For reactions that were only examined by qualitative experiments "major" indicates that the yield for this channel was >50%, while "minor" indicates that the yield was between 10 and 50%, and "trace" indicates that the yield was <10%. [b] Adduct indicates the formation of $(CH_3O)_2P(O)CH_2^-(ROH)$ or an isomer thereof. [c] The absolute rate coefficient for this reaction is 1.20 (±0.12) × 10^{-10} cm^3 $molecule^{-1}$ s^{-1} (EFF = 0.068). [d] The absolute rate coefficient for this reaction is 2.24 (±0.08) × 10^{-10} cm^3 $molecule^{-1}$ s^{-1} (EFF = 0.130).

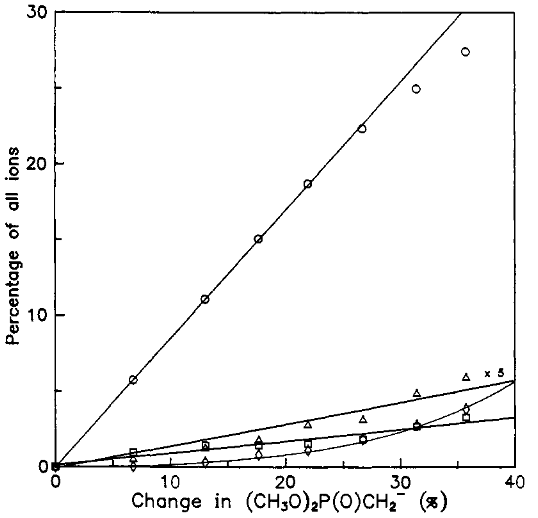

Figure 1. A branching ratio plot for the reaction of the conjugate base of dimethyl methylphosphonate with methanol-d_3 at 0.3 Torr of helium and 298 K. The downward curvature of *m/z* 126 (○) and the upward curvature of *m/z* 129 (◇) indicate the presence of a secondary reaction in which *m/z* 126 reacts with a second molecule of methanol-d_3. The straight lines are those defined by eq 4 in ref 13 and are fitted to the data which correspond to less than 15% conversion; the slopes of these lines yield the "observed amounts" of the three product ions for this *one* measurement: 8.3% *m/z* 109 (□), 3.0% *m/z* 112 (△), and 88.7% *m/z* 126. Note that for clarity, the data for *m/z* 112 are displayed at five times the actual intensity.

Table III. Observed Products for the Gas-Phase Reactions of the Conjugate Base of Dimethyl Methylphosphonate with Carbonyl Compounds at 298 K

carbonyl compd	products obsd[a]	is *m/z* 123 quenched?[b]
CH_3CHO	$H_2C{=}CH{-}O^-$; $(CH_3O)_2PO_2^-$; adduct	yes
PhCHO	$(CH_3O)_2PO_2^-$; adduct	*c*
$CH_2{=}CHCHO$	adduct; $(CH_3O)_2PO_2^-$	yes
$(CH_3)_3CCHO$	$(CH_3O)_2PO_2^-$; adduct	no
$(CH_3)_3CCOC(CH_3)_3$	no reaction obsd	no
CH_3COCH_3	$H_2C{=}C(O^-)CH_3$; $(CH_3O)_2PO_2^-$; adduct	no
$CH_3CO_2CH_3$	$H_2C{=}C(O^-)OCH_3$[d]	no
$CH_3COCOCH_3$	$H_2C{=}C(O^-)COCH_3$; $(CH_3O)_2PO_2^-$	yes
$CH_3COCO_2CH_3$	$(CH_3O)_2P(O)CH(CO)_2CH_3$; $H_2C{=}(O^-)CO_2CH_3$; $(CH_3O)_2PO_2^-$; adduct	yes
CO_2	adduct	yes
CO	no reaction obsd	no

[a] The products are listed in order of decreasing yields with the most abundant product listed first. [b] The reactant ion, $(CH_3O)_2P(O)CH_2^-$, has an *m/z* value of 123; a "yes" indicates that less than 1% of the initial amount of the reactant ion remains upon addition of the neutral at a port 76.7 cm from the entrance to the detection region and with a reservoir pressure of the carbonyl compound of less than or equal to 2.0 Torr. These conditions are such, therefore, that a "yes" indicates that the reaction rate coefficient is greater than or equal to 10^{-13} cm^3 $molecule^{-1}$ s^{-1} while a "no" indicates that the rate coefficient is less than this value. [c] PhCHO is relatively nonvolatile; we cannot add enough PhCHO to the flow tube to attain the conditions noted in footnote *b*. [d] The overall reaction is too slow to determine if the adduct is formed.

Discussion

The Acidity of Dimethyl Methylphosphonate. The experiments on the bracketing of the acidity of dimethyl methylphosphonate (Table I) indicate that the conjugate base of dimethyl methylphosphonate will ***readily*** deprotonate acids as strong or stronger than acetonitrile (i.e., $\Delta G°_{acid}[(CH_3O)_2P(O)CH_3] \geq \Delta G°_{acid}[CH_3CN]$) and will not deprotonate acids similar to or weaker than acetylene (i.e., $\Delta G°_{acid}[(CH_3O)_2P(O)CH_3] \leq \Delta G°_{acid}[HC{\equiv}CH]$). The data in Table I also show that any base stronger than the conjugate base of methylene chloride will ***readily*** deprotonate dimethyl methylphosphonate (i.e., $\Delta G°_{acid}[(CH_3O)_2P(O)CH_3] < \Delta G°_{acid}[H_2CCl_2]$) and bases similar to or weaker than fluoride will not deprotonate dimethyl methylphosphonate (i.e., $\Delta G°_{acid}[(CH_3O)_2P(O)CH_3] \geq \Delta G°_{acid}[HF]$). Thus, on the basis of these reactions of dimethyl methylphosphonate and its conjugate base, we bracket the acidity of dimethyl methylphosphonate between hydrogen fluoride and methylene chloride. Because the conjugate base of dimethyl methylphosphonate readily deprotonates acetonitrile, while the conjugates base of acetonitrile only slowly deprotonates dimethyl methylphosphonate, we conclude $\Delta G°_{acid}[(CH_3O)_2P(O)CH_3]$ = 366.0 ± 3.0 kcal mol^{-1}. Using[29] $\Delta S°_{acid}[(CH_3O)_2P(O)CH_3]$ = 23.7 eu, we obtain $\Delta H°_{acid}[(CH_3O)_2P(O)CH_3]$ = 373.1 ± 3.0 kcal mol^{-1}. Thus, the gas- and liquid-phase acidities of acetonitrile ($\Delta G°_{acid}$ = 365.2 kcal mol^{-1}, pK_a^{DMSO} = 31.3) and dimethyl methylphosphonate ($\Delta G°_{acid}$ = 366.0 kcal mol^{-1}, pK_a^{DMSO} = 33) are in excellent agreement.[30,31]

The heat of formation of the conjugate base of dimethyl methylphosphonate can be determined by using our measured acidity and the definition of the acidity of dimethyl methylphosphonate (eq 6). Using eq 6b, $\Delta H_f°[H^+]$ = 365.7 kcal mol^{-1}, $\Delta H_f°_{est}[(CH_3O)_2P(O)CH_3]$ = −211 ± 3 kcal mol^{-1} (estimated

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[29] Bartmess, J. E.; McIver, R. T., Jr. In *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 2, Chapter 11. The estimate assumes that there is no contribution to the entropy of ionization from translational, vibrational, or electronic considerations while the loss of internal rotations contributes −2.3 eu.

[30] Teulade, M.; Savignac, P.; Aboujaoude, E. E.; Collignon, N. *J. Organomet. Chem.* **1986**, *312*, 283–295.

[31] Concurrent metalation of dimethyl methylphosphonate places the pK_a of dimethyl methylphosphonate ~2 pK_a units more basic than CH_3CN (pK_a = 31.3, DMSO) and 4 pK_a units more basic than phenylacetylene (pK_a = 28.8, DMSO). pK_a values are taken from the following: Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.

Table IV. Product Distributions for the Gas-Phase Reactions of Anions with Dimethyl Methylphosphonate in 0.3 Torr of Helium at 298 K

anion A^-	$\Delta H°_{acid}[HA]$[a] (kcal mol^{-1})	product ion (*m/z*)	obsd amount[b]	n_{BR}[c]	molecular formula	product yields[d] (%)
H_2N^-	403.6	93	0.035 ± 0.007	2	$(C_2H_6O_2P)^-$	3.4
		109	0.033 ± 0.003		$(C_2H_6O_3P)^-$	3.3
		123	0.932 ± 0.002		$(C_3H_8O_3P)^-$	93.3
$CH_3CH_2CH_2NH^-$	398.4	109	0.006 ± 0.001	3	$(C_2H_6O_3P)^-$	0.6
		123	0.994 ± 0.001		$(C_3H_8O_3P)^-$	99.4
HO^-	390.8	109	0.044 ± 0.006	2	$(C_2H_6O_3P)^-$	4.3
		123	0.956 ± 0.006		$(C_3H_8O_3P)^-$	95.7
$H_2C{=}CH{-}CH_2^-$	390.8	109	0.120 ± 0.010	2	$(C_2H_6O_3P)^-$	11.9
		123	0.880 ± 0.010		$(C_3H_8O_3P)^-$	88.1
CD_3O^-	382.0[e]	109	0.032 ± 0.007	2	$(C_2H_6O_3P)^-$	3.2
		123	0.926 ± 0.013		$(C_3H_8O_3P)^-$	92.6
		126	0.042 ± 0.018		$(C_3H_5D_3O_3P)^-$	4.2
$PhCH_2^-$	380.8	109	0.033 ± 0.002	2	$(C_2H_6O_3P)^-$	3.3
		123	0.967 ± 0.003		$(C_3H_8O_3P)^-$	96.7
CH_2CN^-	372.9	109	0.071 ± 0.026	4	$(C_2H_6O_3P)^-$	7.0
		123	0.929 ± 0.025		$(C_3H_8O_3P)^-$	93.0
F^-	371.0	109	0.840 ± 0.008	2	$(C_2H_6O_3P)^-$	84.4
		111	0.160 ± 0.009		$(C_3H_8O_3P)^-$	15.6

[a] Acidities, unless otherwise noted, were obtained from ref 23. [b] The average fractional yield, ±1 standard deviation, based on observation of only the *m/z* values listed for that reaction. [c] The number of independent experimental determinations of the branching ratio (BR). [d] The yield of the product ion of given molecular formula actually formed in the reaction cited (i.e., corrected to include all naturally occurring isotopic variants). These values are calculated by taking the "observed amounts" and dividing them by the "isotope factor" (and when necessary, subtracting for overlapping isotopes) and then renormalizing. The isotope factor is the fraction of the product ion with the given molecular formula that will be detected at the *m/z* value listed (which is the predominant isotopic peak). These values were calculated from values in the Table of the Isotopes in ref 26. The isotope factors for *m/z* 93, 109, 111, 123, 126 are 0.9726, 0.9703, 0.9727, 0.9593, and 0.9598, respectively. [e] Reference 24.

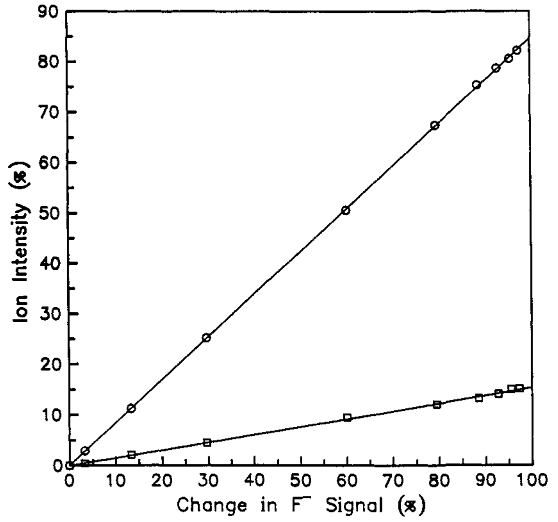
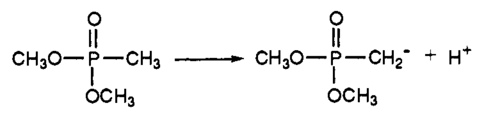


Figure 2. A branching ratio plot for the reaction of fluoride with dimethyl methylphosphonate at 0.3 Torr of helium and 298 K. The lines are those defined by eq 4 in ref 13, and the slopes of these lines yield the "observed amounts" of the two product ions for this *one* measurement: 84.6% *m/z* 109 (○) and 15.4% *m/z* 111 (□).


(6a)

$$CH_3O{-}P(=O)(OCH_3){-}CH_3 \longrightarrow CH_3O{-}P(=O)(OCH_3){-}CH_2^- + H^+ \quad (6a)$$

$$\Delta H° \text{ acid}[(CH_3O)_2P(O)CH_3] = \Delta H_f°[(CH_3O)_2P(O)CH_2^-] + \Delta H_f°[H^+] - \Delta H_f°[(CH_3O)_2P(O)CH_3] \quad (6b)$$

by group additivity),[32,33] and the acidity derived above, $\Delta H_f°[(CH_3O)_2P(O)CH_2^-] = -204 \pm 3$ kcal mol^{-1}.

Reactions of $(CH_3O)_2POCH_2^-$ and ROH. The reactions of the conjugate base of dimethyl methylphosphonate with a series of alcohols (Table II) can be described by a generalized reaction scheme (Scheme I) involving a series of elementary chemical steps terminating in one of three distinct products: proton transfer followed by ion–neutral complex separation (PT, Scheme I), proton transfer followed by nucleophilic substitution at carbon (S_N2-C, Scheme I), and proton transfer followed by nucleophilic substitution at phosphorus (S_N2-P, Scheme I). In Scheme I, the species shown in square brackets are representations of several of the long-lived ion–neutral complexes which may exist along the reaction coordinate, not all of which are shown and none of which are detected. For example, the substitution at phosphorus may proceed via a pentacoordinate intermediate which is not shown. In this general reaction scheme, the conjugate base of dimethyl methylphosphonate and the alcohol initially form an ion–neutral (encounter) complex; within this ion–neutral complex, intermolecular proton transfer occurs (III → IV) producing an alkoxide ion and neutral dimethyl methylphosphonate. The resulting ion–neutral complex, IV, has three pathways in the forward direction. If the alcohol is more acidic than dimethyl methylphosphonate, complex IV can dissociate yielding the separated products from proton transfer (e.g., free alkoxide). Within complex IV the alkoxide could also react at carbon or at phosphorus; these pathways are the only "forward" options for a complex IV formed from an alcohol that is less acidic than dimethyl methylphosphonate. The reaction of the alkoxide at carbon (S_N2) forms complex V, which can only dissociate to yield $(CH_3O)(CH_3)PO_2^-$. Within complex IV, the reaction at phosphorus, through a pentacoordinate transition state (an S_N2-like process), yields an ion–neutral complex, **VI**, containing methoxide and a new phosphonate, $(CH_3O)(RO)(CH_3)PO$. This product ion–neutral complex (VI) can proceed in the forward direction in three ways; methoxide could be observed as a product ion, or much more likely, the strong base methoxide would abstract an acidic proton or methyl group or react at the RO group from $(CH_3O)(RO)(CH_3)PO$ within complex VI, followed by dissociation yielding $(CH_3O)(RO)POCH_2^-$, $(RO)(CH_3)PO_2^-$, and/or $(CH_3O)(CH_3)PO_2^-$ as the observed product ions. Methoxide is not observed as a product ion from the reaction of the conjugate base of dimethyl methylphosphonate and any alcohol examined; thus, this pathway in Scheme I has been crossed out.

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(32) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley & Sons: New York, 1976.

(33) The heats of formation for phosphonates estimated by group additivity are in excellent agreement with the experimentally determined values. For example, for diethyl methylphosphonate $\Delta H_f°_{est}[(CH_3CH_2O)_2(CH_3)PO] \approx -228$ kcal mol^{-1} while $\Delta H_f°_{exptl}[(CH_3CH_2O)_2(CH_3)PO] = -231.2$ kcal mol^{-1} and for diisopropyl ethylphosphonate $\Delta H_f°_{est}[((CH_3)_2CHO)_2(CH_3CH_2)PO] = -249$ kcal mol^{-1} while $\Delta H_f°_{exptl}[((CH_3)_2CHO)_2(CH_3CH_2)PO] = -255.6$ kcal mol^{-1}. The experimental heats of formation are taken from ref 34. The heats of formation used in this work are included in the supplementary material.

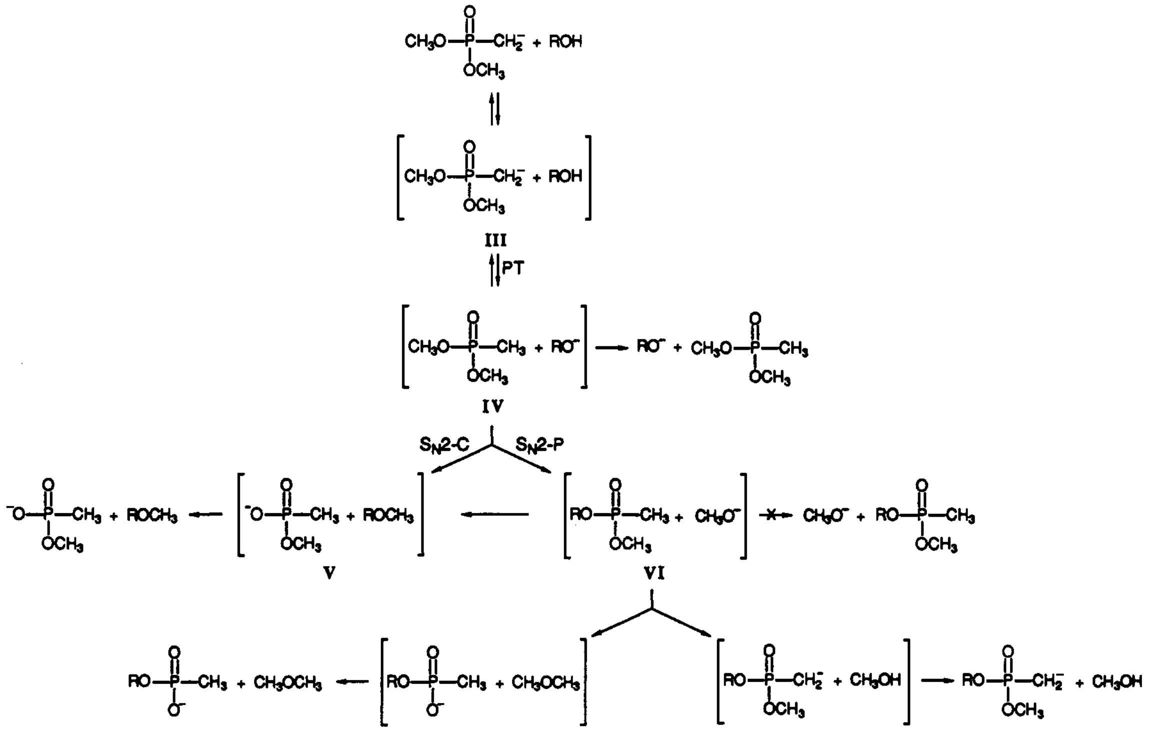
(34) Pedley, J. B.; Rylance, J. *Sussex-N. P. L. Computer Analysed Thermochemical Data: Organic and Organometallic Compounds*; University of Sussex, 1977.

Table V. Partitioning of Observed Product Ions among Available Reaction Pathways for the Interaction of Anions with Dimethyl Methylphosphonate at 298 K[a]

anion A^-	$\Delta H°_{acid}[HA]$[b] (kcal mol^{-1})	proton transfer (*m/z* 123)	$E_{CO}2$ (*m/z* 93)	S_N2-C (*m/z* 109)	S_N2-P
H_2N^-	403.6	94%	3%	3%	
$C_6H_5^-$	400.7	major		minor	
$CH_3CH_2CH_2NH^-$	398.4	99%		1%	
HO^-	390.8	96%		Va	
$H_2C{=}CH_2CH_2^-$	390.8	88%		12%	
CD_3O^-	382.0[d]	93%		3%	4%
$PhCH_2^-$	380.8	97%		3%	
$HC{\equiv}C^-$	376.7	major		minor	
$(CH_3)_3CO^-$	374.6	major		minor	
Cl_2CH^-	374.6	major		minor	
H_2CCN^-	372.9	93%		7%	
$H_2C{=}C(OCH_3)O^-$	371.9			major[e]	
F^-	371.0			84%	16%
$FCH_2CH_2O^-$	370.1			major[f]	
HS^-	351.2			minor[g]	

[a] For reactions that were only examined by qualitative experiments, "major" indicates that the yield for this channel was >50%, while "minor" indicates that the yield was between 10 and 50%, and "trace" indicates that the yield was <10%. A blank indicates that this product was not observed (≤0.6% of the reaction). [b] Acidities, unless otherwise noted, were obtained from ref 23. [c] Without isotopic labeling of the hydroxide oxygen, we are unable to discern whether the observed product results from reaction at carbon or at phosphorus. [d] Reference 24. [e] A minor amount of adduct/cluster formation is also observed. [f] A trace amount of adduct/cluster formation is also observed. [g] A major amount of adduct/cluster formation is also observed.

Scheme I. A Generalized Scheme for the Reactions of the Conjugate Base of Dimethyl Methylphosphonate with Alcohols

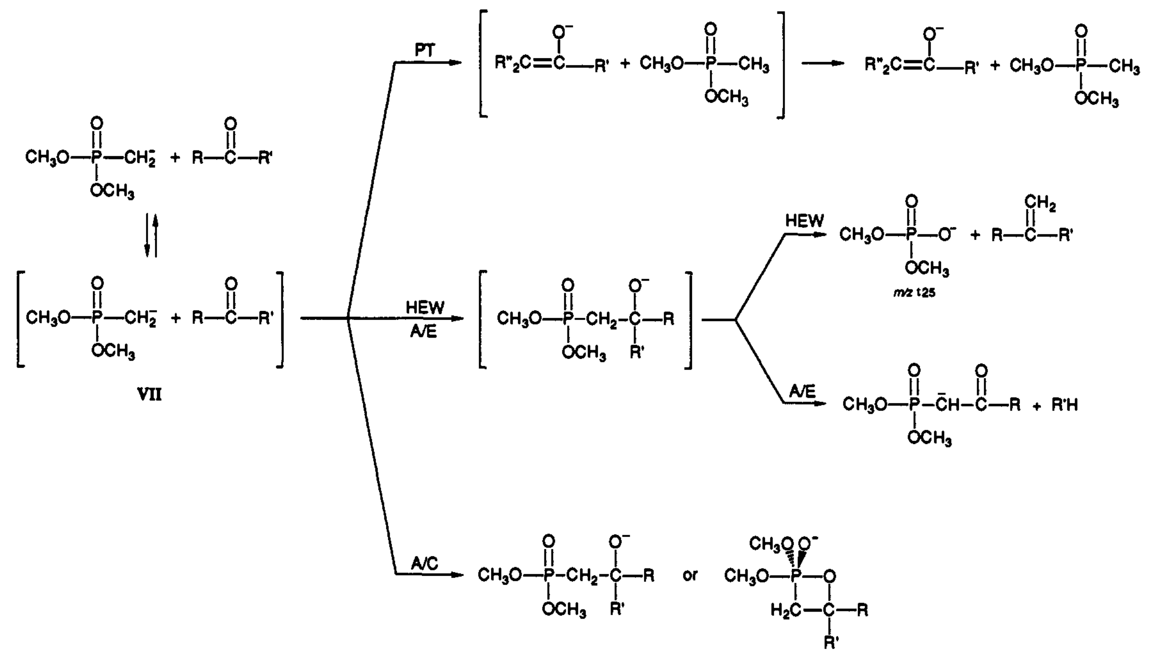


Proton transfer products are observed from the reactions of those alcohols that are more acidic than dimethyl methylphosphonate ($\Delta H°_{acid}[ROH] < 373$ kcal mol^{-1}); however, facile H/D exchange is observed for those alcohols that are up to 20 kcal mol^{-1} less acidic than dimethyl methylphosphonate (e.g., D_2O, CD_3OD, and CD_3CD_2OD). For all alcohols that react by the proton transfer followed by reaction-at-phosphorus channel, $(CH_3O)(RO)POCH_2^-$ is observed as a product; the reaction of CD_3OH also yields a trace amount of $(CD_3O)(CH_3)PO_2^-$. The $(CH_3O)(CH_3)PO_2^-$ observed could be formed from a nucleophilic substitution reaction in either ion–neutral complex IV or VI in Scheme I; both complexes probably generate $(CH_3O)(CH_3)PO_2^-$.

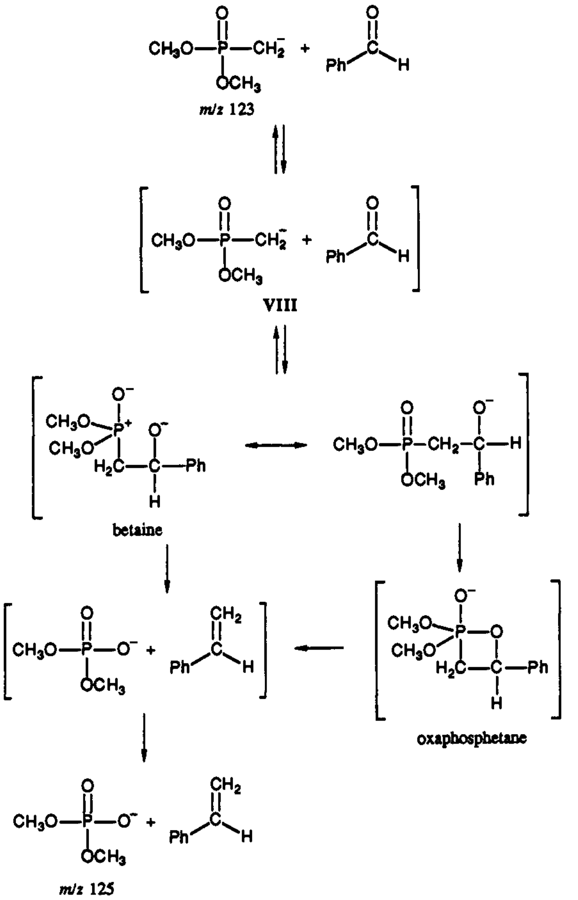
Reactions of $(CH_3O)_2POCH_2^-$ and Carbonyl Compounds. When the conjugate base of dimethyl methylphosphonate is allowed to react with aldehydes, ketones, or esters (Table III), the initial ion–neutral complex (VII, Scheme II) selects from among four reaction channels: proton transfer (PT, Scheme II), Horner–Emmons–Wadsworth reaction (HEW, Scheme II), addition/elimination (A/E, Scheme II), and adduct/cluster formation (A/C, Scheme II). Proton transfer occurs when the aldehyde or ketone contains an acidic hydrogen and the proton transfer reaction is thermodynamically allowed (i.e., $\Delta H°_{acid}$[carbonyl compound] < 373 kcal mol^{-1}). Adduct/cluster formation is observed to some extent for the reaction of the conjugate base of dimethyl methylphosphonate with many of the compounds listed in Table III. When the adduct/cluster ion from the reaction of $(CH_3O)_2P(O)CH_2^-$ with $H_2C{=}CHCHO$ is allowed to react with both acetone and acetaldehyde no exchanged adduct/cluster products are found (i.e., no $(CH_3O)_2P(O)CH_2^-(CH_3COCH_3)$ or $(CH_3O)_2P(O)CH_2^-(CH_3CHO)$ was observed). This observation indicates that the termolecular product from the $(CH_3O)_2P(O)CH_2^-$ with $H_2C{=}CHCHO$ is the adduct.

For most of the carbonyl compounds studied (Table III), we also observe formation of a product ion at *m/z* 125; the reactions of benzaldehyde and 2,3-butanedione yield the most *m/z* 125. We have assigned the structure $(CH_3O)_2PO_2^-$ to the ion at *m/z* 125 and propose that it is formed by a Horner–Emmons–

Scheme II. A Generalized Scheme for the Reactions of the Conjugate Base of Dimethyl Methylphosphonate with Carbonyl Compounds

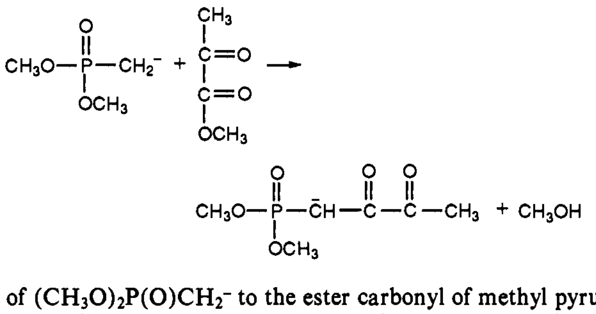


Scheme III. A Mechanistic Scheme for the Horner–Emmons–Wadsworth Reaction between the Conjugate Base of Dimethyl Methylphosphonate and Benzaldehyde



Wadsworth reaction as shown in Scheme III for the reaction of the conjugate base of dimethyl methylphosphonate and benzaldehyde. The mechanism in the gas phase of this Horner–Emmons–Wadsworth reaction should be analogous to that proposed in the liquid phase.[8] Within the first formed ion-neutral complex (VIII), the conjugate base of dimethyl methylphosphonate attacks the carbonyl compound forming a tetrahedral intermediate. The tetrahedral intermediate decomposes, via a betaine intermediate and/or an oxaphosphetane intermediate, effecting a Horner–Emmons–Wadsworth reaction, forming $(CH_3O)_2PO_2^-$ and a terminal olefin. In the liquid phase, it is not known whether the reaction occurs via the betaine intermediate or an oxaphosphetane intermediate;[8] however, recently, it has been reported that the betaine intermediate is unimportant for the related Wittig reaction.[35] An analogous methylene-for-oxygen atom exchange has been reported in the gas-phase reactions of silyl carbanions.[36] Horner–Emmons–Wadsworth reactions involving phosphonate carbanions have been observed in solution for phosphonate carbanions stabilized by an electron-withdrawing group; for phosphonate carbanions without electron-withdrawing groups, the reaction stops at betaine formation.[9] The gas-phase results, however, show that the Horner–Emmons–Wadsworth reaction occurs in the gas phase for the parent phosphonate carbanion, albeit at modest rates compared to other reactions.

An addition/elimination reaction (eq 7) is observed for the reaction of methyl pyruvate and the conjugate base of dimethyl methylphosphonate (it is the major process) in addition to proton transfer and the Horner–Emmons–Wadsworth reaction just mentioned. The tetrahedral intermediate formed by the addition



$$CH_3O-P(O)(OCH_3)-CH_2^- + CH_3-C(=O)-C(=O)-OCH_3 \rightarrow CH_3O-P(O)(OCH_3)-\bar{C}H-C(=O)-C(=O)-CH_3 + CH_3OH \quad (7)$$

of $(CH_3O)_2P(O)CH_2^-$ to the ester carbonyl of methyl pyruvate can collapse by eliminating methoxide. The methoxide that is expelled can then deprotonate the newly formed carbonyl compound in the ion–neutral complex. Methyl acetate is the

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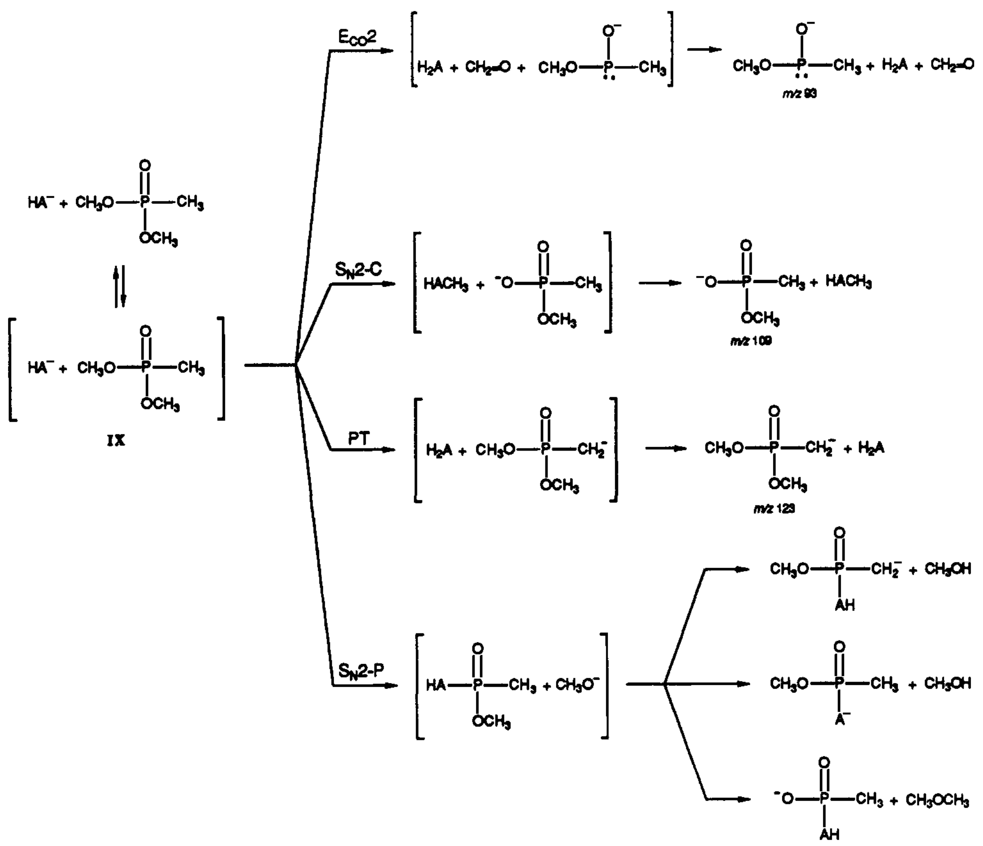
(35) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1990**, *112*, 3905–3909.

(36) (a) Damrauer, R.; DePuy, C. H.; Davidson, I. M. T.; Hughes, K. J. *Organometallics*, **1986**, *5*, 2050–2054. (b) Damrauer, R.; DePuy, C. H.; Davidson, I. M. T.; Hughes, K. J. *Organometallics* **1986**, *5*, 2054–2057. (c) Campanaro, A.; Marvin, C. H.; Morehouse, S. P.; McMahon, T. B. *Org. Mass Spectrom.* **1988**, *23*, 663–668.

Scheme IV. A Generalized Scheme for the Reactions of Anions with Dimethyl Methylphosphonate



only other carbonyl compound examined in which both addition/elimination and methylene transfer pathways are viable. For the reaction of the conjugate base of dimethyl methylphosphonate and methyl acetate, however, proton transfer outcompetes both addition/elimination and methylene transfer.

Reaction of Anionic Nucleophiles with Dimethyl Methylphosphonate. We can account for how anionic nucleophiles react with dimethyl methylphosphonate by using the general reaction scheme shown in Scheme IV which involves four reaction pathways: reductive elimination across a carbon–oxygen bond ($E_{CO}2$, Scheme IV); nucleophilic substitution at carbon (S_N2-C, Scheme IV); proton transfer (PT, Scheme IV); and nucleophilic attack at phosphorus (S_N2-P, Scheme IV). In Table V, we have re-cast the data of Table IV, plus added qualitative observations for the reaction of several additional anions with dimethyl methylphosphonate, in terms of the mechanistic channels followed. A quick perusal of the data in Table V indicates that nucleophiles react with dimethyl methylphosphonate by only two major processes: proton transfer and nucleophilic substitution at carbon. Three nucleophiles, amide, methoxide-d_3, and fluoride, also show small amounts (4-16%) of unique pathways ($E_{CO}2$ or S_N2-P). Adduct formation, which we do not consider a "chemical reaction" but rather just an "association" process, is only observed for those anions that are too weakly basic to undergo bimolecular reaction.

We think about the anions in Table V as belonging to three different classes of reactants, localized heteroatomic bases (e.g., H_2N^-, HO^-), localized carbon nucleophiles (e.g., $C_6H_5^-$), and delocalized carbon nucleophiles (e.g., $H_2C{=}CHCH_2^-$, $PhCH_2^-$). These anions are classified in this manner because of the distinct reactivity that each class displays upon reaction with a variety of organic compounds such as dimethyl disulfide,[14] dimethyl sulfite,[13] and trimethyl phosphate.[6] In contrast to this structure–reactivity relationship in which reactions of ions from the different classes were to have different selectivities even when having identical efficiencies, proton transfer dominates the reaction of dimethyl methylphosphonate (Table V) independent of the type of anion studied (albeit of sufficient base strength to make the proton transfer exothermic). Whether the anion is a localized heteroatomic base, a localized carbon base, or a delocalized carbanion, the proton transfer path is found to predominate, e.g., high yields of m/z 123 are found for tBuO$^-$, Cl_2CH^-, and CH_2CN^- reacting with dimethyl methylphosphonate. This type of behavior is consistent with the proton transfer depending only on the thermodynamics of the reaction, even though delocalized carbanions have been shown to be kinetically poor bases,[37] and provides confidence in acidities derived from bracketing studies.

The second major pathway observed to some extent for every anion that undergoes *chemical* reaction with dimethyl methylphosphonate yields a product ion at m/z 109, $(CH_3O)(CH_3)PO_2^-$, which is formed via nucleophilic substitution at carbon (S_N2-C, Scheme IV). Since $(CH_3O)(CH_3)PO_2^-$ is a weak base[6] and presumably, therefore, an excellent leaving group,[38] when the proton transfer pathway is "turned off" by becoming endothermic (i.e., for anions with PA < 372 kcal mol^{-1}), nucleophilic substitution is still thermochemically allowed and becomes the major pathway by which reaction occurs.

When amide, the strongest base examined, is allowed to react with dimethyl methylphosphonate, a minor pathway observed is reductive elimination across the carbon–oxygen bond yielding m/z 93, $(CH_3)(CH_3O)PO^-$ ($E_{CO}2$, Scheme IV). In some encounters, the resulting phosphonite anion might be expected to add to formaldehyde within the encounter complex, yielding an alkoxide, $(CH_3)(CH_3O)P(O)CH_2O^-$ (m/z 123), as the product ion. Therefore, the ion, m/z 123 that is detected in many of the reactions reported herein, could either be the rearranged alkoxide or the conjugate base of dimethyl methylphosphonate. Two fast

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[37] Farneth, W. E.; Brauman, J. I. *J. Am. Chem. Soc.* **1976**, *98*, 7891–7898.

[38] (a) Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219–4228. (b) Pellerite, M. J.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 5993–5999. (c) Riveros, J. M.; Jose, S. M.; Takashima, K. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic Press: New York, 1985; Vol. 21, pp 197–240. (d) Brauman, J. I.; Dodd, J. A.; Han, C.-C. In *Nucleophilicity*; Harris, J. M., McManus, S. P. Eds.; American Chemical Society: Washington, DC, 1987; Advances in Chemistry Series 215, Chapter 2.

H/D exchanges[39] of the m/z 123 ion with D_2O, CH_3OD, and CD_3CD_2OD, however, indicate that m/z 123 has two acidic protons and therefore must not arise from re-addition of the phosphonite anion to formaldehyde. Re-addition probably does not occur because the resulting alkoxide, $(CH_3)(CH_3O)POCH_2O^-$, is more basic than the starting phosphonite anion, $(CH_3)(CH_3O)PO^-$. Reductive elimination reactions across C–O bonds of organic esters have been noted for the reaction of strong bases with dimethyl sulfite,[13] dimethyl carbonate,[40] methyl pyruvate,[12] and trimethyl phosphate.[6] An analogous reaction involving elimination across the C–S bond of dimethyl disulfide[14] involves re-addition of the leaving group anion to the thioformaldehyde produced. Re-addition of the leaving group anion to the formaldehyde produced in the amide plus methyl pyruvate[12] reaction and in the amide plus dimethyl carbonate[40] reaction has also been noted.

When methoxide-d_3 or fluoride are allowed to react with dimethyl methylphosphonate, product ions arising from attack at phosphorus (S_N2-P, Scheme IV) are observed. Methoxide-d_3 yields 4% of m/z 126, $(CH_3O)(CD_3O)POCH_2^-$, while fluoride yields 16% of m/z 111, $(CH_3O)(F)P(O)CH_2^-$. After the initial formation of an ion–neutral "encounter" complex, the methoxide-d_3 or fluoride attacks phosphorus via an "in-line" displacement[1-3,41] at phosphorus, involving a pentacoordinate transition structure (i.e., a mechanism similar to S_N2 at carbon), to displace methoxide. Within the product ion–neutral complex $[CH_3O^- + (CH_3O)(F)P(O)CH_3]$, methoxide deprotonates the newly formed phosphonate yielding $(CH_3O)(HA)P(O)CH_2^- + CH_3OH$, where HA is either F or CD_3O. The reaction of fluoride with dimethyl methylphosphonate is the *only* reaction of an anion with a P(V) compound that we have studied that yields significant (>10%) reaction at phosphorus.

Why does fluoride yield the largest amount of phosphorus attack with dimethyl methylphosphonate? For F^-, the proton transfer pathway is *endo*thermic and therefore this kinetically facile process is thermochemically negated, which allows slower reaction channels, such as nucleophilic substitution, a chance to compete. Reaction at phosphorus may be due to an enhanced nucleophilicity of fluoride toward phosphorus with respect to the other anions studied herein. In solution, fluoride has been shown to be a better nucleophile in phosphoryl transfer reactions than oxygen-centered nucleophiles having the same base strength.[42] This enhanced nucleophilicity of fluoride toward phosphorus is also observed in the gas phase; 2-fluoroethoxide, a nulceophile with a similar proton affinity to fluoride, reacts exclusively at carbon, rather than in part at phosphorus (Table V).

The reaction of dimethyl methylphosphonate with fluoride yields more products from attack at phosphorus (16%) than the reaction of trimethyl phosphate and fluoride (≤2%).[6] The enhanced reactivity of the phosphonate compared to the phosphate could be due to the electron donating ability of the lone pairs of the additional oxygen in trimethyl phosphate to the P=O group, which lowers the electrophilicity of the phosphate relative to the phosphonate; similar arguments have been used to explain why ketones are more electrophilic and more reactive than carbonyl esters. The decreased reactivity of phosphates relative to phosphonates has also been observed in solution; Hudson and Keay[4] have measured the rate for alkaline hydrolysis of dimethyl methylphosphonate to methyl methylphosphonic acid and found that it is 1.46×10^{-2} M^{-1} s^{-1} at 50 °C, which is an order of magnitude faster than the rate of alkaline hydrolysis of trimethyl phosphate[5] to dimethyl phosphate ($k_{obs} = 1.4 \times 10^{-3}$ M^{-1} s^{-1} extrapolated to 50 °C).

Filley[43] has briefly examined the gas-phase reactions of amide and hydroxide with dimethyl methylphosphonate in a flowing afterglow. He found that the reaction of amide yields 82% $(CH_3O)_2P(O)CH_2^-$, 9% $(CH_3)(CH_3O)PO_2^-$, and 9% $(CH_3)(CH_3O)PO^-$, while the reaction of hydroxide yields 88% $(CH_3O)_2P(O)CH_2^-$ and 12% $(CH_3)(CH_3O)PO_2^-$; these observations are in agreement with our results presented above. He also observed that the reaction of the conjugate base of dimethyl methylphosphonate with benzaldehyde slowly yields $(CH_3O)_2PO_2^-$, which arises from a Horner–Emmons–Wadsworth reaction.

On the basis of the product yields and the thermochemical data (supplementary material) described above we can compose a reaction coordinate diagram that accounts for the reactions of dimethyl methylphosphonate and its conjugate base. One such reaction energy diagram, which contains our bias that the most appropriate way to consider all ion–molecule processes is a series of elementary chemical steps, is shown in Figure 3 for the reaction of methoxide-d_3 with dimethyl methylphosphonate. The solvation energies for the various ion–neutral complexes are estimated by calculating the appropriate potential using ion–neutral separation distances estimated by the van der Waal radii.[44]

All chemical conversions are initiated by the formation of a long-lived ion–neutral complex between CD_3O^- and dimethyl methylphosphonate, **IX**. Four chemical pathways are, in principle, available for this specific complex. First is the trivial dissociation back to reactants; however, this pathway must be relatively unimportant because the reaction is fairly efficient. The three chemically significant processes are (i) proton transfer (PT, Scheme IV) yielding $[(CH_3O)_2P(O)CH_2^- + CD_3OH]$, (ii) nucleophilic substitution at carbon (S_N2-C, Scheme IV) yielding $[(CH_3O)(CH_3)PO_2^- + CD_3OCH_3]$, and (iii) nucleophilic substitution at phosphorus (S_N2-P, Scheme IV) yielding $[CH_3O^- + (CH_3O)(CD_3O)(CH_3)PO]$. These complexes follow the subsequent steps indicated in Figure 3. In order to determine the partitioning of the reaction into the three complexes above, we must consider the heights of the barriers to these complexes from the initial complex, **IX**. Since the branching ratio favors nucleophilic substitution at phosphorus (4%) over nucleophilic substitution at carbon (3%), we expect the barrier leading to $[CH_3O^- + (CH_3O)(CD_3O)(CH_3)PO]$ to be lower but very close in energy to that leading to $[(CH_3O)(CH_3)PO_2^- + CD_3OCH_3]$. We anticipate that the barrier to proton transfer is significantly smaller than the barrier for either substitution at phosphorus or carbon pathways, since proton transfer dominates the reaction of CD_3O^- and dimethyl methylphosphonate.

How does the reaction coordinate diagram in Figure 3 relate to our observations for the reaction of the conjugate base of dimethyl methylphosphonate with methanol-d_3? For this reaction we do not observe products from proton transfer since it is endothermic. We also observe more reaction at phosphorus (89.5%) than reaction at carbon (8.6%). Thus, the barrier for reaction at phosphorus should be lower than that for reaction at carbon. The comparison of the product ratios for the CD_3O^- and $(CH_3O)_2P(O)CH_3$ reaction and the $(CH_3O)_2P(O)CH_2^-$ and CD_3OH reaction indicates that the barriers for both reaction at carbon and at phosphorus should be close to the total energy for the $(CH_3O)_2P(O)CH_2^-$ and CD_3OH reaction. The presence of these high barriers for the $(CH_3O)_2P(O)CH_2^-$ and CD_3OH reaction is confirmed by the inefficiency (EFF = 0.068) of the reaction. Since the barrier between complex IX and complex III is small, facile interconversion between these complexes is expected for $(CH_3O)_2P(O)CH_2^-$ and CD_3OH. The observation of fast H/D exchange when CD_3OD is allowed to react with $(CH_3O)_2P(O)CH_2^-$ reveals that there is indeed rapid intercon-

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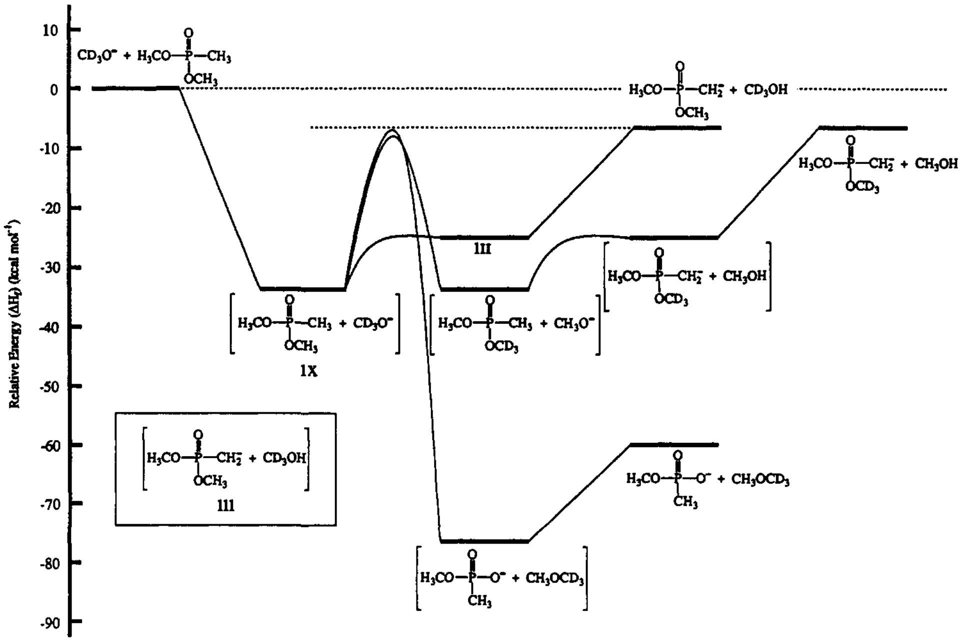

Figure 3. Proposed reaction coordinate diagram for the interaction of CD_3O^- and dimethyl methylphosphonate and $(CH_3O)P(O)CH_2^-$ and methanol-d_3. The heights of the barriers are hypothetical and are inferred from the observed product yields (see text). The structure of ion–molecule complex **III** is shown in the box.

version between complexes IX and III, thereby confirming the small barrier.

The reaction coordinate diagram shown in Figure 3, while qualitative in nature, has a substantial amount of experimental data to support it and can be used to predict the outcome of reactions not yet studied. It is interesting to note that for the reaction of methoxide-d_3 and dimethyl methylphosphonate the barrier for reaction at phosphorus is lower than that for the reaction at carbon, indicating that the reaction at phosphorus is more facile than reaction at carbon, while for the analogous reaction of methoxide-d_3 and trimethyl phosphate the reaction at carbon is much more facile than the reaction at phosphorus. This difference could indicate that the reaction at phosphorus for the phosphonate is more "addition/elimination like" since addition/elimination reactions at phosphorus can compete with substitution reactions at carbon[45] while for the phosphate the reaction at phosphorus is more "substitution-like", a reaction which cannot compete with the substitution reaction at carbon.[6]

Conclusions

The gas-phase reactivity displayed by dimethyl methylphosphonate and its conjugate base is rich and varied. For example, the conjugate base of dimethyl methylphosphonate reacts readily with a wide range of alcohols and carbonyl compounds. The reaction of the conjugate base of dimethyl methylphosphonate and alcohols yields three different products from a series of microscopic steps: proton transfer, proton transfer followed by nucleophilic substitution at carbon, and proton transfer followed by nucleophilic substitution at phosphorus, while the reaction of the conjugate base of dimethyl methylphosphonate with carbonyl compounds leads to the formation of products from proton transfer, Horner–Emmons–Wadsworth reaction, addition/elimination, and adduct formation. Dimethyl methylphosphonate, itself, also undergoes facile reaction with a diverse set of anions. Essentially four reaction pathways are followed: proton transfer, nucleophilic substitution at carbon, reductive elimination across a carbon–oxygen bond, and reaction at phosphorus. Proton transfer and nucleophilic substitution at carbon dominate the reaction of anions with dimethyl methylphosphonate, while reductive elimination is only observed for the strongest base examined. Products from reaction at phosphorus are found in a trace amount when methoxide-d_3 is used as a nucleophile and in a greater amount when fluoride is used as the nucleophile. The significant (>10%) amount of phosphorus reaction for fluoride arises from the enhanced nucleophilicity of fluoride toward phosphorus and enhanced electrophilicity of phosphorus. Combination of the reactions of dimethyl methylphosphonate and its conjugate base leads to a bracketed acidity of $\Delta H^\circ_{acid}[(CH_3O)_2(CH_3)PO] = 373 \pm 3$ kcal mol^{-1} and further to the postulation of a reaction coordinate diagram for the reaction of methoxide with dimethyl methylphosphonate and the reaction of the conjugate base of dimethyl methylphosphonate and methanol.

Acknowledgment. We gratefully acknowledge support of this research by the National Science Foundation (Grant CHE-9196164). R.C.L. thanks Procter and Gamble for a fellowship administered by the Organic Division of the American Chemical Society.

Supplementary Material Available: Table of heats of formation used in this work (2 pages). Ordering information is given on any current masthead page.

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