ment with earlier measurements.[22,23] However, no hydroxamate could be detected during the course of the metal ion catalyzed hydrolysis. The observation of hydroxamate products in other related di- and triester phosphate hydrolyses catalyzed by neighboring carboxyl or carboxylate groups warrants its presence.[30] From this result one may infer that nucleophilic catalysis by carboxylate is limited to di- and triester systems, as for II, and that the occurrence of metal ion catalysis in salicyl phosphate hydrolysis may be attributed to an amplification of the general acid catalysis observed in the absence of metal ion.

One may postulate several alternative mechanisms for the role of the metal ion in the catalysis of II. The metal ion may serve to neutralize the negatively charged phosphoryl oxygen, thereby reducing the electrostatic repulsion encountered by the carboxylate anion, and facilitating displacement. The importance of this effect, however, is apparently a factor of tenfold. This estimate is based on the ratio of the rate constants for phenoxide expulsion by carboxylate from the triester, diphenyl(2-carboxyphenyl) phosphate, and the diester, phenyl(2-carboxyphenyl) phosphate, the latter as the dianion, after correction for differences in the sensitivity of phosphorus to nucleophilic attack in the two systems.[31] Alternatively, the metal ion may act as an effective acid catalyst, lowering the pK_a of the departing phenol.[6] The structure–reactivity correlation for the hydrolysis of substituted aryl(2-carboxyphenyl) phosphates reveals a very high dependency (β −1.26) on the basicity of the leaving phenol.[4] Therefore, a change of 2 pK_a units in the pK_a of the leaving phenol, owing to chelation of the metal ion with the ether oxygen, would rationalize the rate acceleration. However, the pK_a of the stronger La^{3+}–phenolate complex is only 2 units below that for phenol, implying that this rationale is not entirely satisfactory.[29] A third and final argument invokes stabilization of the possible intermediate pentacovalent species by the metal ion and the associated transition states leading to and from this species. The plausibility of this latter suggestion will be the subject of a future communication.

Model systems which feature intramolecular catalysis or catalysis by biologically important Zn^{2+} or Mg^{2+} ions are of particular interest, since the interactions involved may closely resemble those in an enzyme–substrate complex.[32] The results of this study indicate that both of these types of catalysis may be integrated into one model system to confer dramatic reactivity to a normally unreactive phosphate diester.

Registry No.—I, 38401-04-6; II, 28401-05-7; diphenylphosphorochloridate, 2524-64-3; glycine ethyl ester hydrochloride, 623-33-6; diphenyl *N*-(glycyl)-phosphoramidate, 38401-06-8.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health, GM 13306.

(30) S. J. Benkovic in "Comprehensive Chemical Kinetics," C. H. Banford and C. F. Tipper, Ed., American Elsevier, New York, N. Y., 1972.

(31) R. H. Bromilow, S. A. Khan, and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 911 (1972).

(32) G. J. Lloyd and B. S. Cooperman, *J. Amer. Chem. Soc.*, **93**, 4883 (1971). These authors recently have described a model system which features phosphoryl transfer from phosphoryl imidazole to the Zn^{2+}–pyridine-2-carbaldoxime anion *via* a ternary complex.

Phosphorus Derivatives of Nitrogen Heterocycles. 3. Carbon–Phosphorus Bonding in Pyridyl-2- and -4-phosphonates[1]

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A postulate that the extent of d_π–p_π conjugation for a phosphorus substituent on a pyridyl ring is greater for attachment at the 4 position than at the 2 position has been examined in a series of pyridyl-2- and -4-phosphonates by measurement of several physical properties. Although the ^{31}P nmr spectra of the pyridylphosphonate esters suggest the presence of d_π–p_π conjugation for attachment at the 4 position, ultraviolet and mass spectra of these esters and pK_a determinations on the corresponding acids argue strongly against such conjugation. The general conclusion that all the pyridylphosphonates show an absence of d_π–p_π conjugation is based on a comparison of physical properties with those of phenylphosphonates, a system in which d_π–p_π conjugation has been shown to be absent by other workers.

There exists considerable current interest concerning the extent of d_π–p_π bonding in the C–P bond of phosphorus substituents attached to aryl and heteroaryl rings.[2] From the ultraviolet and proton magnetic resonance spectra it has been concluded that d_π–p_π bonding exists in the C–P bonds of furan, thiophene, and pyrrole derivatives but that it is probably absent in pyridine derivatives. Although the spectra for pyridyl-2-phosphonates support this view, the corresponding pyridyl-4-phosphonates give indications of some d_π–p_π interaction.[2,3] To examine this possibility a more detailed examination has been made of the ^{31}P nmr spectra of the esters and acids, the mass spectra of esters, and pK_a and uv measurements for pyridyl phosphonic acids.

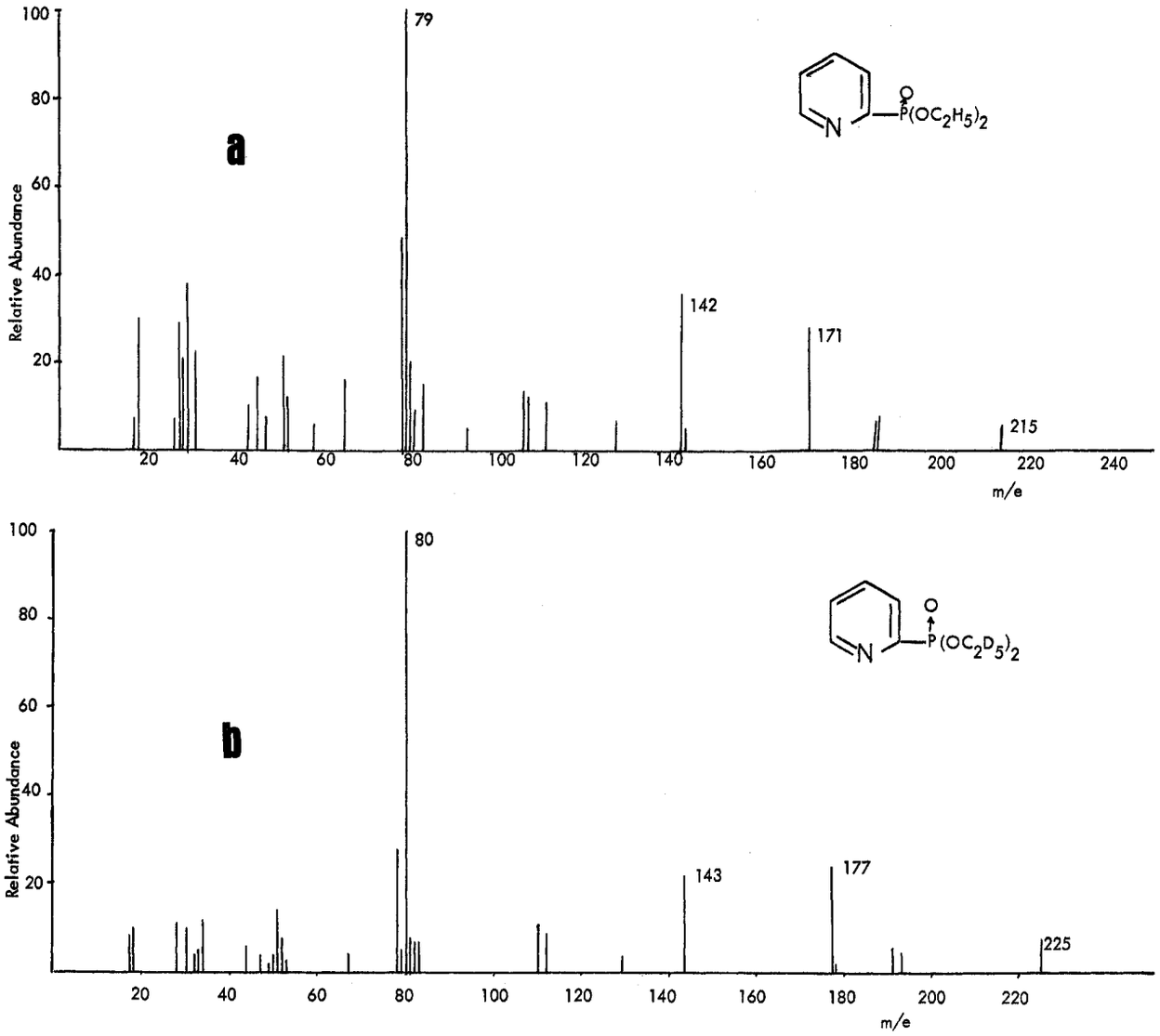
P^{31} Nmr Spectra.—The magnitude of the ^{31}P chemical shift of the phosphonate group can be correlated with the electron-donating ability of the attached organic radical.[4] It should be possible, therefore, to

(1) This work was presented, in part, at the 7th Midwest Regional Meeting of the American Chemical Society, St. Louis, Mo., Oct 1971. The present interpretation of the data differs considerably from this earlier presentation.

(2) D. Redmore, *Chem. Rev.*, **71**, 315 (1971).

(3) D. Redmore, *J. Org. Chem.*, **35**, 4114 (1970).

(4) J. G. Riess, J. R. Van Wazer, and J. Letcher, *J. Phys. Chem.*, **71**, 1925 (1967); C. C. Mitsch, L. D. Freedman, and C. G. Moreland, *J. Magn. Resonance*, **3**, 446 (1970).



Figures 1a and 1b.—Mass spectra of pyridylphosphonates.

TABLE I
^{31}P CHEMICAL SHIFTS OF PYRIDYLPHOSPHONATES AND RELATED COMPOUNDS

Phosphonate	Chemical shift vs. H_3PO_4, ppm
Diethyl pyridyl-2-phosphonate (1)	−8.2
Diethyl 4,6-dimethylpyridyl-2-phosphonate (2)	−10.5
Diethyl 3,5-dimethylpyridyl-2-phosphonate (3)	−11.4
Diethyl 3-chloropyridyl-2-phosphonate (4)	−7.7
Diethyl 2,6-dimethylpyridyl-4-phosphonate (5)	−15.0
Diethyl 2-thienylphosphonate	−10.9[a]
Diethyl phenylphosphonate	−16.7[a]
Pyridyl-2-phosphonic acid (6)	+2.3
2,6-Dimethylpyridyl-4-phosphonic acid (7)	−5.6

[a] Reference 5.

determine whether there are differences in the interaction for a phosphonate group attached to the 2 and 4 positions on the pyridine ring on the basis of the ^{31}P chemical shift. The stronger electron-donating groups will show less shielding of the phosphorus nucleus.[4,5] The data summarized in Table I show that chemical shift differences do exist in the pyridylphosphonates. It can be seen from the ^{31}P chemical shifts that the pyridyl ring in the 4-phosphonate **5** is more strongly electron donating than the pyridyl ring in the isomeric 2-phosphonates **2** and **3**. This is precisely the effect that one would predict if a phosphonate group at the 4 position enters into greater d_π–p_π conjugation than at the 2 position.

Mass Spectra.—The mass spectra of diethyl pyridyl-2-phosphonate (**1**), the perdeuterioethyl ester of **1**, diethyl 4,6-dimethylpyridyl-2-phosphonate (**2**), and diethyl 2,6-dimethylpyridyl-4-phosphonate (**5**) have been determined at 70 eV and are represented in Figure 1. The fragmentation patterns observed for the pyridylphosphonates differ considerably from those observed for diethyl alkylphosphonates.[6] The base peak in the latter appears at M − 55 and represents $[RP(OH)_3]^+$, which is a fragment of low abundance for all the pyridylphosphonates. The base peak for the pyridyl-2-phosphonates **1** and **2** is M − 136 (loss of $C_4H_9O_3P$) and for the perdeuterioethyl ester of **1** M − 145 (loss of $C_4D_9O_3P$). In the case of diethyl 2,6-dimethyl-

(5) D. W. Allen, B. G. Hutley, and M. T. J. Mellor, *J. Chem. Soc., Perkin Trans. 2*, 63 (1972).

(6) J. L. Occolowitz and G. L. White, *Anal. Chem.*, **35**, 1179 (1963); see also J. G. Pritchard, *Org. Mass Spectrom.*, **3**, 163 (1970).

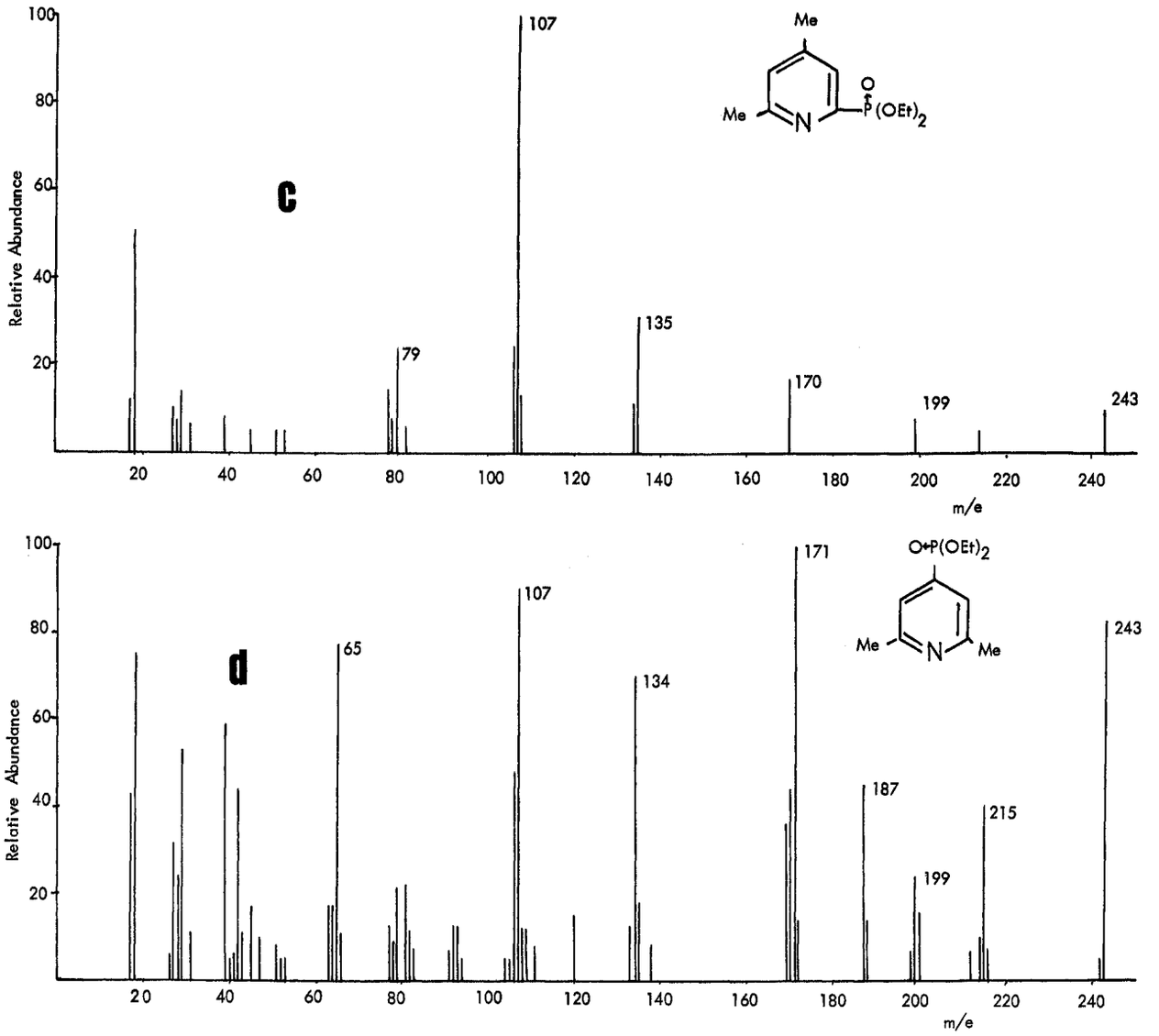


Figure 1c and 1d.—Mass spectra of pyridylphosphonates.

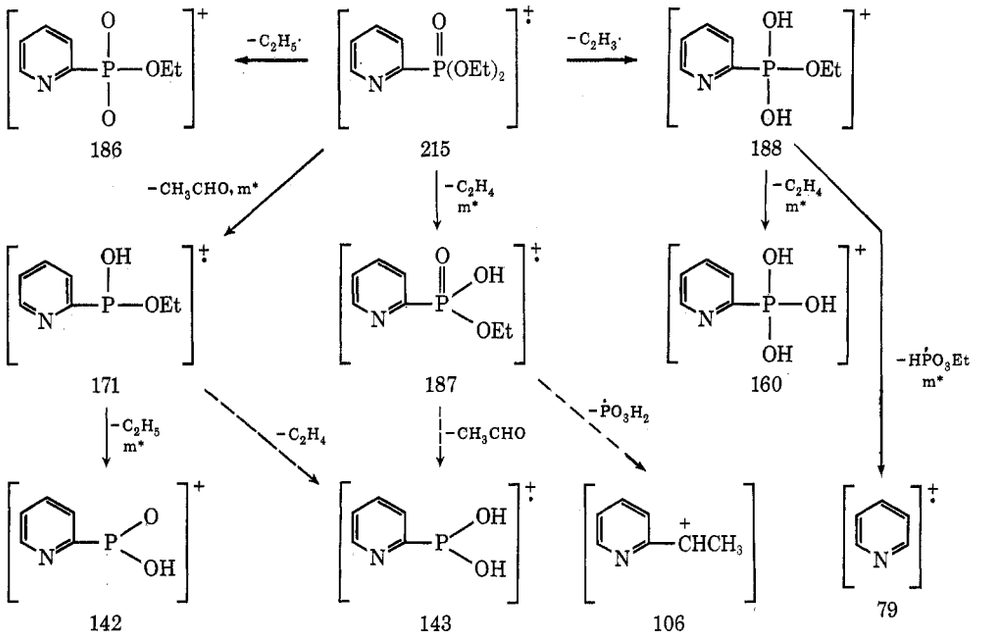
pyridyl-4-phosphonate (**5**) the base peak is M − 72, although M − 136 is still a fragment of high relative intensity (90%). Schemes I and II represent the postulated fragmentation pathways for compounds **1** and **5**, respectively. In these schemes fragmentations for which there are good precedents or for which the appropriate metastable peaks are observed (indicated by m*) are shown by a solid arrow, while the broken arrow is used where strong evidence is lacking. However, the structures shown in these schemes are firmly established; the spectrum of the perdeuterated ester was particularly important in this respect. In both **1** and **5** the loss of C_2H_4 and CH_3CHO is a well-established fragmentation identified by the presence of the appropriate metastable peaks. The genesis of the phosphorus-free ions, *m/e* 107, 106, and 79 in Scheme I and *m/e* 134 and 107 in Scheme II, is not unequivocally established. For diethyl pyridyl-2-phosphonate (**1**) ion *m/e* 79 appears to come from ion *m/e* 188, as indicated by a metastable peak at *m/e* 33.2. The corresponding ion at *m/e* 107 for phosphonate **5** appears to come from ion *m/e* 171 (metastable at *m/e* 66.9). The ions of *m/e* 107 and 106 in Scheme I are "ethylated" pyridines, since in the perdeuterio compound they appear at *m/e* 112 and 110, respectively, and thus involve a rearrangement. The appearance of a metastable peak at *m/e* 83.5 for compound **5** suggests that "ethylated" pyridine *m/e* 134 arises from ion *m/e* 215, Scheme II.

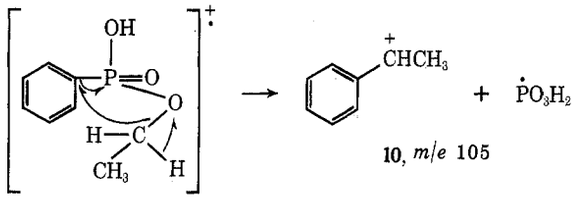
In an attempt to clarify the structures of the ions *m/e* 107 and 106 derived from **1**, the mass spectrum of diethyl phenylphosphonate (**8**) was measured as shown in Figure 2. The base peak for this ester has *m/e* 158 (M − 56) and, as in the case of the pyridylphosphonates, "ethylated" aryl peaks are present at *m/e* 106 and 105 with relative intensities of 5 and 43%. The presence of these ions in the phenyl ester shows that the "ethyl" group can be carbon bound and that this is not a feature unique to the pyridylphosphonates. It is suggested that ion **10**, *m/e* 105, in the phenylphosphonate arises by fragmentation and rearrangement of ion **9** as shown.

In examining Figures 1 and 2 it can be seen that fragmentation patterns for these aryl phosphonates differ considerably. In the 2-pyridylphosphonates **1** and **2** the base peak is the pyridinium ion, and no ions retaining the C–P bond have a higher relative intensity than 35%. On the other hand, in the 4-phosphonate **5** many ions retaining the C–P bond have a high relative

SCHEME I

FRAGMENTATION PATHWAY FOR DIETHYL PYRIDYL-2-PHOSPHONATE





intensity, including the molecular ion. Table II, which lists the relative intensity of the main fragments of the

TABLE II

RELATIVE INTENSITIES OF THE MAJOR FRAGMENTS OF THE PHOSPHONATE ESTERS

Ion	1	2	5	8	—Perdeuterio 1—	
M	6	10	83	75	M	8
M − 27	2	2	8	19	M − 30	2
M − 28	8	2	41	19	M − 32	5
M − 29	7	5	11	14	M − 34	6
M − 44	28	8	24	18	M − 48	24
M − 55	4	2	14	66	M − 62	2
M − 56	2	2	45	100	M − 64	2
M − 72	5	4	100	77	M − 80	2
M − 73	36	17	43	90	M − 82	22
M − 108	12	32	18	5	M − 113	9
M − 109	14	11	70	43	M − 115	11
M − 136	100	100	90	46	M − 145	100
M − 137	48	24	48	59	M − 147	27

phosphonates studied, brings out these differences and further shows that the 4-phosphonate **5** is much more like diethyl phenylphosphonate (**8**) in its fragmentation than are the 2-phosphonates.

We conclude, therefore, from the mass spectra that the C–P bonding in pyridyl-2- is different from that in pyridyl-4-phosphonates and that the 4-phosphonate is a typical aryl phosphonate by comparison with phenylphosphonate. Since other types of measurements have indicated an absence of d_π–p_π bonding in phenylphosphonates,[7] the difference in the mass spectra

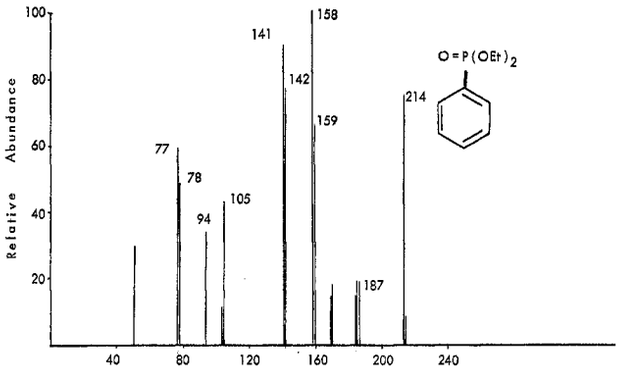
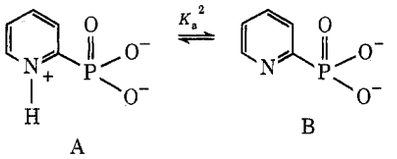


Figure 2.

of 2- and 4-pyridylphosphonates is not ascribable to d_π–p_π bonding. In fact, the differences in ease of C–P cleavage in the mass spectra would appear to arise from its facilitation by adjacent nitrogen in the 2-phosphonates rather than from C–P bond strengthening by d_π–p_π conjugation in the pyridyl-4-phosphonates.

pK_a Determinations on Pyridylphosphonic Acids.—Pyridylphosphonic acids are high-melting solids existing as zwitterions which titrate as dibasic acids. The pK_a values of these acids have been determined by potentiometric titration with 0.1 *N* sodium hydroxide and are presented in Table III.

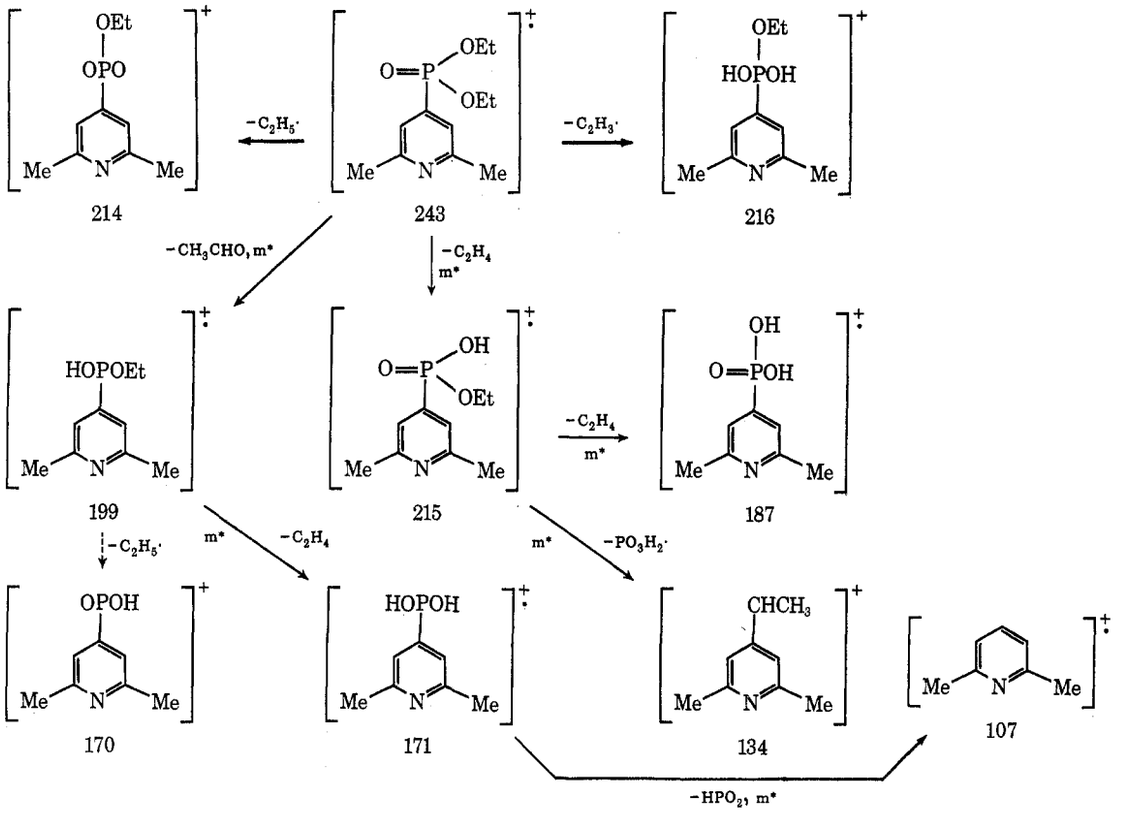
The correlation obtained by plotting the pK_a^2 values for the pyridylphosphonic acids against the pK_a of the parent pyridines (Figure 3) shows that the second ionization step is A ⇄ B.



(7) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, London, 1965, pp 67–85.

SCHEME II

FRAGMENTATION PATHWAY FOR DIETHYL 2,6-DIMETHYLPYRIDYL-4-PHOSPHONATE



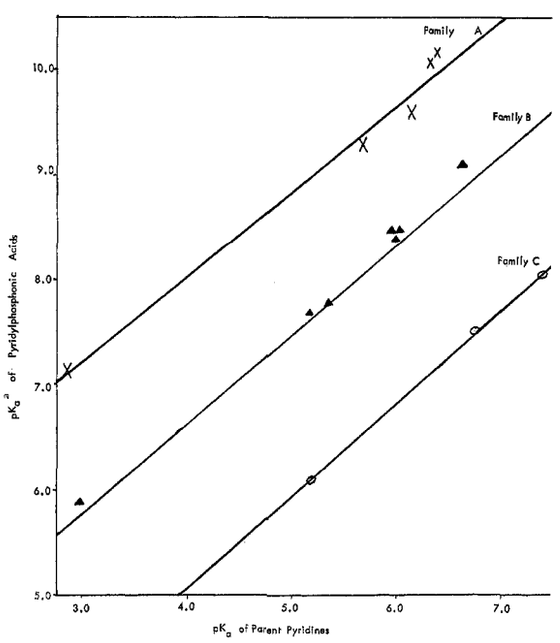


Figure 3.

The phosphonic acids are seen to fall into three families (Figure 3), which from the least squares method of analysis are described by the following equations: family A, $pK_A = 4.81 + 0.81\ pK_p$, correlation coefficient $r = 0.993$; family B, $pK_A = 3.24 + 0.85\ pK_p$, $r = 0.925$; family C, $pK_A = 1.58 + 0.88\ pK_p$, $r = 0.999$, where pK_p is the pK_a of the pyridine and pK_A is pK_{a_2} for the pyridylphosphonic acid.

TABLE III

pK_a OF PYRIDYLPHOSPHONIC ACIDS[a]

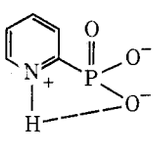
Phosphonic acid		pK_{a_1}	pK_{a_2}	pK_a of parent pyridine
Pyridyl-2-	6	4.13	7.71	5.17[b]
6-Methylpyridyl-2-	11	4.31	8.49	5.94[c]
4-Methylpyridyl-2-	12	4.25	8.47	6.03[c]
4-Phenylpyridyl-2-	13	4.24	7.80	5.35[d]
4-*tert*-Butylpyridyl-2-	14	4.44	8.41	5.99[c]
4,6-Dimethylpyridyl-2-	15	4.64	9.10	6.63[b]
4-Benzylpyridyl-2-	16	4.28	7.04	5.59[d]
3-Fluoropyridyl-2-	17	2.38	5.90	2.97[c]
3-Methylpyridyl-2-	18	4.39	9.32	5.67[c]
3,5-Dimethylpyridyl-2-	19	4.75	9.60	6.14[d]
3-Ethyl-6-methylpyridyl-2-	20		10.07	6.33
3,6-Dimethylpyridyl-2-	21	4.41	10.17	6.40[c]
3-Chloropyridyl-2-	22	3.49	7.15	2.84[c]
2,6-Dimethylpyridyl-4-	7	5.12	7.52	6.75[b]
2,3,6-Trimethylpyridyl-4-	23	5.06	8.04	7.40[e]
Pyridyl-4-	24		6.10[f]	5.17[b]

[a] These values are nonthermodynamic. Strictly speaking, these dissociation constants should be designated pK_{a_2} and pK_{a_3}, since further protonation to $C_6H_4NH^+P{=}O(OH)_2$ (pK_{a_1}) could be brought about in strong acid. [b] A. Albert in "Physical Methods in Heterocyclic Chemistry," Vol. 1, Academic Press, New York, N. Y., 1963. [c] "Handbook of Tables for Organic Compound Identification," 3rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967. [d] A. Fischer, W. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964). [e] N. Ikekawa, Y. Sato, and T. Maeda, *Chem. Pharm. Bull.*, **2**, 205 (1950); *Chem. Abstr.*, **50**, 994 (1956). [f] Calculated value; *vide infra*.

Family C, the least basic, is a family of pyridyl-4-phosphonates; family B and family A both are 2-phosphonates, the latter all bear 3 substituents.

Several groups of workers have applied the Hammett equation to the basicity of pyridines and have obtained excellent correlations.[8] Using the value 5.77 for the reaction constant (ρ) in the pyridine protonation[8a] with σ_{para} for PO_3^{2-} of -0.16,[9] the calculated pK_a^2 for 4-pyridylphosphonic acid (**24**) is 6.10. Unfortunately, the synthesis of this acid has so far been unsuccessful so that the calculated pK_a^2 has been used in Figure 3 to obtain the line for family C. The excellent fit of this calculated value with the experimental values for **7** and **23** indicates that the 4-pyridylphosphonic acids and phenylphosphonic acid have equal d_π–p_π conjugation in their C–P bonding. Further, we can conclude that this contribution of d_π–p_π bonding is zero since the pK_a^2 value for phenylphosphonic acid calculated from the Taft–Ingold relationship $\log K_2 = -7.77 + 1.177\sigma^*$ determined for aliphatic phosphonic acids (and hence purely inductive) is precisely the experimentally determined value.[10] Justification for the use of the Hammett relationship to calculate the pK_a^2 for **24** is obtained by the result of its application to 4-trimethylsilylpyridine. Using a σ_{para} value for $SiMe_3$ of -0.07 (determined from benzoic acid ionization in water),[11] the calculated pK_a for 4-trimethylsilylpyridine is 5.57, exactly equal to the experimental value.[12] The absence of a d_π–p_π conjunctive contribution from the $-SiMe_3$ group in 4-trimethylsilylbenzoic acid has been cogently argued on the basis of the thermodynamic parameters for the dissociation process.[13]

Since it was concluded that there is no d_π–p_π conjugation in the 4-pyridylphosphonic acids, the higher basicity of the pyridyl ring in the 2-phosphonates compared with the 4-phosphonates must arise from an effect other than d_π–p_π conjugation, since this is a base-weakening effect. Intramolecular hydrogen bonding as in **26**, stabilizing the N-protonated form and hence



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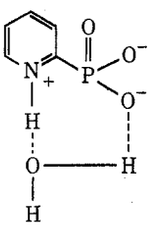

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increasing the pK_a, offers a reasonable explanation of this higher basicity. It would appear that the geometry in **26** is somewhat unfavorable for H bonding[14] and that interpolation of a water molecule as in **27** may be desirable.

The higher basicity of 3-substituted pyridyl-2-phosphonic acids (family A) compared with unsubstituted pyridyl-2-phosphonic acids (family B) can be explained by hindrance to solvation of the PO_3^{2-} by this substituent, bringing about a strengthening of the intramolecular hydrogen bonding. Hindrance to solvation of $-PO_3^{2-}$ ions by adjacent groups has been proposed to explain the lower than expected acidities in aliphatic acids.[10]

Ultraviolet Spectra.—Ultraviolet spectra have been used in a number of compounds to determine the presence of d_π–p_π conjugation between an unsaturated system and an attached phosphorus substituent.[7] In electron-rich aryl or heteroaryl phosphonates, bathochromic shifts have been observed, providing evidence for d_π–p_π interaction.[2]

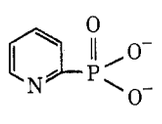
The uv spectra of pyridyl-2-phosphonic acid (**6**) and 2,6-dimethylpyridyl-4-phosphonic acid (**7**) and their ethyl esters **1** and **5** have been measured in water and the data are summarized in Table IV. The spectral data for the parent pyridines also are included as reference points. From the data it can be seen that for both **6** and **7** there is only a slight bathochromic shift from the parent pyridines. Thus, there is no evidence for a difference in conjugative interaction in the two series.

TABLE IV
ULTRAVIOLET SPECTRA OF PYRIDYLPHOSPHONATES

Compd	Absorption, nm (ε)
Pyridine (0.1 *N* NaOH)	262 (1800), 257 (2750),[a] 251 (2450)[a]
Pyridine (0.1 *N* HCl)	256 (5300)[a]
Pyridyl-2-phosphonic acid (pH 10)	268 (4050), 262 (5660), 256 (4700)
Pyridyl-2-phosphonic acid (pH 6.0)	264 (6570)
Pyridyl-2-phosphonic acid (pH 2.0)	263 (8410)
Diethyl pyridyl-2-phosphonate	267 (1970), 259 (2790)
2,6-Lutidine (0.1 *N* NaOH)	267 (4510)[a]
2,6-Lutidine (0.1 *N* HCl)	270 (8540)[a]
2,6-Dimethylpyridyl-4-phosphonic acid (pH 10.0)	280 (3560) (s), 273 (4330)
2,6-Dimethylpyridyl-4-phosphonic acid (pH 6.30)	283 (6410) (s), 278 (7380)
2,6-Dimethylpyridyl-4-phosphonic acid (pH 3.0)	283 (6510) (s), 278 (7420)
Diethyl 2,6-dimethylpyridyl-4-phosphonate	279 (3200)

[a] H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).

From the measurements on the acids at different pH's it can be seen that the position of the absorption maximum is almost independent of pH. From the pK_a determinations we know that at pH 10 the acid exists in form **28** and at pH 2 in form **29** (or possibly further



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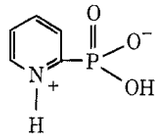

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protonated). In form **29** the opportunity for d_π–p_π conjugation is minimal, since both protonation of the nitrogen and the inductive effect of the PO_3H^- group[9] will reduce electron density in the pyridyl ring. However, in **28** the pyridyl ring is unprotonated and the substituent $-PO_3^{2-}$ is electron donating,[9] favoring d_π–p_π conjugation. Since both species show almost identical absorption properties, we conclude that there

(8) (a) H. H. Jaffe and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964); (b) A. Fischer, W. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964).

(9) H. H. Jaffe, L. D. Freedman, and G. O. Doak, *J. Amer. Chem. Soc.*, **75**, 2209 (1953).

(10) D. J. Martin and C. E. Griffin, *J. Organometal. Chem.*, **1**, 292 (1964).

(11) R. A. Benkeser and H. R. Krysiak, *J. Amer. Chem. Soc.*, **75**, 2421 (1953).

(12) D. G. Anderson, J. R. Chipperfield, and D. E. Webster, *J. Organometal. Chem.*, **12**, 323 (1968).

(13) J. M. Wilson, A. G. Briggs, J. E. Sawbridge, P. Tickle, and J. J. Zuckerman, *J. Chem. Soc. A*, 1024 (1970).

(14) G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, pp 263–265; P. A. Kollman and L. C. Allen, *Chem. Rev.*, **72**, 283 (1972).

is an absence of d_π–p_π bonding between the pyridyl ring and the phosphorus substituent.

Conclusions.—Although the ^{31}P nmr chemical shift data can be interpreted as supporting d_π–p_π conjugation in pyridyl-4-phosphonates, all other measurements, mass spectra, ultraviolet spectra, and pK_a measurements, offer no evidence for any d_π–p_π conjugation in pyridylphosphonates.

Experimental Section

Melting points, determined on a Fisher-Johns melting point apparatus, and boiling points are uncorrected. The elemental analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill., and the staff of Dr. F. J. Ludwig, Petrolite Corp., Physical-Analytical Section. Proton nmr spectra were obtained with a Varian Associates A-60 spectrometer, using TMS as an internal standard. ^{31}P nmr spectra were obtained with a Varian HR-100 spectrometer operating at 40.5 MHz, using H_3PO_4 as an external reference or with a Joel spectrometer operating at 24.3 MHz, using P_4O_6 as a reference. Infrared spectra were determined on a Beckman IR-4 spectrometer.

Mass spectra of the pyridylphosphonates were determined by West Coast Technical Service with a Hitachi Perkin-Elmer Model RMU-6D spectrometer at 70 eV. The mass spectrum of diethyl phenylphosphonate (**8**) was determined at Washington University through the courtesy of Dr. C. D. Gutsche with a Varian M-66 spectrometer at 70 eV. The ultraviolet spectra were determined on a Beckman DK-2 spectrometer.

All new pyridylphosphonate esters used in this study were prepared by the general method previously described.[3] In many cases these esters were not characterized but converted directly to the corresponding acids by hydrolysis in the normal manner.[3] The analytical data used in the characterization of the pyridylphosphonic acid derivatives are summarized below.

Diethyl 4,6-Dimethylpyridyl-2-phosphonate (2).—This ester was obtained in 40% yield: bp 110–112° (0.03 mm); nmr (neat) δ 1.32 (t, 6, J = 7 Hz, CH_3CH_2O), 2.35 (s, 3, CH_3Ar at C_4), 2.52 (s, 3, CH_3Ar at C_6), 4.25 (quintet, 4, J = 7 Hz, OCH_2CH_3), 7.30 (s, 1, H at C_5), 7.68 (d, 1, J = 7.5 Hz, H at C_3).

Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.41; N, 5.76; P, 12.76. Found: C, 54.09; H, 7.22; N, 5.92; P, 12.79.

4,6-Dimethylpyridyl-2-phosphonic Acid (15).—Hydrolysis of the above ester (**2**) yielded 4,6-dimethylpyridyl-2-phosphonic acid (**15**) after crystallization from aqueous ethanol, mp <300°.

Anal. Calcd for $C_7H_{10}NO_3P$: C, 44.92; H, 5.35; N, 7.49; P, 16.58. Found: C, 44.89; H, 5.00; N, 7.64; P, 16.66.

Disodium 3-Ethyl-6-methylpyridyl-2-phosphonate.—3-Ethyl-6-methylpyridine N-oxide was converted into diethyl 3-ethyl-6-methylpyridyl-2-phosphonate in 18% yield and subjected to hydrolysis in 18% hydrochloric acid in the normal manner. The product obtained upon crystallization from aqueous ethanol, mp 278–284°, was not the expected acid but rather the corresponding anhydride on the basis of the following data: ir (KBr disc) 1195 (P=O), 920 (POP), and 740 cm^{-1} (POP).[15]

Anal. Calcd for $C_{16}H_{22}N_2O_5P_2 \cdot H_2O$: C, 47.76; H, 5.97; N, 6.96; P, 15.42. Found: C, 48.36; H, 6.42; N, 6.90; P, 15.11; equiv wt (KOH titration) 205 (calcd 201); pK_a 4.16 (one break only).

Dissolution of the above anhydride (1 g) in water (25 ml) containing sodium hydroxide (0.4 g) gave disodium 3-ethyl-6-methylpyridyl-2-phosphonate after evaporation of the solvent. Recrystallization from aqueous ethanol yielded the pure salt: mp >300°; nmr (D_2O) δ 1.24 (t, 3, J = 8 Hz, CH_3CH_2–), 2.53 (s, 3, CH_3 at C_6), 3.09 (q, 2, J = 8 Hz, CH_3CH_2–), 7.31 (m, 1, H at C_5), 7.75 (m, 1, H at C_4).

Anal. Calcd for $C_8H_{10}NO_3PNa_2$: C, 39.18; H, 4.08; N, 5.71. Found: C, 39.09; H, 3.58; N, 5.78.

Disodium 3,6-Dimethylpyridyl-2-phosphonate.—Diethyl 3,6-dimethylpyridyl-2-phosphonate, obtained from 2,5-dimethylpyridine N-oxide in 40% yield, was hydrolyzed with 18% hydrochloric acid. The product, mp 296–302°, crystallized from aqueous ethanol, was the anhydride of 3,6-dimethylpyridyl-2-phosphonic acid: ir (KBr disc) 1185 (P=O), 926 (POP), and 746 cm^{-1} (POP).[15]

Anal. Calcd for $C_{14}H_{18}N_2O_5P_2 \cdot H_2O$: C, 44.92; H, 5.35; N, 7.49; P, 16.58. Found: C, 45.00; H, 5.47; N, 7.69; equiv wt (KOH titration) 190 (calcd 187); pK_a 4.20.

Dissolution of the above anhydride (1 g) in water (25 ml) containing sodium hydroxide (0.4 g) gave disodium 3,6-dimethylpyridyl-2-phosphonate upon evaporation of the solvent. Recrystallization from aqueous ethanol gave the pure salt: mp <300°; nmr (D_2O) δ 2.54 (s, 3, CH_3Ar at C_3), 2.58 (s, 3, CH_3Ar at C_6), 7.30 (m, 1, H at C_5), 7.67 (m, 1, H at C_6).

Diethyl 3-Chloropyridyl-2-phosphonate (4).—This ester was obtained in 63% yield: bp 125–126° (0.2 mm); nmr (neat) δ 1.45 (t, 6, J = 7 Hz, CH_3CH_2O), 4.40 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.72 (m, 1, ArH at C_5), 8.15 (m, 1, ArH at C_4), 8.90 (m, 1, ArH at C_6); ir (liquid film) 1250 (P=O), 790 cm^{-1} (3 adjacent aryl hydrogen).

Anal. Calcd for $C_9H_{13}ClNO_3P$: C, 43.29; H, 5.21; N, 5.61; P, 12.42: Found: C, 43.59; H, 5.43; N, 5.34; P, 12.56.

3-Chloropyridyl-2-phosphonic Acid (22).—This acid was obtained by hydrolysis of ester **4**, mp 252–254° (aqueous ethanol).

Anal. Calcd for $C_5H_5ClNO_3P$: C, 31.01; H, 2.58; Cl, 18.35; N, 7.24; P, 16.02. Found: C, 30.12; H, 2.65; Cl, 18.11; N, 7.07; P, 15.61.

Diethyl 3-Fluoropyridyl-2-phosphonate.—3-Fluoropyridine N-oxide, mp 61–64° (lit.[16] mp 64°), was converted into diethyl 3-fluoropyridyl-2-phosphonate in 68% yield: bp 124–127° (0.1 mm); nmr ($CDCl_3$) δ 1.39 (t, 6, J = 7 Hz, CH_3CH_2O), 4.40 (quintet, 4, J = 7 Hz, CH_3CH_2O), 7.83 (m, 2, H at C_4 and C_5), 8.50 (m, 1, H at C_6).

Anal. Calcd for $C_9H_{13}FNO_3P$: C, 46.35; H, 5.58; N, 6.01; P, 13.30. Found: C, 45.25; H, 5.68; N, 5.97; P, 13.98.

3-Fluoropyridyl-2-phosphonic Acid (17).—Hydrolysis of the above ester and crystallization from aqueous ethanol yielded 3-fluoropyridyl-2-phosphonic acid, mp 220–222°.

Anal. Calcd for $C_5H_5FNO_3P \cdot {}^1/_2H_2O$: C, 32.26; H, 3.23; N, 7.52; P, 16.67. Found: C, 32.08; H, 3.44; N, 7.55; P, 16.33.

4-Phenylpyridyl-2-phosphonic Acid (13).—Hydrolysis of the corresponding ethyl ester yielded pure acid upon crystallization from aqueous ethanol, mp 268–271°.

Anal. Calcd for $C_{11}H_{10}NO_3P$: C, 56.17; H, 4.68; N, 5.96; P, 13.19. Found: C, 56.44; H, 4.38; N, 5.90; P, 13.35.

Di(perdeuterioethyl) Pyridyl-2-phosphonate.—Phosphorus pentachloride (20.8 g, 0.1 mol) was added to diethyl pyridyl-2-phosphonate (10.8 g, 0.05 mol) at 60° during 0.5 hr. Evolution of gas (ethyl chloride) was vigorous during the addition. The mixture was heated at 165–170° for 6 hr, during which time 11 g of distillate ($POCl_3$) was collected. The residue was distilled under reduced pressure to yield pyridyl-2-phosphonic dichloride (3.5 g, 33%), bp 88–90° (0.1 mm), ir (liquid film) 1270 cm^{-1} (P=O).

To pyridyl-2-phosphonic dichloride (3.4 g, 0.016 mol) in benzene (25 ml) was added a solution of ethanol-d_6 (1.8 g, 0.032 mol) and triethylamine (3.2 g, 0.032 mol) in benzene (30 ml) during 1 hr at 20°. After filtration of the precipitated amine hydrochloride the benzene solution was washed with sodium carbonate solution. Evaporation of the benzene yielded an oil which, upon distillation, yielded pure di(perdeuterioethyl) pyridyl-2-phosphonate: bp 93–95° (0.03 mm); ir (liquid film) 3050 (aryl CH), 2230 (CD_3), 2155 (CD_2), 2120 (CD_3?), 2080 (CD_3),[17] 1260 cm^{-1}; mass spectrum M^+ 225 (see Figure 1b).

4-Benzylpyridyl-2-phosphonic Acid (16).—4-Benzylpyridine N-oxide (49 g, 0.26 mol) was converted in the normal manner to diethyl 4-benzylpyridyl-2-phosphonate, which was purified by chromatography on alumina and elution with benzene, yield 12.7 g (16%). This oil was subjected to hydrolysis with 18% hydrochloric acid without further purification. The resulting oil was crystallized from aqueous ethanol to yield pure 4-benzylpyridyl-2-phosphonic acid: mp 269–272°; yield 2.1 g (20%); nmr (D_2O) δ 4.13 (s, 2, CH_2Ph), 7.50 (s, 5, PhH), 7.3 (m, 1, H at C_5), 7.9 (m, 1, H at C_3), 8.5 (m, 1, H at C_6).

Anal. Calcd for $C_{12}H_{12}NO_3P$: C, 57.83; H, 4.82; N, 5.62; P, 12.45. Found: C, 58.15; H, 5.27; N, 5.75; P, 12.68.

(15) The anhydride absorptions are absent in the spectra of other pyridylphosphonic acids, for example, the spectrum of pyridyl-2-phosphonic acid recorded on Documentation of Molecular Spectroscopy card no. 21442.

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Registry No.—**1,** 23081-78-9; **1** perdeuterioethyl ester, 38605-80-0; **2,** 38605-81-1; **3,** 26384-92-9; **4,** 38605-83-3; **5,** 26384-85-0; **6,** 26384-86-1; **7,** 26394-19-4; **8,** 1754-49-0; **13,** 38605-87-7; **15,** 38605-88-8; **16,** 38605-89-9; **16** diethyl ester, 38605-90-2; **17,** 38605-91-3; **17** diethyl ester, 38605-92-4; **20,** 38605-93-5; **20** anhydride, 38605-94-6; **20** diethyl ester, 38605-95-7; **20** disodium salt, 38605-96-8; **21** anhydride, 38605-97-9; **21** diethyl ester, 38605-98-0; **21** disodium salt, 38605-99-1; **22,** 38606-00-7; 3-ethyl-6-methylpyridine *N*-oxide, 768-44-5; 2,5-dimethylpyridine *N*-oxide, 4986-05-4; 3-fluoropyridine *N*-oxide, 695-37-4; phosphorus pentachloride, 10026-13-8; pyridyl-2-phosphonic dichloride, 38606-04-1; 4-benzylpyridine *N*-oxide, 7259-53-2.

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Nuclear Magnetic Resonance Spectroscopy. Carbon-13 Nuclear Magnetic Resonance for Some Six-Membered Aromatic Nitrogen Heterocycles[1a]

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High-resolution, natural-abundance ^{13}C spectra have been obtained for pyridine, pyridazine, pyrimidine, pyrazine, and *s*-triazine and some methyl derivatives. Geminal and vicinal carbon–proton coupling has been related to proton–proton coupling in substituted ethylenes.

Although one-bond carbon–proton coupling constants in aromatic systems are well characterized,[2,3] long-range carbon–proton coupling constants have not been extensively studied. Direct observation of the inner satellites in the proton spectrum is hampered by the strong resonances from molecules having no ^{13}C. If the proton spectrum is particularly simple, these satellites can be observed,[4] but they cannot always be assigned to a particular carbon. The analysis of the outer satellites is dependent on the differences in the long-range carbon–proton coupling constants, but the magnitudes cannot be determined.[5] Homonuclear tickling of the inner satellites while observing the outer satellites gives all the transitions for a complete iterative analysis.[6] If all the proton–proton coupling constants are known (from studies of the unlabeled materials), all the carbon–proton coupling constants can be determined from the ^{13}C spectrum.

Lauterbur[2] has measured the ^{13}C chemical shifts of six-membered nitrogen heterocycles, but the spectra were low resolution and long-range couplings were not resolved. High-resolution ^{13}C spectra of pyridine have been published but not interpreted in detail.[7] Long-range carbon–proton coupling constants of benzene[8] and the five-membered heterocycles[9] have been reported. This paper concerns the nmr spectra of six-membered nitrogen heterocycles.

Experimental Section

All samples were obtained from commercial sources. Liquid samples were diluted with 5% acetone for an internal lock. Spectra of solid samples were taken as saturated acetone solutions. The spectra were obtained with the previously described Varian DFS-60 spectrometer.[8,9] Theoretical spectra were calculated by trial and error using the computer programs NMRIT, or by iteratative techniques with the LAOCOON programs.[10]

Results

The ^{13}C spectra of pyridine, pyridazine, and pyrazine are shown in Figures 1–6. The ^{13}C spectra of all of the carbons of pyrimidine and *s*-triazine are first order. Only the low field half of the pyrazine spectrum is shown because the high field half is simply its mirror image. The carbon–proton coupling constants for the parent heterocycles are summarized in Table I. Long-range coupling constants are accurate to ±0.2 Hz.

TABLE I

CARBON–PROTON COUPLING CONSTANTS IN THE SIX-MEMBERED NITROGEN HETEROCYCLES

Compound	Registry no.	Carbon	H-2	H-3	H-4	H-5	H-6
Pyridine	110-86-1	2	175.3	3.3	6.4	±1.6	10.9
		3	8.7	162.5	1.0	6.4	±1.6
		4	6.4	0.0	169.2	0.0	6.4
Pyridazine	289-80-5	3		182.5	6.5	2.0	−1.4
		4		6.7	169.9	0.0	5.2
Pyrimidine	289-95-2	2	202.7		10.3	0.0	10.3
		4	9.1		182.8	1.9	5.3
		5	1.9		9.5	166.2	9.5
Pyrazine	290-37-9		182.7	10.4		−1.5	9.8
s-Triazine	290-87-9		207.5		7.95		7.95

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