

## The Direct Synthesis of $\alpha$ -Aminomethylphosphonic Acids. Mannich-Type Reactions with Orthophosphorous Acid

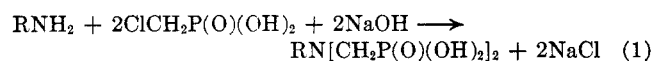
KURT MOEDRITZER AND RIYAD R. IRANI

Research Department, Inorganic Chemicals Division, Monsanto Company, St. Louis, Missouri

Received September 20, 1965

A direct reaction is described to prepare  $\alpha$ -aminomethylphosphonic acids,  $R_{3-n}N[CH_2P(O)(OH)_2]_n$ , from orthophosphorous acid, formaldehyde, and amines. The amines employed in this reaction were ammonia, primary or secondary amines, polyamines, and functionally substituted amines. The  $\alpha$ -aminomethylphosphonic acids prepared in this study exhibit chelating properties for polyvalent metal ions. Nmr spectra are discussed.

Since the discovery<sup>1</sup> of the extraordinary chelating properties of compounds containing in the molecule one or more "nitrilodiacetate" groups,  $-N(CH_2COOH)_2$ , such as ethylenedinitrilotetraacetic acid (ethylenediaminetetraacetic acid, EDTA) and nitrilotriacetic acid (NTA), considerable effort has been undertaken to synthesize new and different chelating agents. Bersworth,<sup>2</sup> as well as Banks and Yerick,<sup>3</sup> prepared compounds with "nitrilodimethylene diphosphonate" groups,  $-N[CH_2P(O)(OH)_2]_2$ , and studied their chelating properties. These authors synthesized ethylenebis(nitrilodimethylene)tetraphosphonic acid and 1,2-cyclohexanebis(nitrilodimethylene)tetraphosphonic acid and noted their chelating ability for polyvalent metals ions, particularly for alkaline earth metal ions. Utilizing a synthetic method described earlier by Schwarzenbach<sup>4</sup> these compounds were prepared by the reaction of the corresponding diprimary amine with chloromethylphosphonic acid in alkaline solution, according to eq 1. The method requires long reaction



times at relatively high temperatures, several days at ca. 80°, and a pH of 10–11. We found that under these conditions, however, hydrolysis of the chlorine-carbon bond in the chloromethylphosphonic acid to give hydroxymethylphosphonic acid, according to eq 2, is



quite significant. The latter contaminates the desired aminomethylphosphonic acid with a difficultly separable component.

Of importance is also a series of papers by Kabachnik and Medved<sup>5</sup> describing the preparation of various  $\alpha$ -aminomethylphosphonic acids by hydrolysis of the corresponding  $\alpha$ -aminomethylphosphonic esters.

After completion of our work an additional generally applicable method<sup>6</sup> for the preparation of  $\alpha$ -aminomethylphosphonic acids appeared which utilizes the Curtius reaction of phosphonacetic acids. However, this method depends on the availability of suitable

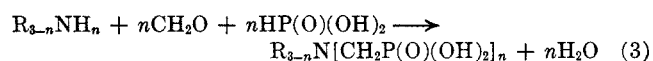
phosphonoacetic esters. Additional methods for preparing  $\alpha$ -aminomethylphosphonic acids from other less common starting materials are the reactions of Chavane<sup>7</sup> (bromomethylphthalimide and sodium dialkylphosphite) and Pıkl and Engelmann<sup>8</sup> (acetamido-methanol and phosphorus trichloride).

Although certain  $\alpha$ -aminophosphonic acids may be considered to be phosphorus analogs of amino acids, none have been found in biological materials. Recent reports<sup>9</sup> have shown, however, that a  $\beta$ -aminophosphonic acid was isolated from protein fractions of sea animals.

This paper reports a new and direct method for the preparation of a class of  $\alpha$ -aminomethylphosphonic acids in high yields by a Mannich-type reaction using phosphorous acid, formaldehyde, and ammonia or amines as reactants.

### Results and Conclusions

The Mannich-type reaction of an amine, formaldehyde, and phosphorous acid proceeds according to the general equation given below



where  $n = 1, 2, \text{ or } 3$ . The hydrogen atom directly bonded to the phosphorus in phosphorous acid is the "acidic" hydrogen required for this type of reaction. Although other classes of phosphorus compounds having P-H bonds have been found to undergo Mannich-type reactions, no previous references are available for the reaction using phosphorous acid. The phosphorus compounds of which Mannich-type products have been reported earlier are phosphines,<sup>10</sup>  $H_nPR_{3-n}$ ; hypophosphorous acid,<sup>11</sup>  $H_2P(O)(OH)$ ; secondary phosphine oxides,<sup>12</sup>  $HP(O)R_2$ ; alkyl alkylphosphinates,<sup>13</sup>  $HP(O)R(OR')$ ; dialkylphosphonates,<sup>14</sup>  $HP(O)(OR)_2$ ; and dialkylphosphonothioates,<sup>15</sup>  $HP(S)(OR)_2$ .

The reaction of eq 3 proceeds almost quantitatively. As no special efforts have been made to isolate quantitatively the resulting aminomethylphosphonic acids from the reaction mixtures, the yields reported in

(1) G. Schwarzenbach, W. Biedermann, and F. Bangertner, *Helv. Chim. Acta*, **29**, 811 (1946).

(2) F. C. Bersworth, U. S. Patent 2,599,807 (June 10, 1952); *Chem. Abstr.*, **47**, 4360b (1953).

(3) C. V. Banks and R. E. Yerick, *Anal. Chim. Acta*, **20**, 301 (1959).

(4) G. Schwarzenbach, H. Ackermann, and P. Ruckstuhl, *Helv. Chim. Acta*, **32**, 1175 (1944).

(5) M. I. Kabachnik and T. Y. Medved, *Dokl. Akad. Nauk SSSR*, **83**, 689 (1952); *Chem. Abstr.*, **47**, 2724 (1953); T. Y. Medved and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR*, **84**, 717 (1952); *Chem. Abstr.*, **47**, 3226 (1953); M. I. Kabachnik and T. Y. Medved, *Bull. Acad. Sci. USSR*, 769 (1953); T. Y. Medved and M. I. Kabachnik, *ibid.*, 255 (1954); M. I. Kabachnik and T. Y. Medved, *ibid.*, 843 (1954).

(6) J. R. Chambers and A. F. Isbell, *J. Org. Chem.*, **29**, 832 (1964).

(7) V. Chavane, *Bull. Soc. Chim. France*, **27**, 774 (1948).

(8) J. Pıkl, U. S. Patent 2,328,358 (Jan 23, 1941); *Chem. Abstr.*, **38**, 754 (1944); M. Engelmann and J. Pıkl, U. S. Patent 2,304,156 (March 7, 1940); *Chem. Abstr.*, **37**, 3261 (1943).

(9) L. D. Quin, *Science*, **144**, 1133 (1964).

(10) H. Coates and P. T. Hoyer, British Patent 854,182 (Nov 16, 1960); *Chem. Abstr.*, **56**, 1482 (1962).

(11) H. Schmidt, *Chem. Ber.*, **81**, 477 (1948).

(12) N. Kreutzkamp and K. Storck, *Naturwiss.*, **47**, 497 (1960).

(13) M. I. Kabachnik and T. Y. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1024 (1954); *Chem. Abstr.*, **50**, 219 (1956).

(14) E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).

(15) M. I. Kabachnik, T. Y. Medved, and T. A. Mastryukova, *Dokl. Akad. Nauk SSSR*, **92**, 959 (1953); *Chem. Abstr.*, **49**, 839 (1955).

TABLE I  
ANALYTICAL AND OTHER DATA OF ALKYLIMINODIMETHYLENEDIPHOSPHONIC ACIDS  
 $RN[CH_2P(O)(OH)_2]_2$

R	Mp, °C	Yield, <sup>a</sup> %	Equiv wt		Carbon, %		Hydrogen, %	
			Calcd	Found	Calcd	Found	Calcd	Found
CH <sub>3</sub>	210–212 <sup>b</sup>	67.0 <sup>c</sup>	73.0	73.5	16.45	16.65	5.06	5.05
C <sub>2</sub> H <sub>5</sub>	205 <sup>b</sup>	62.2 <sup>c</sup>	77.1	78.6	20.61	21.50	5.62	5.98
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	183 <sup>b</sup>	81.0 <sup>c</sup>	82.4	84.2	24.30	24.30	6.12	6.46
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	196 <sup>b</sup>	74.5 <sup>c</sup>	87.1	87.5	27.59	27.33	6.56	6.82
<i>n</i> -C <sub>5</sub> H <sub>11</sub>	186 <sup>b</sup>	73.3 <sup>d</sup>	91.7	93.8	30.55	30.69	6.92	6.82
<i>n</i> -C <sub>6</sub> H <sub>13</sub>	205–207 <sup>b</sup>	82.3 <sup>d</sup>	96.4	97.0	33.22	33.29	7.32	7.76
<i>n</i> -C <sub>7</sub> H <sub>15</sub>	215 <sup>b</sup>	89.7 <sup>d</sup>	101.1	102.5	35.64	35.78	7.65	7.88
<i>n</i> -C <sub>8</sub> H <sub>17</sub>	213–215 <sup>b</sup>	89.5 <sup>d</sup>	105.7	106.5	37.85	38.78	7.94	8.03
<i>n</i> -C <sub>9</sub> H <sub>19</sub>	215 <sup>b</sup>	68.2 <sup>d</sup>	110.4	110.7	39.88	39.70	8.22	8.67
<i>n</i> -C <sub>10</sub> H <sub>21</sub>	247 <sup>b,e</sup>	70.2 <sup>d</sup>	115.1	116.3	41.73	41.25	8.49	8.61
<i>n</i> -C <sub>12</sub> H <sub>25</sub>	215 <sup>o</sup>	91.0 <sup>f</sup>	124.5	125.6	45.03	45.30	8.91	9.08
<i>n</i> -C <sub>14</sub> H <sub>29</sub>	216 <sup>o</sup>	90.5 <sup>f</sup>	133.8	137.1	47.87	48.74	9.29	9.64
<i>n</i> -C <sub>16</sub> H <sub>33</sub>	215 <sup>o</sup>	91.3 <sup>f</sup>	143.2	142.5	50.34	50.43	9.62	9.88
<i>n</i> -C <sub>18</sub> H <sub>37</sub>	219 <sup>o</sup>	93.7 <sup>f</sup>	152.5	158.2	52.50	52.30	9.91	9.31
(CH <sub>3</sub> ) <sub>2</sub> CH	235 <sup>b</sup>	60.3 <sup>c</sup>	82.4	83.2	24.30	24.26	6.12	6.64
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	224 <sup>b</sup>	82.1 <sup>c</sup>	87.1	86.5	27.59	27.26	6.56	6.27
(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> CH <sub>2</sub> )CH	189 <sup>b</sup>	65.3 <sup>d</sup>	87.1	87.5	27.59	27.29	6.56	7.26
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub>	212 <sup>b</sup>	68.5 <sup>d</sup>	91.7	94.0	30.55	30.45	6.96	6.89
CH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> CH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	191 <sup>b</sup>	61.5 <sup>d</sup>	105.8	106.5	37.85	37.18	7.94	8.22
CH <sub>2</sub> =CHCH <sub>2</sub>	190 <sup>b</sup>	49.0 <sup>b</sup>	81.7	81.5	24.50	24.52	5.32	5.47
<i>c</i> -C <sub>6</sub> H <sub>11</sub>	237 <sup>i</sup>	84.0 <sup>d</sup>	97.5	97.8	33.45	32.87	6.67	6.94
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	248 <sup>b</sup>	85.7 <sup>d</sup>	98.4	102.0	36.62	36.47	5.12	5.14
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	237 <sup>i</sup>	71.5 <sup>d</sup>	103.1	103.5	38.84	38.70	5.54	5.53
HOCH <sub>2</sub> CH <sub>2</sub>	255 <sup>i</sup>	68.2 <sup>j</sup>	83.0	80.7	19.28	20.06	5.26	5.12
HOOCCH <sub>2</sub> <sup>k</sup>	203 <sup>i</sup>	53.6 <sup>c</sup>	65.8	68.4	18.26	18.25	4.21	4.84
HOCH <sub>2</sub> CH <sub>2</sub> <sup>l</sup>	246 <sup>i,m</sup>	53.5 <sup>n</sup>	199.2	201.0	30.13	32.83	7.09	6.83
HOOCCH <sub>2</sub> <sup>l,o</sup>	210 <sup>i</sup>	65.0 <sup>c</sup>	75.7	77.7	26.44	26.32	4.44	4.77

<sup>a</sup> The P<sup>31</sup> nmr spectra in all cases indicate a better than 95% conversion of phosphorous acid to form NCH<sub>2</sub>P(O)(OH)<sub>2</sub> groups. <sup>b</sup> Melts with evolution of bubbles. <sup>c</sup> The concentrated reaction mixture is recrystallized from ethanol-water. <sup>d</sup> Recrystallized from water. <sup>e</sup> Sample becomes transparent at ca. 220° but does not flow. <sup>f</sup> Purified by dissolution in hot concentrated HCl and separation by dilution with water. <sup>g</sup> Sample becomes transparent at this temperature but is too viscous to flow. Turns into liquid at ca. 260° and gradually decomposes turning brown. <sup>h</sup> Crystallizes from the concentrated reaction mixture after several days in a refrigerator. <sup>i</sup> Melts with evolution of bubbles and turns yellowish brown. <sup>j</sup> Addition of methanol to the syrupy concentrate of the reaction initiates crystallization within several days at room temperature. <sup>k</sup> Anal. Calcd: N, 5.32; P, 23.55. Found: N, 4.88; P, 24.37. <sup>l</sup> Acids of the type R<sub>2</sub>NCH<sub>2</sub>P(O)(OH)<sub>2</sub>. <sup>m</sup> This melting point does not agree with the value of 144–146 reported<sup>18</sup> for a product of this composition obtained from diethanolamine and chloromethylphosphonic acid. <sup>n</sup> Addition of 250 ml of dimethylformamide to the syrupy concentrate of the reaction mixture and slight warming initiated crystallization. <sup>o</sup> Anal. Calcd: N, 6.17; P, 13.64. Found: N, 6.40; P, 14.42.

TABLE II  
ANALYTICAL AND OTHER DATA OF POLYMETHYLENEBIS(NITRILODIMETHYLENE)TETRAPHOSPHONIC ACIDS  
[(HO)<sub>2</sub>(O)PCH<sub>2</sub>]<sub>2</sub>NR'N[CH<sub>2</sub>P(O)(OH)<sub>2</sub>]<sub>2</sub>

R'	Mp, °C	Yield, %	Equiv wt		Carbon, %		Hydrogen, %	
			Calcd	Found	Calcd	Found	Calcd	Found
(CH <sub>2</sub> ) <sub>2</sub> <sup>a</sup>	214 <sup>b</sup>	49.6	72.0	71.8	16.52	17.05	4.62	4.81
(CH <sub>2</sub> ) <sub>4</sub>	237–238 <sup>b</sup>	77.5	77.5	78.2	20.70	20.92	5.21	5.00
(CH <sub>2</sub> ) <sub>6</sub>	249 <sup>c</sup>	82.0	82.0	81.6	24.40	24.29	5.73	5.62
(CH <sub>2</sub> ) <sub>8</sub>	241 <sup>b</sup>	85.0	85.0	84.2	27.70	27.90	6.20	6.13
(CH <sub>2</sub> ) <sub>9</sub>	217 <sup>d</sup>	89.0	89.0	88.7	29.22	29.25	6.41	6.49
(CH <sub>2</sub> ) <sub>10</sub>	225 <sup>b</sup>	91.4	91.4	90.6	30.66	30.73	6.62	6.76
(CH <sub>2</sub> ) <sub>11</sub>	205 <sup>d</sup>	93.7	93.7	93.3	32.03	32.57	6.81	7.05
(CH <sub>2</sub> ) <sub>12</sub>	212 <sup>d</sup>	96.1	96.1	98.4	33.34	33.90	6.99	7.01
CH <sub>2</sub> -1,4-C <sub>6</sub> H <sub>10</sub> CH <sub>2</sub>	262 <sup>b</sup>	86.4	86.4	88.0	27.81	28.09	5.83	6.15

<sup>a</sup> Anal. Calcd: N, 6.42; P, 28.41. Found: N, 6.49; P, 27.09. <sup>b</sup> Melting under frothing with subsequent decomposition. <sup>c</sup> Substance starts to decompose at 238–241°. <sup>d</sup> Melting with frothing.

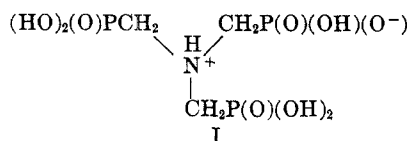
Tables I and II are somewhat low for the more water-soluble compounds and are approaching 100% for the more water-insoluble products. Reaction 3 proceeds equally well with ammonia, primary amines, secondary amines, polyamines, and functionally substituted amines or their hydrochlorides. Optimum results are obtained when the reaction is carried out at low pH values, such as in the presence of ca. 2–3 moles of concentrated hydrochloric acid/mole of amine hydrochloride. It was found that high acidity increases the rate of re-

action and improves the yield. Low pH also aids in inhibiting the oxidation of phosphite to phosphate.

The solutions of the amine hydrochloride, phosphorous acid, and concentrated hydrochloric acid are heated to reflux temperature (ca. 110–125°) and a 100% excess of aqueous formaldehyde solution or paraformaldehyde is added dropwise in the course of 1–2 hr. After refluxing for an additional period of 1–2 hr, the resulting aminomethylphosphonic acid is isolated by standard procedures. Analytical and other data of

the compounds prepared are listed in Tables I and II.

**The Reaction with Ammonia.**—For  $n = 3$  in eq 3 nitrilotrismethylenetriphosphonic acid is obtained. This compound in water titrates as a pentabasic acid having two strongly dissociated protons and three weakly dissociated protons, with the sixth available proton probably coordinated to the central nitrogen atom, resulting in a zwitterion structure. The acid



recently has been prepared by two other methods which, however, involve a series of steps. One of these methods is based on the hydrolysis of the corresponding hexaalkyl ester,<sup>16</sup>  $\text{N}[\text{CH}_2\text{P}(\text{O})(\text{OR})_2]_3$ , with the latter being obtained in *ca.* 20% yield from the reaction of ammonia, formaldehyde, and dialkyl phosphonate. According to the second method<sup>17</sup> the reaction product of ammonia and chloromethylphosphonic acid,  $\text{N}[\text{CH}_2\text{P}(\text{O})(\text{OH})]_3$ , is oxidized to give nitrilotrismethylenetriphosphonic acid. Both methods involve several steps and give low over-all yields.

**The Reaction with Primary Amines.**—Alkyliminodimethylenediphosphonic acids are obtained for  $n = 2$  in the reaction of eq 3. For  $\text{R} = \text{CH}_3$  to  $\text{C}_4\text{H}_9$  the resulting acids are very soluble in water and therefore have to be recrystallized from ethanol or ethanol-water mixtures. When  $\text{R}$  is an alkyl group equal to or higher than  $\text{C}_5\text{H}_{11}$ , the resulting acids crystallized from the cooled reaction mixture and on recrystallization from water yielded pure materials. The acids with long-chain alkyl groups,  $\text{R} \geq \text{C}_{12}$ , are rather poorly soluble in water and to a great extent precipitate from the reaction mixture during the reaction. They are soluble in concentrated hydrochloric acid. As seen in Table I straight-chain, branched, unsaturated, cycloalkyl as well as arylalkyl primary amines have been employed successfully in the reaction of eq. 3. These acids probably exist as zwitterions with three titratable protons, a strongly dissociated proton and two weak ones, with the fourth available proton being coordinated to the central nitrogen atom.

**The Reaction with Secondary Amines.**—For  $n = 1$  in eq 3 it could be shown by  $\text{P}^{31}$  nmr that more than 98% of the reacting phosphorous acid was used up to form the aminomethylphosphonic acid derivative. Upon evaporation of the reaction mixture, syrupy liquids resulted which resisted crystallization. A similar behavior has been observed<sup>14</sup> for the same class of compounds prepared by a different method. Furthermore, significant amounts of hydrochloric acid were retained by these products and could not be stripped by repeated addition of water and evaporation. This is probably due to the increased basicity of the nitrogen in dialkylaminomethylphosphonic acids as compared to acids having two or more methylphosphonate groups attached to the nitrogen. Crystalline aminomethyl-

phosphonic acid derivatives could be isolated only in the case of iminodiacetic acid and diethanolamine. Both of these compounds have been prepared previously<sup>4,18</sup> by the method of eq 1.

**The Reaction with Other Amines.**—In addition to the types of amines described above, our reaction with phosphorous acid has been applied successfully to other types of amines, such as polyamines. Using  $\alpha,\omega$ -polymethylenediamines a series of polymethylenebis(nitrilodimethylene)tetrphosphonic acids have been prepared, the properties of which are described in Table II. These compounds titrate as hexabasic acids and their solubility in water decreases with increasing number of methylene groups separating the two nitrilodimethylenediphosphonic acid groups. Although  $\text{P}^{31}$  nmr indicated over 95% conversion of phosphorous acid to aminomethylphosphonic acid groups, the yields listed in Table II are somewhat lower since no effort has been made to separate quantitatively the products from the reaction mixtures. The lower members of the series having an odd number of methylene groups between the two nitrogen atoms (3, 5, and 7) were found to form, as evidenced by  $\text{P}^{31}$  nmr, but attempts to crystallize the viscous reaction products resulting upon evaporation failed.

Other amines which have been found to give aminomethylphosphonic acid derivatives are the poly(ethylenediamines), such as triethylenetetramine which results in a product having six methylenephosphonic acid groups in the molecule. Furthermore, amines having other functional groups in the molecule, such as aminoethanol, aminoacetic acid, and others were observed to undergo the Mannich-type reaction with phosphorous acid.

**Nmr Spectra.**—In the proton nmr spectra the characteristic feature seen for all  $\alpha$ -aminomethylphosphonic acids is a doublet centering in a range of -4.3 to -4.1 ppm relative to tetramethylsilane. The doublet with a coupling constant of *ca.* 13 cps results from coupling of the methylene protons with the phosphorus nucleus.

In the  $\text{P}^{31}$  nmr spectra the signal of the phosphorus atom in the acids  $\text{R}_{3-n}\text{N}[\text{CH}_2\text{P}(\text{O})(\text{OH})_2]_n$  is split into a triplet due to coupling of the phosphorus atoms with the two protons of the neighboring methylene group. For the acids in aqueous solution the triplet centers in the range of -11 to -8 ppm for all cases studied and the coupling constant was determined to be 13 cps. The relatively narrow range of the  $\text{P}^{31}$  chemical shifts observed in the total series of compounds indicates that the shielding effect on the phosphorus atom by atoms beyond nitrogen is negligible.

The  $\text{P}^{31}$  chemical shifts of  $\alpha$ -aminomethylphosphonic acids are greatly dependent upon the acidity of the solution in which they are measured. As seen in Figure 1 for nitrilotrismethylenetriphosphonic acid, addition of sodium hydroxide up to an amount of 5 equiv/mole of acid has only a very slight effect on the chemical shift. However, addition of sodium hydroxide in excess of 5 moles causes a shift of the signal from the -8-ppm region to *ca.* -18 ppm, a value which is reached after 6 moles of sodium hydroxide have been added. Further addition of sodium hydroxide, again,

(16) K. A. Petrov, F. L. Maklyaev, and N. K. Bliznyuk, *J. Gen. Chem. USSR*, **29**, 587 (1959).

(17) E. H. Uhing and A. D. F. Toy, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, Abstracts, p 68 Q; U. S. Patent 3,160,632 (Dec 8, 1964).

(18) W. M. Ramsay and C. Kezerian, U. S. Patent 2,917,528 (Aug 24, 1956); *Chem. Abstr.*, **54**, 24399 (1960).

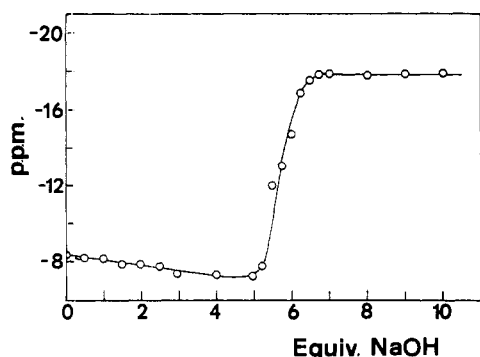


Figure 1.—Variation of the nmr chemical shift of the  $P^{31}$  nucleus in  $N[CH_2P(O)(OH)_2]_3$  upon neutralization with sodium hydroxide.

changes the observed shift only within the limits of experimental error. This effect is interpreted to mean that upon addition of the sixth mole of sodium hydroxide per mole of the acid the proton coordinated to the central nitrogen atom, as shown in I, is neutralized, thus converting the quaternary nitrogen to amine nitrogen. This change in the electronic structure of the nitrogen atom results in a change in the shielding of the phosphorus atom and consequently in a different chemical shift. This assumption is in agreement with the observed  $P^{31}$  chemical shift values for esters of  $\alpha$ -aminomethylphosphonic acids which truly are compounds of triply connected nitrogen. The nmr signals of the latter type of compounds have been found<sup>19</sup> in the range from  $-22$  to  $-24$  ppm, *e.g.*,  $N[CH_2P(O)(OC_2H_5)_2]_3$ ,  $-22.6$  ppm, and  $HN[CH_2P(O)(OC_2H_5)_2]_2$ ,  $-23.3$  ppm. This is in agreement with the value of  $-18$  ppm found for the completely neutralized nitrilotrismethylenetriphosphonic acid, *i.e.*, the hexasodium salt in which the nitrogen is also triply connected.

Furthermore,  $P^{31}$  nmr has been proven to be a valuable analytical means for studying quantitatively the course of the reaction of eq 3. The spectrum of phosphorous acid in the reaction mixture is a doublet with peaks at *ca.*  $-19$  and  $+7$  ppm. The formation of aminomethylphosphonic acid moieties was signalled by the appearance of the triplet at *ca.*  $-10$  to  $-8$  ppm. There was also a small peak at 0 ppm, but usually representing less than 5% of the total phosphorus, due to phosphoric acid formed from phosphorous acid in a side reaction. Quantitative evaluation of  $P^{31}$  nmr spectra obtained during the course of the reaction helped to establish the preferred reaction conditions given earlier in this paper.

**Physical and Chemical Properties.**—The melting points observed for the acids listed in Tables I and II display a surprising uniformity. Regardless of the nature of the groups R in  $R_{3-n}[CH_2P(O)(OH)_2]_n$  the compounds melted in the range *ca.*  $200$ – $250^\circ$  under evolution of bubbles and subsequent decomposition.

The compounds were found to be quite resistant to chemical attack. Extended refluxing of samples of the acids in dilute or concentrated acids or bases did not result in a change in the  $P^{31}$  or  $H^1$  nmr spectra of these solutions. For analytical purposes the acids may be decomposed by ashing in perchloric acid media.

Preliminary studies demonstrated the outstanding chelating properties of  $\alpha$ -aminomethylphosphonic acids.

Their alkali metal salts were found to form stable complexes with alkaline earth and polyvalent metal ions. In general, one metal ion is complexed by two to three aminomethylphosphonate groups. The stability constant for a given complexed ion decreases upon substitution of methylenephosphonic groups in  $N[CH_2P(O)(OH)_2]_3$  by organic groups to give  $RN[CH_2P(O)(OH)_2]_2$  or  $R_2NCH_2P(O)(OH)_2$ . Furthermore, in a series of each of the latter two compounds, the stability of a complex decreases with increasing chain length of the organic group R. A more detailed account of the complexing behavior of  $\alpha$ -aminomethylphosphonic acids will be published elsewhere.

**Mechanism.**—Mannich-type reactions with phosphorus compounds having P–H bonds in the past have been interpreted in terms of a base-catalyzed mechanism,<sup>20</sup> as reported for the reactions with dialkyl phosphonates,  $HP(O)(OR)_2$ . As, however, the reaction with phosphorous acid requires strongly acidic media and as a matter of fact, does not proceed in neutral or basic solution, a different type of mechanism must be considered.

### Experimental Section

**Reagents.**—The amines or amine hydrochlorides as well as the functionally substituted amines were commercial products of highest available purity and were used as received. Aqueous formaldehyde solution (37%) or paraformaldehyde and crystalline phosphorous acid or 70% solution were obtained from Fisher Scientific.

**Nmr Measurements.**—Proton nmr spectra were obtained on a Varian A-60 spectrometer. The  $P^{31}$  nmr measurements were made on a Varian high-resolution spectrometer system using a Model V-4311 fixed-frequency RF unit operating at 24.288 Mc in a magnetic field of 14,092 gauss. Referencing was done by an audio side band modulation technique using, as an external reference, 85%  $H_3PO_4$  in a sealed 1.0-mm od capillary tube inserted in the sample.

**Hydrolysis of Chloromethylphosphonic Acid.**—A sample of  $ClCH_2PO(OH)_2$  in an aqueous NaOH solution of pH 11.5 after 14 days at  $80^\circ$  yielded an amount of titratable chlorine equivalent to 33% hydrolysis according to eq 2. In the  $P^{31}$  nmr spectrum of this solution the presence of the hydrolysis product  $HOCH_2P(O)(OH)_2$  was indicated<sup>19</sup> by the appearance of a new peak at  $-23.5$  ppm [ $ClCH_2P(O)(OH)_2$ :  $-18.5$  ppm.] When chloromethylphosphonic acid was treated with a primary amine according to eq 1 under the conditions given above, also about 30% of the acid had hydrolyzed to form hydroxymethylphosphonic acid as described by eq 2.

**Nitrilotrismethylenetriphosphonic Acid.**—A quantity of 17.8 g (0.33 mole) of ammonium chloride, 82 g (1 mole) of crystalline phosphorous acid dissolved in 100 ml of water and 100 ml of concentrated HCl were heated to reflux in a three-necked flask fitted with thermometer, stirrer, condenser, and dropping funnel. In the course of *ca.* 1 hr 160 ml of 37% aqueous formaldehyde solution (2 mole, 100% excess) was added dropwise, and the reaction mixture was kept at reflux temperature for 1 additional hr. Upon standing at room temperature overnight the acid crystallized partially. The crystals of this fraction were filtered, washed with acetone–water (5:1), and dried at  $120^\circ$ . The filtrate can be worked up in a similar fashion. The yield based on the first fraction is 74.9 g (75%), mp  $210$ – $215^\circ$ . Contrary to a previous report<sup>16</sup> which describes the acid as a glassy mass, our product is a free-flowing crystalline material. The compound titrated as pentabasic acid with inflection points at pH 3.5 (2 equiv) and pH 9.5 (3 equiv).

*Anal.* Calcd for  $C_3H_{12}NO_5P_3$ : C, 12.05; H, 4.04; N, 4.68; P, 31.06; mol wt, 299. Found: C, 12.28; H, 3.92; N, 4.47; P, 31.65; mol wt (by titration), 303.

**Alkyliminodimethylenediphosphonic Acids.**—A quantity of 0.5 mole of the alkylamine or the alkylamine hydrochloride, 1

(19) K. Moedritzer, L. Maier, and L. C. D. Groenweghe, *J. Chem. Eng. Data*, **7**, 307 (1962).

(20) M. I. Kabachnik and T. Y. Medved, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 893 (1954); *Chem. Abstr.*, **50**, 219, 1550 (1956).

mole of crystalline phosphorous acid dissolved in 100 ml of water, and 100 ml of concentrated HCl is treated with 2 moles of aqueous 37% formaldehyde solution (100% excess) as described in the preceding preparation. The resulting acids with alkyl groups lower than C<sub>5</sub> were isolated by evaporation of the reaction mixture to a syrupy state and subsequent dissolution in hot ethanol. Upon cooling to room temperature the acids crystallized. The acids having alkyl groups with five or more carbon atoms crystallized from the reaction mixture upon cooling to room temperature. They may be recrystallized from hot dilute hydrochloric acid solution. All acids of this class titrated as tribasic acids with inflection points at pH 4.5 (1 equiv) and pH 9 (2 equiv). Analytical data and melting points are listed in Table I.

**Polymethylenebis(nitrilodimethylene)tetrakisphosphonic Acids.**—A quantity of 0.25 mole of the diamine H<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, 1 mole of crystalline phosphorous acid dissolved in 100 ml of water, and 100 ml of concentrated HCl was treated with 2 moles of 37% aqueous formaldehyde solution as described above. Upon cooling of the reaction mixture to room temperature, the acids generally separated as white crystalline materials. In some instances, when diamines with a large value of *n* were used, the corresponding acids crystallized from the solution during the reaction. The products were washed with cold water and dried at 120°. The yields recorded in Table II represent the amounts

of product that separated from the reaction mixture upon cooling to room temperature. Evaporation of the filtrate generally yielded additional fractions. However, no efforts have been made to isolate quantitatively the reaction products from the solution although P<sup>31</sup> indicated 95% conversion of the phosphorous acid to aminomethylphosphonic acids. All acids of this class titrated as hexabasic acids with inflection points at pH 4 (2 equiv) and pH 9 (4 equiv). Analytical data and melting points are listed in Table II.

**Triethylenetetraminehexa(methylenephosphonic Acid).**—A quantity of 48 g (0.33 mole) of triethylenetetramine was dissolved in 75 ml of concentrated HCl and a concentrated aqueous solution of 162 g (2 moles) of phosphorous acid. The resulting solution was heated to reflux temperature and 320 ml of 37% aqueous formaldehyde solution (4 moles) was added dropwise in the course of 1 hr. Ethanol precipitated 75 g (35.4%) of a slightly yellow product from the concentrated reaction solution.

*Anal.* Calcd for C<sub>12</sub>H<sub>34</sub>N<sub>4</sub>O<sub>18</sub>P<sub>6</sub>: C, 20.29; H, 5.11; N, 7.89; P, 26.17; mol wt, 710. Found: C, 19.94, H, 5.69; N, 8.53; P, 25.42; mol wt (by titration), 700.

**Acknowledgment.**—We wish to thank Dr. T. L. Westman for helpful discussions and J. P. Brennan for experimental assistance.

## Hydride Transfer. Reactions of Triphenylcarbonium Fluoroborate and Triphenylmethyl Bromide with Tertiary Amines

RALPH DAMICO AND C. D. BROADDUS

*The Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239*

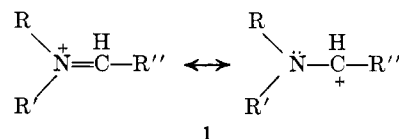
Received February 7, 1966

Trialkylamines undergo hydride transfer reactions with triphenylcarbonium fluoroborate and triphenylmethyl bromide in chlorinated hydrocarbons, acetonitrile, excess amine solvents, and diluents at room temperature. If an amine contains only  $\alpha$  hydrogens the corresponding ternary iminium salt can be isolated. When  $\beta$ -hydrogen atoms are present the intermediate ternary iminium salt reacts with tertiary amine to produce an enamine and amine hydroanion salt. Enamines transfer hydride ions very rapidly to triphenylcarbonium fluoroborate and triphenylmethyl bromide. A mechanism is proposed to account for high yields of amine hydroanion salts and triphenylmethane from reactions of trialkylamines and trityl salts.

During the past decade triphenylcarbonium ion has been used to abstract hydride ions from a variety of olefinic and oxygen-containing compounds.<sup>1,2</sup> For example, Dauben and co-workers have prepared tropenium ion salts<sup>1a</sup> and tropenium-metal carbonyl complex ion salts<sup>1b,c</sup> from cycloheptatriene compounds, while Deno and collaborators<sup>2</sup> have examined acyclic and cyclic alcohols, ethers, and some esters with this reagent. Other workers have oxidized alcohols,<sup>3</sup> ethers,<sup>3,4</sup> and formic acid<sup>5</sup> with triphenylcarbonium ion. The facile hydride transfers from oxygen compounds can be attributed to stabilization of the incipient carbonium ions by resonance contributions of nonbonding electrons on oxygen.

In view of these various reports on hydride transfer reactions of oxygen compounds it is somewhat surprising that there is little work reported on the use of trityl salts<sup>6</sup> to abstract hydride ions from the isoelec-

tronic nitrogen compounds. For example, extraction of hydride ion from tertiary amines would be expected to be assisted by the formation of the stable ternary iminium salts (1)



Recently Meerwein and co-workers<sup>4</sup> oxidized tribenzylamine with triphenylcarbonium fluoroborate to obtain a 94% yield of the corresponding iminium salt; however, extension of this reaction to amines containing  $\beta$ -hydrogen atoms has not been reported. We have attempted to prepare dodecylidinedimethylaminium fluoroborate (1, R, R' = CH<sub>3</sub>; R'' = C<sub>11</sub>H<sub>23</sub>) by the reaction of dimethyldodecylamine with triphenylcarbonium fluoroborate in dichloromethane; however, despite a 62% yield of triphenylmethane, no ternary iminium salt was recovered. Instead, a 70% yield of dimethyldodecylamine hydrofluoroborate was realized (eq 1).

(6) Trityl salts will be used synonymously with triphenylcarbonium fluoroborate and triphenylmethyl bromide in this paper, since the reactive species in both of these compounds is probably the triphenylcarbonium ion.

(1) (a) H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon, and D. L. Pearson, *J. Am. Chem. Soc.*, **79**, 4557 (1957); (b) H. J. Dauben, Jr., and D. J. Bertelli, *ibid.*, **83**, 497 (1961); (c) H. J. Dauben, Jr., and L. R. Honnen, *ibid.*, **80**, 5570 (1958); (d) L. M. McDonough, Ph.D. Thesis, University of Washington, 1960, and references therein.

(2) N. Deno, *Progr. Phys. Org. Chem.*, **2**, 129 (1964), and references therein.

(3) P. D. Bartlett and J. D. McCollum, *J. Am. Chem. Soc.*, **78**, 1441 (1956).

(4) H. Meerwein, J. Hederich, H. Morschel, and K. Wunderlich, *Ann.*, **635**, 1 (1960).

(5) R. Stewart, *Can. J. Chem.*, **35**, 766 (1957).