Acylphosphonic Acids and Methyl Hydrogen Acylphosphonates: Physical and Chemical Properties and Theoretical Calculations

Rafik Karaman, Amiram Goldblum, and Eli Breuer *
Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy, Jerusalem, Israel
Haim Leader
The Israel Institute for Biological Research, Ness Ziona, Israel

Acylphosphonic acids (**5**) and methyl hydrogen acylphosphonates (**3**) were synthesized by di- and mono-demethylation of dimethyl acylphosphonates (**1**). Spectroscopic data (i.r., ^{31}P and ^{1}H n.m.r.) are reported for these types of compounds for the first time. Examination of their hydrolytic stability under acidic and basic conditions revealed that except for methyl hydrogen acylphosphonates (**3**) that are unstable under highly alkaline pH conditions, the C–P bond in these types of compounds is stable in most cases. Nucleophilic reagents, *e.g.* amines, borohydride, or hydroxylamine react with the carbonyl group of ionized acylphosphonates with the preservation of the C–P bond, to yield α-imino-, α-hydroxy-, or α-oxyimino-alkylphosphononate anions, respectively. Semi-empirical quantum mechanical (MNDO/H) calculations were performed on benzoylphosphonic acid (**5c**) and on the esters and anions derived from it, as representatives of their classes, in order to assess bond lengths and preferred conformations, and to estimate charges on the carbonyl and phosphoryl groups. Calculations show that for both neutral and ionized (anions) compounds free rotation around the C–P bond is expected due to the low energy barriers.

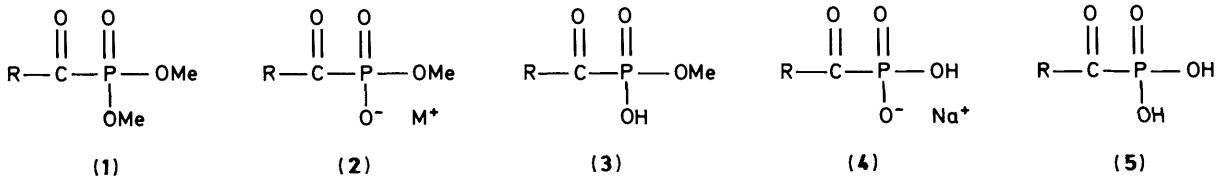
Phosphonic acid analogues of naturally occurring phosphates or of carboxylic acids have attracted considerable interest as potential regulators, mediators, or inhibitors of metabolic processes.[1,2] In the large group of compounds prepared and studied, there is an abundance of analogues of lipids, sugar phosphates, nucleotides, or amino acids,[2] *etc.*, containing C–P bonds in a variety of structures. However, the compounds hitherto studied belong almost entirely to the class of alkylphosphonates with only a handful of examples of acylphosphonates among them.[3] The few instances of reported acylphosphonic acids or monoesters have been prepared, characterized, and used as salts, mostly for studying their biochemical properties. The free alkyl hydrogen acylphosphonates and dihydrogen acylphosphonates (acylphosphonic acids) have never been reported, and their chemical and physical properties have not been described. Assumptions about the chemical properties of acylphosphonic acids and of their monoesters have been based on the properties of the diesters.[4] Such extrapolations cannot be justified since ionization of the phosphoryl group should influence considerably the reactivity of the whole molecule. There exists information in the recent literature regarding the hydrolytic behaviour of specific and unusual acylphosphonic acids (see below), that can hardly be considered as representative compounds of their classes. In view of this, a systematic study of these acids is required, as it is a prerequisite to the design of novel biologically active compounds based upon these functional groups. Consequently we describe in this paper the preparation and physical and chemical properties of some representative acylphosphonic acids and monoesters. We have recently reported that acylphosphonic acids and monoesters undergo thermal and acid catalyzed fragmentation,[5] while their oximes can serve as phosphorylating agents.[6]

Results and Discussion

Synthesis.—The standard synthetic procedure for the synthesis of acylphosphonates is the Arbuzov reaction of acyl halides with trialkyl phosphites.[4,7] Using this method we have synthesized a series of aliphatic and aromatic acylphosphonates, as well as the previously reported α,β-unsaturated derivatives, dimethyl *trans*-but-2-enoylphosphonate (**1d**)[8] and dimethyl 2,2-dimethylacryloylphosphonate (**1e**).[9] In contrast to problems that were observed in the preparation of the unsubstituted α,β-unsaturated diethyl propenoylphosphonate,[8] we encountered no difficulty in the preparation of the terminally unsaturated (but not conjugated) dimethylpent-4-enoylphosphonate (**1f**) and dimethyl undec-10-enoylphosphonate (**1g**), which could be obtained *via* the Arbuzov reaction in good yields. The Arbuzov reaction was also applicable to the preparation of halogeno-acylphosphonates, such as dimethyl 2-chloropropionyl-(**1h**)[10] and 4-chlorobutyryl-phosphonate (**1k**), but yielded unstable and impure products when it was attempted using 3-chloropropionyl chloride, 2,3-dichloropropionyl chloride, and 3,4-dichlorobutyryl chloride. Other dichloroacetylphosphonates, 2,3-dichlorobutyryl- and 2,3-dichloro-3-methylbutyryl-phosphonate (**1i**) and (**1j**), were obtained by the addition of chlorine to the double bonds of the corresponding unsaturated alkenoylphosphonates (**1d**) and (**1e**). Attempted syntheses of (**1i**) and (**1j**) by the Arbuzov reaction of trimethyl phosphite and the corresponding dichloroacyl chlorides led to mixtures of phosphorus-containing products.

The salts of methyl hydrogen acylphosphonates (**2**) were conveniently obtained, usually in analytically pure state, through monodemethylation of dimethyl acylphosphonates (**1**) by sodium iodide in acetone,[3c] or lithium bromide in acetonitrile. While both reagents were effective in the dimethylation of alkanoyl-, alkenoyl-, and aroyl-phosphonates, lithium bromide was clearly the preferred reagent for the demethylation of chloroalkanoylphosphonates because of less interference by halogen exchange.

The free acids, methyl hydrogen acylphosphonates (**3**), were obtained by simple acidification of the corresponding salts (**2**) or by passing their methanolic solutions through a cation exchanger. All such compounds obtained in this work were oils that decomposed to the corresponding alkyl carboxylates upon attempted distillation.[5] Consequently no elemental analytical data are available for these. Their structure assignment is based upon n.m.r. and i.r. spectroscopic data that clearly differ from those of the alkyl carboxylates. Methyl hydrogen acylphos-



(1) (2) (3) (4) (5)

M = Li, except for (**2a**) and (**2c**), M = Na

a; R = Me
b; R = Hexyl
c; R = Ph
d; R = MeCH=CH–
e; R = Me_2C=CH–
f; R = CH_2=$CH(CH_2)_2$–
g; R = CH_2=$CH(CH_2)_8$–
h; R = MeCH(Cl)
i; R = MeCH(Cl)CH(Cl)
j; R = $Me_2C(Cl)CH(Cl)$
k; R = $Cl(CH_2)_3$

phonates (**3a**) and (**3c**) were further dealkylated to the mono salts of the dibasic acylphosphonic acids (**4a**) and (**4c**) by treatment with sodium iodide in refluxing acetone. Alternatively, didemethylation of dimethyl acylphosphonates could be achieved by their treatment with trimethylsilyl bromide in acetonitrile, followed by methanolysis of the resulting bistrimethylsilyl acylphosphonates.[11] The acylphosphonic acids (**5**) obtained in this work are oils, except for benzoylphosphonic acid (**5c**), m.p. 211 °C. They are soluble in water and insoluble in chloroform and ether and decompose upon heating to the corresponding carboxylic acids.[5]

Spectra of Acylphosphonates.—The i.r. spectra of the various diesters of acylphosphonates have been studied previously.[12] The results of these studies (showing that the carbonyl absorptions of acylphosphonates appear at lower frequency than those of the corresponding α-diketones; see Table 1 and Experimental section) served as basis for speculations regarding the rotational conformation as well as electronic interactions and conjugation in the acylphosphonic group.

Anions of acylphosphonate monoesters (**2**) show lower absorption frequencies for the C=O and P=O bonds than the corresponding diesters (**1**) and acids (**3**) (see Table 1 and Experimental section). These low C=O and P=O frequencies in the series of (**2**) are consistent with an alteration in the electronic ground-state of C=O and P=O. The negative charge, located on the oxygens of the phosphoryl group, interacts with the carbonyl group and shifts the carbonyl stretching absorption to a longer wavelength. Similarly, delocalization of the negative charge on the oxygen results in lowering the stretching frequency of P=O, as in the case of other types of phosphoryl derivatives.[13]

The vibrational frequencies calculated (see below) for the C=O bond in the three molecules (**1c**), (**2c**), and (**3c**) are too high. The value of 2 180 cm^{-1} is obtained for both un-ionized species (**1c**) and (**3c**). Ionization leads to a lowering by 60 cm^{-1} [in (**2c**)], in agreement with the trend observed experimentally. The phosphoryl vibrations contain many contributions and are not easily compared.

In the ^1H n.m.r. spectrum, the P–O–Me protons of dimethyl and of monomethyl esters (**1**) and (**3**) appear as doublets in the region of δ 3.9 p.p.m. Ionization of the phosphoryl group causes a significant change in the methoxy proton shifts, as can be seen from the values of δ 3.6—3.7 obtained for the salts (**2**). This shift is caused by the electron donation from the negatively charged oxygen which results in an increase in the electron density on the methoxy protons. This is confirmed by MNDO/H calculations, as shown in Table 1. Both ^1H n.m.r. spectra and theoretical calculations of the diesters and monoesters [of type (**1**) and (**3**)] as well as those of anions (**2**) indicate the existence of free rotation around the C–P bond in these molecules.

In Table 2 there is a summary of ^{31}P chemical shifts of two representative acylphosphonic acids, mono- and di-methyl esters (**5**), (**3**), and (**1**), and the corresponding ionized acylphosphonates [(**2**), (**4**), and the di-ionized (**5c**) Na_2]. The data show that the phosphorus nucleus adjacent to a negative charged oxygen resonates at a lower field by *ca.* 2—4 p.p.m. than the phosphorus of an un-ionized analogue. This is consistent with the results of MNDO/H calculations which indicate that the phosphorus in anions (**2c**) and (**5c**) Na_2 has a larger *positive* charge than the phosphorus in the un-ionized derivatives (**1c**), (**3c**), and (**5c**) (see Table 1).*

Quantum Mechanical Calculations.—We carried out semi-empirical calculations on benzoylphosphonates (**1c**), (**2c**), (**3c**), (**5c**), and the dianion of (**5c**) with a modified version of MNDO,[14] which was recently corrected for its failures to describe hydrogen bonding appropriately.[15] Total geometry optimizations were done with estimations of second derivatives (Hessian matrix) for each of the $3n - 6$ parameters in each species. The optimizations started from a few conformations in order to verify global minima. Rotational barriers were checked by the 'reaction co-ordinate' method,[16] where a torsional angle was kept 'frozen' at each of a few angular variation steps (10—30°) leading to full rotations. In addition to the enthalpies obtained by MNDO (at 298.15 K), entropies were calculated by adding their translational, rotational, and vibrational components.[17] Vibrational frequencies were obtained through the diagonalization of the force constant matrix, including mass weights.

With regard to conformational stabilities, the energies of many conformers of compound (**1c**) were calculated by rotating P=O with respect to C=O. This compound was found to be most stable in its s-*trans* carbonyl-phosphoryl arrangement (ΔH_f = 141.18 kcal/mol). The s-*cis* conformation is at a maximum on the rotational energy co-ordinate, but only 1.8 kcal above the minimum. The phenyl ring is nearly perpendicular to the average plane of O=C–P=O and has a rotational barrier of *ca.* 5.2 kcal, but it may rotate ± 50° from its minimum with less than 2.0 kcal. Methyl (OMe) equilibrium conformations are ± 30° with respect to the O–P=O plane (rotational barrier of 3.7 kcal/mol). Bond lengths, bond angles, and Mulliken atomic charges for (**1c**) (Figure 1) are given in Table 3. The calculated dipole moment for the most stable conformation is μ = 2.177 Debye.

Our theoretical calculations substantiate previous observations of free rotation around the C–P bond in benzoylphosphonate by Berlin and Taylor.[12a] These authors attributed the large reduction in the carbonyl i.r. frequency in the phosphonate (with respect to α-dicarbonyl compounds) to an

* Similar influence of the ionization upon the ^{31}P chemical shifts has been observed in the case of orthophosphoric acid: V. Mark, C. H. Dungan, M. M. Crutchfield, and J. R. Van Wazer, in 'Topics in Phosphorus Chemistry,' eds. M. Grayson and J. Griffith, Interscience, N.Y., N.Y. 1967, vol. 5, pp. 227—457, and refs. 50, 89, and 95 therein.

Table 1. Comparison of i.r., ^{1}H n.m.r., and ^{31}P n.m.r. data with results of MNDO/H calculations of (**1c**), (**2c**), (**3c**), and (**5c**)

	(**1c**)	(**2c**)[a]	(**3c**)	(**5c**)	(**5c**)-Na_2[a,b]
Calcd. length of C=O (Å)	1.2033	1.2213	1.2032	1.2031	1.2277
Calcd. length of P=O (Å)	1.4971	1.5096	1.4497	1.5025	1.5260
Observed ν(C=O)/cm^{-1}	1 655	1 620	1 650	1 650	1 605
Observed ν(P=O)/cm^{-1}	1 260	1 215	1 230	1 230	1 200
Calcd. charge on C=O	0.291	0.108	0.297	0.299	0.068
Calcd. charge on phosphorus	1.159	1.293	1.124	1.093	1.312
δ ^{31}P (p.p.m.)	−0.87	2.16	−0.55	−1.29	2.55
Average calcd. charge on OMe H's	0.023	−0.025	0.023		
Calcd. charge on OMe C	0.185	0.243	0.185		

[a] Anions of (**2c**) and of (**5c**) were calculated without counter-ions. [b] (**5c**)Na_2 was prepared from (**5c**) by the addition of 2 equiv. of sodium hydroxide in methanol, in which this disodium salt is insoluble.

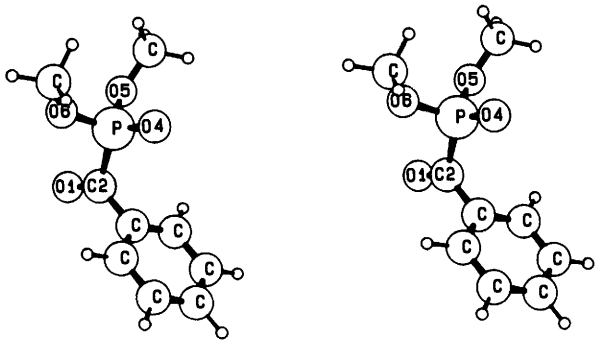


Figure 1. Stereoview of dimethyl benzoylphosphonate (**1c**)

interaction between the lone pair of the P=O oxygen and the carbonyl carbon orbital, which is mostly possible in a perpendicular conformation of O=P–C with respect to the P–C=O plane. To test the prediction of Berlin and Taylor we calculated dimethyl benzoylphosphonate (**1c**) by limiting O=C–P=O conformations to 90° and to 0°, with geometry optimization of all other parameters. In the 90° conformer, the only support for their suggestion is an appreciable reduction of the C=O vacant orbital energy (LUMO + 1) by *ca.* 4 kcal with respect to this orbital in the 180° conformer. However, no participation of the O-4 atomic orbitals is found. To further test the validity of the calculations for the molecular conformation we combined the results for conformational energy and for dipole moment of 36 conformers (at 10° intervals) around the C–P bond of (**1c**) (Figure 2) and calculated the resultant dipole moment from the contribution of each conformer, due to its molar fraction in the mixture. Equations (**1**) and (**2**) have been used towards these calculations.

$$\mu = \sum_{J=1}^{36} \mu_J \cdot \bar{X}_J \qquad (1)$$

$$\bar{X}_J = e^{-\Delta H_j/RT} / \sum_{n=1}^{36} e^{-\Delta H_n/RT} \qquad (2)$$

RT = 0.6 kcal at room temperature

Table 2. ^{31}P Chemical shifts of representative acylphosphonic derivatives

Un-ionized compound ($CDCl_3$)	δ ^{31}P/ p.p.m.	Ionized compound (D_2O)	δ ^{31}P/ (p.p.m.)
(**1a**)	−2.93	(**2a**)	−0.83
(**3a**)	−2.51	(**4a**)	−0.63
(**5a**)	−2.10		
(**1c**)	−0.87	(**2c**)	2.16
(**3c**)	−0.55	(**4c**)	2.13
(**5c**)	−1.29	(**5c**)Na_2	2.55

Table 3. Calculated structure and charge parameters of dimethyl benzoylphosphonate (**1c**)

Bond length (Å)		Bond angle (°)		Atomic charge (e$^-$)	
O(1)–C(2)	1.203	O=C–P	119.8	O(1)	−0.210
C(2)–P	1.861	C–P=O	119.6	C(2)	0.291
				P	1.159
P–O(4)	1.497	C–P=O	103.8	O(4)	−0.696
P–O(5),O(6)	1.614	P–O–methyl	126.9	O(5,6)	−0.567
O–methyl	1.389				

[a] See Figure 1 for the equilibrium structure and atom numbers.

The value of μ = 2.932 Debye thus calculated for (**1c**) is in striking similarity to the measured value of μ = 2.93 ± 0.05 D.[12a] This corresponds to a mean dihedral angle (O=P–C *vs.* P–C=O) of *ca.* 115°, close to the conformation suggested by Berlin and Taylor. Additional confirmation for the calculated structure was recently obtained from crystallography,[18] which found the phenyl ring out-of-the-plane of the carbonyl sp^2 bonds in a series of related α-oximinophosphonic derivatives. The barrier of rotation about the C–P bond in the anion of (**2c**) had similar values to those of (**1c**), and we may safely assume that the acid also has corresponding energy values. While the optimized structure of the neutral compounds [di- and mono-methyl esters (**1c**) and (**3c**)] is s-*trans* for the O=C–P=O group, the anion (**2c**) prefers a conformation with the two oxygens, which share the additional negative charge, at an angle of ≈ ±130° with respect to the O=C–P plane (Figure 3).*

Anion (**2c**) has longer C=O and P=O bonds than the neutral compounds (**1c**), (**3c**), and (**5c**). This is reflected in the lower vibrational frequencies (Table 1). This is also accompanied by minor shortening of the C–P bond in anion (**2c**). The molecular orbitals of the neutral compounds (**1c**), (**3c**), and (**5c**), are quite similar, with HOMO and HOMO-1 being mostly degenerate π orbitals of the phenyl ring. The degeneracy is removed in the anion which has the three phosphoryl oxygens (O-4, O-5, and O-6) contributing to the three highest occupied orbitals (lone pairs). The HOMO of the anion has a contribution from the carbonyl which is nearly perpendicular to the P–O$^-$ bonds, and antibonding in character (Figure 4). This orbital may be singled out as the clearest source for the reduction in C=O Mulliken bond density in the anion (**2c**) (0.625) *vs.* the neutral compounds (**1c**) and (**3c**) (0.674).

Chemical Properties of Acylphosphonates.—Information regarding the hydrolytic stabilities of acylphosphonate esters

* Previous crystallographic study of monosodium acetylphosphonate showed the P=O and C=O groups nearly parallel in the crystal. However, this compound cannot be compared to our calculations owing to the presence of counterions and ionic interactions: P. G. Jones and O. Kennard, *Acta Crystallogr., Sect. B*, 1978, **34**, 2309.

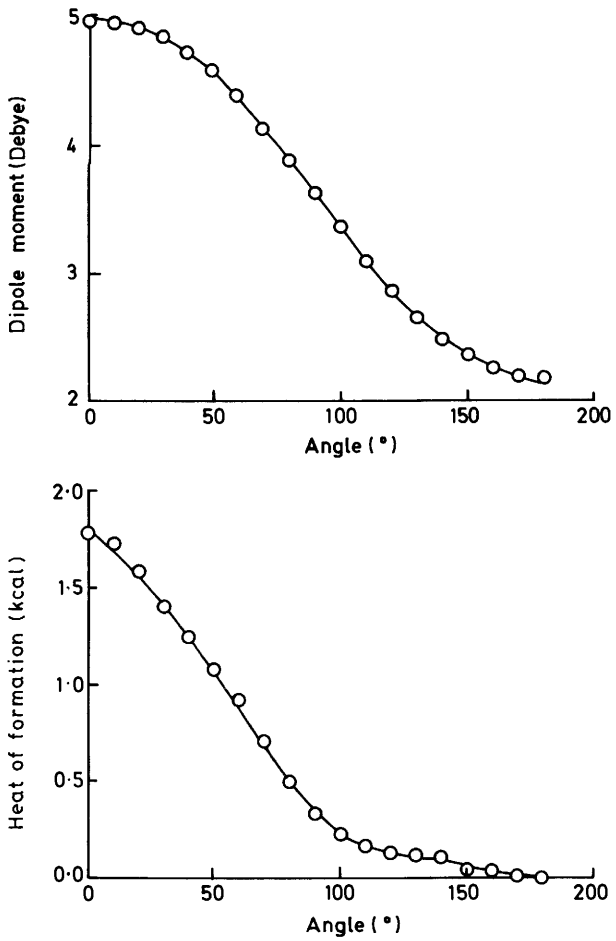


Figure 2. Dipole moments and heats of formation of rotamers of (**1c**)

or acids is needed so that these compounds can be used for biological or technological purposes. The acid catalysed hydrolysis of diethyl benzoylphosphonate was studied from a mechanistic standpoint by Narayanan and Berlin,[19] who found that this reaction leads mainly to benzoic acid and diethyl hydrogen phosphonate, in addition to small amounts of benzoylphosphonic acid and ethyl hydrogen benzoylphosphonate. We have examined the stability of dimethyl benzoylphosphonate (**1c**), methyl hydrogen benzoylphosphonate (**3c**), and benzoylphosphonic acid (**5c**) in aqueous hydrogen chloride for 96 h at room temperature by ^{31}P n.m.r. spectroscopy. Similarly to Narayanan and Berlin we have found that dimethyl benzoylphosphate (**1c**) hydrolysed (to the extent of 50%) to dimethyl hydrogen phosphonate (δ ^{31}P = 10.9 p.p.m., d septet, J 728 Hz) as the main product (40%) in addition to methyl dihydrogen phosphonate (δ ^{31}P = 7.51 p.p.m., dq, J 600 Hz, 10%). In contrast, methyl hydrogen acylphosphonates (**3b**) and (**3c**) and acylphosphonic acids (**5b**) and (**5c**) were stable under these conditions. It seems reasonable to assume that the stability of (**3**) and (**5**) is a consequence of hydrogen bonding.[19]

In order to gain information regarding the comparative hydrolytic stabilities of the different types of acylphosphonates in base, we examined by ^{31}P n.m.r. spectroscopy and high performance liquid chromatography the stabilities of dimethyl acylphosphonates (**1b**) and (**1c**), monomethyl acylphosphonates (**2b**), (**2c**), and (**2d**) and acylphosphonic acids (**5b**) and (**5c**) as representative compounds under three standard conditions: (i) borate buffer of pH 7.4, (ii) borate buffer of pH 9.0, and (iii) 1M NaOH (pH $\approx$ 14), at room temperature.

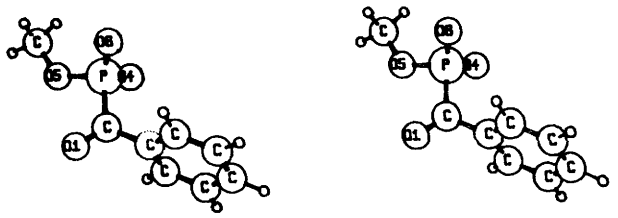


Figure 3. Stereoview of methyl benzoylphosphonate anion (**2c**)

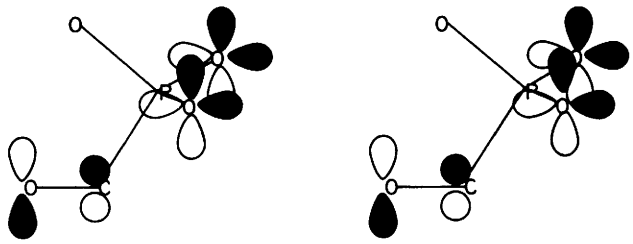
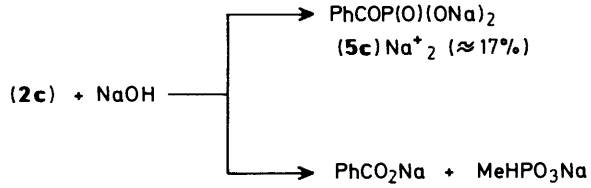


Figure 4. H.O.M.O. Orbitals of methyl benzoylphosphonate anion (**2c**)

We found that acylphosphonic acids (**5b**) and (**5c**) are completely resistant to basic hydrolysis, in contrast to the dialkyl esters (**1b**) and (**1c**) that are completely unstable in all basic media,* and hydrolyse to the corresponding carboxylic acid (>90%) and methyl dihydrogen phosphonate ($\approx$90%) as the major products.† In contrast, monomethyl acylphosphonates (**2b**), (**2c**), and (**2e**) were stable at pH 9 but hydrolysed, at pH 14 to give acylphosphonate dianion (**5**), sodium carboxylates, and methyl sodium phosphonate in the approximate ratio of 1:5:5 [in the case of (**2c**)] as determined by high performance liquid chromatography and ^{31}P n.m.r. spectroscopy (Scheme 1).

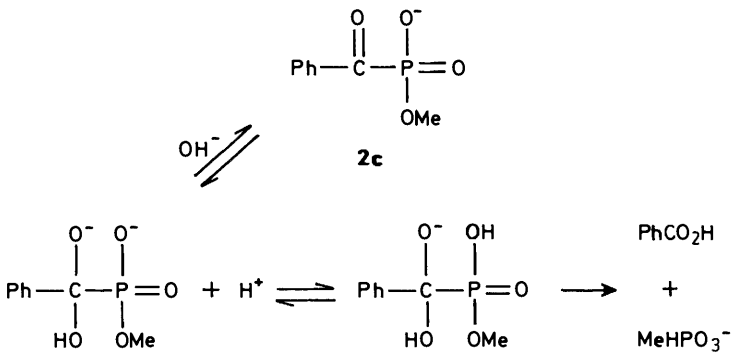


Scheme 1.

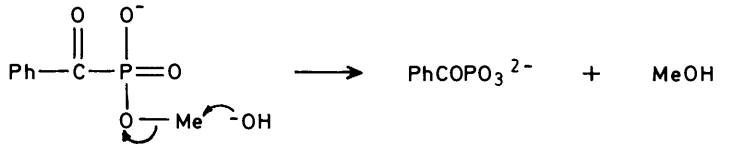
The formation of these products indicates that in (**2c**) there are two electrophilic sites at which there is a possibility for a nucleophilic attack by a hydroxide anion. Judging by the relative amounts of the products, the most reactive site is the carbonyl carbon which reacts with hydroxide to give, reversibly, a tetrahedral intermediate, which in turn may be protonated and suffer cleavage of the C–P bond to form benzoate and monomethyl hydrogen phosphonate (Scheme 2). Alternatively, hydroxide anion may also attack the P–O–Me group (Scheme

* Dimethyl acetylphosphonate has been shown to hydrolyse with a half-life of seconds at pH 7: R. Kluger, D. C. Pike, and J. Chin, *Can. J. Chem.*, 1978, **56**, 1792; see also: W. Jugelt, S. Andreae, and G. Schubert, *J. Prakt. Chem.*, 1971, **313**, 83; S. Andreae and W. Jugelt, *Z. Chem.*, 1973, **13**, 136.

† We assume that methyl hydrogen phosphonate is the secondary hydrolysis product of dimethyl hydrogen phosphonate that has been shown to hydrolyse rapidly, presumably by a dissociative mechanism involving methyl phosphenite (MeOP=O): F. H. Westheimer, Shaw Huang, and F. Covitz, *J. Am. Chem. Soc.*, 1988, **110**, 181. Methyl phosphenite has been postulated previously: C. J. R. Fookes, M. J. Gallagher, and H. Honnegger, *J. Chem. Soc., Chem. Commun.*, 1978, 324.



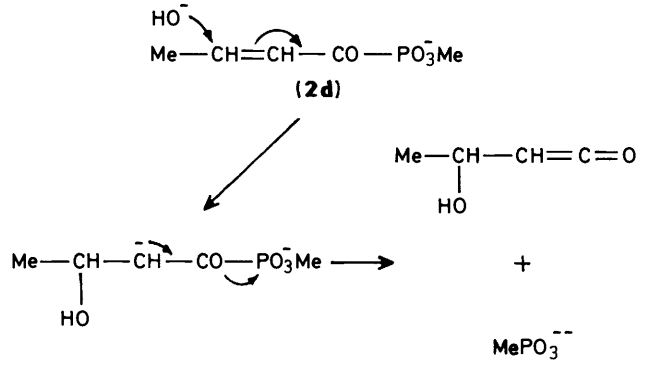
Scheme 2.



Scheme 3.

3) and displace benzoylphosphonate, which as a dianion is expected to be a very poor leaving group. Therefore it is not surprising that this is the less favoured course of the reaction.*

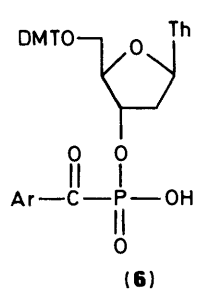
It is noteworthy that among the monoesters of type (**2**) that are stable at pH 7.4, the crotonyl derivative (**2d**) is exceptional in its instability at this pH. It seems reasonable to assume that the decomposition of (**2d**) is initiated by a Michael type addition of hydroxide ion to the double bond, to form an enolate anion, which would decompose by analogy to what was observed for α-carbanions derived from acylphosphonates (Scheme 4).[20] The addition of hydroxide ion to the double bond in (**2e**) would be greatly hindered by the two β-methyl groups, thereby preventing the reaction.[21] This assumption is supported by the results obtained from monitoring the reaction of methyl crotonylphosphonate anion with sodium hydroxide by ^{1}H n.m.r. spectroscopy in deuterium oxide. During the progress of the reaction there is a gradual decrease in the intensities of the vinylic protons (multiplets centred at δ 7.49 and δ 6.49) and of the allylic β-methyl group (δ 2.02, d, *J* 6.8 Hz), accompanied by the appearance of a new doublet at δ 1.23 (d, *J* 6.3 Hz) which is attributed to the terminal methyl group of the addition product of hydroxide to the double bond.



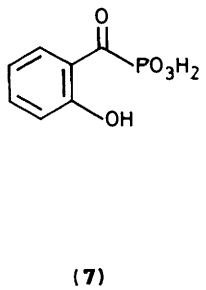
Scheme 4.

* The alternative mechanism, by which a hydroxide ion would attack the phosphorus in (**2c**), is regarded as less likely, since this would lead to a higher density of negative charge around the phosphorus in the transition state and is therefore expected to have a higher activation energy.

In this context previous results concerning the behaviour of two unique acylphosphonate derivatives under hydrolytic conditions should be mentioned. Hata and co-workers used the aroylphosphonic group as a protecting group in the synthesis of nucleotides.[22] In the course of their work they determined the stability of a series of 5′-(dimethoxytrityl)thymidine-3′-aroylphosphonates (**6**) in '1 M sodium hydroxide–pyridine (1 : 1, v/v)', and found that these aroylphosphonate monoesters were resistant to hydrolysis. We subjected methyl sodium benzoylphosphonate (**2c**) to these conditions and found that it underwent complete hydrolysis to benzoic acid in 18 h at 25 °C. Another unique case is that of *o*-hydroxybenzoylphosphonic acid (**7**). Calvo reported recently that this compound hydrolyses to the extent of 15% 'at 100 °C, pH 8.8'.[23] In contrast to this, we observed no decomposition when we kept benzoylphosphonic acid at the same conditions. It seems therefore that neither compound (**6**) nor (**7**) can be considered as representative models for acylphosphonic acids and monoesters. It appears reasonable to assume that the excessive stability of the monoester (**6**) is the result of steric hindrance due to the large nucleoside bound to the phosphoryl group. On the other hand the increased reactivity of (**7**) as compared to the unsubstituted



(**6**)

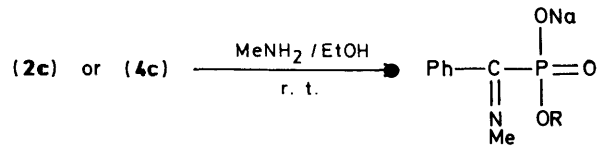


(**7**)

benzoylphosphonate indicates that the *ortho*-hydroxy group probably participates intramolecularly in the fission of the C–P bond.

Treatment of (**2c**) and (**4c**) with alcoholic methylamine at room temperature gave the imino derivatives (**8**) and (**9**) in high yields (92 and 87% respectively) (Scheme 5). The two products, (**8**) and (**9**), crystallized from their reaction mixtures and were identified on the basis of elemental analysis and spectroscopic evidence. In their ^{1}H n.m.r. spectra they showed doublets at δ

3.16 and at 3.19, which were attributed to MeN= groups ($J_{PC=NCH}$ 4.4 and 4.5 Hz, respectively), while in their ^{31}P n.m.r. spectra compound (**8**) appears at δ 6.66 p.p.m. as a quartet and (**9**) at 5.92 as a singlet. These spectra indicate that the imines are single geometric isomers around the C=N bond; their configurations are unassigned. In the i.r. spectra, (**8**) and (**9**) show the absence of the carbonyl absorption of the starting materials and the presence of new bands at 1 620 and 1 615 cm^{-1} which are characteristic for imines. The facile imine formation from the carbonyl groups of ionized acylphosphonates (**2c**) and (**4c**) can be taken as an indication that these carbonyl groups have retained their electrophilicity at least toward methylamine, which is an uncharged nucleophile. Imines (**8**) and (**9**) are reactive compounds that hydrolyse rapidly in aqueous solution to the starting ketones, (**2c**) and (**4c**), but not to the corresponding carboxamides, as could be established by ^1H and ^{31}P n.m.r. spectroscopy. This behaviour confirms the increased stability of the C–P bond in acylphosphonate anions [type (**2**) and (**4**)] as compared to that in acylphosphonate diesters [of type (**1**)].[4,24]

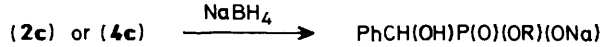


(**8**) R = Me

(**9**) R = H

Scheme 5.

Similarly to dialkyl acylphosphonates (**1**) that have been reported to react rapidly with sodium borohydride,[25] methyl sodium benzoylphosphonate (**2c**) could also be reduced to the corresponding α-hydroxyalkylphosphonate (**10**) (Scheme 6). In order to determine whether the carbonyl group of the doubly ionized benzoylphosphonate would still be reactive towards borohydride anion, its reaction was monitored by ^{31}P n.m.r. spectroscopy. In this experiment it was found that the carbonyl group of (**4c**) was completely reduced in 30 min at pH 10. While the reaction products of the dialkyl acylphosphonates have been reported to undergo fragmentation at pH 6—7 to yield aldehydes,[25] the anions of α-hydroxyalkylphosphonic acids were stable, and the corresponding acid (**10**) could be isolated after acidification. ^{31}P N.m.r. spectra of the two products show peaks at 20.07 p.p.m. for (**10**) and 16.94 p.p.m. for (**11**) which are characteristic for alkylphosphonates.



(**10**) R = Me (**11**) R = Na

Scheme 6.

The latter result clearly indicates that the carbonyl group of ionized acylphosphonates remains a reactive electrophilic centre even towards an anionic nucleophile (borohydride anion), in addition to what has been shown earlier with regard to noncharged nucleophiles (methylamine, hydroxylamine). However, in contrast to the behaviour of dialkyl acylphosphonates [*e.g.* (**1c**)] which easily suffer C–P bond cleavage, in ionized acylphosphonates, *e.g.* (**2**) or (**4**), this addition step is not followed by cleavage of the C–P bond because the ionized phosphoryl moiety cannot serve as a leaving group.

We employed MNDO/H calculations in order to improve our understanding of these experimental results, which show

Table 4. Stabilization energy [$E(\beta^2)$] in frontier orbital interactions

Electrophilic site in compound	Nucleophile	
	OH^-	H^-
P in (**1c**)	−0.063	−0.0942
C in (**1c**)	−0.187	−0.2710
C in $(\mathbf{5c})^{2-}$	−0.051	−0.0610

that the dianion of (**5c**) reacts with sodium borohydride but not with sodium hydroxide. The calculations demonstrate that, for both the diester (**1c**), and the dianion of (**5c**), nucleophilic attack by H^- * or OH^- is directed more easily towards the carbonyl carbon, than to the phosphorus atom. We found that in vacant orbitals with lower energy, carbon participates more than phosphorus (as evident from the relevant atomic orbital coefficients in the molecular orbitals). Smaller stabilization is found for the interaction of nucleophiles with the phosphorus atom of dianion (**5c**) with respect to similar interaction with the carbonyl carbon. Equation (**3**)[26] gives the approximate stabilizing energy due to nucleophile-electrophile interaction, based on frontier orbital terms. Only a few orbitals of the electrophile (LUMO, LUMO + 1, LUMO + 2) and HOMO from the nucleophile were considered for attack on (**1c**). With the dianion of (**5c**), the most important contribution to stabiliz-

$$E = \sum_s \sum_r \frac{2\left(\sum_{ab} C_{ra} C_{sb} \beta_{ab}\right)^2}{E_r - E_s} \qquad (3)$$

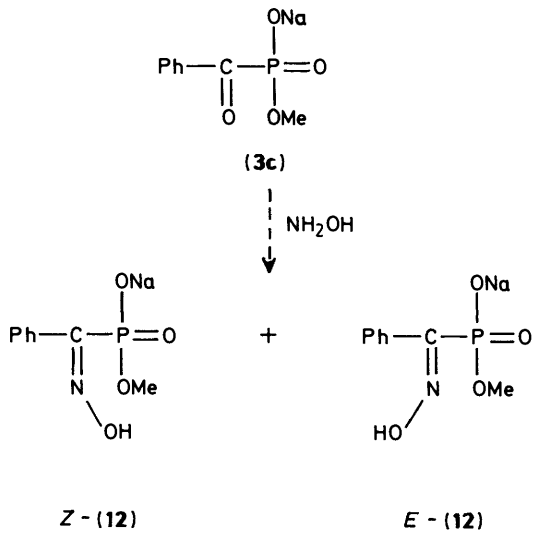
ation is from LUMO + 4 with the nucleophile's HOMO. In this equation r stands for the electrophile's vacant orbitals, s for the occupied orbitals of the nucleophile, c for the orbital's coefficient, β the resonance integral (1.5—6.5 eV),[27] C_a is the coefficient of H^- or OH^- in their HOMO only (we assumed $C_a = 1$ for both H^- and OH^-, the latter being concentrated on the oxygen), and C_b is the coefficient of either carbonyl or phosphorus. E_r For H^- and OH^- were calculated by MNDO, as were also the E_s values for the relevant molecular orbitals. Table 4 gives the values for the stabilization energies expected from the attack by H^- or OH^- on electrophilic sites. The results in Table 4 demonstrate that: (i), the carbonyl of (**1c**) is more easily attacked by nucleophiles than the dianion of (**5c**), which is expected; (ii), H^- attacks both (**1c**) and the dianion of (**5c**) more than OH^- [the difference between the two is smaller in the case of (**5c**) dianion]. Contrary to the experimental results, this approach suggests that attack by OH^- on (**5c**) dianion should be nearly as effective as the attack by H^-.† The discrepancy between the calculations and the experiments may have two sources. (a) Experiments by ^{31}P n.m.r. may not be adequate to show the attack by OH^- on (**5c**) dianion if an intermediate which is in fast equilibrium with the starting materials, is formed. This explanation is supported by the well known fast equilibrium of ketones forming hydrates in basic medium, while the reaction with H^- leads to secondary alcohols. (b) The

* Although hydride and borohydride are quite different reagents, we justify the calculation of this simplified model, because the most crucial interaction to consider is that of the carbonyl with the hydride. However, it is clear that this approach is approximate in its very nature.

† The addition of hydroxide to the carbonyl should give a tetrahedral intermediate, which should be observable by ^{31}P n.m.r. spectroscopy, similar to the tetrahedral intermediate we observed in the reactions of acylphosphonates with alcohols. (J. Katzhendler, R. Karaman, and E. Breuer, in preparation.) No change was seen in the ^{31}P n.m.r. spectrum of (**5c**) in highly basic solution.

calculations only treat the initial interaction of nucleophile with electrophile and are insufficient to be applied to later steps along the reaction pathway, in particular to the transition state. The essence of frontier orbital theory[28] as it was here applied, is to extend the expected influence of an initial stabilization of reactants towards stabilization of the transition state. As is well known for some cases, such as 1,2- *vs.* 1,4-addition to conjugated systems, this correlation is not always operative and a difference between thermodynamic and kinetic control is found.[29]

Treatment of dialkyl acylphosphonates with a methanolic solution of hydroxylamine hydrochloride in the presence of 1 equiv. of pyridine has been shown by Berlin over 20 years ago to give mixture of the *E* and *Z* oximes.[30] However, when this reaction was attempted using methyl benzoylphosphonate anion (**2c**), the formation of benzonitrile and dimethyl hydrogen phosphate were observed. Further study disclosed that when



Scheme 7.

hydroxylamine was used in this reaction as a free base, the *E* and *Z* oximes (**12**) of the monoanions of acylphosphonate monoesters [*E*-(**12**) and *Z*-(**12**)] could be obtained (*E*/*Z* = 73/27)* (Scheme 7), and proved that the formation of benzonitrile in the presence of pyridine hydrochloride is a secondary fragmentation of the α-oxyiminophosphonic acids.[6a]

Experimental

All m.p.s were determined by a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Laboratories, Givat-Ram, The Hebrew University, Jerusalem. I.r. spectra were determined on a Perkin-Elmer Model 457 spectrophotometer. N.m.r. spectra were obtained on a Varian XL-100 or a Bruker-WH-300 instrument, ^{1}H n.m.r. and ^{31}P n.m.r. were recorded in deuteriochloroform or in deuterium oxide solutions. Chemical shifts are reported in p.p.m. from TMS or TSP as internal standards in ^{1}H n.m.r. and from 10% H_3PO_4 as external standard in ^{31}P n.m.r., positive chemical shifts are at low field with respect to the standard. High pressure liquid chromatographic work was carried out using a Merck-Hitachi instrument with an R_p-18 or an R_p-8 column. Gas chromatographic work was carried out with a Varian model 1400 gas chromatograph equipped with a copper tube (1.5m × 0.25 in o.d.) packed with 10% Carbowax 20M on Chromosorb W 60–80, peak areas were determined by the internal standard method.

Materials. Trimethyl phosphite, trimethylsilyl bromide, acetyl chloride, benzoyl chloride, heptanoyl chloride, propionyl chloride, lauroyl chloride, 2,3-dichloropropionyl chloride, 3,4-dichlorobutyryl chloride, 2-chloropropionyl chloride, 3-chlorobutyryl chloride, 3-chloropropionyl chloride, but-2-enoyl chloride, 3-methylbut-2-enoyl chloride and undec-11-enoyl chloride were obtained from Aldrich Chemical Company and were distilled before use. Other acyl chlorides were prepared by treatment of acids with the excess of thionyl chloride.

General Procedure for the Synthesis of Dimethyl Acylphosphonates (**1a—g**) *and* (**1k**) *from Trimethyl Phosphite and Acyl Chloride.*—A modification of the method described by Kabachnik [7a] was used. To acyl chloride (0.5 mol) stirred at 5 °C was added dropwise trimethyl phosphite (0.5 mol). After the addition was completed the cooling bath was removed and the mixture was stirred for 2 h at the ambient temperature. The products were purified by vacuum distillation.

Dimethyl acetylphosphonate (**1a**).[7c] Yield 91%, b.p. 65 °C/1.5 mmHg; $\nu_{max.}$(neat) 1 695s, 1 260s, and 1 025s cm^{-1}; δ_H($CDCl_3$) 2.40 (3 H, d, *J* 5.1 Hz), and 3.95 (6 H, d, *J* 11 Hz); δ_P −2.93 p.p.m. (sept).

Dimethyl heptanoylphosphonate (**1b**). Yield 90%, b.p. 110 °C/0.7 mmHg; $\nu_{max.}$(neat) 1 695s, 1 260s, and 1 025s cm^{-1}; δ_H($CDCl_3$) 1.00 (3 H, t, *J* 7 Hz), 1.52 (8 H, m), 2.83 (2 H, t, *J* 7 Hz), and 3.85 (6 H, d, *J* 11 Hz); δ_P −2.64 p.p.m. (sept).

Dimethyl benzoylphosphonate (**1c**). Yield 83%, b.p. 120 °C/1 mmHg; $\nu_{max.}$(neat) 1 655s, 1 595m, 1 260s, and 1 030s cm^{-1}; δ_H($CDCl_3$) 3.89 (6 H, d, *J* 10.63 Hz), 7.51 (3 H, m), and 8.16 (2 H, m); δ_P −0.87 p.p.m. (sept).

(E)-*Dimethyl but-2-enoylphosphonate* (**1d**). This was prepared by the standard procedure, but in order to minimize polymerization, the bath temperature during the distillation was not allowed to exceed 150 °C. With such precautions the compound was obtained in 35% yield, b.p. 99 °C at 2 mmHg; $\nu_{max.}$(neat) 1 640s, 1 600s, 1 250s, and 1 020s cm^{-1}; δ_H($CDCl_3$) 2.06 (3 H, d, *J* 6.9 Hz), 3.89 (6 H, d, *J* 10.7 Hz), 6.50 (1 H, d, *J* 16 Hz), and 7.6 (1 H, m) (lit.,[8] b.p. 92—94.5 °C/0.4 mmHg).

Dimethyl 3-methylbut-2-enoylphosphonate (**1e**). Yield 82%, b.p. 110—115 °C/0.5 mmHg; $\nu_{max.}$(neat) 1 650s, 1 585s, 1 250s, and 1 020s cm^{-1}; δ_H($CDCl_3$) 2.04 (3 H, s), 2.26 (3 H, s), 3.89 (6 H, d, *J* 10.7 Hz), and 6.73 (1 H, br); δ_P −1.11 p.p.m. (septet) (lit.,[9] b.p. 86 °C/0.23 mmHg).

Dimethyl pent-4-enoylphosphonate (**1f**). Yield 83%, b.p. 100 °C/1 mmHg; $\nu_{max.}$(neat) 1 690s, 1 640m, and 1 260s; δ_H($CDCl_3$) 2.45 (2 H, t, *J* 7 Hz), 3.88 (6 H, d, *J* 10.7 Hz), 5.17 (2 H, d, *J* 5.2 Hz), and 5.60 (1 H, m).

Dimethyl undec-11-enoylphosphonate (**1g**). Yield 63%, b.p. 130 °C/1 mmHg; $\nu_{max.}$(neat) 1 690s, 1 640s, 1 255s, and 1 020s cm^{-1}; δ_H($CDCl_3$) 1.30 (10 H, m), 1.60 (2 H, m), 2.03 (2 H, m), 2.81 (2 H, t, *J* 7 Hz), 3.89 (3 H, d, *J* 10.7 Hz), 5.03 (2 H, m), and 5.84 (1 H, m); δ_P −2.55 p.p.m. (sept).

Dimethyl 2-chloropropionylphosphonate (**1h**). This was prepared by dropwise addition of trimethyl phosphite (24.8 g, 0.2 mol) to 2-chloropropionyl chloride (25.6 g, 0.2 mmol) cooled in an ice-bath. The reaction mixture was kept at 0 °C for 24 h and the product was isolated by distillation (21 g, 53%), b.p. 110 °C/2 mmHg; $\nu_{max.}$(neat film) 1 705s, 1 270s, and 1 025s cm^{-1}; δ_H($CDCl_3$) 1.85 (3 H, d, *J* 7 Hz), 3.91 (6 H, d, *J* 11 Hz), and 4.85 (1 H, q, *J* 7 Hz). A second fraction, b.p. 155 °C/2 mmHg (14 g), was also obtained. This fraction showed i.r. absorption at 1 640w, 1 270s, 1 035s cm^{-1} and ^{1}H n.m.r. signals at δ 2.04 (3 H, d, *J* 7 Hz), 3.80 (6 H, d, *J* 12 Hz), 3.83 (6 H, d, *J* 12 Hz), and 6.48 (1 H, m).

Dimethyl 4-chlorobutyrylphosphonate (**1k**). Yield 75%, b.p.

* The configurations of oximes (**12**) were assigned previously by *X*-ray crystallography of dimethyl α-hydroxyiminobenzylphosphonates.[18]

135 °C/0.5 mmHg; $\nu_{max.}$(neat film) 1 700s, 1 260s, and 1 030s cm^{-1}; $\delta_H(CDCl_3)$ 2.12 (2 H, m), 3.05 (2 H, t, *J* 7 Hz), 3.59 (2 H, t, *J* 7 Hz), and 3.89 (6 H, d, *J* 10.7 Hz); δ_P −2.99 p.p.m. (septet) (lit.,[9] b.p. 110 °C/0.13 mmHg).

Synthesis of Dimethyl 2,3-*Dichlorobutyrylphosphonate* (**1i**) *and Dimethyl* 2,3-*Dichloro*-3-*methylbutyrylphosphonate* (**1j**).—Chlorine gas was passed at room temperature into a solution of (**1d**) or (**1e**) (0.1 ml) in dichloromethane (50 ml) and the reaction was monitored by i.r. spectroscopy by observing changes in the carbonyl absorption. After completion of the reaction the dichloromethane was evaporated to dryness and the residue was vacuum distilled.

Dimethyl 2,3-*dichlorobutyrylphosphonate* (**1i**). This was obtained in crude form in 91% yield but decomposed upon attempted distillation with evolution of hydrogen chloride. Spectra were determined on the undistilled product; $\nu_{max.}$(neat film) 1 710s, 1 255s, and 1 015s cm^{-1}; $\delta_H(CDCl_3)$ 1.72 (3 H, d, *J* 7 Hz), 3.91 (6 H, d, *J* 11 Hz), 4.33 (1 H, m), and 4.66 (1 H, m).

Dimethyl 2,3-*dichloro*-3-*methylbutyrylphosphonate* (**1j**). This was obtained in a yield of 93%, b.p. 115 °C/0.5 mmHg; $\nu_{max.}$(neat film) 1 710s, 1 260s, and 1 015s cm^{-1}; $\delta_H(CDCl_3)$ 1.72 (6 H, s), 3.90 (6 H, d, *J* 11 Hz), and 5.31 (1 H, d, *J* 1.5 Hz).

General Procedure for the Synthesis of Methyl Acylphosphonate Monosalts (**2**).—Dimethyl acylphosphonate (0.05 mol) was dissolved in dry acetonitrile (or dry acetone) (50 ml), and the solution was added to a solution of lithium bromide (0.55 mol) in dry acetonitrile (30 ml) (or sodium iodide in acetone). The reaction mixture was stirred for 12 h at room temperature after which the precipitate was filtered off, washed with dry acetone, and dried.

Methyl sodium acetylphosphonate (**2a**). Yield 93%, m.p. 191—192 °C; $\nu_{max.}$(KBr) 1 670s, 1 210s, 1 090s, and 1 025s cm^{-1}; $\delta_H(D_2O)$ 2.50 (3 H, d, *J* 4.8 Hz) and 3.69 (3 H, d, *J* 10.63 Hz); δ_P −0.83 p.p.m. (q) (Found: C, 22.5; H, 4.15. Calc. for $C_3H_6NaO_4 \cdot 0.5H_2O$: C. 21.30; H, 4.14%). This compound was reported previously without any characteristics.[3c]

Methyl lithium heptanoylphosphonate (**2b**). Yield 87%, m.p. >270 °C; $\nu_{max.}$(KBr) 1 670s, 1 205s, 1 090s, and 1 020s cm^{-1}; $\delta_H(D_2O)$ 0.85 (3 H, t, *J* 6.9 Hz), 1.32 (6 H, m), 2.82 (2 H, t, *J* 7 Hz), and 3.57 (3 H, d, *J* 10.3 Hz); δ_P −0.98 p.p.m. (q).

Methyl sodium benzoylphosphonate (**2c**). Yield 98%, m.p. 283 °C (decomp.); $\nu_{max.}$(KBr) 1 620m, 1 580m, 1 215s, 1 080s, and 1 020s cm^{-1}; $\delta_H(D_2O)$ 3.67 (3 H, d, *J* 10.63 Hz), 7.56 (3 H, m), and 8.17 (2 H, m); δ_P −2.16 p.p.m. (q) (Found: C, 43.0; H, 3.6. Calc. for $C_8H_8NaO_4P$: C, 43.24; H, 3.60%).

Methyl lithium but-2-*enoylphosphonate* (**2d**). Yield 98%, m.p. >270 °C (becomes yellow at 200 °C); $\nu_{max.}$(KBr) 1 620m, 1 575s, 1 215s, 1 075s, and 1 015s cm^{-1}; $\delta_H(D_2O)$ 7.49 (1 H, m), 6.49 (1 H, apparent t, *J* 15 Hz), 3.62 (3 H, d, *J* 10.63 Hz), and 2.02 (3 H, d, *J* 7 Hz) (Found: C, 34.85; H, 4.7. Calc. for $C_5H_8LiO_4P$: C, 35.29; H, 4.71%).

Methyl lithium 3-*methylbut*-2-*enoylphosphonate* (**2e**). This was obtained in quantitative yield, m.p. >270 °C (becomes yellow at *ca.* 200 °C); $\nu_{max.}$(KBr) 1 600br s, 1 215s, 1 075s, and 1 025s cm^{-1}; $\delta_H(D_2O)$ 6.68 (1 H, br s), 3.60 (3 H, d, *J* 10.63 Hz), 2.15 (3 H, s), and 2.01 (3 H, s); δ_P 3.08 p.p.m. (q) (Found: C, 38.85; H, 5.3. Calc. for $C_6H_{10}LiO_4P$: C, 39.13; H, 5.43%).

Methyl lithium pent-4-*enoylphosphonate* (**2f**). Yield 96%, m.p. >270 °C; $\nu_{max.}$(KBr) 1 660m, 1 630m, 1 200s, 1 090s, and 1 000s cm^{-1}; $\delta_H(D_2O)$ 2.34 (2 H, m), 2.62 (2 H, t, *J* 7 Hz), 3.56 (3 H, d, *J* 10.63 Hz), 5.23 (2 H, d, *J* 5.2 Hz), and 5.70 (1 H, m).

Methyl lithium undec-10-*enoylphosphonate* (**2g**). Yield 92%, m.p. >270 °C; $\nu_{max.}$(KBr) 1 660m, 1 630m, 1 200s, 1 080s, and 1 000s cm^{-1}; $\delta_H(D_2O)$ 1.28 (12 H, br s), 1.57 (2 H, m), 2.00 (2 H, t, *J* 7 Hz), 3.57 (3 H, d, *J* 10.5 Hz), 5.01 (2 H, m), and 5.82 (1 H, m); δ_P −0.60 p.p.m. (q).

Methyl lithium 2-*chloropropionylphosphonate* (**2h**). M.p. 225 °C (decomp.); $\nu_{max.}$(KBr) 1 665, 1 215s, 1 090s, and 1 025s cm^{-1}; $\delta_H(D_2O)$ 5.33 (1 H, m), 3.63 (3 H, d, *J* 10.63 Hz), and 1.65 (3 H, d, *J* 7 Hz) (Found: C, 24.4; H, 3.5. Calc. for $C_4H_7ClLiO_4P$: C, 24.93; H, 3.64%).

Methyl lithium 2,3-*dichlorobutyrylphosphonate* (**2i**). Yield 96%, m.p. >270 °C; $\nu_{max.}$(KBr), 1 680s, 1 220s, 1 090s, 1 025s, and 770s cm^{-1}; $\delta_H(D_2O)$ 1.75 (3 H, s), 3.63 (3 H, d, *J* 10.63 Hz), and 5.26 (1 H, d, *J* 1.1 Hz).

Methyl lithium 2,3-*dichloro*-3-*methylbutyrylphosphonate* (**2j**). Yield 82%, m.p. >270 °C; $\nu_{max.}$(KBr) 1 680s, 1 220s, 1 090s, and 1 025s cm^{-1}; $\delta_H(D_2O)$ 5.26 (1 H, d, *J* 1.1 Hz), 3.63 (3 H, d, 10.63 Hz), and 1.75 (6 H s).

Methyl lithium 4-*chlorobutyrylphosphonate* (**2k**). Yield 96%, m.p. 250 °C (decomp.); $\nu_{max.}$(KBr) 1 660m, 1 200s, 1 100s, and 1 010s cm^{-1}; $\delta_H(D_2O)$ 3.69 (2 H, t, *J* 7 Hz), 3.66 (3 H, d, *J* 10.63 Hz), 3.05 (2 H, t, *J* 7 Hz), and 2.10 (2 H, q, *J* 7 Hz); $\delta_P(D_2O)$ 0.30 p.p.m. (q) (Found: C, 29.35; H, 4.6. Calc. for $C_5H_9ClLiO_4P$: C, 29.06; H, 4.36%).

Synthesis of Methyl Hydrogen Acylphosphonates (**3**).—Methyl sodium acylphosphonate (**2**) (0.5 mol) was dissolved in distilled water (20 ml) and transferred to a 250 ml separating funnel. Concentrated aqueous hydrochloric acid (20 ml) was added, and the solution was extracted (×3) with chloroform (70 ml). The combined chloroform layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure while the temperature was kept <40 °C.

Methyl hydrogen acetylphosphonate (**3a**). Yield 90%, viscous oil; $\nu_{max.}$(neat) 3 500—3 200br, 1 690m, 1 230br s, and 1 050—1 000br s cm^{-1}; $\delta_H(CDCl_3)$ 2.49 (3 H, d, *J* 4.7 Hz), 3.82 (3 H, d, *J* 10.95 Hz), and 8.91 (1 H, br); δ_P −2.51 (q).

Methyl hydrogen heptanoylphosphonate (**3b**). Yield 86%, viscous oil; $\nu_{max.}$(neat) 3 500—3 200br, 1 690s, 1 230s, and 1 040—1 000br s cm^{-1}; $\delta_H(CDCl_3)$ 1.00 (3 H, t, *J* 4.7 Hz), 1.52 (8 H, m), 2.82 (3 H, t, *J* 7 Hz), 3.83 (3 H, d, *J* 10.7 Hz), and 9.1 (1 H, br); δ_P −2.12 (q).

Methyl hydrogen benzoylphosphonate (**3c**). Yield 95%, viscous oil; $\nu_{max.}$(neat) 3 500—3 100br, 1 650s, 1 600w, 1 230s, and 1 040—1 000br s cm^{-1}; $\delta_H(CDCl_3)$ 3.85 (3 H, d, *J* 11 Hz), 7.52 (3 H m), and 8.19 (2 H, m); δ_P −0.55 (q).

Methyl hydrogen 3-*methylbut*-2-*enoylphosphonate* (**3e**). Viscous oil; $\nu_{max.}$(neat) 3 500—3 200br, 1 650m, 1 595m, 1 230br, and 1 050—1 000br cm^{-1}; $\delta_H(CDCl_3)$ 8.11 (1 H, b), 6.69 (1 H, s), 3.85 (3 H, d, *J* 10.7 Hz), 2.22 (3 H, s), and 2.01 (3 H, s); δ_P −0.55 (q, *J* 10.7 Hz).

Methyl hydrogen 4-*chlorobutyrylphosphonate* (**3k**). Viscous oil; $\nu_{max.}$(neat film) 3 550—3 200br, 1 690m, 1 230br s, and 1 050—1 000br s cm^{-1}; $\delta_H(CDCl_3)$ 9.82 (1 H, br s), 3.83 (3 H, d, *J* 10.8 Hz), 3.60 (2 H, t, *J* 6.3 Hz), 3.04 (2 H, t, *J* 6.3 Hz), and 2.09 (2 H, m); δ_P −1.52 p.p.m. (q, *J* 10.8 Hz).

Synthesis of Sodium Hydrogen Acylphosphonates (**4a**) *and* (**4c**).—A solution of (**3b**) or (**3c**) (0.01 mol) in dry acetone (30 ml) was added to a solution of sodium iodide (0.011 mol) in dry acetonitrile (20 ml). The reaction mixture was refluxed with stirring for 48 h. The precipitate was filtered off, washed with dry acetonitrile (50 ml), and dried.

Sodium hydrogen acetylphosphonate (**4a**). Yield 67%, m.p. >270 °C; $\nu_{max.}$(KBr) 1 660s, 1 215s, 1 190—1 080br s, and 1 000s cm^{-1}; $\delta_H(D_2O)$ 2.38 (d, *J* 4.5 Hz); δ_P −0.63 p.p.m. (s).

Sodium hydrogen benzoylphosphonate (**4c**). Yield 74%, m.p. >270 °C; $\nu_{max.}$(KBr) 1 620m, 1 580m, 1 215s, 1 180s, 1 150s, and 1 020s cm^{-1}; $\delta_H(D_2O)$ 7.57 (2 H, m), 7.69 (1 H, m), and 8.18 (2 H, m); δ_P −1.55 p.p.m. (s).

General Procedure for Synthesis of Acylphosphonic Acids (**5**).—Trimethylsilyl bromide (0.2 mol) was slowly added to a

solution of dimethyl acylphosphonate (**1**) (0.1 mol) in dry acetonitrile (100 ml). The reaction mixture was allowed to stand at room temperature for 3 h after which the acetonitrile was evaporated and methanol (50 ml) was added to the residue. The mixture was stirred for 30 min and then evaporated to give the product.

Acetylphosphonic acid (**5a**). Yield 92%, viscous oil; $\nu_{max.}$(neat) 3 500—3 200br, 1 690m, and 1 230br s cm^{-1}; $\delta_H(D_2O)$ 2.31 (d, *J* 4.6 Hz); δ_P −2.1 p.p.m. (s).

Heptanoylphosphonic acid (**5b**). Yield 87%, viscous oil; $\nu_{max.}$(neat) 3 450—3 200br, 1 685s, and 1 255br s cm^{-1}; $\delta_H(D_2O)$ 0.98 (3 H, t, *J* 7 Hz), 1.46 (8 H, m), and 2.75 (2 H, t, *J* 7 Hz); δ_P −1.84 (s).

Benzoylphosphonic acid (**5c**). Yield 55%, m.p. 213 °C; $\nu_{max.}$(KBr) 3 500—3 100br, 1 650s, 1 600w, 1 230s, and 1 210s cm^{-1}; $\delta_H(D_2O)$ 7.55 (3 H, m) and 8.12 (2 H, m); δ_P −1.29 p.p.m. (s) (Found: C, 42.1; H, 3.9; P, 15.0. Calc. for $C_7H_7O_4P{\cdot}H_2O$: C, 41.15; H, 4.41; P; 15.19%).

3-*Methylbut-2-enoylphosphonic acid* (**5e**). Viscous oil; $\nu_{max.}$(neat film) 3 500—3 200br, 1 640m, 1 600m, and 1 230s cm^{-1}; $\delta_H(D_2O)$ 6.53 (1 H, s), 1.98 (3 H, s), and 1.84 (3 H, s); δ_P −0.27 p.p.m. (s).

4-*Chlorobutyrylphosphonic acid* (**5k**). Viscous oil; $\nu_{max.}$(neat film) 3 500—3 200br, 1 685m, and 1 225br s cm^{-1}; $\delta_H(D_2O)$ 3.54 (2 H, t, *J* 7 Hz), 2.93 (2 H, t, *J* 7 Hz), and 1.97 (2 H, apparent quintet); δ_P −1.30 p.p.m. (s).

Base Hydrolyses of Acylphosphonate Derivatives.—Solutions of acylphosphonate (1 mmol) in aqueous borate buffer pH 7.4, aqueous borate buffer pH 9 or 1M aqueous sodium hydroxide (4 ml) were stirred at room temperature for 24 h.

(**1b**) at pH 14 gave dimethyl phosphonate (5%, δ ^{31}P: 10.5 p.p.m., *J* 720 Hz, d septet), methyl hydrogen phosphonate (92%, δ 7.3 p.p.m., *J* 602 Hz, dq), phosphonic acid (3%, δ 4.9 p.p.m., *J* 695 Hz, d).

(**1c**) (R_t 2.8 min) at pH 7.4, 9, and 14 gave benzoic acid (96%, R_t 1.8 min), (**2c**) (4%, R_t 1.19 min) using an R_p-8 column, MeOH–water (6:4). The pH experiment was also examined by ^{31}P n.m.r. that showed the presence of MeH_2PO_3 (90%) and H_3PO_3 (10%).

(**2b**) at pH 14, examined by ^{31}P n.m.r., gave MeH_2PO_3 (81%) and (**5b**)$^{2-}$ (19%, δ 2.21 p.p.m., s).

(**2c**) at pH 14, examined by ^{31}P n.m.r., gave MeH_2PO_3 (83%), (**5c**)$^{2-}$ (δ 2.53 s), examination by h.p.l.c. [R_p-8 MeOH–water (6:4)] showed benzoic acid (85%).

(**2d**) Described in the 'Results and Discussion'.

(**2e**) (R_t 2.22 min) at pH 14, determined by h.p.l.c. [R_p-18, MeOH–water (9:1)], gave 3-methylbutenoic acid (quantitative, R_t 3.12 min).

Reaction of Methyl Sodium Benzoylphosphonate (**2c**) *with an Ethanolic Solution of Methylamine.*—An ethanolic solution (30%, w/v) of methylamine (10 ml) was added to a solution of methyl sodium benzoylphosphonate (2.22 g, 0.01 mol) in absolute ethanol (30 ml). The reaction mixture was stirred at the ambient temperature for 24 h. The white precipitate was filtered off, washed with absolute ethanol (20 ml), and dried to yield (**8**) (2.16 g, 9.2 mmol), m.p. >270 °C; $\nu_{max.}$(KBr) 1 620m, 1 250s, and 1 070—1 020s cm^{-1}; $\delta_H(D_2O)$ 7.4 (5 H, m), 3.58 (3 H, d, *J* 11.0 Hz), and 3.16 (3 H, d, *J* 4.4 Hz); δ_P 6.66 p.p.m. (Found: C, 53.2; H, 5.9. Calc. for $C_9H_{11}NO_3PNa$: C, 53.66; H, 5.85%).

Reaction of Monosodium Benzoylphosphonate (**4c**) *with Ethanolic Methylamine.*—As described under the reaction of (**2c**) with methylamine, using (**4c**) (2.07 g, 0.01 mol), yielding compound (**9**) (2.1 g, 8.5 mmol), m.p. >270 °C; $\nu_{max.}$(KBr) 1 615m, 1 600w, and 1 240s, cm^{-1}; $\delta_H(D_2O)$ 7.43 (5 H, m), and 3.19 (3 H, d, *J* 4.5 Hz); δ_P 5.92 p.p.m. (q).

Reaction of Methyl Sodium Benzoylphosphonate (**2c**) *with Sodium Borohydride.*—A solution of sodium borohydride (0.45 g, 12 mmol) in a mixture of 0.02M potassium hydrogen phosphate (10 ml) and distilled water (5 ml) was added to a solution of methyl sodium benzoylphosphonate (2.22 g, 0.01 mol) in methanol (15 ml). The reaction mixture was stirred at room temperature for 2 h. The excess of methanol was evaporated and the aqueous layer was acidified with 1M hydrochloric acid (40 ml) and extracted (×5) with ether (70 ml). The combined ether layers were dried (Na_2SO_4), filtered and evaporated to yield (**10**) (1.5 g, 7.5 mmol), m.p. 127—132 °C; $\nu_{max.}$(KBr) 3 500—3 200br, 1 600w, and 1 240s cm^{-1}; $\delta_H(D_2O)$ 7.45 (5 H, m), 5.05 (1 H, d, *J* 12.0 Hz), and 3.33 (3 H, d, *J* 10.3 Hz); δ_P 20.07 p.p.m.

Reaction of Monosodium Benzoylphosphonate (**4c**) *with Sodium Borohydride.*—A solution of monosodium benzoylphosphonate (**4c**) (0.416 g, 2 mmol) in 1M aqueous sodium hydroxide (2 ml) was added to a solution of sodium borohydride (0.09 g, 2.4 mmol) in deuterium oxide (2 ml). The reaction mixture was monitored by ^{31}P n.m.r. spectroscopy. After 30 min the signal at 2.13 p.p.m. vanished and a new signal appeared at 16.94 p.p.m. (d, *J* 12.5 Hz).

Reaction of Methyl Sodium Benzoylphosphonate (**2c**) *with Hydroxylamine Hydrochloride.*—A solution of methyl sodium benzoylphosphonate (2.22 g, 0.11 mol) in absolute methanol (80 ml) was added to a solution of hydroxylamine hydrochloride (0.695 g, 0.01 mol) in methanol (70 ml). The reaction mixture was stirred at room temperature for 72 h, filtered and evaporated under reduced pressure (temperature <40 °C). The viscous liquid which formed was triturated with hexane (4 × 75 ml). The combined hexane layers were evaporated yielding benzonitrile (1.03 g, 92%, determined by gas chromatography. The hexane-insoluble residue was dissolved in chloroform (75 ml), dried (Na_2SO_4), filtered, and evaporated to yield a viscous residue (1.82 g) which was identified as dimethyl phosphate by comparing its i.r., ^{1}H n.m.r., and ^{31}P n.m.r. spectra with those of dimethyl phosphate obtained by independent synthesis.

Reaction of Methyl Sodium Benzoylphosphonate with Hydroxylamine.—Hydroxylamine free base (3.3 mmol) was prepared by neutralizing hydroxylamine hydrochloride (231 mg) in methanol (3 ml) with sodium hydroxide (132 mg). The precipitated sodium chloride was filtered off and methyl sodium benzoylphosphonate (**2c**) (444 mg, 3 mmol) was added to the filtrate: the latter was then examined by ^{31}P n.m.r. after 24 h at ambient temperature. This examination revealed the presence of two quartets at 6.43 (73%) and 1.83 p.p.m. (27%).

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