(73.8), 27 (61.5), 26 (20.9), 25 (3.4). The nmr spectrum was obtained in $CDCl_3$ solution and is described in the text.

Anal. Calcd for $C_8H_{15}ClN_2O_4$: C, 40.25; H, 6.29; N, 11.72; Cl, 14.90%. Found: C, 40.07; H, 6.29; N, 11.62; Cl, 15.05%.

Registry No.—2, 5336-13-0.

Studies Concerning the Neutralization of Tetrakis(hydroxymethyl)phosphonium Chloride and the Reaction of Tris(hydroxymethyl)phosphine with Formaldehyde

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The unusual behavior of tetrakis(hydroxymethyl)phosphonium chloride (tetrakis) toward base has been a subject of interest since its original synthesis.[1] Most tetraalkylphosphonium salts require temperatures above 100° in order to react with metal hydroxides, giving phosphine oxide plus hydrocarbon.[2] However, tetrakis reacts facilely with base; in fact it is a monoprotic acid, having an apparent[7] pK_a of 5.5 and a true[3] pK_d of 7.06. Many authors have written the neutralization reaction as

$$R_4P^+OH^- \longrightarrow R_3P{=}O + RH$$

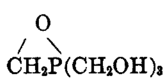
$$\underset{\text{tetrakis}}{(HOCH_2)_4PCl} + NaOH \longrightarrow NaCl + HCHO + H_2O + \underset{\text{THP}}{(HOCH_2)_3P}$$

since there is ample chemical evidence for the formation of tris(hydroxymethyl)phosphine (THP) and formaldehyde.[3-7,19b]

Various other species have been suggested as being in equilibrium with tetrakis and THP. In his study of the hydroxide-induced oxidation of the THPC to tris(hydroxymethyl)phosphine oxide (THPO), Grayson[7] proposed an equilibrium between THP and structure **1** or, less favorably, **2** or **3**.

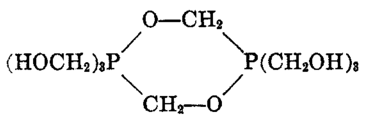
$^{-}OCH_2\overset{+}{P}(CH_2OH)_3$

1



$$\overset{O}{\overbrace{CH_2P}}(CH_2OH)_3$$

2



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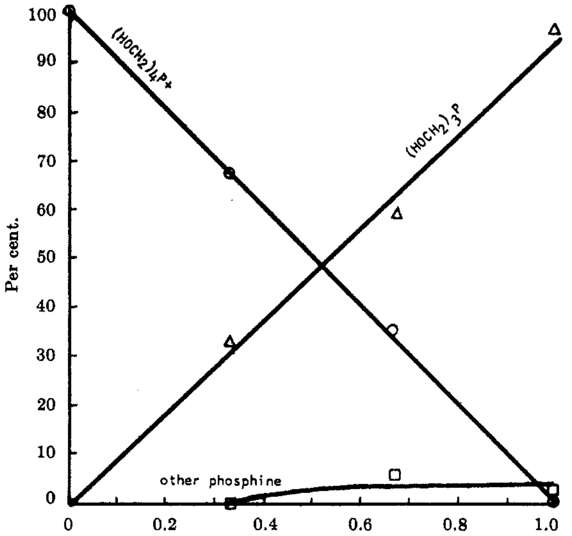

Figure 1.—Neutralization of tetrakis by NaOH in methanol.

French workers,[8] and more recently Filspescu, *et al.*,[9] proposed an equilibrium between THP and tetrakis(hydroxymethyl)phosphonium hydroxide (THPOH).

$$(HOCH_2)_4PCl \xrightarrow[\text{or MOH}]{PbCO_3} (HOCH_2)_4POH$$

$$(HOCH_2)_3POH \rightleftharpoons (HOCH_2)_3P + H_2O + HCHO$$

The synthesis of THPOH by the reaction of phosphine with formaldehyde in the presence of transition metal halide catalysts[10a,b] or pressure[10c] has recently been reported.

We were therefore encouraged to study the neutralization of tetrakis by ^{31}P nuclear magnetic resonance spectroscopy. The chemical shifts of tetrakis (−27 ppm), THP (+25 ppm), and THPO (−48 ppm) are widely different. Phosphonium salts absorb over a fairly narrow range[11] around −30 ppm, so that zwitterion **1** and THPOH, should it be ionic, would be recognized either by a less than quantitative reduction in the −27-ppm peak or by a new peak very near. It is not possible to predict with certainty where pentacovalent structures **2** and **3** and a pentacovalent THPOH might absorb owing to the lack of suitable models.[12]

The course of the neutralization of tetrakis by sodium hydroxide in water and in methyl alcohol using ^{31}P nuclear magnetic resonance spectroscopy was followed. The results are shown in Figures 1 and 2 and may be summarized as follows: (1) in methyl alcohol the concentration of tetrakis diminishes in direct proportion to the amount of base added. During the early portion of the neutralization THP is the only species produced. After a third of a mole of base has been added, a new peak appears at +29.1 ppm, amounting to about

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(1) A. Hoffman, *J. Amer. Chem. Soc.*, **43**, 1684 (1921); **52**, 2995 (1930).

(2) A. Cahours and A. W. Hofmann, *Ann.*, **104**, 1 (1957).

(3) L. M. Fodor, Ph.D. Thesis, Cornell University, Ithaca, N. Y., 1963.

(4) H. Hellman and O. Schumacker, *Angew. Chem.*, **72**, 211 (1960).

(5) K. A. Petrov, V. A. Parshina, and M. B. Luzanova, *J. Gen. Chem. USSR*, **32**, 553 (1962).

(6) W. J. Vullo, *Ind. Eng. Chem. Prod. Res. Develop.*, **5**, 344 (1966).

(7) M. Grayson, *J. Amer. Chem. Soc.*, **85**, 79 (1963).

(8) French Patent 1,011,978 (1952).

(9) N. Filipescu, L. M. Kindley, H. E. Podall, and F. A. Serafin, *Can. J. Chem.*, **41**, 821 (1963).

(10) (a) M. Reuter and L. Orthner, German Patent 1,041,957 (1958); (b) M. Reuter, German Patent 1,064,061 (1960); (c) Kh. R. Raver, A. B. Brecker, and L. Z. Soborovski, *J. Gen. Chem. USSR*, **32**, 588 (1961).

(11) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer in "Topics in Phosphorus Chemistry," Vol. V, "P^{31} Nuclear Magnetic Resonance," M. Grayson and C. Griffith, Ed., Interscience Publishers Inc., New York, N. Y., 1967, Chapter 4.

(12) A positive (to phosphoric acid reference) chemical shift might be expected by analogy with phosphoranes and oxyphosphoranes, ref 11, pp 434–442.

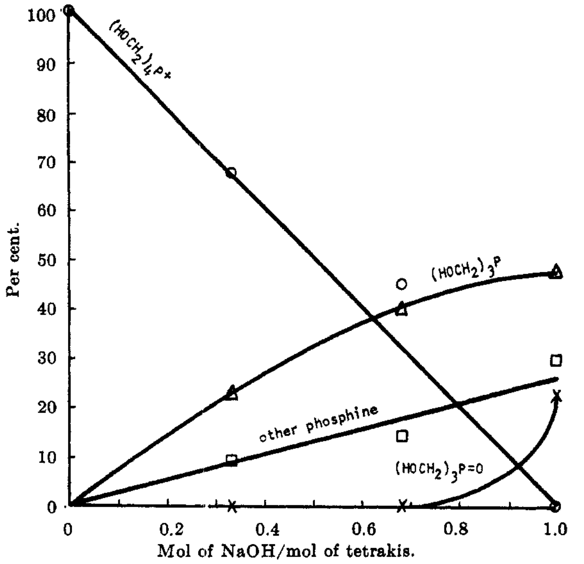


Figure 2.—Neutralization of tetrakis by NaOH in water.

5% at the equivalence point. (2) In water, as in methanol, the phosphonium peak is diminished in direct proportion to the amount of base added. The new peak is produced in even greater amount here than in methanol, reaching about 29% at the equivalence point. At or near the equivalence point THPO begins to form.

Owing to the proximity of the new peak to THP we suspected a *t*-phosphine rather than a pentacovalent species. It is felt that the new product is probably a hemiacetal resulting from reaction of THP with the by-

$$(HOCH_2)_3P + HCHO \rightleftharpoons HOCH_2OCH_2P(CH_2OH)_2$$

product formaldehyde. Alcohols have been shown to compete more favorably for formaldehyde than does water, *i.e.*, hemiacetals are more stable than hydrates.[13] Therefore, the tetrakis hemiacetal should be more stable in water than in methanol, explaining the solvent effect. Additional evidence for the formation of hemiacetal is the proton magnetic resonance spectrum of the residue obtained by evaporating to dryness a neutralized solution of tetrakis. This shows, in addition to a major amount of THP, a sharp singlet at 4.74 ppm (to tetramethylsilane reference) and a complex pattern just upfield from the THP methylene protons at around 4.08 ppm in a ratio of *ca.* 1:2.8. The singlet is in the correct place for OCH_2O, the complex pattern could be two types of OCH_2P protons in the monohemiacetal, and the ratio agrees fairly well with the ratio of 1:3 calculated for the monohemiacetal.

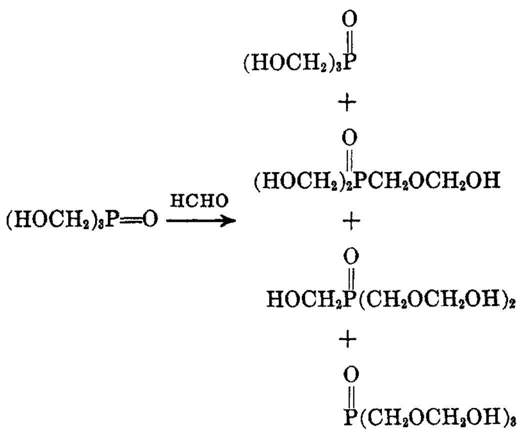
To obtain more information concerning the reaction between THP and formaldehyde, the ^{31}P nmr of solutions of THP and THPO in aqueous formaldehyde was studied. The THP employed was a mixture of THP, *ca.* 52%, and phosphine oxides, mainly THPO, and the molar ratio of formaldehyde to phosphorus compound was about 1.8. Results are shown in Table I and may be summarized as: (1) THPO shows a singlet (unresolved multiplet) in water but three to four closely lying peaks in aqueous formaldehyde, and (2) THP likewise shows one peak in water and three to four peaks in aqueous formaldehyde. No phosphonium peaks are present.

TABLE I

^{31}P NMR ANALYSIS OF THPO AND THP IN WATER AND AQUEOUS FORMALDEHYDE

THPO + water			THPO + formaldehyde	
Chemical shift	%		Chemical shift	%
−48.1	100		−49.6	24
			−48.5	42
			−47.8	34
			Ca. −47	Trace, appears to be increasing with time
THP + water			THP + formaldehyde	
Chemical shift	%		Chemical shift	%
+24.8	52		+25.5	16
			+29.0	28
			+33.7	15
			+38.5	Trace, appears to be increasing with time
−52	14	Phosphine oxide impurities	−52.4	10
−48.6	29		−50.1	17
−46.5	5		−49.0	8
			−47.8	6

It is concluded that THPO reacts with formaldehyde to give a mixture of THPO and mono-, bis-, and tris-hemiacetals. Since THP also shows one peak in water



$$(HOCH_2)_3P{=}O \xrightarrow{HCHO} (HOCH_2)_3\overset{O}{\overset{\|}{P}} + (HOCH_2)_2\overset{O}{\overset{\|}{P}}CH_2OCH_2OH + HOCH_2\overset{O}{\overset{\|}{P}}(CH_2OCH_2OH)_2 + \overset{O}{\overset{\|}{P}}(CH_2OCH_2OH)_3$$

and three to four peaks in formalin, the reaction between THP and formaldehyde is most likely hemiacetal formation also. The neutralization of tetrakis can, therefore, best be presented as

$$(HOCH_2)_4PCl + NaOH \longrightarrow (HOCH_2)_3P + HCHO + NaCl + H_2O$$

$$(HOCH_2)_3P + HCHO \rightleftharpoons HOCH_2OCH_2P(CH_2OH)_2$$

The reaction of formaldehyde with the hydroxyl group rather than the phosphorus atom of THP is attributed to the low nucleophilicity and basicity of phosphorus in this compound owing to the inductive effects of the hydroxymethyl groups. THP much more closely resembles triphenylphosphine than tributylphosphine in nucleophilicity. Thus, the second-order rate constant for the reaction with ethyl iodide (35°) is calculated, from the equation of Henderson, to be 4.5×10^{-5} as compared with the experimental values[14] of 162×10^{-5} for tributylphosphine and 3.78×10^{-5} for triphenylphosphine.

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[13] J. F. Walker, "Formaldehyde," 3rd ed, American Chemical Society Monograph No. 159, Reinhold Publishing Corp., New York, N. Y., 1964 p 78.

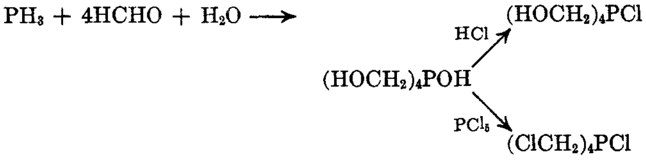
[14] W. A. Henderson, Jr., and S. A. Buckler, *J. Amer. Chem. Soc.*, **82**, 5794 (1960).

Some data concerning the equilibrium between *t*-phosphines and aqueous formaldehyde have been obtained.

$$R_3P + HCHO + H_2O \rightleftharpoons R_3\overset{+}{P}CH_2OH\ \overset{-}{O}H$$

When tributylphosphine was added to a neutral solution of formaldehyde in alcohol–water, approximately 1 mol of hydroxide ion was produced (by titration). However, triphenylphosphine or THP produced no increase in pH. The above equilibrium, therefore, lies far to the right for tributylphosphine but far to the left for THP and triphenylphosphine.

Our finding that neutralization of tetrakis and the reaction of THP with formaldehyde produces a mixture of THP and THP hemiacetal makes questionable the structure of THPOH.[15-17] The synthesis,[10] from phosphine and aqueous formaldehyde, most likely proceeds through the intermediacy of THP. The syrup isolated was identified by elemental analyses, reaction with hydrochloric acid, and reaction with phosphorus pentachloride.[10c] These same results, however, would be



obtained from a more probable mixture of hydrated hemiacetals of THP, for example, approximated by

$$(HOCH_2)_2PCH_2OCH_2OH \cdot H_2O$$

Experimental Section

The nmr spectra were recorded on a Varian Associates Model HA-100 spectrometer at 40.47 MHz; chemical shifts are in parts per million from external phosphoric acid reference. Chemical shifts are accurate to about 0.5 ppm and integrated areas to about 5%.[18] The initial scans were run at a sweep rate of 1.2 ppm/sec, covering the range of −75 to +50 ppm, and the analytical scans were run at a sweep rate of 0.5 ppm/sec.

Materials.—The THPO and THP were gifts of our sample preparation laboratory and were prepared by methods of Gordon.[19a,b] The THPO analyzed for greater than 98% purity by ^{31}P nmr spectroscopy. The THP analyzed for about 52% THP and 48% of a mixture of phosphine oxides, mainly THPO (see Table I). The formaldehyde was a Fisher Scientific product, 40% aqueous formaldehyde. The tetrakis was plant grade material, mp 141–143° (lit.[1] mp 151°).

The Neutralization of Tetrakis by Sodium Hydroxide in Methanol and in Water.—The following solutions were prepared: 2.16 *M* aqueous tetrakis, 2.89 *M* methanolic tetrakis, 2.95 *M* aqueous sodium hydroxide, and 3.21 *M* methanolic sodium hydroxide. The concentration of tetrakis was determined by titration with standard sodium hydroxide to a phenolphthalein end point, and the concentration of sodium hydroxide was determined by titration with standard hydrochloric acid. To a small volume of the tetrakis solution in a test tube was added the calculated volume of base. The tube was stoppered under nitrogen, shaken well, and after allowing about 1 hr for equilibration the ^{31}P nmr spectrum was obtained. In methanol solution the chemical shifts were tetrakis, −27.6; THP, +24.8; and other phosphine, +29.1. In aqueous solution the chemical shifts were tetrakis, −26.5; THP, +24.8; other phosphine, +27.7; and THPO −48. Results of these experiments are shown in Figures 1 and 2. Owing to the high noise level no attempt was made to investigate coupling constants by ^{31}P magnetic resonance spectroscopy. However, the residue obtained by neutralization of an ethanolic water solution of tetrakis, removal of salt, and careful evaporation of solvent to constant weight was investigated by proton magnetic resonance spectroscopy. The spectrum, taken in deuterioacetone with tetramethylsilane as an internal reference, showed a singlet at 4.74 ppm (area 1.0), the THP methylene protons as a doublet at 4.18 ppm (J_{P-H} = 6.6 MHz) above the broad hydroxyl peak (total area approximately 9.5), and a complex pattern (approximate area 2.8) centered about 4.08 ppm and partly overlapping the THP doublet. The 4.74-ppm singlet is in the region expected for OCH_2O.[20]

The Reaction of Formaldehyde with THPO and with THP.—The following solutions were prepared using oxygen-free water, oxygen-free 40% aqueous formaldehyde, and maintaining a nitrogen atmosphere: 50% THPO in 40% aqueous formaldehyde, 50% THP in 40% aqueous formaldehyde, 50% THPO in water, 50% THP in water. After allowing about 1 hr for equilibration the ^{31}P nmr spectra were determined. Results are shown in Table I.

The Reaction of *t*-Phosphines with Formaldehyde as Determined Titrimetrically.—An *ca.* 0.3 *M* stock solution of tributylphosphine (Carlisle Chemical Works) was prepared by dissolving 6 ml of the phosphine in about 100 ml of denatured alcohol. A 10-ml aliquot of this dissolved in alcohol required 50.5 ml of 0.101 *N* aqueous iodine, corresponding to a concentration of 0.252 *M*. A 10-ml aliquot of the stock solution was added to a solution of 5 ml of 40% formaldehyde in 20 ml of 2B alcohol which had been made just neutral to phenolphthalein. The pink phenolphthalein color immediately appeared. The solution was swirled a few minutes, 20 ml of distilled water was added, and then it was titrated with 0.1012 *M* hydrochloric acid. A total of 24.50 ml of acid was required to discharge the phenolphthalein color, corresponding to a concentration of 0.248 *M* for the stock tributylphosphine solution.

When THP and triphenylphosphine were similarly treated, they did not produce a phenolphthalein color.

Registry No.—Tetrakis, 16980-25-9; THP, 2767-80-8; THPO, 1067-12-5; formaldehyde, 50-00-0.

Acknowledgment.—The author thanks the spectroscopy laboratory of Hooker Chemical Corporation, in particular Dr. James Colson, for invaluable assistance in obtaining and interpreting the ^{31}P nmr spectra.

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[15] One wonders whether THPOH can exist as a stable compound. A pentacovalent structure seems unlikely in view of the greater stability of quadruple- over quintuple-bonded phosphorus[16] and the hydrolytic instability of oxyphosphoranes.[17] An ionic structure also seems unlikely in that it would contain both a strong base and a moderately strong acid.

[16] J. R. Van Wazer, "Phosphorus and Its Compounds," Vol. I, Interscience Publishers, Inc., New York, N. Y., p 73.

[17] F. Ramirez, International Union of Pure and Applied Chemistry, Organic Chemistry Division Special Symposium on Organo Phosphorus Compounds, Heidelberg, Germany, 1964, p 368.

[18] J. Colson and A. Davis, "Quantitative Analysis by ^{31}P NMR," presented at the Applied Spectroscopy Meeting, Chicago, Ill., June 1967.

[19] (a) I. Gordon, U. S. Patent 3,076,034 (1963); (b) I. Gordon and G. M. Wagner, U. S. Patent 3,257,460 (1966).

[20] High Resolution NMR Spectra Catalog, Vol. 2, Varian Associates, 1963, spectra no. 437 and 445.

A New Synthesis of Lysine

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Numerous papers have been published on the synthesis of lysine.[1] The present paper reports a new method of synthesis of lysine starting from β-cyano-

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[1] J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 2097.