THE PREPARATION AND PROPERTIES OF PHOSPHONIC ACIDS

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I. Introduction

Among the organic derivatives of phosphorus the phosphonic acids occupy a prominent position. Together with their amides and esters they probably outnumber all other compounds containing the carbon–phosphorus bond. Prior to 1950 no important new methods for preparing this class of compounds had appeared in several decades. In two excellent reviews (127, 128) which cover the chemical literature on organic phosphorus compounds through 1949, the prin-

cipal methods given for preparing phosphonic acids were the Friedel–Crafts and the Michaelis–Arbuzov reactions, first described in 1879 and 1898, respectively.

After the appearance of these two reviews, however, vastly improved methods for the synthesis of phosphonic acids appeared. With the use of these new methods the number of phosphonic acids prepared has increased tremendously. Since 1950 approximately as many aromatic phosphonic acids have been prepared as were prepared during the previous seventy years.

It is the purpose of this review to cover those methods of preparing phosphonic acids which have appeared since publication of Kosolapoff's two reviews. A list of phosphonic acids prepared since 1950, together with new data on the physical and biological properties of this class of compounds, is included. The phosphonic acids listed are those for which analyses were given or those which were isolated as a syrup and identified by the analysis of a solid derivative. *Chemical Abstracts* is covered through September 25, 1956. Acids mentioned in the literature as having been prepared by the hydrolysis of esters but without further characterization are not listed. The patent literature has been searched, but only those phosphonic acids which have been described in detail are included.

NOMENCLATURE

The nomenclature of organic phosphorus compounds underwent a radical change in 1952. Prior to that year the naming of a new organic phosphorus compound was left largely to the preference of the individual author. *Chemical Abstracts* used a fairly well defined system based on I.U.C. Rule 34, but many authors, writing in American chemical journals, did not follow these rules. In British chemical journals an entirely different system was used, so that the same name was frequently used for describing two different compounds in the two countries. In reading older books on organic phosphorus compounds it is often impossible to ascertain the structure of a compound when only the name is given.

In 1949 an Advisory Committee on the Nomenclature of Organic Phosphorus Compounds was organized within the framework of the Nomenclature Committee of the Division of Organic Chemistry of the American Chemical Society. Several joint sessions were held with a committee of the (British) Chemical Society and a number of compromises were made in an effort to satisfy chemists in both countries. A report was submitted at the meeting of the American Chemical Society in New York in September, 1951. This report was divided into two sections, one dealing with compounds containing one phosphorus atom and the other with compounds containing two or more phosphorus atoms. Tentative acceptance of the first section only was recommended, since full agreement on the second section had not been reached. The report was published almost simultaneously in both *Chemical and Engineering News* (3) and the *Journal of the Chemical Society* (4). The Chemical Society now requires that this nomenclature be used in the *Journal of the Chemical Society*. Although no such definite policy has been officially stated in the various journals published by the American

Chemical Society, the editors of the journals are requesting that this new nomenclature be used. *Chemical Abstracts* also uses this new nomenclature with one or two exceptions. The new system has not been adopted by the International Union of Chemistry nor have chemical journals in countries other than Britain and the United States adopted it. There has been some criticism of the system. It is the opinion of the present authors that the system must be used for some time in order to determine how satisfactory it will be. Undoubtedly, the system is often cumbersome and unwieldy and names many hypothetical classes of compounds which probably never will be prepared. Nevertheless, it does bring order to a very confused state and may well be adopted, at least in part, by the International Union of Chemistry.

Throughout this review the new phosphorus nomenclature has been used, except that "phosphono" is used rather than "dihydroxyphosphinyl" for the radical —PO_3H_2. This is in accord with the usage of *Chemical Abstracts*. Further, the compound $[PO(OR)_2]^-Na^+$ is named as a sodium dialkyl phosphite. This type of compound is prepared by the reaction between sodium and a dialkyl phosphonate, $HPO(OR)_2$. The name sodium dialkyl phosphite regards this compound as being derived from phosphorous acid, $(HO)_3P$, and is probably in accord with the actual structure of the compound. In a few cases the rules do not exactly delineate the name to be used. One such example is the compound $(C_5H_{10}N)_2POCl$, which the authors have called phosphorodipiperididic chloride, a name which is certainly within the spirit of the new rules (183).

II. Newer Methods for the Preparation of Phosphonic Acids

A. Reaction of Lithium or Grignard Reagents with Inorganic Derivatives of Phosphorus

In 1950 Mikhailov and Kucherova (173) reported that a readily separable mixture of arylphosphonic and diarylphosphinic acids can be obtained by the reaction between an aryllithium reagent and phosphoropiperididic dichloride ($C_5H_{10}NPOCl_2$). This discovery was of great importance, for it was the first really new method of preparing arylphosphonic acids since the classical work of A. Michaelis at the end of the nineteenth century. In 1951 the same authors (174) modified the reaction by using phosphorodipiperididic chloride and obtained excellent yields of the arylphosphonic acids. The following reaction sequence was employed:

$$RLi + (C_5H_{10}N)_2POCl \rightarrow RPO(NC_5H_{10})_2 + LiCl$$
$$RPO(NC_5H_{10})_2 + 2H_2O \xrightarrow{HCl} RPO(OH)_2 + 2C_5H_{11}N$$

This procedure was used to prepare several new phosphonic acids derived from polynuclear hydrocarbons.

About the same time that Mikhailov and Kucherova announced their first method for preparing arylphosphonic acids, Kosolapoff (126) reported that the reaction of alkylmagnesium halides with *N*,*N*-diethylphosphoramidic dichloride could be used for preparing alkylphosphonic acids such as butylphosphonic acid.

Kosolapoff pointed out that this method cannot in general be expected to compete with the older methods for the preparation of alkylphosphonic acids but suggested that this reaction might be extended to the preparation of substituted aromatic phosphonic acids.

In 1951 Burger and Dawson (44) reported that the addition of diethyl phosphorochloridate to ortho-substituted arylmagnesium halides yields diethyl arylphosphonates, while sterically unhindered Grignard reagents form triarylphosphine oxides. It was further found that hindered or unhindered arylmagnesium halides can be converted to esters of phosphonic acids by "reverse addition," i.e., the addition of the Grignard compound to the dialkyl phosphorochloridate. They also reported that aryllithium compounds can be used in place of the Grignard reagents.

Since dialkyl arylphosphonates can be readily hydrolyzed to the corresponding phosphonic acids, the method of Burger and Dawson seems to be very convenient and has been used for preparing a considerable number of arylphosphonic acids (16, 44, 65, 130).

Independently of Burger and Dawson, Morrison (175) also discovered that Grignard reagents can be used for the preparation of arylphosphonic acids. It was found that the interaction of arylmagnesium halides and *N*,*N*′-diphenylphosphorodiamidic chloride gives fair yields of arylphosphonic dianilides. By hydrolysis of these anilides with concentrated hydrochloric acid, the corresponding phosphonic acids were obtained. No new phosphonic acids have been prepared by this procedure, which apparently has no advantages over the method of Burger and Dawson.

Morrison also noted that diphenyl arylphosphonates can be formed to a moderate extent by the addition of an aryl Grignard compound to a cooled ethereal solution of diphenyl phosphorochloridate. The free phosphonic acid can be obtained from its diphenyl ester by prolonged alkaline hydrolysis.

B. REACTION OF DIAZONIUM SALTS WITH PHOSPHORUS TRIHALIDES

The convenience of the Bart and related reactions for preparing arylarsonic and stibonic acids (103) has induced a number of investigators to attempt the preparation of arylphosphonic acids from diazonium salts. Nijk (179, p. 475) in 1922 made a determined but unsuccessful effort to prepare organophosphorus compounds by the interaction of aqueous solutions of diazonium salts and inorganic derivatives of phosphorus. Davies and Morris (64) have recorded similar unsuccessful attempts. Plets (188), on the other hand, has reported the preparation of arylphosphinic acids from diazonium salts and sodium hypophosphite. Other workers have been unable to duplicate these results (75; 127, p. 142; 146, 237, 242).

In 1951 a new general method for the preparation of arylphosphonic and diarylphosphinic acids was described (67). The method consisted in the interaction of a diazonium fluoborate and phosphorus trichloride in an anhydrous organic solvent in the presence of copper or one of its salts. The solvents used included dioxane and several aliphatic acetates. The major reaction product was

usually the arylphosphonic acid; by proper choice of solvent and catalyst, a fair yield of the symmetrical phosphinic acid could also be obtained. It was later discovered that phosphorus tribromide can be used in place of the trichloride (69) and that other stable diazonium salts such as the fluosilicates and the chlorozincates can be used instead of the fluoborates (78). Only in the case of *o*-nitrobenzenediazonium and *o*-toluenediazonium fluoborates has the reaction failed to produce either the expected arylphosphonic or diarylphosphinic acid (16, 67, 79). The diazo method has now been used in several laboratories for the preparation of a considerable number of new phosphonic acids and makes readily available a wide variety of organophosphorus compounds which hitherto have been difficult if not impossible to prepare (16, 24, 37, 38, 67, 68, 69, 78, 79, 84, 101, 102, 132, 133, 136).

C. REACTION OF ALKYL HALIDES WITH PHOSPHORUS TRICHLORIDE

In 1951 Clay (54) reported a new method for the preparation of alkylphosphonic acids. The method may be illustrated by the following reactions:

$$RCl + PCl_3 + AlCl_3 \rightarrow RCl \cdot PCl_3 \cdot AlCl_3 \text{ (insoluble complex)}$$
$$RCl \cdot PCl_3 \cdot AlCl_3 + 7H_2O \rightarrow AlCl_3 \cdot 6H_2O + RPOCl_2 + 2HCl$$
$$RPOCl_2 + 2H_2O \rightarrow RPO_3H_2 + 2HCl$$

The melting point of the insoluble complex is high (about 370°C. for $C_2H_5Cl \cdot PCl_3 \cdot AlCl_3$), and solutions of the complex in nitromethane conduct an electric current and produce an abnormal lowering of the freezing point. These facts suggest that the complex is ionic in character and has a structure such as $[RPCl_3]^+[AlCl_4]^-$.

Since ethyl, isopropyl, and *tert*-butyl chlorides all yielded phosphonic dichlorides, Clay believed that this method was a general one, applicable to the alkylation of phosphorus with primary, secondary, or tertiary alkyl groups. It was soon found (120, 187), however, that the reaction of *n*-propyl, *n*-butyl, and isobutyl chloride yields isopropyl-, *sec*-butyl-, and *tert*-butylphosphonic dichloride, respectively. This type of isomerization, which is somewhat analogous to that occurring when alkyl chlorides are condensed with benzene by the Friedel–Crafts reaction, seriously limits the utility of Clay's procedure. Another complication was discovered by Crofts and Kosolapoff (62), who found that *tert*-amyl chloride yields *tert*-butylphosphonic dichloride. The elimination of a methylene group by a reaction occurring at or below room temperature seems very remarkable.

Attempts to prepare diphosphonic acids by this procedure have failed (120). Thus, 1,5-dichloropentane gives 4-chloro-1-methylbutylphosphonic dichloride and no trace of higher-boiling material. Carbon tetrachloride gives a good yield of trichloromethylphosphonic dichloride, but no diphosphonic acid (119, 120).

Kinnear and Perren have found that aliphatic ethers also react with phosphorus trichloride and aluminum trichloride to give alkylphosphonic dichlorides. The preparation of alkoxymethylphosphonic acids by the reaction between

formals, phosphorus trihalides, and aluminum trichloride has been described in the patent literature (43).

D. SYNTHESIS OF AMINOALKYLPHOSPHONIC ACIDS FROM CARBONYL COMPOUNDS

Until 1952 amino-substituted alkylphosphonic acids could not be made in a single step from readily available starting materials (104). In that year Kabachnik and Medved (105) described a new synthetic method based on the reaction of aldehydes with ammonia and dialkyl phosphonates:

$$RCHO + NH_3 + HPO(OR')_2 \rightarrow RCH(NH_2)PO(OR')_2 + H_2O$$

The esters of the aminophosphonic acids were isolated as hydrochlorides. Hydrolysis of these esters with hydrochloric acid yielded the free amino acids. It was soon found that ketones undergo the above reaction more readily than aldehydes (160, 161). Aliphatic ketones react most vigorously, alicyclic and mixed aliphatic-aromatic ketones react with more difficulty, while aromatic ketones react only under drastic conditions. Chalmers and Kosolapoff (47) discovered that the yields of the esters are higher if the anhydrous ammonia and the carbonyl compound are mixed before the dialkyl phosphonate is added. The free aminophosphonic acids, which are of course zwitter ions, are colorless, high-melting substances which crystallize from water with one or two molecules of solvent of crystallization.

Fields (73) has described a method of synthesizing esters of substituted aminophosphonic acids by the interaction of an aldehyde or ketone, a dialkyl phosphonate, and a primary or secondary amine. This reaction is exothermic and vigorous, and the esters can be isolated in excellent yields. However, the free aminophosphonic acids could not be prepared in pure form; generally, noncrystallizing, hygroscopic syrups were obtained.

The mechanism of the reaction discovered by Kabachnik and Medved is not clear. It has been suggested (107) that the reaction proceeds through the hydroxyphosphonates formed by the addition of the dialkyl phosphonates to the carbonyl group. If the reaction mixture is not heated, the product is in fact the hydroxyphosphonate, which can be readily converted to the amino compound by heating with ammonia. Fields (73), on the other hand, has reported that diethyl α-hydroxymethylphosphonate does *not* react with diethylamine. It seems strange that ammonia and diethylamine apparently react so differently with the hydroxy compounds.

It has also been found that Schiff bases react vigorously with dialkyl phosphonates to form esters of substituted aminophosphonic acids (73, 196, 209). This reaction is general for Schiff bases derived from both aldehydes and ketones and takes place simply upon the mixing of equimolar quantities of the two reactants.

The reactions reviewed in this section produce compounds in which both the amino group and the phosphono group are attached to the same carbon atom.

It is therefore now possible to synthesize aminophosphonic acids analogous to the biologically important α-aminocarboxylic acids.

E. PHOSPHONATION OF AROMATIC COMPOUNDS WITH PHOSPHORIC ANHYDRIDE

The first nitration of an aromatic compound was performed in 1834, when Mitscherlich prepared nitrobenzene by the action of fuming nitric acid on benzene (227). In contrast, the phosphonation of aromatic compounds by phosphoric acid or its anhydrides was unsuccessful (179, p. 473) until 1954, when it was found that benzene, chlorobenzene, *o*-xylene, and naphthalene can be phosphonated by phosphorus pentoxide at a temperature of about 275–325°C. (144, 145). The primary product of this reaction has a composition corresponding to the formula $ArHP_4O_{10}$. In some cases there are also formed secondary reaction products, which are anhydrides of the type $(ArPO_2)_n$. The primary and secondary reaction products can easily be separated, since only the latter type is soluble in the aromatic compound. For practical purposes it is not necessary to work up the insoluble and soluble reaction products separately, since both types of products can be hydrolyzed to the phosphonic acid or can be converted to the phosphonic dichloride by treatment with phosphorus pentachloride.

The phosphonation reaction produces good yields only if a large excess of the aromatic compound is used. Thus, when 20 moles of benzene was used per mole of phosphorus pentoxide (P_4O_{10}), the yield of phenylphosphonic acid was 75.5 per cent (calculated for one molecule of phenylphosphonic acid from one molecule of P_4O_{10}). When the ratio was 5 moles of benzene per mole of P_4O_{10}, the yield was only 38 per cent.

When the reaction products from chlorobenzene and phosphorus pentoxide were hydrolyzed, a mixture of chlorophenylphosphonic acids was obtained. The main component of this mixture was the para isomer, which could be obtained in a pure state by recrystallization. The other constituent, which was isolated as an *o*-toluidine salt, was probably *o*-chlorophenylphosphonic acid.

The reaction between naphthalene and phosphorus pentoxide produced considerable amounts of nonphosphonated by-products, e.g., 2,2′-binaphthyl. The phosphonated compounds formed included 2-naphthylphosphonic acid and an unknown naphthalenediphosphonic acid.

During the phosphonation of *o*-xylene, considerable amounts of water-insoluble, tarry condensation products were formed. A small yield of a phosphonic acid was also isolated. The structure of this compound was not determined, but it may be 3,4-dimethylphenylphosphonic acid as suggested by the authors.

F. SYNTHESIS OF ALKYLPHOSPHONIC ACIDS FROM ALCOHOLS

Alkyl halides can be converted to alkylphosphonic acids by means of several different reactions (127, p. 121). In 1949 Chavane (49) found that alkyl deriva-

tives other than the halides can also be used. Thus, methylphosphonic acid can be prepared from dimethyl sulfate and a sodium dialkyl phosphite. It was also found that ethylphosphonic acid can be prepared from ethyl *p*-toluenesulfonate:

$$p\text{-}CH_3C_6H_4SO_3C_2H_5 + NaPO(OR)_2 \rightarrow p\text{-}CH_3C_6H_4SO_3Na + C_2H_5PO(OR)_2$$
$$C_2H_5PO(OR)_2 + H_2O \xrightarrow{HCl} C_2H_5PO_3H_2 + 2ROH$$

Later work (90, 178) has shown that sulfonate esters of a number of primary and secondary alcohols can be converted to phosphonic acids. This method promises to be a useful one, since the reaction conditions are mild and the alcohols used as starting materials can easily be converted to their sulfonate esters.

With *p*-toluenesulfonate esters of primary alcohols, the reaction, which is performed in tetrahydrofuran or dioxane solution, occurs smoothly at room temperature. Methanesulfonic esters react similarly except that gentle warming is required. Sulfonate esters of secondary aliphatic alcohols also react satisfactorily, but the yield of alkylphosphonate is lower than that obtained with sulfonate esters of primary alcohols. Cyclohexyl *p*-toluenesulfonate reacts only slowly, and the yield of dialkyl cyclohexylphosphonate is rather low. The *p*-toluenesulfonate esters of both phenol and *p*-nitrophenol also react with sodium diethyl phosphite. However, the course of these reactions has not been elucidated, and the products are apparently *not* derivatives of arylphosphonic acids.

The direct conversion of certain alcohols to phosphonic acids has been described in the patent literature (53). There has also been reported a reaction in which a lactone and a trialkyl phosphite react to yield the corresponding dialkyl carboalkoxy alkylphosphonate (59):

$$(C_2H_5O)_3P + \underset{\text{O}}{\text{RCHCH}_2\text{CH}_2\text{CO}} \rightarrow (C_2H_5O)_2P(O)CH(R)CH_2CH_2COOC_2H_5$$

A similar reaction between lactams and phosphites has recently been described (158).

G. SYNTHESIS OF γ-OXOPHOSPHONIC ACIDS FROM MANNICH BASES

β-Dialkylaminoketones, commonly referred to as Mannich bases, are readily prepared by the treatment of ketones with formaldehyde and a secondary amine. It has recently been found (177) that heating triethyl phosphite with the methiodide of a Mannich base derived from a methyl ketone causes the ammonio group to be eliminated and produces an ester of a γ-oxophosphonic acid:

$$[RCOCH_2CH_2\overset{+}{N}(C_2H_5)_2CH_3]I^- + P(OC_2H_5)_3 \rightarrow$$
$$RCOCH_2CH_2PO(OC_2H_5)_2 + [(C_2H_5)_3NCH_3]^+I^-$$

The ester can be converted by hydrolysis to the corresponding free acid. Thus, there is now available a convenient and apparently general procedure for the

preparation of γ-oxoalkylphosphonic acids; another method for preparing such compounds is discussed in Section II,I.

Hydrochlorides of Mannich bases react with triethyl phosphite in a manner similar to that of the methiodides, although the yields are slightly lower and the products more difficult to purify. No reaction is observed between triethyl phosphite and the free Mannich bases. Sodium dialkyl phosphites react with both the free bases and their methiodides to produce esters of γ-oxophosphonic acids. However, the interaction of the quaternary salts and triethyl phosphite gives higher yields.

H. SYNTHESIS OF HETEROCYCLIC PHOSPHONIC ACIDS

Few compounds are known in which a phosphono or a dialkylphosphono group is attached directly to a heterocyclic ring. Kosolapoff (123) has described the preparation of diethyl acridine-9-phosphonate by the reaction between 9-chloroacridine and triethyl phosphite (the Michaelis–Arbuzov reaction). This phosphonic ester could not be obtained, however, by the interaction of 9-chloroacridine and sodium dibutyl phosphite (the Nylen reaction). Arbuzov and Lugovkin (11) have reported unsuccessful attempts to introduce the diethyl phosphono group into pyridine, but they (10) were able to prepare a number of compounds in which the diethylphosphono group is linked to oxygen heterocycles. However, the corresponding free phosphonic acids could not be obtained, since attempts at hydrolysis opened the rings.

Both the Michaelis–Arbuzov and the Nylen reactions have been tried with 2-chloro- and 2-bromopyridine, but no conversion seemed to occur (45). However, it was found that 2-chloroquinoline and 2-chlorolepidine will react with sodium dibutyl phosphite, and the resulting esters can be hydrolyzed to the corresponding free acids. By contrast, 2-chloro-4,8-dimethylquinoline could not be converted to a phosphonic ester by the Nylen reaction.

The preparation of two phosphonic acid derivatives of dihydrocoumarin has recently been described (14). These compounds were synthesized by the method of Pudovik, which is reviewed in the next section.

I. MISCELLANEOUS METHODS

A considerable number of organophosphorus compounds have been prepared by the addition of dialkyl phosphonates to ethylenic double bonds conjugated with certain "activating" groups. These groups include the dialkylphosphono (141, 193, 202, 206, 207, 217, 222), oxo (35, 36, 140, 192, 194, 198, 203, 204, 212), cyano (35, 36, 199, 203, 205, 213), carboalkoxy (35, 36, 195, 197, 199, 200, 203, 205, 213), carbamyl (199), and carboxy (199) groups. This method was first described by Pudovik but was discovered independently in a number of other laboratories. The dialkyl alkylphosphonates obtained by this reaction are usually colorless, viscous, high-boiling liquids, which can be obtained in good yields and hydrolyzed to give the corresponding phosphonic acids. The addition reaction is exothermic and is promoted by basic catalysts, especially sodium dialkyl phosphites and sodium alkoxides. Alkyl groups attached to the

vinyl radical generally inhibit the addition of the dialkyl phosphonate, and the reaction then requires larger amounts of the basic catalyst. The addition occurs in a direction contrary to Markownikoff's rule and thus resembles the Michael type of reaction. Unsaturated aldehydes first combine with the dialkyl phosphonates at the carbonyl group to form α-hydroxyphosphonic esters (208), while unsaturated ketones first react at the carbon–carbon double bond to form keto phosphonic esters (194). If an excess of the dialkyl phosphonate is used, unsaturated aldehydes and ketones yield hydroxydiphosphonic esters. Addition reactions have been carried out also with compounds containing activated acetylenic bonds (199, 213). In this case two moles of the dialkyl phosphonate add to the triple bond to form a diphosphonic ester, regardless of whether the reagents are used in equimolar or other proportions.

Closely related to the reactions discussed above is the peroxide-catalyzed addition of diethyl phosphonate to an enol ester (191). Hydrolysis of the addition product yields a β-hydroxyphosphonic acid. The addition of phosphine to olefins is also catalyzed by peroxides as well as by ultraviolet light (20, 42, 229) and by strong non-oxidizing acids (42). The free-radical-initiated reaction yields mixtures of primary, secondary, and tertiary phosphines. The primary phosphines can be separated from the mixtures by fractional distillation and can be oxidized to the corresponding phosphonic acids with nitric acid or 30 per cent hydrogen peroxide. The acid-catalyzed addition reaction yields mainly primary phosphine, a little secondary phosphine, and no tertiary phosphine. Alkylphosphines can be prepared also by the interaction of olefins, white phosphorus, and hydrogen at a temperature above 200°C. and under a pressure of 700–3000 atm. (181).

The use of diazoalkanes for the preparation of organophosphorus compounds has been recently reviewed (226).

Phosphonic acids have been synthesized by the interaction of yellow phosphorus and alkyl or aryl halides, but this procedure seems to have little preparative importance (137).

III. Reactions of Phosphonic Acids

A. Acid dissociation constants

1. Aliphatic and alicyclic phosphonic acids

Although it has been known for a long time that phosphonic acids are moderately strong and dibasic, no information concerning their dissociation constants was available until 1930, when Nylen (180) reported the pK values of several alkylphosphonic acids. Later workers have determined the acidity constants of a considerable number of phosphonic acids. The recorded acid dissociation constants of unsubstituted alkylphosphonic acids are collected in table 1. These acids are weaker than phosphoric acid (pK_1 = 1.97; pK_2 = 6.82) and its monoalkyl esters (139). The pK values of the phosphonic acids increase with an increase in the number of carbon atoms in the alkyl group and with the degree of branching of the carbon chain. This effect is obviously due to the electron-

repelling characteristics of the saturated carbon atom. The median difference between the first and second pK's of the alkylphosphonic acids is 5.62 units. The equation used by Branch and Calvin (39) for calculating the dissociation constants of nonresonating acids predicts a pK difference of 4.9.

The recorded dissociation constants of substituted aliphatic phosphonic acids are collected in table 2. The symbol pK_1 used in tables 1 and 2 refers to the first dissociation constant of the phosphono group, i.e., to the equilibrium constant of the reaction:

$$RPO_3H_2 \rightleftharpoons H^+ + RPO_3H^-$$

Similarly, the symbol pK_2 refers to the reaction:

$$RPO_3H^- \rightleftharpoons H^+ + RPO_3^{--}$$

The acid dissociation constants of other functional groups (e.g., COOH and NH_3^+) are not given in table 2; in many cases, however, they have been determined and can be found in the references. There appears to be no ambiguity about the assignments of the experimental pK values to given acid functions. The last pK's of the aminoalkylphosphonic acids range from 10.0 to 11.25 and, accordingly, have been assigned to the ammonio group. The first pK obtained by titration of 3-anilinopropylphosphonic acid, $C_6H_5NH_2^+(CH_2)_3PO_3H^-$, with alkali is 4.25; this value is undoubtedly the pK_a of the substituted anilinium group. Since the pK_a of N-propylanilinium ion is 5.05, the PO_3H^- group of 3-anilinopropylphosphonic acid must be acid-strengthening and hence electron-attracting. The median of the pK_2 − pK_1 values listed in table 2 is 5.05. This

TABLE 1

Acid dissociation constants of alkylphosphonic acids

Alkyl Group	pK_1	pK_2	pK_2 − pK_1	References
Methyl	2.33	7.76	5.43	(180)
	2.35	7.1	4.75	(52, 218)
	2.38	7.74	5.36	(62)
	2.48	7.34	4.86	(30)
Ethyl	2.39	7.98	5.59	(180)
	2.45	7.85	5.40	(52, 218)
	2.43	8.05	5.62	(62)
n-Propyl	2.45	8.06	5.61	(180)
	2.49	8.18	5.69	(62)
Isopropyl	2.55	7.75	5.20	(52)
	2.66	8.44	5.78	(62)
n-Butyl	2.59	8.19	5.60	(62)
Isobutyl	2.70	8.43	5.73	(62)
s-Butyl	2.74	8.48	5.74	(62)
t-Butyl	2.79	8.88	6.09	(62)
Neopentyl	2.84	8.65	5.81	(62)
1,1-Dimethylpropyl	2.88	8.96	6.08	(62)
n-Hexyl	2.6	7.9	5.3	(52, 218)
	2.4	8.25	5.85	(148)
n-Dodecyl	*	8.25	—	(52, 218)
	4.22†	9.81†	5.59	(246)

* The first pK was not determined because of the low solubility of this compound in acid solutions.

† These values are on the molal scale and were obtained in 50 per cent by weight ethanol.

TABLE 2

Acid dissociation constants of substituted aliphatic phosphonic acids

RPO_3H_2 R =	pK_1	pK_2	pK_2 − pK_1	References
$CH_3(CH_2)_5CH(COOH)$	1	—	—	(52)
CF_3	1.16	3.93	2.77	(30)
CCl_3	1.63	4.81	3.18	(63)
$NH_3^+CH_2$	2.35*	5.9	3.55	(218)
	1.85*	5.35	3.50	(48, 52)
$(^-OOCCH_2)_2NH^+CH_2$	—	5.57	—	(221)
$CHCl_2$	1.14	5.61	4.47	(63)
CH_2Cl	1.40	6.30	4.90	(63)
CH_2Br	1.14	6.52	5.38	(63)
$(^-OOCCH_2)_2NH^+(CH_2)_2$	—	6.54	—	(221)
CH_2I	1.30	6.72	5.42	(63)
$NH_3^+CH_2CH_2$	2.45*	7.00	4.55	(52, 218)
$C_6H_5CH{=}CH$	2.00	7.1	5.10	(52)
$HOCH_2$	1.91	7.15	5.24	(63)
$C_5H_5NH_2^+(CH_2)_2$	2.1*	—	—	(218)
$C_6H_5NH(CH_2)_3$	—	7.17	—	(218)
$Br(CH_2)_2$	2.25	7.3	5.05	(52)
$CH_3(CH_2)_5CH(COO^-)$	—	7.5	—	(52)
$C_6H_5CH_2$	2.3	7.55	5.25	(52)
	1.85	7.4	5.55	(148)
$NH_3^+(CH_2)_4$	2.55*	7.55	5.00	(52, 218)
$NH_3^+(CH_2)_5$	2.6*	7.6	5.0	(218)
	2.6*	7.65	5.05	(52)
$NH_3^+(CH_2)_{10}$	†	8.00	—	(52, 218)
$^-OOC(CH_2)_{10}$	—	8.25	—	(52)
$(CH_3)_3SiCH_2$	3.22	8.70	5.48	(118)
$C_6H_5CH_2$	3.3‡	8.4‡	5.1	(52)
$(C_6H_5)_3C$	3.85‡	9.00‡	5.15	(52)

* Determined by titration of the aminophosphonic acid with hydrochloric acid.

† The first pK was not determined because of the low solubility of this compound in acid solutions.

‡ These values were obtained in 50 per cent ethanol.

is close to the theoretical value of 4.9; however, the stronger acids in table 2 tend to have pK_2 − pK_1 values which are considerably lower than the median value.

The pK values of several alicyclic phosphonic acids also have been measured. Cyclohexylphosphonic acid was first prepared by Clayton and Jensen (55) by the chlorophosphonation of cyclohexane. The acid was reported to melt at 166–167°C. and have dissociation constants of 4×10^{-5} and 2×10^{-10}. Since these dissociation constants differ considerably from those of hexylphosphonic acid, some doubt existed concerning the identity of the acid prepared by Clayton and Jensen. Accordingly, Lesfauries and Rumpf (146, 148, 237) repeated the chlorophosphonation of cyclohexane and obtained an acid with a melting point of 168°C. and pK values of 2.2 and 8.35. Subsequent to this work cyclohexylphosphonic acid was prepared in several laboratories by a number of different methods (72, 82, 88, 178, 229). There is now no doubt whatever that the chlorophosphonation reaction *does* yield cyclohexylphosphonic acid. However, the acid dissociation constants reported by Clayton and Jensen must be in error, since the first ionizable hydrogen of cyclohexylphosphonic acid can be titrated stoichiometrically with the aid of methyl purple (endpoint at pH 5.4) (82). The

dissociation constants reported by Lesfauries and Rumpf for cyclohexylphosphonic acid seem quite reasonable. The preparation and pK values of a tetrahydronaphthylphosphonic acid and a decahydronaphthylphosphonic acid obtained by the chlorophosphonation of tetralin and decalin, respectively, were reported. The phosphonic acid prepared from decalin was presumably a mixture, but gave a titration curve like that of a pure dibasic acid with pK values of 2.5 and 8.2. Tetralin yielded, apparently, a single derivative (m.p. 209°C.) with pK values of 2.0 and 8.0. The PO_3H_2 group is probably in the 2-position, since the tetrahydronaphthylphosphonic acid, although stronger than the acids derived from hexane, cyclohexane, or decalin, is weaker than phenylmethylphosphonic acid. Therefore, the acid-strengthening effect of the aromatic ring (32) is presumably further removed from the PO_3H_2 group than in the case of phenylmethylphosphonic acid.

The pK values of several diphosphonic acids have been measured and are listed in table 3. These acids dissociate according to the following scheme:

$$H_2O_3P—R—PO_3H_2 \overset{K_1}{\rightleftharpoons} H^+ + (H_2O_3P—R—PO_3H)^-$$

$$(H_2O_3P—R—PO_3H)^- \overset{K_2}{\rightleftharpoons} H^+ + (HO_3P—R—PO_3H)^{--}$$

$$(HO_3P—R—PO_3H)^{--} \overset{K_3}{\rightleftharpoons} H^+ + (HO_3P—R—PO_3)^{-3}$$

$$(HO_3P—R—PO_3)^{-3} \overset{K_4}{\rightleftharpoons} H^+ + (O_3P—R—PO_3)^{-4}$$

It is seen from table 3 that the values of both pK_2 and pK_3 decrease as the distance between the phosphorus atoms becomes smaller. This generalization can be explained by the conclusion that the PO_3H^- group, which is a constant substituent in equilibria 2 and 3, is electron-attracting and consequently acid-strengthening. By contrast the value of the pK_4 tends to *increase* as the distance between the phosphorus atoms becomes smaller. The acidity of the last ionizable hydrogen must therefore be weakened by the PO_3^{--} group, which must, accordingly, have an electron-repelling inductive effect.

The dissociation constants of a tetraphosphonic acid, ethylenebis(nitrilodimethylene)tetraphosphonic acid, have recently been reported (245). The eight pK values were found to be 1.46, 2.72, 5.05, 6.18, 6.63, 7.43, 9.22, and 10.95.

The dissociation constants discussed in this section were determined by

TABLE 3

Acid dissociation constants of aliphatic diphosphonic acids

Compound	pK_1	pK_2	pK_3	pK_4	References
$H_2O_3P(CH_2)_4PO_3H_2$	<2	2.75	7.54	8.38	(223)
$H_2O_3P(CH_2)_3PO_3H_2$	<2	2.65	7.34	8.35	(223)
$H_2O_3PCH_2CH(CH_3)PO_3H_2$	<2	2.6	7.00	9.27	(222)
$H_2O_3PCH_2PO_3H_2$	<2	2.57	6.87	10.33	(223)

potentiometric titration. No activity corrections were made, nor were liquid-junction potentials estimated. Hence the experimental results are nonthermodynamic or "apparent" dissociation constants. In some of the papers it is not clear whether the reported pK values have been calculated by means of the appropriate equations (87) or are merely the pH values at the midpoints of the titration curves. This uncertainty does not affect the values given for the second dissociation constants of the PO_3H_2 group, but the values given for the first dissociation constants may be considerably in error if the midpoint pH's were assumed equal to the pK's.

Since the last pK's of many of the aliphatic and alicyclic phosphonic acids are greater than 8, none of the commonly used indicators can be relied upon for determining the neutral equivalents of these acids. Thymolphthalein, which changes from colorless to blue at about pH 9.3, can probably be used for many of the aliphatic phosphonic acids with strongly electron-attracting substituents.

2. Arylphosphonic acids

The first measurements of the acid dissociation constants of arylphosphonic acids were performed by Lesfauries and Rumpf (146, 147, 237), who reported the pK values of several phosphonic acids and concluded that the effects of substituents on the acidity of benzoic acid and of phenylphosphonic acid are very similar. This conclusion suggests that the Hammett equation (91) applies to the acid dissociation constants of arylphosphonic acids and that the reaction constants (ρ) for both series of acids are approximately the same. The correctness of these suggestions was demonstrated by later workers (101), who determined the dissociation constants of twenty-five meta- and para-substituted arylphosphonic acids by potentiometric titration in water and 50 per cent

TABLE 4

Reaction constants (ρ) for the acid dissociation of arylphosphonic acids of the type 2-X-4(or 5)-$RC_6H_3PO_3H_2$

X	Solvent	ρ	s*	n†	$-\log k^0$‡	References
		$-PO_3H_2 \rightleftharpoons H^+ + -PO_3H^-$				
H	H_2O	0.755	0.030	10	1.84	(101)
Cl, Br	H_2O	0.749	0.090	3	1.70	(102)
H	50% C_2H_5OH	0.986	0.059	12	3.13	(101)
Cl, Br	50% C_2H_5OH	0.995	0.031	4	2.94	(102)
		$-PO_3H^- \rightleftharpoons H^+ + -PO_3^=$				
H	H_2O	0.949	0.058	12	6.97	(101)
Cl, Br	H_2O	0.908	0.152	6	6.90	(102)
CH_3O	H_2O	0.881	0.105	3	7.69	(102)
H	50% C_2H_5OH	0.991	0.063	12	8.23	(101)
Cl, Br	50% C_2H_5OH	1.191	0.033	5	8.25	(102)
CH_3O	50% C_2H_5OH	1.108	0.057	3	8.82	(102)

* The standard deviation from the best straight line.

† The number of compounds on which the calculation of ρ is based.

‡ The intercept of the plot of σ vs. $-\log K$.

TABLE 5

Substituent constants of the phosphono anions

Substituent	σ meta	σ para
PO_3H^-	0.25,* 0.24†	0.17,* 0.29†
PO_3^{--}	−0.02‡	−0.16‡

* Calculated from the acid dissociation constants, in water, of the carboxy group of *m*- and *p*-carboxyphenylphosphonic acids.

† Calculated from the acid dissociation constants, in 50% ethanol, of the carboxy group of *m*- and *p*-carboxyphenylphosphonic acids.

‡ Calculated from the acid dissociation constants, in water, of the hydroxy group of *m*- and *p*-hydroxyphenylphosphonic acids

ethanol. Reaction constants (ρ) calculated from these data are included in table 4. Several of the arylphosphonic acids used in this investigation contain substituents which are acid functions. The pK values of these functions were determined and used to calculate the substituent constants (σ) of the PO_3H^- and PO_3^{--} groups. These values, which are listed in table 5, indicate that the PO_3H^- group is electron-attracting and that the PO_3^{--} group is electron-repelling. Similar conclusions were reached by Schwarzenbach and Zurc (223) in their study of the pK's of aliphatic diphosphonic acids.

The pK values of a considerable number of *o*-substituted arylphosphonic acids have also been measured and are listed in table 6. Although the Hammett equation does not apply to ortho substituents, it can be used for the effect of substituents (R) on the reactivity of side chains (Y) in series of compounds of the type 2-X-4(or 5)-RC_6H_3Y, if the ortho substituent (X) is constant throughout the series (97, 98, 216). Some of the compounds listed in table 6 can be grouped into two such series with X = Cl (or Br) and CH_3O. The justification for combining compounds with *o*-chloro and *o*-bromo substituents into a single series depends on the fact that both substituents equally affect the pK of phenylphosphonic acid and that reaction constants are insensitive to the nature of the ortho substituent (X). Reaction constants for the two series are included in table 4. Many of the ortho-substituted acids have pK's which differ significantly from the pK's of the corresponding para isomers. In a few cases these differences can be explained by the assumption that the inductive effect from the ortho position is somewhat larger than from the para position. Most of the "ortho effects", however, are probably due to intramolecular hydrogen bonding and can be elucidated by mechanisms discussed in detail in reference 102.

The dissociation constants reviewed above were determined by potentiometric measurements of cells containing liquid junctions. The ionic strengths of the solutions used were about 0.1, but no attempt was made to keep the ionic strength constant during a determination. The acid dissociation constants of phenylphosphonic acid at a constant ionic strength of 1.0 have been determined by both potentiometric and spectroscopic methods (17, p. 428). A recent paper describes the measurement by a spectroscopic method of the dissociation constants in water of several para-substituted phenylphosphonic acids (189). In

TABLE 6

Acid dissociation constants of the ortho-substituted arylphosphonic acids

2-X-$RC_6H_3PO_3H_2$		$pK_{PO_3H_2}$		$pK_{PO_3H^-}$		References
X	R	In H_2O	In 50% C_2H_5OH	In H_2O	In 50% C_2H_5OH	
Cl	4-O_2N	1.12	2.18	6.14	7.31	(102)
Br	5-O_2N	(a)	(a)	6.14	7.47	(102)
Cl	5-Cl	(a)	2.55	6.63	7.84	(102)
Cl	H	1.63	2.94	6.98	8.21	(102)
Br	H	1.64	2.91	7.00	8.22	(102)
Br	5-CH_3	1.81	3.04	7.15	8.35	(102)
Cl	4-NH_2	—	—	7.33	(a)	(102)
CH_3O	4-O_2N	1.53	2.61	6.96	7.94	(102)
CH_3O	H	2.16	3.62	7.77	8.87	(102)
CH_3O	4-NH_2	—	—	8.22	9.53	(102)
HO[b]	4-O_2N	1.22	1.95	5.39	6.59	(102)
O_2N	H	1.45	—	6.74	—	(80)
F	H	1.64	2.84	6.80	7.99	(102)
I	H	1.74	3.06	7.06	8.40	(102)
NH_2[c]	H	—	—	7.29	8.34	(102)
CH_3	H	2.10	—	7.68	—	(16)
C_6H_5	H	(a)	3.78	8.13	(d)	(102)
HOOC[e]	H	1.71	2.47	9.17[f]	10.03[f]	(102)

[a] The compound was not sufficiently soluble.
[b] $pH_{OH} > 12$ in water; > 13 in 50% ethanol.
[c] $pK_{NH_3^+} = 4.10$ in water.
[d] The sodium salt precipitated during titration.
[e] $pK_{COOH} = 3.78$ in H_2O and 4.89 in 50% ethanol.
[f] The substituent is actually COO^-.

neither this study nor the earlier studies were activity corrections or liquid-junction potentials estimated; hence all the reported pK's are nonthermodynamic values.

The neutral equivalents of practically all arylphosphonic acids which do not have interfering acid functional groups (i.e., groups such as SO_2NH_2 and OH, the pK's of which are near 9) can be determined by titration in aqueous or alcoholic solution with thymolphthalein as an indicator (102). Only three exceptions to this rule have been found: namely, *o*-carboxyphenylphosphonic acid, 2-methoxy-4-aminophenylphosphonic acid, and 2-biphenylylphosphonic acid. The last pK values of these acids in water are greater than 8.1. The weakest arylphosphonic acid which has given a theoretical neutral equivalent with thymolphthalein is *o*-methoxyphenylphosphonic acid, which has a second pK in water of 7.77.

B. SALTS OF PHOSPHONIC ACIDS

Phosphonic acids, being dibasic, form both acid and neutral salts, often occurring with water of crystallization. Many of these salts are insoluble in water and have been used since the earliest days of organic phosphorus chemistry for the isolation and purification of phosphonic acids (93, 171). However, because salts of phosphonic acids vary widely in their solubility it is difficult to generalize as to the best salt to use for the isolation of any particular phosphonic acid.

Ammonium salts and salts of the alkali metals are usually very soluble in water, although the monosodium salt of 2-phosphonoöctanoic acid is only slightly soluble (49, p. 361). They are customarily prepared by evaporation of half-neutralized or neutralized solutions of the acids (166). Freeze-drying methods have recently been used for isolating water-soluble salts of phosphonic acids (30, 71). Dipotassium 9-(9-phenyl)fluorenyl- and (phenyl di-*p*-tolyl)methylphosphonates have been obtained from the corresponding acids by crystallization from aqueous potassium hydroxide (92). Many of the water-soluble alkali metal salts can be recrystallized from alcohol. The dipotassium salt of D-glucopyranose-6-deoxy-6-phosphonic acid precipitates from methanol solution when the corresponding tetraacetyl compound is hydrolyzed with potassium methoxide (90). Several alkali metal salts have been characterized by means of their infrared spectra (30, 71).

The lithium salts of a wide variety of phosphonic acids have been added to lithium base greases (46). The claim is made that the resulting greases have greater mechanical stability and resistance to shear during working or milling. There is also less tendency for separation of oil from the grease during storage. The most satisfactory additives have been the dilithium salts of 2-ethylhexyl-, tetradecyl-, octadecyl-, and phenylphosphonic acids.

Heavy metal salts in particular have been useful for the isolation and purification of soluble phosphonic acids. The salt most frequently used has been the lead salt (137, 156, 221). In several cases phosphonic acids have been isolated only as the lead salts (57). Silver salts (214) have also been used for isolating phosphonic acids; however, disilver trichloromethylphosphonate explodes on slight heating in the dry state (250).

Calcium and barium salts have frequently been used for the isolation of phosphonic acids. Many such salts are more soluble in cold water than in hot (190). The barium and calcium salts of different phosphonic acids vary widely in their solubility in water. Barium trifluoromethylphosphonate is sparingly soluble; the lead, silver, mercurous, and calcium salts of this acid, however, are apparently soluble (30). This varying solubility has been used for the separation of a mixture of two phosphonic acids, one of whose barium salts is soluble while the other is insoluble in water (171, p. 276).

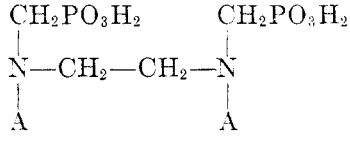
Magnesium salts of phosphonic acids have been more thoroughly investigated than other metallic phosphonates. It has long been known that the magnesium salts of aromatic arsonic acids are precipitated only on heating, whereas the inorganic salt (magnesium ammonium arsenate) precipitates in the cold. This phenomenon has frequently been used for the separation of inorganic from organic arsenic acids. That a similar phenomenon occurs with phosphonic and phosphoric acids was suggested by Bauer (22) when phosphanilic acid was found to give a magnesium salt which precipitated from hot water. The magnesium salt technique has also been used for the separation of phosphate ion from a phosphonic acid (57). The magnesium salts of aromatic phosphonic acids have recently been the subject of a more comprehensive examination (80). It was shown that in a large series of acids only two acids gave insoluble magnesium salts in the cold.

All para-substituted and all but one meta-substituted acid gave copious precipitates when heated with magnesia mixture. *o*-Methyl-, *o*-amino-, *o*-hydroxy-, and *o*-fluorophenylphosphonic acids gave sparse precipitates when heated with magnesia mixture; all other ortho-substituted acids failed to give an insoluble magnesium salt. This difference between ortho-substituted and the meta- and para-substituted phosphonic acids was then used as the basis for the separation of *o*-nitrophenylphosphonic acid from its meta isomer; the ortho isomer was thus prepared in a pure state for the first time. It seems probable that this technique could be used for separating other ortho isomers from mixtures of isomeric phosphonic acids.

It has been suggested that thallous salts might prove useful for the characterization of phosphonic acids (86). Both thallous hydrogen and dithallous phenylphosphonate were prepared and found to melt at 200–201°C. and 317–320°C., respectively. It would seem probable that the melting points of thallous salts of most substituted aromatic phosphonic acids would be too high to be of value for characterizing these acids. It should be noted that thallous formate and ammonia give a precipitate of thallous phosphate with orthophosphoric acid; no precipitate is obtained with phenylphosphonic acid (145).

The use of phenylphosphonic acid as a reagent for the quantitative determination of thorium has been recommended (17). Phenylphosphonic acid precipitates thorium quantitatively from solution at pH values of 0.5 and above. The resulting salt, $Th(C_6H_5PO_3)_2 \cdot 3H_2O$, is stable to 240°C.; above this temperature one mole of water is lost.

Compounds containing phosphonic acid groups have been prepared as chelating agents for metal ions. Closely related to ethylenediaminetetraacetic acid (Versene) is a group of compounds of the type shown in formula I,



I

where A may be a $—CH_2PO_3H_2$ group, a $—CH_2COOH$ group, or a hydrogen atom (33, 34, 245). These compounds are used in the form of their alkali metal salts to chelate with a wide variety of heavy metal ions, forming complexes in which the ionic properties of the metal ion are greatly suppressed.

A similar chelating agent, bis(carboxymethyl)aminomethylphosphonic acid, has been prepared by condensing chloromethylphosphonic acid with iminodiacetic acid (221). Calcium, magnesium, strontium, and barium ions have been found to chelate with this compound.

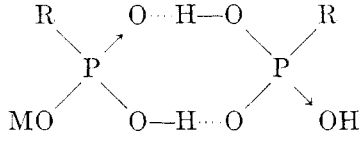
Salts with aromatic amines have been used for the isolation, purification, and characterization of phosphonic acids, but again the type of salt produced varies with the acid used. Bromomethyl- and chloromethylphosphonic acids form the monoanilinum salt (249, 252) even when an excess of aniline is used, whereas trichloromethylphosphonic acid forms both mono- and dianilinium salts (248,

250). The neutral salt, however, loses a mole of aniline on storage or recrystallization to form the acid salt (250). Anilinium hydrogen chloromethylphosphonate, m.p. 199–200°C., has been used for characterizing the acid (120). Bengelsdorf and Barron (29) obtained this salt, as well as other monoamine salts of chloromethylphosphonic acid, by addition of the amine to a benzene solution of the free acid. *p*-Toluidine, however, gave an equimolar mixture of the mono- and di-salts. *o*-Phenylenediamine gave a salt with a molar ratio of amine to acid of 2:1, whereas the corresponding para isomer gave a salt with a ratio of amine to acid of 1:1. These authors suggest that, since salts of phosphonic acids with weakly basic aromatic amines can be readily titrated with standard alkali to give reproducible neutralization equivalents, these salts may well prove to be valuable for characterization of the acids. Since all but one of the amine salts of trichloromethylphosphonic acid melted with decomposition at temperatures above 200°C., the melting points of these salts are not of value for characterization purposes. Trifluoromethylphosphonic acid also gave both mono- and dianilinium salts which decompose without melting when heated; they were characterized by means of their infrared spectra (71).

The precipitation of phosphonic acids as their *p*-toluidine salts has been suggested as a desirable method for the isolation of the acids from complex reaction mixtures (38). The *p*-toluidine salts of a series of aromatic phosphonic acids were obtained, some as the pure neutral salt, others as a mixture of mono- and di-salts. Where the free acid was required, the *p*-toluidine salt was dissolved in sodium hydroxide, the toluidine removed by steam distillation, and the sodium ion removed in an ion-exchange column. The resulting solution was then evaporated to incipient crystallization in order to obtain the free acid. Although this method undoubtedly gives good results with certain phosphonic acids, the present authors have experienced difficulties when the acids were very soluble. Our difficulties have arisen from the fact that phosphoric acid also gives an insoluble *p*-toluidine salt. Since crude reaction mixtures from the synthesis of phosphonic acids often contain phosphoric acid, the isolation of soluble phosphonic acids is not readily accomplished by this method.

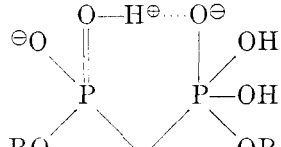
In addition to the expected mono- and di-salts, phosphonic acids also form a series of hemi-salts of the general formula $RPO_3HM \cdot RPO_3H_2$, where M is usually sodium or potassium. Although these hemi-salts were first observed by Michaelis (172, p. 226), they were not used extensively until recent years. It has been discovered that the hemi-sodium or hemi-potassium salts of aromatic phosphonic acids are usually less soluble in water than the free acids and hence precipitate from solution when an alkaline solution of the acid is acidified to Congo red (67, 144). This fact has been used extensively as a means of isolating the acids from complex reaction mixtures and is probably the best means of obtaining the acids under many circumstances. The fact that a hemi-alkali salt may be obtained when an alkaline solution of the acid is acidified has been overlooked by various authors; it is quite probable that many compounds described as hydrated free acids or as acid salts are in reality the hemi-alkali salts (15, 155). A determination of the neutral equivalent would distinguish between these possibilities.

The structure of the hemi-salts has not been established with certainty. Kosolapoff (129) has performed experiments designed to elucidate the structure of these and other salts of phosphonic acids; the results are discussed in the section on molecular weights. Although the exact formulation of the steps involved in the progressive neutralization of phosphonic acids is a matter of opinion, the structure (II) proposed for the hemi-salts may well be correct.



II

Friedman and Seligman (85) have suggested structure III and various resonance hybrids of this structure for the "half-salts" of naphthyl acid phosphates. These "half-salts" of naphthyl acid phosphates are undoubtedly analogous to the hemi-



III

salts of the phosphonic acids. In all of the structures proposed by Friedman and Seligman one phosphorus atom is bonded to five oxygen atoms. Similar structures for other phosphorus compounds have been justifiably criticized by other workers (184, 185); the present evidence does not seem to warrant analogous structures for the hemi-salts of phosphonic acids.

C. PROBLEMS OF ORIENTATION IN ARYLPHOSPHONIC ACIDS

1. Nitration

Phenylphosphonic acid was first nitrated in 1875 with fuming nitric acid in a sealed tube (169). The nitrophenylphosphonic acid, which was isolated by a tedious procedure involving the barium salt, was believed to be a single isomer (170, 171). However, no information about the position of the nitro group was obtained. The melting point was first (169) reported to be 140°C., but in other papers (170, 171) it was given as 132°C. In 1922 the nitration of phenylphosphonic acid was reinvestigated by Nijk (179, p. 464), who showed that *m*-nitrophenylphosphonic acid is formed; the presence of either ortho or para isomers was not detected. Hence, it seemed that the sample of nitrophenylphosphonic acid which melted at 140°C. was the pure meta isomer. This conclusion was accepted without question for a long time, and the nitrophenylphosphonic acid obtained by Nijk's procedure has been used whenever the *m*-nitro compound was desired (124). In 1949, however, evidence was presented (125) that the material melting at 140°C. was not a single compound but contained, in addition

to *m*-nitrophenylphosphonic acid, a considerable proportion of either the ortho or the para isomer. This possibility was strengthened by the later observation that pure *m*-nitrophenylphosphonic acid (prepared from *m*-nitrobenzenediazoniumfluoborate) has a melting point of 155–156°C. (67). Finally, both *o*-nitro- and *m*-nitrophenylphosphonic acids were isolated from the mixture of isomers obtained by nitrating phenylphosphonic acid (80). It is now obvious that phenylphosphonic acid does *not* undergo nitration exclusively in the meta position, although the meta isomer predominates.

The literature also contains descriptions of nitro compounds prepared by the nitration of *p*-chlorophenylphosphonic acid (37; 168, p. 230; 179, p. 471), *p*-bromophenylphosphonic acid (24; 168, p. 243), *p*-tolylphosphonic acid (168, pp. 270, 273), *o*-tolylphosphonic acid (168, p. 298), *p*-methoxyphenylphosphonic acid (24; 168, p. 254), 2,4-dimethylphenylphosphonic acid (243, p. 1722), 2,5-dimethylphenylphosphonic acid (244), and 3-chloro-4-methylphenylphosphonic acid (164). In these cases it has been assumed that the nitro group enters meta to the phosphono group. This assumption is, of course, very reasonable but no unequivocal proof of the structure or purity of any of these nitrated products has been reported. Nitration products of 3,5-dimethylphenylphosphonic acid (243, p. 1723) and *m*-ethoxycarbonylaminophenylphosphonic acid (179, p. 479) have also been described; in these cases the nitro group probably entered either the 2- or the 4-position.

2. The Friedel–Crafts reaction

The Friedel–Crafts reaction has been long used for the preparation of phosphonic acid derivatives of aromatic compounds. A serious disadvantage of this method is that mixtures of arylphosphonic acids are sometimes obtained, which are in general very difficult to separate. Furthermore, it is necessary to establish the position occupied by the phosphono group relative to other substituents in the benzene ring. Some of the structural problems that have arisen concerning arylphosphonic acids prepared by the Friedel–Crafts reaction are discussed below.

The Friedel–Crafts reaction between phosphorus trichloride and toluene was first described in 1879 by Michaelis (167), who isolated *p*-tolylphosphonic acid and determined its structure. It was later suggested that the ortho isomer may also be formed in this reaction (172, p. 210). Recently, Kosolapoff (130) has isolated *o*-tolyl-, *m*-tolyl-, and *p*-tolylphosphonic acids in the ratio 10:27:63 from a mixture of isomeric acids obtained through the Friedel–Crafts reaction. It is possible that other alkylbenzenes behave analogously to toluene. Thus, from 0.5 mole of ethylbenzene were obtained 35 g. of *p*-ethylphenylphosphonic acid (m.p. 174.5–175.0°C.) and 4 g. of another phosphonic acid, m.p. 116–117°C. Kosolapoff suggested that the latter acid might be the meta isomer. However, it is now known that the meta isomer melts at 128–129.5°C. and that the ortho isomer melts at 145.5–147°C. (79). It seems probable, therefore, that the low-melting material reported by Kosolapoff was a mixture of isomeric ethylphenylphosphonic acids.

In 1929 Lindner and Strecker (150) subjected naphthalene to the Friedel–Crafts reaction and obtained a naphthylphosphonic acid which melted at 188–189°C. and gave no significant melting-point depression with authentic 2-naphthylphosphonic acid (m.p. 193–194°C.). On the basis of other evidence, however, Lindner and Strecker were led to believe that the phosphonic acid obtained in the Friedel–Crafts reaction was the 1-isomer. This conclusion was generally accepted until 1953, when it was definitely established that the reaction between naphthalene and phosphorus trichloride yields the pure 2-isomer (242, p. 1318).

From a Friedel–Crafts reaction between bromobenzene and phosphorus trichloride Michaelis (168, p. 244) isolated *p*-bromophenylphosphonic acid and an acidic material (m.p. 265°C.) which was presumed to be an isomeric bromophenylphosphonic acid. This inference cannot be correct, for the melting points of *o*-bromophenyl-, *m*-bromophenyl-, and *p*-bromophenylphosphonic acid are all below 265°C. Since the unknown compound was precipitated from ammoniacal solution by the addition of hydrochloric acid, it seems possible that this unidentified material was the hemi-ammonium salt of a bromophenylphosphonic acid.

D. THE DYE AND INDICATOR PROPERTIES OF PHOSPHONIC ACIDS

Relatively few dyes have been prepared which contain phosphonic acid groups. This may be due to the paucity in the past of good methods for preparing such compounds. With the better synthetic methods which have been developed in recent years the number of dyes containing phosphonic acid groups will probably increase.

In 1952 Klotz, Burkhard, and Urquard (121), while studying the reaction of bovine and human serum albumins with methyl orange, prepared dyes in which the SO_3^- group of methyl orange was replaced by the COO^-, PO_3H^-, or AsO_3H^- group. Sodium 3- and 4-(4-dimethylaminophenylazo)phenylphosphonates were prepared by coupling diazotized 3-aminophenylphosphonic or phosphanilic acids with *N*,*N*-dimethyl-*p*-phenylenediamine. The structure of the resulting azo compounds was not determined, and the authors state "analyses for carbon and hydrogen were considerably below theoretical, but it is probable that the impurity was merely sodium chloride."

Dickey (66) has patented a large number of dyes prepared by condensing 4-chloro-3-nitrophenylphosphonic acid with aniline or a substituted aniline to yield a 4-anilino-3-nitrophenylphosphonic acid. By using an ester or an amide rather than the phosphonic acid the corresponding phosphonic amides or esters were obtained. The resulting yellow dyes were of particular value in dyeing cellulose acetate textiles, but also dyed silk, wool, nylon, and other materials.

The dye and indicator properties of a limited series of phosphonic and arsonic acids containing azo groups have been recently reported (136). The compounds prepared were the phosphonic and arsonic acid analogs of methyl orange, ethyl orange, and Congo red. The various fabrics dyed with these dyes were subsequently laundered with commercial detergents; excellent fastness without running or fading was reported for each dye deposited on the particular fabric (cotton, silk, or wool) for which the dye showed an affinity. All of the arsonic

acids and all but one of the phosphonic acids were indicators with two distinct color changes, as would be expected from the structure of these compounds. The phosphonic analog of ethyl orange, however, showed only a single color change from red to orange-red between pH 3.5 and 5.8.

E. REDUCTION OF PHOSPHONIC ACIDS

The difficulty in reducing phosphoric acid and its derivatives is well known; theoretical reasons for this have been discussed by Latimer (143). It is accordingly not surprising that the direct reduction of phosphonic acids has not been accomplished, although some evidence exists that benzylphosphonic acid may have been reduced to the corresponding phosphine with a large excess of phosphorous acid; the benzylphosphine itself was not characterized other than by its typical odor (149). Phosphorous acid in excess, as well as hypophosphorous acid, might possibly serve to reduce phosphonic acids to phosphines; this point should be investigated. An attempt to reduce phosphonic acids with a wide variety of other reducing agents proved unsuccessful (77). It was found, however, that phenylphosphonic dichloride, readily obtained by the reaction between phenylphosphonic acid and phosphorus pentachloride, could be easily reduced to phenylphosphine by the use of either lithium aluminum hydride or lithium borohydride. At about the same time, Karrer and Jucker (116) observed that when organic esters of phosphoric acid are treated with lithium aluminum hydride, the corresponding alcohol and a mixture of phosphoric acid and phosphine are obtained. In recent papers the reduction of phenyldichlorophosphine (94, 240) and phenylphosphinic acid (241) with lithium aluminum hydride to phenylphosphine has been reported. However, it has been stated that arylphosphonic acids cannot be reduced to the corresponding phosphines with lithium aluminum hydride (241).

By contrast with phenyldichlorophosphine, bis(trifluoromethyl)iodophosphine was not reduced by lithium aluminum hydride but was readily reduced by hydrogen in the presence of Raney nickel (31, p. 3898).

The difficulty in reducing phosphonic acids allows the use of a wide variety of reducing agents for effecting the reduction of other groups in the molecule. Such reductions can be brought about either chemically or catalytically. It has recently been found possible to reduce arylphosphonic acids to the corresponding cyclohexylphosphonic acids by the use of hydrogen and a rhodium-on-alumina catalyst at low pressure (82). Although there is no reduction of the phosphono group, halogen substituents are cleaved from the ring.

F. PHOSPHONIC ACID CATION-EXCHANGE RESINS

The discovery of synthetic ion-exchange resins is one of the most important chemical discoveries of the past twenty years. Resins which contain sulfonic acid, carboxylic acid, or phenol groups are generally employed for the removal of cations from solution. It is not surprising that, with the increasing interest in phosphorus chemistry in recent years, phosphonic acid resins have been synthesized and tested. The first announcement of this type of resin was early in 1952

(41). Both phosphonic and phosphinic type resins were described in a preliminary communication. These resins were found to show a selectivity for sodium over potassium. Although the details of preparation of these materials have not been announced and a personal communication from the National Aluminate Corporation has indicated that they are no longer available, a later paper by Bregman reveals some of the properties of these interesting ion-exchange resins (40). As would be expected, titration of the phosphonic acid resin gives two breaks in the titration curve corresponding to the expected breaks for the phosphonic acid group. At low pH values the resin preferentially removes potassium rather than sodium, while at pH values above 6 sodium is removed preferentially over potassium. Carboxylic, phosphonic, and sulfonic acid type resins were compared; the reaction rate of these resins with cations is in the order $SO_3H > PO_3H_2 > COOH$.

A phosphonic acid type resin has been tested for its ability to remove sodium from the animal body (230). In contrast to the carboxylic and sulfonic acid type resins, the phosphonic acid resins had only a minimal effect in removing either potassium or sodium ions when administered to the extent of 10 per cent of the diet of rats. The resin used in this experiment was stated to be a "phosphonic type" of the structure $ROPO_3H_2$. If this formula is correct, the resin contains not phosphono but rather phosphoric ester groups.

The preparation of ion-exchange resins containing phosphonic acid groups is described in considerable detail in a recent paper (239). The resins were prepared by condensing various phenoxymethylphosphonic acids with formaldehyde. In alkaline solution a monomer of the type $HOCH_2C_6H_4OCH_2PO_3Na_2$ is first formed. When this salt is acidified in an excess of formaldehyde and heated at 140°C., an insoluble thermosetting resin, having ion-exchange properties, is formed. The same type of resin is obtained by heating a phenoxymethylphosphonic acid with an excess of formaldehyde. The resins are highly cross-linked in those cases where there are no substituents ortho or para to the phosphono group.

Several polystyrene phosphonic acids have been prepared as cation-exchange resins (2). The syntheses were accomplished by the reaction between either styrene or polystyrene, phosphorus trichloride, and aluminum chloride. The maximum cation-exchange capacity of the resulting resins was 250 millimoles of sodium per gram of resin, or 23 per cent of the theoretical capacity.

Another phosphonic acid cation-exchange resin is Duolite C-60, manufactured by the Chemical Process Company, Redwood, California; however, the only information obtainable on this resin is the statement that it is a phosphonic acid type resin (232).

G. CLEAVAGE OF THE CARBON–PHOSPHORUS BOND

Unsubstituted aromatic and aliphatic phosphonic acids are thermally stable compounds. This is in accord with the bond energy of the carbon–phosphorus bond which has been calculated as 62 kcal., compared with 57 kcal. for the carbon–arsenic bond, 68 kcal. for the carbon–silicon bond, and 64 kcal. for the

carbon–carbon bond (95). Heating for long periods at relatively high temperatures does result in splitting of the carbon–phosphorus bond; 2-naphthylphosphonic acid, when heated in a sealed tube at 275°C. for 24 hr., gave naphthalene and metaphosphoric acid (144, 145). The carbon–phosphorus bond of phosphonic acids is resistant to chemical attack. Phenylphosphonic acid has been nitrated with nitric acid at 100°C. (171, p. 276), while it is common practice to recrystallize certain phosphonic acids from hot 6 *N* hydrochloric acid in order to ensure conversion of the sodium or potassium salts to the free acids (67). Octadecylphosphonic acid has been boiled for 8 hr. in sodium hydroxide solution or for 12 hr. in alcoholic potassium hydroxide and the free acid recovered in almost theoretical yield (50, p. 366).

Although the majority of substituted phosphonic acids are also quite stable, there are certain exceptions in both the aromatic and the aliphatic series. With aromatic phosphonic acids the presence of strongly electron-repelling groups in the ortho and para position to the phosphono group apparently weakens the carbon–phosphorus bond; such phosphonic acids are readily hydrolyzed to phosphoric acid and the substituted hydrocarbon under a variety of experimental conditions. *p*-Methoxyphenylphosphonic acid has been cleaved to anisole and phosphoric acid by 66 per cent hydrobromic acid in glacial acetic acid (146, 237) and by heating with 57 per cent hydriodic acid (24). *p*-Hydroxyphenylphosphonic acid, however, can be obtained in low yield, admixed with starting material, when *p*-methoxyphenylphosphonic acid is heated with 47 per cent hydrobromic acid (24). Similarly the carbon–phosphorus bond in 2-methoxy-4-nitrophenylphosphonic acid was cleaved when this acid was refluxed in 48 per cent hydrobromic acid, whereas the ether linkage only was cleaved in 40 per cent hydrobromic acid (70). 2-Methoxy-4-nitrophenylphosphonic acid was readily reduced to the corresponding amino compound by Raney nickel and hydrogen in alkaline solution, but 2-hydroxy-4-nitrophenylphosphonic acid was converted to *m*-aminophenol and phosphoric acid under the same conditions; the latter phosphonic acid was successfully reduced with platinum and hydrogen in dilute hydrochloric acid solution (70). The hydrolysis of *p*-methoxyphenylphosphonic acid to anisole and phosphoric acid in sulfuric acid solution has been studied kinetically (238). The reaction was found to be first order in phosphonic acid but was more complex in H^+. Thus, in sulfuric acid of concentrations from 9 to 30 per cent, the reaction rate increased as the square of the acid concentration, but above 30 per cent the rate of increase became slower and was even more markedly slowed as the concentration approached 60 per cent.

The instability of *p*-dimethylaminophenylphosphonic acid in aqueous solution was noted by Schenk and Michaelis many years ago (220). These same authors also noted that the corresponding phosphinic acid, $p\text{-}(CH_3)_2NC_6H_4PO_2H_2 \cdot 2H_2O$, was hydrolyzed to phosphorous acid and dimethylaniline by warming in aqueous solution. The hydrolysis was faster in acid solution, but the compound was stable in alcoholic or in alkaline solution. In contrast to these findings, the cleavage of the carbon–phosphorus bond in a number of alkylaminophenylphosphonic acids in alkaline solution has been described (69). The phenomenon

was noted in an attempt to prepare *o*- and *p*-alkylaminophenylphosphonic acids by the reaction between the corresponding bromo acids and various alkylamines in aqueous solution in the presence of cuprous oxide. *p*-Methylaminophenylphosphonic acid and a few others were successfully prepared. In the majority of cases, however, no alkylaminophenylphosphonic acid could be isolated, although bromide-ion analyses indicated that all the bromine had been split from the ring. Analysis of reaction mixtures indicated that usually from 10 to 25 per cent of the phosphorus was present as phosphoric acid; failure to isolate the desired phosphonic acid was attributed to the solubility of these compounds in aqueous phosphoric acid. No difficulty was experienced in preparing *m*-alkylamino compounds, and analyses of the reaction mixtures indicated that essentially no phosphoric acid was present.

Aminophenylphosphonic acids are apparently more stable than the alkylamino compounds discussed above. However, the carbon–phosphorus bond in these compounds can be broken under some circumstances. *o*-Aminophenylphosphonic acid (and presumably also the para isomer) gives a quantitative yield of tribromoaniline when treated with bromine water (68, 125), whereas the meta compound is brominated without rupture of the carbon–phosphorus bond (179, p. 468). Bell and Kosolapoff (24) have stated that *p*-aminophenylphosphonic acid shows a "low order of stability of the carbon-to-phosphorus link," but no experimental evidence is given. *p*-Aminophenylphosphinic acid is unstable and is cleaved to aniline and phosphorous acid by prolonged boiling in acid solution (146). *p*-Hydroxyphenylphosphonic acid also is unstable in aqueous acid solution; it gives tribromophenol when treated with bromine water (24).

In contrast to the situation in arylphosphonic acids, in which the carbon–phosphorus bond is weakened by electron-releasing substituents, the carbon–phosphorus bond in alkylphosphonic acids appears to be weakened by certain electron-attracting groups in close proximity to the phosphono group. In particular, compounds in which a carbonyl group is attached directly to the phosphono group are rather unstable (50). Thus, dialkyl acylphosphonates cannot be hydrolyzed to the corresponding acids without cleavage of the carbon–phosphorus bond; acetyl- and benzoylphosphonic acids have, however, been prepared from the esters by the use of anhydrous hydrogen bromide (58). When the carbonyl group is in the α-position, the carbon–phosphorus bond is probably more stable but may be cleaved by acid hydrolysis (50). The possibility of rupture of the carbon–phosphorus bond in α-carbonylphosphonic esters has been used to help in establishing the structure of several compounds. Diethyl phosphonate adds to α,β-unsaturated ketones to give saturated oxophosphonic diesters. Hydrolysis of these esters gives the free phosphonic acids and not phosphoric acid. From these results it has been concluded that the diethylphosphono group added β to the carbonyl group (203, 204).

In addition to the carbonyl group a few other groups have been found to affect the stability of the carbon–phosphorus bond in aliphatic phosphonic acids. Diethyl α-methyl-β-styrylphosphonate is cleaved to α-methylstyrene and

phosphoric acid when heated with hydrochloric acid (8). It was originally claimed that when dialkyl trichloromethylphosphonates were hydrolyzed with 15 per cent hydrochloric acid the carbon–phosphorus bond was cleaved to give the alkyl chloride, carbon dioxide, and phosphorous acid (114). More recent work on this subject, however, has disproved this claim, and it has now been shown that trichloromethylphosphonic acid can be readily obtained by the hydrolysis of its esters by hydrochloric acid (29, 63, 248, 250, 252). In contrast to the stability of trichloromethylphosphonic acid to acid hydrolysis, the carbon–phosphorus bond in esters of this compound is readily cleaved when warmed in alkaline solution (27, 248, 251).

It is of interest to note that trifluoromethylphosphonic acid is an extremely stable compound, whereas other phosphorus compounds containing the trifluoromethyl group, e.g., CF_3PH_2, $(CF_3)_2PH$, $(CF_3)_2POH$, are decomposed in alkaline solution with rupture of the carbon–phosphorus bond (31).

An interesting difference exists between α-hydroxyphosphonic acids and their esters. The acids have long been known and are extremely stable substances. After being boiled in concentrated alkali solutions 1-hydroxyisopentylphosphonic acid was recovered unchanged, and even repeated evaporations with nitric acid or aqua regia failed to completely break the carbon–phosphorus bond (74). The carbon–phosphorus bond in the esters is also quite stable towards acids, and the corresponding phosphonic acids can be readily obtained from the esters by acid hydrolysis. By contrast with the acids, however, the esters are rapidly cleaved by alkali to give the aldehyde and the dialkyl phosphonate (1, 56, 176):

$$RCHOHPO(OR')_2 \rightleftharpoons RCHO + HPO(OR')_2$$

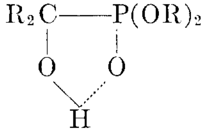
Some of the esters are similarly cleaved merely by warming (1). It should be noted that this reaction, unlike those previously described, is not a hydrolysis. Thus, a dialkyl phosphonate and a carbonyl compound are formed rather than a dialkyl phosphate and an alcohol.

The reason for the difference in stability between the α-hydroxyphosphonic acids and their esters has been the subject of considerable discussion (176). A mechanism for the alkaline-catalyzed cleavage of the esters has been proposed (1). This involves the following steps: (*a*) addition of a sodium ion to the oxygen of the PO group, (*b*) an electron flow from the carbon–phosphorus linkage facilitated by an electron shift from the hydroxyl group, and (*c*) rupture of the carbon–phosphorus bond. This mechanism seems highly improbable.

In order to account for the thermal dissociation of these esters, these same authors suggest an equilibrium between the dialkyl α-hydroxyphosphonate and the aldehyde (or ketone) plus dialkyl phosphonate:

$$R_2COHPO(OR)_2 \rightleftharpoons R_2CO + HPO(OR)_2$$

They further suggest that an intramolecular hydrogen bond exists in the ester (IV), which facilitates transfer of the hydrogen from the carbonyl group to the oxygen of the P—O group.



IV

The hydrolytic cleavage of the α-hydroxyphosphonic esters in alkaline solution takes an entirely different course in the case of dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate. With this compound, hydrogen chloride is eliminated, the phosphorus–carbon bond is ruptured, and the compound rearranges to a phosphate ester (19, 151, 157).

$$CCl_3CHOHPO(OR)_2 \xrightarrow{OH^-} Cl_2C{=}CHOPO(OR)_2 + HCl$$

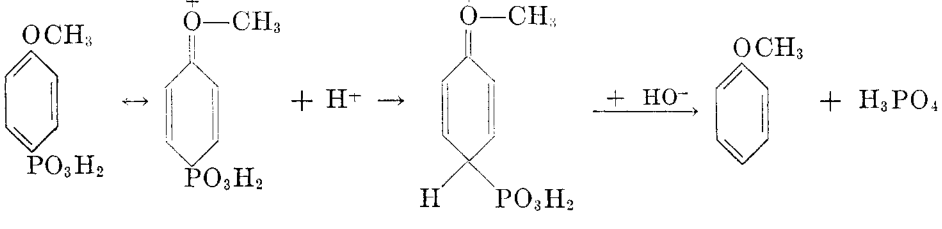
Bengelsdorf (28) has advanced evidence to show that this type of reaction is quite general for certain types of α-hydroxyphosphonic diesters. The first step in the reaction is probably the removal of a proton from the α-hydroxy group:

$$(RO)_2(O)P\underset{\displaystyle OH}{\underset{|}{C}}HCX_3 \quad + \quad B \quad \rightarrow \quad BH^+ \quad + \quad (RO)_2(O)P\underset{\displaystyle O^-}{\underset{|}{C}}HCX_3$$

If X is a group which is capable of leaving as an anion, then rearrangement to a vinyl phosphate will occur as the next step. Alternatively, where the ionization of X is energetically unfavorable, the ester will be cleaved to the dialkyl phosphonate and the aldehyde.

Although these suggestions by Abramov and by Bengelsdorf may be correct, they do not offer any explanation for the thermal instability of these esters, nor any reason why the acids are so much more stable than the esters in alkaline solution. The diethylphosphono group has been shown, at least in reactions of aromatic compounds, to be strongly electron-attracting, with Hammett σ-constants of 0.55 and 0.66 for the meta and para positions, respectively (83). By contrast, the PO_3^{--} group is electron-repelling in both aliphatic (223) and aromatic (101) compounds, with σ-constants of −0.02 and −0.16 in the meta and para positions. This marked difference in the electrical effects of the two groups may well be a contributing factor to the difference in stability between the two classes of compounds.

There has been very little theoretical investigation as to the reasons for the instability of the carbon–phosphorus bond in some substituted aryl and alkyl phosphonic acids. Lesfauries (146) has proposed the following mechanism for the hydrolytic cleavage of aromatic phosphonic acids substituted with electron-repelling groups:



The cleavage of the phosphorus as a positively charged phosphonyl group, $PO_3H_2^+$, is facilitated by electron-repelling groups. Presumably then the $PO_3H_2^+$ group would react with the solvent to give phosphoric acid and a proton. The proposed mechanism also is believed to account for the decreased stability of the arylphosphinic acids as compared with the phosphonic acids, since the phosphorus is more positive in the former compounds. In amino-substituted phosphonic acids, however, the substituent is present largely as a positively charged ammonio group. The instability of aminophosphonic acids in acid solution must then be due to the small proportion of the compound which contains an uncharged amino group.

Any mechanism for the instability of the carbon–phosphorus bond in some phosphonic acids must account for the fact that electron-repelling substituents apparently weaken the bond in aromatic compounds, while electron-attracting substituents weaken the bond in aliphatic compounds. Obviously the question of the stability of the carbon–phosphorus bond in substituted phosphonic acids requires further investigation.

IV. Physical Properties and Structure of Phosphonic Acids

A. ABSORPTION SPECTRA

The ultraviolet absorption spectra of a considerable number of arylphosphonic acids have been determined in 95 per cent ethanol (76, 80, 99, 100). The spectra of some of these compounds have been measured in water also (189). In general the phosphono group causes no profound change in the characteristics of the spectrum of the parent compound. The absorption maxima of most arylphosphonic acids show bathochromic shifts of about 10 mμ, and the intensity of absorption is increased by a factor between 1.5 and 5. Any fine structure found in the spectrum of the parent compound is usually unaltered by the presence of the phosphono group. It seems likely that the slight bathochromic shift and the moderate hyperchromic effect should be ascribed to *weak* resonance interaction between this group and the benzene ring.

Two cases have been recorded in which the phosphono group *does* have a marked effect on the spectrum of the parent compound. The ultraviolet absorption of *o*-nitrophenylphosphonic acid is much less intense than that of nitrobenzene. This effect has been attributed to steric interference with the resonance between the nitro group and the benzene ring (80). Similarly, a PO_3H_2 group in the ortho position of biphenyl greatly reduces the intensity of the biphenyl absorption (76). Presumably, therefore, the *o*-phosphono group interferes with the attainment of a planar arrangement of the two phenyl rings, and thus hinders resonance interaction between them.

The ultraviolet absorption spectra of the species $C_6H_5PO_3H_2$, $C_6H_5PO_3H^-$, and $C_6H_5PO_3^{--}$ in perchlorate solutions of ionic strength 1.0 have also been determined (17, p. 429).

No systematic study of the infrared spectra of phosphonic acids has been published. The scanty information available on this subject has been recently reviewed (25).

B. MOLECULAR WEIGHTS

It is well known that organic compounds which contain groups such as —OH, —NH_2, —COOH, =NOH, and =NH are generally polymeric in nonpolar solvents and that the apparent molecular weight increases as the concentration increases. This phenomenon has been explained by intermolecular hydrogen bonding (142). It is therefore not surprising to find that phosphonic acids are associated in nonpolar solvents. Both *n*-butyl- and *n*-hexylphosphonic acids have been found to be associated in naphthalene solution and their molecular weights increase with increasing concentration (134). Similarly, *o*- and *m*-tolylphosphonic acids were associated in naphthalene solution, and *o*- and *p*-tolylphosphonic acids were associated both in acetone and in camphor (16).

In accordance with the well-known properties of compounds associated by hydrogen bonding, both aliphatic and aromatic phosphonic acids have been found to be monomolecular in acetic acid (81). In water the molecular-weight determinations were complicated by ionization of the strong phosphonic acid group, but in all cases the apparent molecular weight was less than the formula weight (16).

In two other papers two phosphonic acids, tetralinphosphonic acid (2) and trimethylsilylmethylphosphonic acid (118), have been reported as monomolecular, but in neither case was the solvent given. (A personal communication from Dr. W. H. Keeber indicates that the molecular weight of the latter compound was determined only by potentiometric titration and is thus a neutral equivalent rather than a true molecular weight.)

Kosolapoff has proposed that phosphonic acids are associated in long chains through intermolecular hydrogen bonding and that this association persists in aqueous solution (129), so that the neutralization of a phosphonic acid solution by aqueous alkali consists of a neutralization of the free chain ends with preservation, in whole or in part, of the essential structure of the chain, until one formula weight is one-quarter neutralized, whereupon the dimeric hemi-alkali salt is formed. Kosolapoff neutralized a solution of *n*-butylphosphonic acid with small increments of alkali and evaporated the solutions to dryness after each step. The wax-like solids which were obtained up to one-quarter neutralization melted below the melting point of the free acid. Kosolapoff has interpreted these results as being consistent with the foregoing association concept.

As suggested previously in this review, the hydrogen-bonded dimeric form for the hemi-alkali salts may well be correct. However, the energy of the hydrogen bond is so weak—on the order of 5 kcal.—that compounds associated by hydrogen bonds are rapidly dissociated when dissolved in polar solvents such as water, acetic acid, or formic acid. It is true that benzoic acid is partially dimeric in aqueous solution (117) and it has been proposed that in certain favorable cases intramolecular hydrogen bonds are maintained with some acids in aqueous solutions (159). However, in these cases steric considerations greatly favor the hydrogen bonding, and even with benzoic acid the polymerization does not exceed the dimeric form. The molecular weights of phosphonic acids in acetic acid show these compounds to be monomeric in that solvent. The low melting

points and wax-like character of partially neutralized *n*-butylphosphonic acid seem insufficient evidence for assigning a polymeric structure to phosphonic acids in aqueous solution, especially since many phosphonic acids can be readily crystallized from aqueous solution. More experimental data are needed to settle this question.

C. THE CHARACTER OF THE PHOSPHORUS–OXYGEN BOND

The nature of the phosphorus–oxygen bond in the phosphoryl (≡PO) group has long been a subject of controversy. Before the Lewis theory of electronic structure, compounds such as phosphonic acids were believed to contain pentavalent phosphorus and the oxygen of the phosphoryl group was thought to be linked to the phosphorus by a double bond. The octet theory of Lewis required that the phosphorus–oxygen bond be semipolar, and this view has been widely accepted. However, there is considerable evidence that the phosphorus atom can expand its valence shell to ten electrons and be involved in multiple-bond formation. For example, it has been shown that the wavelength of the phosphoryl stretching vibration in a variety of organic phosphorus compounds varies (from 7.0 to 8.5 μ) with the electron-repelling power of the groups linked to the phosphorus atom (23). Such a change in wavelength implies a change in the force constant of the bond and a corresponding change in the bond order. In compounds containing strongly electron-repelling substituents, the phosphoryl bond probably approaches the nature of a pure single bond. On the other hand, when the substituents are strongly electron-attracting, the phosphoryl group may take on appreciable multiple-bond character. Cyclohexylphosphonic acid is the only phosphonic acid for which infrared data have been published (26). The wavelength of the phosphoryl absorption in this compound is 8.2 μ, which is near the highest values observed for the ≡PO bond. Accordingly, the infrared evidence suggests that the phosphoryl bond of the phosphono group is primarily a single covalent bond.

Chemical studies have also provided evidence that the phosphorus atom can expand its valence shell. As has been mentioned in the section on nitration, the principal by-product of the nitration of phenylphosphonic acid is *o*-nitrophenylphosphonic acid. This fact indicates that the phosphono group is conjugated with the ring, since purely inductive meta-directing substituents favor the formation of the para isomer as a by-product, while the ortho isomer is favored only when resonance is possible between the meta-directing substituent and the ring (96). Therefore, the phosphorus atom in the phosphono group must have π-orbitals which can interact with the π-electrons of the benzene ring.

It has been reported that tetraethyl methylenediphosphonate reacts readily with potassium and that the resulting potassium derivative can be alkylated with *n*-butyl bromide (131). The enhanced reactivity of the hydrogen in the methylene group of the diphosphonate has been cited as evidence for a "keto-enol" type of tautomerism in the compound:

$$(C_2H_5O)_2(O)PCH_2P(O)(OC_2H_5)_2 \rightleftharpoons (C_2H_5O)_2(O)PCH{=}P(OH)(OC_2H_5)_2$$

Obviously, such an equilibrium can exist only if the phosphorus atom can expand its valence shell to at least ten electrons.

Studies of compounds that do not contain the phosphoryl group have also produced evidence that the phosphorus can expand its valence shell. Thus, the preparation of pentaphenylphosphorus shows that stable, truly pentavalent organophosphorus compounds can exist (215, 247). Evidence for phosphorus-to-phosphorus double bonds is provided by the fact that phosphorobenzene ($C_6H_5P{=}PC_6H_5$) is unassociated in camphor solution (240).[1]

V. Biological Properties of Phosphonic Acids

In contrast to the organic arsenicals, no systematic investigation into the possible therapeutic properties of organic phosphorus compounds has ever been undertaken. Earlier workers tested phosphanilic (*p*-aminophenylphosphonic) acid and a number of related compounds against a few microörganisms, usually *in vitro*. Several were found to show antibacterial activity (21, 115, 122, 138, 228). A preliminary investigation also revealed that phosphanilic acid is very nontoxic to laboratory animals (186). A more thorough investigation of a larger series of aromatic phosphonic and phosphinic acids against fifteen different microörganisms *in vitro* has revealed that many of these compounds possess antibacterial activity (233). Phosphanilic acid was the most active compound tested; it was superior to sulfanilamide against many organisms, although inferior to sulfathiazole. None of the compounds tested possessed any fungicidal activity. One phosphinic acid possessed some activity against *Treponema pallidum*, the causative agent of syphilis. In testing a large series of compounds against *Borrelia novyi*, the causative agent of relapsing fever, *p*-aminobenzylphosphonic acid was found to be without activity (234).

A number of aminoalkylphosphonic acids have been found to be toxic in high concentration to silk worms and chick embryos (219). These same compounds also repressed tobacco mosaic virus and tobacco rootlets. The compounds did not act as competitors of amino acids. Kidney, liver, and plant tissue did not split the carbon–phosphorus bond in the phosphonic acids tested.

In an investigation into the effect of various substances on the uptake of methionine by *Escherichia coli*, it was found that aminomethylphosphonic acid was a weak inhibitor of methionine uptake, although aminomethanesulfonic and α-aminoethanesulfonic acids stimulated the methionine uptake (165).

Phosphonic acids are active as inhibitors of certain enzymes. Thus, in testing a fairly large series of aromatic phosphonic and phosphinic acids and their esters against cholinesterase, it was found that many of these compounds possessed anticholinesterase activity (84, 231). The most active phosphonic acid was the *o*-iodo derivative. None of the organic phosphorus compounds tested approached

[1] Note added in proof: A recent note by W. Kuchen and H. Buchwald (Angew. Chem. **68,** 791 (1956)) suggests that phosphorobenzene may be decomposed in molten camphor and hence may not be monomolecular in that solvent. H. Mahler and A. B. Burg (J. Am. Chem. Soc. **79,** 251 (1957)) have recently proposed that phosphorobenzene actually has a ring structure.

TABLE 7

Aliphatic and alicyclic phosphonic acids

Phosphonic Acid	Formula	Melting Point	References
		°C.	
C_1 acids			
Bromomethyl-	$BrCH_2PO_3H_2$	62	(63)
Chloromethyl-	$ClCH_2PO_3H_2$	89-90	(63, 111, 112, 113, 120, 190, 249, 252)
Dichloromethyl-	$Cl_2CHPO_3H_2$	116-119	(63, 248)
Iodomethyl-	$ICH_2PO_3H_2$	89	(63)
Trichloromethyl-	$Cl_3CPO_3H_2$	163.5	(29, 63, 119, 240, 250, 252)
Trifluoromethyl-	$F_3CPO_3H_2$	81-82	(30)
C_2 acids			
Acetyl-	$CH_3COPO_3H_2$	108-114	(58)
1-Aminoethyl-	$CH_3CH(NH_2)PO_3H_2$	>340	(47)
1-Chloroethyl-	$CH_3CHClPO_3H_2$	99-100	(111, 249)
2-Hydroxyethyl-	$HOCH_2CH_2PO_3H_2$	—	(190)
C_3 acids			
1-Amino-1-methylethyl-	$(CH_3)_2C(NH_2)PO_3H_2 \cdot H_2O$	258	(109, 160, 161)
1-Aminopropyl-	$C_2H_5CH(NH_2)PO_3H_2$	>350	(47)
3-Chloropropyl-	$ClCH_2CH_2CH_2PO_3H_2$	95-97.5	(229)
2,3-Dihydroxypropyl-	$HOCH_2CHOHCH_2PO_3H_2$		(10, 191)
2-Hydroxypropyl-	$CH_3CHOHCH_2PO_3H_2$		(191)
3-Hydroxypropyl-	$HOCH_2CH_2CH_2PO_3H_2$		(229)
β-Phosphonoalanine-	$HOOCCH(NH_2)CH_2PO_3H_2$		(51)
Propylenedi-	$CH_3CH(PO_3H_2)CH_2PO_3H_2$	123	(191, 222)
C_4 acids			
1-Amino-1-methylpropyl-	$C_2H_5(CH_3)C(NH_2)PO_3H_2 \cdot H_2O$	262	(160, 161)
sec-Butyl-	$C_2H_5CH(CH_3)PO_3H_2$	54-56	(62)
tert-Butyl-	$(CH_3)_3CPO_3H_2$	191.5-192	(62)
1-Chlorobutyl-	$C_3H_7CHClPO_3H_2$	86-87	(111)
1-Hydroxybutyl-	$C_3H_7CHOHPO_3H_2$	154.5-155.0	(176)
1-Methylamino-1-methylethyl-	$CH_3NHC(CH_3)_2PO_3H_2$	140	(163)
3-Oxobutyl-	$CH_3COCH_2CH_2PO_3H_2$	81-82	(177)
3-Phosphonobutyric acid	$HOOCCH_2CH(CH_3)PO_3H_2$	141-143	(35, 36, 197, 200)
Tetramethylenedi-	$(CH_2)_4(PO_3H_2)_2$	—	(223)
Trimethylammoniomethyl-	$(CH_3)_3\overset{+}{N}CH_2PO_3H^-$	267	(108)
Trimethylsilylmethyl-	$(CH_3)_3SiCH_2PO_3H_2$	119-121	(118)
C_5 acids			
1-Acetamido-1-methylethyl-	$CH_3CONHC(CH_3)_2PO_3H_2$	199-200	(162)
1-Amino-1-methylbutyl-	$C_3H_7C(CH_3)(NH_2)PO_3H_2 \cdot H_2O$	262-263 (d.)	(161)
1-Dimethylamino-1-methylethyl-	$(CH_3)_2NC(CH_3)_2PO_3H_2$	220-223	(163)
1,1-Dimethylpropyl-	$C_2H_5C(CH_3)_2PO_3H_2$	139-141	(62)
Furfuryl-	$C_5H_5OPO_3H_2$	—	(10)
Hydroxy-[4-(2,6-dihydroxy)pyrimidyl]-methyl-	$2,6\text{-}(HO)_2C_4HN_2CHOHPO_3H_2$	204-205.5 (d.)	(45)
Hydroxy-[4-(6-hydroxy)pyrimidyl]-methyl-	$6\text{-}HOC_4H_2N_2CHOHPO_3H_2$	226 (d.)	(45)
2-Methyl-4-thiazolylmethyl-, hydrochloride	$C_4H_4NSCH_2PO_3H_2 \cdot HCl$	142	(9)
4-Oxopentyl-	$CH_3CO(CH_2)_3PO_3H_2$	—	(12)
Pentylidenedi-	$CH_3(CH_2)_3CH(PO_3H_2)_2$	163-165	(131)
(Phosphonomethylimino)diacetic acid	$(HOOCCH_2)_2NCH_2PO_3H_2$	—	(221)
Tetrahydrofurfuryl-	$C_5H_9OPO_3H_2$	—	(10)

TABLE 7—*Continued*

Phosphonic Acid	Formula	Melting Point	References
	C_6 acids		
		°C.	
1-Aminocyclohexyl-	$C_6H_{10}(NH_2)PO_3H_2 \cdot H_2O$	238	(160, 161)
4-Aminocyclohexyl-	4-$NH_2C_6H_{10}PO_3H_2$	>300	(82)
1-Cyclohexen-1-yl-	$C_6H_9PO_3H_2$	132–133	(72)
2-Cyclohexen-1-yl-	$C_6H_9PO_3H_2$	104–106	(72)
1,2-Dibromocyclohexyl-	$C_6H_9Br_2PO_3H_2$	162–163	(72)
2,3-Dibromocyclohexyl-	$C_6H_9Br_2PO_3H_2$	195–195.5	(72)
1,1-Dimethyl-3-oxobutyl-	$CH_3COCH_2C(CH_3)_2PO_3H_2$	—	(198)
1,2-Dimethyl-3-oxobutyl-	$CH_3COCH(CH_3)CH(CH_3)PO_3H_2$	—	(198)
Ethylenebis(nitrilodimethylene)tetra-	$[CH_2N(CH_2PO_3H_2)_2]_2$	—	(33, 245)
2-Ethyl-4-thiazolylmethyl-, hydrochloride	$C_5H_7NSCH_2PO_3H_2 \cdot HCl$	130–135	(9)
1-Hydroxycyclohexyl-	1-$HOC_6H_{10}PO_3H_2$	191–192	(72)
Hydroxy(4-pyridyl)methyl-	4-$C_5H_4NCHOHPO_3H_2 \cdot H_2O$	226–227 (d.)	(45)
5-Methoxy-2-pentenyl-	$CH_3OCH_2CH_2CH{=}CHCH_2PO_3H_2$	—	(202)
2-(4-Methyl-5-thiazolyl)ethyl-, hydrochloride	$C_6H_8NSPO_3H_2 \cdot HCl$	155–156	(45)
1-Methyl-1-(trimethylammonio)ethyl-	$(CH_3)_3\overset{+}{N}C(CH_3)_2PO_3H^- \cdot H_2O$	230–231 (d.)	(163)
2-Phosphonohexanoic acid	$CH_3(CH_2)_3CH(COOH)PO_3H_2$	170–172	(135)
(2-Phosphonoethylimino)diacetic acid	$(HOOCCH_2)_2NCH_2CH_2PO_3H_2$	—	(221)
	C_7 acids		
α-Amino-*o*-hydroxybenzyl-	*o*-$HOC_6H_4CH(NH_2)PO_3H_2$	—	(47)
α-Amino-*p*-hydroxybenzyl-	*p*-$HOC_6H_4CH(NH_2)PO_3H_2$	150–152	(47)
1-Amino-1-propylbutyl-	$(C_3H_7)_2C(NH_2)PO_3H_2$	192	(161)
Benzoyl-	$C_6H_5COPO_3H_2$	—	(58)
o-Bromobenzyl-	*o*-$BrC_6H_4CH_2PO_3H_2$	182–183	(152)
p-Bromophenoxymethyl-	*p*-$BrC_6H_4OCH_2PO_3H_2$	166–168	(239)
α-Chlorobenzyl-	$C_6H_5CHClPO_3H_2$	98–99	(111)
α-Chloro-*p*-chlorobenzyl-	*p*-$ClC_6H_4CHClPO_3H_2$	152–153	(111)
o-Chlorophenoxymethyl-	*o*-$ClC_6H_4OCH_2PO_3H_2$	133–134	(153)
p-Chlorophenoxymethyl-	*p*-$ClC_6H_4OCH_2PO_3H_2$	156–157	(153, 239)
2,4-Dichlorophenoxymethyl-	2,4-$Cl_2C_6H_3OCH_2PO_3H_2$	141–143	(153, 239)
2,5-Dimethyl-3-oxocyclopentyl-	2,5-$(CH_3)_2$-3-$OC_5H_5PO_3H_2$	—	(106)
2-Hydroxy-5-nitrobenzyl-	2-HO-5-$NO_2C_6H_3CH_2PO_3H_2$	224–229	(152)
4-Hydroxy-3-nitrobenzyl-	4-HO-3-$NO_2C_6H_3CH_2PO_3H_2$	238	(152)
4-Methylcyclohexyl-	$CH_3C_6H_{10}PO_3H_2$	107–110	(82)
1-Methyl-3-oxocyclohexyl-	1-CH_3-3-$OC_6H_5PO_3H_2$	—	(106)
5-Methyl-3-oxo-4-hexenyl-	$(CH_3)_2C{=}CHCOCH_2CH_2PO_3H_2$	—	(204)
Nicotinamidomethyl-	$C_5H_4NCONHCH_2PO_3H_2 \cdot H_2O$	232–233 (d.)	(53)
Phenoxymethyl-	$C_6H_5OCH_2PO_3H_2$	141–142	(153, 239)
2,4,5-Trichlorophenoxymethyl-	2,4,5-$Cl_3C_6H_2OCH_2PO_3H_2$	179–180	(153, 239)
2,4,6-Trichlorophenoxymethyl-	2,4,6-$Cl_3C_6H_2OCH_2PO_3H_2$	217–218	(153)
	C_8 acids		
α-Amino-*p*-methoxybenzyl-	*p*-$CH_3OC_6H_4CH(NH_2)PO_3H_2$	215–218	(47)
α-Amino-(3-methoxy-4-hydroxy)-benzyl-	3-CH_3O-4-$HOC_6H_3CH(NH_2)PO_3H_2$	215	(107)
α-Amino-α-methybenzyl-	$C_6H_5C(CH_3)(NH_2)PO_3H_2 \cdot H_2O$	235	(161)
α-Amino-*p*-methylbenzyl-	*p*-$CH_3C_6H_4CH(NH_2)PO_3H_2$	276	(107)
1-Amino-2-phenylethyl-	$C_6H_5CH_2CH(NH_2)PO_3H_2$	225–227	(47)
α-Aminopiperonyl-	3,4-$CH_2O_2C_6H_3CH(NH_2)PO_3H_2$	255	(105, 107)
Benzamidomethyl-	$C_6H_5CONHCH_2PO_3H_2$	185–186 (d.)	(104)
α-Chloro-*p*-methylbenzyl-	*p*-$CH_3C_6H_4CHClPO_3H_2$	150–151	(111)
2-Chlorostyryl-	$C_6H_5CCl{=}CHPO_3H_2$	159–160	(253)
2-Ethylcyclohexyl-	2-$C_2H_5C_6H_{10}PO_3H_2$	135–138	(82)
4-Ethylcyclohexyl-	4-$C_2H_5C_6H_{10}PO_3H_2$	103–106	(82)
N,*N*′-Ethylenebis(*N*-phosphonomethylglycine)	$[(HOOCCH_2)(CH_2PO_3H_2)NCH_2]_2$	—	(34)

TABLE 7—*Continued*

Phosphonic Acid	Formula	Melting Point	References
	C₈ acids—*continued*		
		°C.	
α-Methylbenzyl-	$C_6H_5CH(CH_3)PO_3H_2$	—	(58)
(*N*-Methylnicotinamido)methyl-	$C_5H_4NCON(CH_3)CH_2PO_3H_2$	180–181	(53)
2-Oxo-2-phenylethyl-	$C_6H_5COCH_2PO_3H_2$	143	(201)
Phenylethylenedi-	$C_6H_5CH(PO_3H_2)CH_2(PO_3H_2)$	212–214	(8)
o-Tolyloxymethyl-	o-$CH_3C_6H_4OCH_2PO_3H_2$	157–158	(239)
m-Tolyloxymethyl-	m-$CH_3C_6H_4OCH_2PO_3H_2$	115–117	(239)
	C₉ acids		
α-Acetamidobenzyl-	$C_6H_5CH(NHCOCH_3)PO_3H_2$	188	(162)
α-Dimethylaminobenzyl-	$C_6H_5CH[N(CH_3)_2]PO_3H_2$	230 (d.)	(163)
2,4-Dimethylbenzyl-	$2,4$-$(CH_3)_2C_6H_3CH_2PO_3H_2$	184–186	(152)
α,β-Diphosphonodihydrocinnamic acid	$C_6H_5CH(PO_3H_2)CH(PO_3H_2)COOH$	113–115	(213)
(*N*-Ethylnicotinamido)methyl-	$C_5H_4NCON(C_2H_5)CH_2PO_3H_2$	185–186	(53)
1-Hydroxy-3-phenylpropyl-	$C_6H_5CH_2CH_2CHOHPO_3H_2$	174.5–175	(176)
3-Oxo-3-phenylpropyl-	$C_6H_5COCH_2CH_2PO_3H_2$	123–124	(177)
α-Phosphonocinnamic acid	$C_6H_5CH{=}C(COOH)PO_3H_2$	132	(210)
4-Phosphono-3,4-dihydrocoumarin	$C_6H_4OCOCH_2CHPO_3H_2$	218–220	(14)
β-Phosphonodihydrocinnamic acid	$C_6H_5CH(PO_3H_2)CH_2COOH$	204	(35, 36, 197)
Phthalimidomethyl-	o-$C_6H_4(CO)_2NCH_2PO_3H_2$	280–285	(108)
	C₁₀ acids		
α-Amino-*p*-isopropylbenzyl-	p-$(CH_3)_2CHC_6H_4CH(NH_2)PO_3H_2$	267 (d.)	(107)
1-Benzamido-1-methylethyl-	$C_6H_5CONHC(CH_3)_2PO_3H_2$	197	(162)
α-Butyl-α-phosphonocaproic acid	$(n$-$C_4H_9)_2C(COOH)PO_3H_2$	140–141	(135)
α^1,α^4-Durenedi-	$2,5$-$(CH_3)_2C_6H_2$-$1,4$-$(CH_2PO_3H_2)_2$	340–350	(152)
α^1,α^5-Durenedi-	$2,4$-$(CH_3)_2C_6H_2$-$1,5$-$(CH_2PO_3H_2)_2$	—	(152)
Hydroxy(3-isoquinolyl)methyl-	$C_9H_6NCHOHPO_3H_2$	238–239 (d.)	(45)
4-Methyl-4-phosphono-3,4-dihydrocoumarin	$C_6H_4OCOCH_2C(CH_3)PO_3H_2$	192–193	(14)
2-Phenyl-4-thiazolylmethyl-, hydrochloride	$C_6H_5C_3HNSCH_2PO_3H_2\cdot HCl$	180–181	(9)
2,3-Quinoxalinebis(methyl-)	$C_8H_4N_2(CH_2PO_3H_2)_2$	234 (d.)	(13)
2-(1,2,3,4-Tetrahydronaphthyl)-*	$C_{10}H_{11}PO_3H_2$	209	(148)
	C₁₁ acids		
p-tert-Butylphenoxymethyl-	p-$(CH_3)_3CC_6H_4OCH_2PO_3H_2$	132–134	(239)
Carvacrylmethyl-	2-CH_3-5-$(CH_3)_2CHC_6H_3CH_2PO_3H_2$	175–177	(152)
10-Chloro-11-phosphonohendecanoic acid	$HOOC(CH_2)_9CHClCH_2PO_3H_2$	116–117	(50)
Hydroxy-1-naphthylmethyl-	$C_{10}H_7CHOHPO_3H_2$	156–158	(60)
2-(*p*-Methoxyphenyl)-4-thiazolylmethyl-, hydrochloride	p-$CH_3OC_6H_4C_3HNSCH_2PO_3H_2\cdot HCl$	184–186	(9)
1-Naphthylmethyl-	$C_{10}H_7CH_2PO_3H_2$	212	(60)
2-Naphthylmethyl-	$C_{10}H_7CH_2PO_3H_2$	229–230	(7)
	C₁₂ acids		
1-Acenaphthenol-1-	$C_{12}H_9OPO_3H_2$	195	(61)
1-Acenaphthenyl-	$C_{12}H_9PO_3H_2$	220	(61)
1,4-Naphthalenebis(methyl-)	$1,4$-$C_{10}H_6(CH_2PO_3H_2)_2$	229–230	(7)
1,2,3,4-Tetrahydro-5,8-naphthalenebis(methyl-)	$5,8$-$C_{10}H_{10}(CH_2PO_3H_2)_2$	296–300	(7)
2,3,4-Tri-*O*-acetyl-D-glucopyranose-6-deoxy-6-	$C_{12}H_{17}O_8PO_3H_2\cdot 2(C_4H_{10}O)$	187–191	(90)

TABLE 7—*Concluded*

Phosphonic Acid	Formula	Melting Point	References
	C_{13} acids		
		°C.	
Aminodiphenylmethyl-	$(C_6H_5)_2C(NH_2)PO_3H_2 \cdot 2H_2O$	232	(160, 161)
Diphenylmethyl-	$(C_6H_5)_2CHPO_3H_2$	169–170	(5)
	C_{14} acids		
α-Benzamidobenzyl-	$C_6H_5CONHCH(C_6H_5)PO_3H_2 \cdot H_2O$	105–107	(162)
1,2,3,4-Tetra-*O*-acetyl-β-D-glucopyranose-6-deoxy-6-	$C_{14}H_{19}O_9PO_3H_2 \cdot 2H_2O$	171–172	(90)
	C_{18-21} acids		
Phenylosazone of D-glucopyranose-6-deoxy-6	$C_{18}H_{21}N_4O_3PO_3H_2$	170–172	(90)
Benz[*a*]anthracen-7-ylmethyl-	$C_{19}H_{13}PO_3H_2$	—	(6)
9-Phenyl-9-fluorenyl-	$C_{19}H_{13}PO_3H_2$	268	(92)
o-Methoxy-α,α-diphenylbenzyl-	$o\text{-}CH_3OC_6H_4C(C_6H_5)_2PO_3H_2$	239–240	(92)
12-Methylbenz[*a*]anthracen-7-ylmethyl-	$C_{20}H_{15}PO_3H_2$	—	(6)
o-Methyl-α,α-diphenylbenzyl-	$o\text{-}CH_3C_6H_4C(C_6H_5)_2PO_3H_2$	264	(92)
α,α-Di-*p*-tolylbenzyl-	$C_6H_5C(p\text{-}CH_3C_6H_4)_2PO_3H_2$	272–273	(92)
Tri-*p*-tolylemethyl-	$(p\text{-}CH_3C_6H_4)_3CPO_3H_2$	262–264	(92)

* No analyses or proof of orientation on this compound.

the activity of such well-known toxic agents as tetraethyl pyrophosphate (TEPP) or diisopropyl phosphorofluoridate (DFP).

Trisodium 3-phosphonopropionate has been found to be an active inhibitor of the succinic dehydrogenase of certain protozoa (224, 225). Trisodium arsonoacetate also inhibits the dehydrogenase in these protozoa. Both the arsono and phosphono compounds probably act in a similar manner to sodium malonate, a strong inhibitor of succinic dehydrogenase. Neither the succinic dehydrogenase of rat tissue (224) nor the succinic oxidase of mouse liver (235) was inhibited by the phosphono or arsono compound.

In addition to their antibacterial activity and their effect on isolated enzyme systems, phosphonic acids have been tested as plant auxins. One such series of compounds comprised 1-naphthylmethylphosphonic acid, 1-naphthalenehydroxymethylphosphonic acid, and a mixture of 1,2,3,4-tetrahydro-5(and6)-naphthylmethylphosphonic acids (60). Another series consisted of 1-acenaphthenylphosphonic acid and 1-acenaphthenol-1-phosphonic acid (61). All of these compounds were found to have marked activity in various plants. The compounds were stimulatory in very dilute solution, but markedly toxic in more concentrated solution (182). Other workers, however, have found 1-naphthylmethylphosphonic acid to be only slightly active as a plant-growth regulator (236).

Examples of another type of phosphonic acid, analogous to the chlorophenoxyacetic acids which are known to have plant-growth-regulating activity, have recently been prepared (153, 154). These were synthesized by condensing either

TABLE 8

Aromatic and heterocyclic phosphonic acids

Phosphonic Acid	Formula	Melting Point	References
	Compounds containing halogens		
		°C.	
o-Bromophenyl-	*o*-$BrC_6H_4PO_3H_2$	199–201	(24, 68, 69)
o-Chlorophenyl-	*o*-$ClC_6H_4PO_3H_2$	186.5–188	(44, 67, 133, 144, 145)
o-Fluorophenyl-	*o*-$FC_6H_4PO_3H_2$	146–149	(65, 84)
m-Fluorophenyl-	*m*-$FC_6H_4PO_3H_2$	129–130	(133)
p-Fluorophenyl-	*p*-$FC_6H_4PO_3H_2$	125–127	(38, 133)
o-Iodophenyl-	*o*-$IC_6H_4PO_3H_2$	219–222	(84)
	Compounds containing alkyl groups		
6-Bromo-*m*-tolyl-	2-Br-5-$CH_3C_6H_3PO_3H_2$	199–203	(84)
p-*tert*-Butylphenyl-	*p*-$(CH_3)_3CC_6H_4PO_3H_2$	199–200	(132)
p-α-Chlorotolyl-	*p*-$ClCH_2C_6H_4PO_3H_2$	161	(155)
o-Ethylphenyl-	*o*-$C_2H_5C_6H_4PO_3H_2$	145.5–147	(16, 79)
m-Ethylphenyl-	*m*-$C_2H_5C_6H_4PO_3H_2$	128–129.5	(16, 79, 130)
3,4-Xylyl-*	3,4-$(CH_3)_2C_6H_3PO_3H_2$	150–151.5	(144, 145)
	Phenols and ethers		
3-Chloro-4-methoxyphenyl-	3-Cl-4-$CH_3OC_6H_3PO_3H_2$	192	(146, 237)
p-(Ethylthio)phenyl-	*p*-$C_2H_5SC_6H_4PO_3H_2$	159–160	(38)
m-Hydroxyphenyl-	*m*-$HOC_6H_4PO_3H_2$	226–229	(68)
p-Hydroxyphenyl-	*p*-$HOC_6H_4PO_3H_2$	178	(24, 68)
o-Methoxyphenyl-	*o*-$CH_3OC_6H_4PO_3H_2$	215†	(24, 65, 84)
3,4-Methylenedioxyphenyl-	3,4-$CH_2O_2C_6H_3PO_3H_2$	160–161	(38)
	Amino and azo compounds		
3-Amino-4-bromophenyl-	3-H_2N-4-$BrC_6H_3PO_3H_2$	>280 (d.)	(24)
4-Amino-2-chlorophenyl-	4-H_2N-2-$ClC_6H_3PO_3H_2$	>200†	(84)
p-(2-Aminoethoxy)phenyl-	*p*-$H_2NCH_2CH_2OC_6H_4PO_3H_2$	>300	(69)
4-Amino-2-hydroxyphenyl-	4-H_2N-2-$HOC_6H_3PO_3H_2$	210–212	(70)
4-Amino-2-methoxyphenyl-	4-H_2N-2-$CH_3OC_6H_3PO_3H_2$	212–214	(70)
o-Aminophenyl-	*o*-$H_2NC_6H_4PO_3H_2$	199–200	(68)
5-Benzimidazolyl-	$C_7H_5N_2PO_3H_2$	>250	(37)
6-Benzoxazolyl-	3,4-CH(O)(N)$C_6H_3PO_3H_2$	204–205	(37)
m-(Butylamino)phenyl-	*m*-$C_4H_9NHC_6H_4PO_3H_2$	198–201	(69)
p-(*p*-Diethylaminophenylazo)-phenyl-	*p*-$[p\text{-}(C_2H_5)_2NC_6H_4N_2]C_6H_4PO_3H_2$	—	(136)
p-(*p*-Dimethylaminophenylazo)-phenyl-	*p*-$[p\text{-}(CH_3)_2NC_6H_4N_2]C_6H_4PO_3H_2$	—	(121, 136)
m-(Ethylamino)phenyl-	*m*-$C_2H_5NHC_6H_4PO_3H_2$	238–241	(69)
m-Hydrazinophenyl-	*m*-$H_2NNHC_6H_4PO_3H_2$	>248	(69)
p-Hydrazinophenyl-	*p*-$H_2NNHC_6H_4PO_3H_2$	>212	(69)
p-(2-Hydroxyethylnitrosoamino)-phenyl-	*p*-$HOCH_2CH_2N(NO)C_6H_4PO_3H_2$	>140 (d.)	(69)
m-(Methylamino)phenyl-	*m*-$CH_3NHC_6H_4PO_3H_2$	226.5–228.5	(69)
p-(Methylamino)phenyl-	*p*-$CH_3NHC_6H_4PO_3H_2$	177.5–179.5	(69)
2-Methyl-5-benzimidazolyl-	2-$CH_3C_7H_4N_2PO_3H_2$	>320	(37)
p-(Propylamino)phenyl-, hydrochloride	*p*-$C_3H_7NHC_6H_4PO_3H_2 \cdot HCl$	180.5–183.5	(69)
	Tetracovalent sulfur compounds		
p-Sulfamylphenyl-	*p*-$H_2NSO_2C_6H_4PO_3H_2$	224–225	(67)
p-(Ethylsulfonyl)phenyl-	*p*-$C_2H_5SO_2C_6H_4PO_3H_2$	177–178	(38)

TABLE 8—*Concluded*

Phosphonic Acid	Formula	Melting Point	References
	Nitro compounds		
		°C.	
4-Anilino-3-nitrophenyl-	$4\text{-}C_6H_5NH\text{-}3\text{-}O_2NC_6H_3PO_3H_2$	—	(66)
2-Bromo-4-nitrophenyl-	$2\text{-}Br\text{-}4\text{-}O_2NC_6H_3PO_3H_2$	217–220	(24)
2-Bromo-5-nitrophenyl-	$2\text{-}Br\text{-}5\text{-}O_2NC_6H_3PO_3H_2\cdot H_2O$	>230 (d.)	(84)
2-Chloro-4-nitrophenyl-	$2\text{-}Cl\text{-}4\text{-}O_2NC_6H_3PO_3H_2$	221.5–224	(84)
2-Hydroxy-4-nitrophenyl-	$2\text{-}HO\text{-}4\text{-}O_2NC_6H_3PO_3H_2$	202–204	(70)
3-Hydroxy-4-nitrophenyl-	$3\text{-}HO\text{-}4\text{-}O_2NC_6H_3PO_3H_2$	201–202	(37)
2-Methoxy-4-nitrophenyl-	$2\text{-}CH_3O\text{-}4\text{-}O_2NC_6H_3PO_3H_2\cdot H_2O$	226.5–227.5	(84)
p-(*p*-Nitrophenoxy)phenyl-	$p\text{-}(p\text{-}O_2NC_6H_4O)C_6H_4PO_3H_2$	288	(155)
o-Nitrophenyl-	$o\text{-}O_2NC_6H_4PO_3H_2$	200–203	(80)
p-Nitrophenyl-	$p\text{-}O_2NC_6H_4PO_3H_2$	197–198	(67, 78)
3-Nitro-4-(*p*-toluidino)phenyl-	$4\text{-}(p\text{-}CH_3C_6H_4NH)\text{-}3\text{-}O_2NC_6H_3PO_3H_2$	—	(66)
	Naphthalene derivatives		
4-Amino-1-naphthyl-	$4\text{-}H_2N\text{-}1\text{-}C_{10}H_6PO_3H_2$	170 (d.)	(136)
2,6(or 7)-Naphthylenedi-	$2,6(\text{or }7)\text{-}C_{10}H_6(PO_3H_2)_2$	338–345	(144, 145)
4-Nitro-1-naphthyl	$4\text{-}O_2N\text{-}1\text{-}C_{10}H_6PO_3H_2$	220 (d.)	(136)
Sodium trihydrogen 3,3′-(4,4′-biphenylenebisazo)bis(4-amino-1-naphthylphosphonate)	$C_{22}H_{23}N_6NaO_6P_2$	—	(136)
	Biphenyl and other polynuclear hydrocarbon derivatives		
3,3′-Biphenyldi-	$3,3'\text{-}(C_6H_4C_6H_4)(PO_3H_2)_2$	246–252	(76)
4,4′-Biphenyldi-	$4,4'\text{-}(C_6H_4C_6H_4)(PO_3H_2)_2$	>300	(76)
2-Biphenylyl-	$2\text{-}C_6H_5C_6H_4PO_3H_2$	203–205	(44, 102)
4-Biphenylyl-	$4\text{-}C_6H_5C_6H_4PO_3H_2$	218–220	(102)
9-Phenanthryl-	$9\text{-}C_{14}H_9PO_3H_2$	228–230	(173, 174)
3-Pyrenyl-	$3\text{-}C_{16}H_9PO_3H_2$	233–234	(174)
	Heterocyclic compounds		
4-Methyl-2-quinolyl-	$4\text{-}CH_3\text{-}2\text{-}C_9H_5NPO_3H_2$	>300	(45)
2-Quinolyl-	$2\text{-}C_9H_6NPO_3H_2\cdot H_2O$	>300	(45)

* Orientation uncertain.

† Approximate melting point, since the melting point varies with the rate of heating.

sodium phenoxide or various chlorine-substituted sodium phenoxides with diethyl iodomethylphosphonate to yield ethyl hydrogen phenoxymethylphosphonates. Hydrolysis of the acid esters with hydrochloric acid gave the free acids. Ethyl hydrogen 2,4-dichlorophenoxymethylphosphonate is reported to have slight auxin activity in the split pea and the pea epicotyl tests (89). With wheat seedlings, sodium ethyl 2-chlorophenoxymethylphosphonate and sodium ethyl 2,4-dichlorophenoxymethylphosphonates possessed slight growth-promoting properties. Disodium methylphosphonate in low concentration was found to markedly depress the dry weight of the tops of rape seedlings. In view of the commercial value of disodium methylarsonate as a selective herbicide, the corresponding phosphonate should obviously be further investigated.

The diammonium salt of 12-methylbenz[*a*]anthracen-7-ylmethylphosphonic acid is carcinogenic (6).

VI. Tables of New Phosphonic Acids

Table 7 lists aliphatic and alicyclic phosphonic acids, while table 8 presents aromatic and heterocyclic phosphonic acids.

VII. References

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