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THE STRUCTURE OF THE SO-CALLED "ETHYLMETAPHOSPHATE" (LANGHELD ESTER)

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Phosphorus pentoxide reacts with ether to form bicyclotetraphosphate ester (II), cyclotetraphosphate ester (III), isocyclotetraphosphate ester (IV), and tetraphosphate ester (V). Phosphorus n.m.r. measurements show the content of the mixtures. The so-called "ethyl metaphosphate" (Langheld ester) is a mixture of III (50% to 45%), IV (36% to 25%), and V (14% to 30%).

The product of the reaction of ether and phosphorus pentoxide[3] has recently become interesting as a reagent for the synthesis of polysaccharides, polypeptides, and polynucleotides.[4] Unfortunately, the

(3) K. Langheld, Chem. Ber. 43, 1857 (1910); 44, 2076 (1911).

(4) G. Schramm, H. Grötsch a. W. Pollmann, Angew. Chem. 74, 53 (1962).

nature of this product, which is usually called ethylmetaphosphate, is not certainly known. Heretofore the proposal of Rätz and Thilo[5] that

(5) R. Rätz a. E. Thilo, Liebigs Ann. Chem. 572, 173 (1951).

the ester is a mixture of cyclotetraphosphate ester (Fig. 1, structure III) and isocyclotetraphosphate ester (Fig. 1, structure IV) has been accepted. But the phosphorus n.m.r. spectrum of the product obtained by several groups does not conform to that assignment.[6,7] In this paper

(6) J. R. Van Wazer, C. F. Callis, J. N. Shoolery a. R. C. Jones, J. Am. Chem. Soc. 78, 5715 (1956).

(7) G. Weill, M. Klein a. M. Calvin, Nature 200, 1005 (1963).

studies are described which were made to determine the actual composition of the so-called "ethylmetaphosphate".

Langheld[3] first prepared "ethylmetaphosphate" by refluxing phosphorus pentoxide with ether. This synthesis was improved by Steinkopf and Schubart[8] using chloroform as a solvent. Since then several additional

(8) W. Steinkopf a. I. Schubart, Liebigs Ann. Chem. 424, 1, esp. 19 (1921).

methods have been described in the literature.[4,5,9] They differ mainly

(9) W. Pollmann a. G. Schramm, Biochim. et Biophys. Acta 80, 1 (1964).

in the time of heating and in the ratio of ether and chloroform in the reaction mixture.

However, in our experiments various products were obtained by heating ether and phosphorus pentoxide in chloroform, depending on the time of heating and on the amount of ether which was used. They ranged from a rubber-like material (B) through a very heavy oil (C) to an oil of lower viscosity (D) (Table I). The refractive index of the liquids varied from 1.441 (C) to 1.438 (D) (20° C) and the viscosity from

TABLE I

Properties and phosphorus n.m.r. peaks of the materials which were obtained by reaction of P_4O_{10} with ether.

Material description (all soluble in $CHCl_3$, colorless to slightly brown)		$n_D 20°$	density (20°)	viscosity (20°) (poise)	P_m %	P_b %	P_t %
A	plastic-like	-	-	-	71.9	22.9	5.2
B	rubber-like	-	-	-	78.7	9.8	11.5
C	heavy oil	1.441	1.462	237.44	75.2	8.9	15.9
D	viscous oil	1.438	1.413	19.45	73.4	6.2	20.4
E	light oil	1.437	1.408	9.76	69.8	4.0	26.2
F	oil	1.434	-		62.7	3.1	34.2
G	oil	1.433	-		55.8	1.8	42.4

237.44 (C) to 19.45 poise (D) (20° C). Therefore, the description of the product as a mixture of ca. 10% of compound III and ca. 90% of compound IV[5] cannot be entirely correct. This does not describe the different properties of our materials prepared by various methods. Furthermore, for the preparation of the "ethylmetaphosphate" two equivalents of ether are necessary. If we used only one equivalent of ether or less, we got a plastic-like solid material (A), which was soluble in $CHCl_3$. Refluxing the solid compound with an excess of ether gave an oil with the refractive index 1.438 and with a viscosity of 25.23 poise. Thus, the new solid product could be an intermediate in the preparation of the "ethylmetaphosphate".

An insight into this problem is possible by means of phosphorus n.m.r. measurements. A phosphorus atom which is bonded to another phosphorus atom via an oxygen atom shows a different chemical shift in the n.m.r. spectrum than an atom which is bonded to zero, two or three phosphorus atoms via oxygen. Thus each type of phosphorus should show a separate line and the compounds with structures II to V can be expected to show three different peaks corresponding to the branched bonded (P_b), the middle bonded (P_m), and the terminal bonded phosphorus (P_t).[6]

If the "Langheld ester" were a mixture of III and IV,[5] the n.m.r. spectrum would show a large peak of middle bonded phosphorus (P_m), and two smaller, but equal, peaks of terminal (P_t) and branched bonded phosphorus (P_b). But the spectrum obtained by Van Wazer[6] showed only 3% P_b compared to 25% P_t. However, while G. Weill, M. Klein, and M. Calvin[7] get a similar result from one preparation (with 6% P_b and 32% P_t), from

another sample a value of 13% P_b and 15% P_t was obtained. It was thought that hydrolysis had taken place in those samples where a difference in the sizes of the P_b and P_t peaks was found. In our experiments all materials showed a very small proton peak of an OH group at 12.1 p.p.m. in the proton n.m.r. spectra. This peak did not increase during the experiments. On the contrary, the ratio of the OH and the C_2H_5 groups calculated from the areas under the n.m.r. peaks changed to higher values of the ethyl groups in the series from material A to G. It ranged from 1 : 8.3 (OH : C_2H_5) for material A through 1 : 13.7 for material D to 1 : 17.7 for material G. These values are not constant for each material; they changed slightly for each actual preparation. The contamination of the "ethylmetaphosphate" with a small amount of OH groups (which probably replace some of the ethyl groups of compounds II to V to a slight extent) must result from impurities of the phosphorus-pentoxide.

Therefore, no hydrolysis could have taken place during the experiments (see also experimental part), but the phosphorus n.m.r. spectra generally showed different sizes of the P_b and P_t peaks, as can be seen from Table I and Figure 2.

Consequently, it can be concluded from the preparative and the n.m.r. results that:

1. The material A, resulting from one equivalent of ether or less is a mixture of compounds II[10] (35.4%), III (43.8%), and IV (20.8%).

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(10) The possible formation of a compound with the structure II as a result of the reaction of P_4O_{10} with ether has already been suggested (M. Calvin, American Inst. of Biolog. Science, Bull. 12, p. 29, Fig. 8, Oct. 1962).

The mixture can contain only a very small amount of compound V, if it does contain any at all, since the P_b peak is much larger than the P_t peak. This means that P_4O_{10} (I) reacts with ether to form compound II. At the same time, a further reaction of II to III and IV takes place. Compound II, therefore, is highly sensitive to an attack by ether. The content of the compounds II, III, IV, or V in the mixture, as given in the parenthesis and in Table II, can be easily calculated from the n.m.r. results as explained in the experimental part.

2. Material B, which was obtained with two equivalents of ether, is a mixture of III (57.4%) and IV (39.2%), with a small amount of V (3.4%). The observation that the reaction of P_4O_{10} with a single equivalent of ether, producing material A, implies that a further reaction of II with ether occurred, leading to the formation of III and IV. Thus, no appreciable amount of II can be expected to remain in material B. The rings of compounds III and IV are opened by ether to form the chain compound V to some extent, giving rise to a larger amount of terminal phosphorus (P_t) than branched phosphorus (P_b). Compounds III and IV must be very sensitive to nucleophilic substances, since they were even attacked slowly by such a very weak nucleophile as is ether. This is confirmed by hydrolytic studies.[7,11]

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(11) Unpublished results from this laboratory.

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3. With an excess of ether we get a mixture, mainly of III with smaller amounts of V and IV. This is the material which has been observed most often and is called "ethylmetaphosphate" (in our experiments, materials C and D).

Table II

Composition of the materials A, B, C, D, E, F, G

Material	Compounds			
	II	III	IV	V
A	35.4%	43.8%	20.8%	-
B	-	57.4%	39.2%	3.4%
C	-	50.4%	35.6%	14.0%
D	-	46.8%	24.8%	28.4%
E	-	39.6%	16.0%	44.4%
F	-	25.4%	12.4%	62.2%
G	-	11.6%	7.2%	81.2%

4. Refluxing of the ester with ether converts more of the compounds III and IV into V. The material E obtained by refluxing for 65 hours consists of III (39.6%) and V (44.4%) with a smaller amount of IV (16.0%). After a longer time of refluxing, materials were obtained which consist mainly of V (materials F and G). There can be no considerable attack by ether of compound V leading to 2 moles of tetraethyl pyrophosphate: Extraction of material E with carbon tetrachloride gave a liquid (n_D^{20} = 1.431) which showed 44.0% P_t, 55.5% P_m and 0.5% P_b in the phosphorus n.m.r. spectrum. Tetraethyl pyrophosphate (100% P_t) is easily soluble in carbon tetrachloride but compounds III (100% P_m) and IV (50% P_m, 25% P_t, 25% P_b), as contained in material B, are nearly insoluble in this solvent. Thus, the CCl_4 extract, which was small, cannot be a mixture of tetraethyl pyrophosphate and compound III and a trace of IV, but must consist of compound V (50% P_t, 50% P_m) contaminated with a small amount of III and a trace of IV. This indicates that no considerable amount of tetraethyl pyrophosphate is present in the mixture and shows that hexaethyl tetraphosphate is soluble to some extent in CCl_4.

Further investigations of this separation are in progress.

5. P_4O_{10} does not react with V, IV, and III to form II. Only decomposition of the esters takes place.

In earlier papers[5,9] the composition of "ethylmetaphosphate" was studied by using hydrolytic destruction of the ester. By this method an amount of isocyclotetraphosphate ester (IV) is estimated higher than is actually present--i.e., total hydrolysis of compound III gives 4 moles of ethylphosphoric acid or 4 primary and 4 secondary acid groups; compound IV gives 2 moles of ethylphosphoric acid, 1 mole of diethylphosphoric acid, and 1 mole of phosphoric acid, or 4 primary, 3 secondary

acid groups and 1 tertiary acid group; and compound V gives 2 moles of ethylphosphoric acid and 2 moles of diethylphosphoric acid, or 4 primary and 2 secondary acid groups. If the amounts of compounds III and IV are calculated from the amount of diethylphosphoric acid,[5] or from the amount of secondary groups,[9] total hydrolysis of pure compound V would appear to have more of compound IV in the mixture than is actually present. Thus, in previous measurements, 85%[9] and 90%[5] of compound IV for two actual preparations were inferred.

Although the methods used in references 3, 5 and 8 for the preparation of mixtures of tetraphosphate esters (or Langheld ester) give up to 70% yield, they are unsatisfactory because they often lead to a rubber-like material, as we have found. This may result from a loss of ether during refluxing. The method used in reference 4 requires an excess of ether and a very long refluxing time. We found that at 25 hr. the reaction is still incomplete. The reason for this is the following: "Ethylmetaphosphate" is soluble in chloroform but insoluble in the solvent mixture here employed. "Ethylmetaphosphate" covers the surface of the P_4O_{10} and prevents further reaction of P_4O_{10} with ether. A more satisfactory procedure, as described in the experimental part, leading to a nearly 100% yield of tetraphosphate esters, results from reacting most of the P_4O_{10} with a small amount of ether in chloroform to form first compound II and then to react compound II with additional ether to form III, IV, and V.

It is to be expected that compounds II, III, IV, and V will differ in their capabilities and effectiveness in producing the dehydration

polymerization reaction. The compounds and polymers produced by the use of "ethylmetaphosphate" may therefore be expected to depend sharply upon the methods used in preparing and handling the "ethylmetaphosphate", a suggestion which would account for the variable results reported.[4,12,13,14]

(12) G. Weill, University of California, Lawrence Radiation Laboratory, Bio-Organic Chemistry Quarterly Report, UCRL-10934, July 29, 1963, p. 79.

(13) N. K. Kochetkov, E. I. Budowsky, V. D. Domkin, a. N. N. Khromov-Borissov, Biochim. et Biophys. Acta 80, 145 (1964).

(14) T. M. Jacob a. H. G. Khorana, J. Am. Chem. Soc. 86, 1630 (1964).

We are currently attempting to separate each of the compounds from the mixture and will study the susceptibility of each of the separate polyphosphate esters, as well as their mixtures, to nucleophylic reactions with ethers, alcohols, amines, esters, sulfides, etc..

EXPERIMENTAL

All experiments were carried out under nitrogen, which had been dried over P_4O_{10}, in an apparatus which had previously been dried by heating under vacuum and which then was closed with a $CaCl_2$ tube.[15,16]

(15) H. Metzger a. E. Müller in Methoden der Organischen Chemie I/2, p. 321 (Houben-Weyl), George Thieme Verlag, Stuttgart, 1959.

(16) K. Ziegler and co-workers, Liebigs Ann. Chem. 629, 1 and following (1960).

The n.m.r. tubes were dried by heating and were sealed as soon as filled. The viscosity was measured with a falling ball viscometer (Hoeppler Viscosimeter HV 303), the density by weighing 25 ml of the ester, and the refractive index with an Abbé refractometer (Spencer Refractometer). The chloroform was purified from ethanol by shaking with water, then dried by shaking and by refluxing with P_4O_{10}; after distillation phosgene was

removed by refluxing with diphenylamine; and HCl was removed by addition of aniline and distillation through a column. The ether was dried with sodium and then distilled over lithium aluminium hydride.

Phosphorus pentoxide (Baker and Adamson) was used.

Material A.--124 g (0.437 mole) P_4O_{10}, 150 ml $CHCl_3$ and 32.4 g (45.4 ml, 0.437 mole) ether were refluxed for 10 hr. The mixture was filtered and from the filtrate the solvent evaporated under vacuum to a final pressure of 0.5 mm Hg. A slightly yellow plastic resulted which was soluble in $CHCl_3$. Yield: 62 g (39.6%, calculated for $C_4H_{10}O_{11}P_4$).

Analysis:--Theoretical for $C_8H_{20}O_{12}P_4$ (432.16)

C, 22.24%; H, 4.66%; P, 28.67%;

and for $C_4H_{10}O_{11}P_4$ (358.04) C, 13.42%; H, 2.82%; P, 34.61%;

Found: C, 16.1% H, 3.9% P, 32.0%

Molecular weight determinations with an osmometer were attempted but gave unsatisfactory results. There seems to be aggregation, since the molecular weight was found to be nearly three times that of the calculated value and changed with the concentration.

Material B.--50 g (0.176 mole) P_4O_{10}, 100 ml chloroform and 28.5 g (40 ml, 0.385 mole) ether were refluxed for 15 hr. Filtration and evaporation of the solvent from the filtrate gave a heavy oil. Removal of the rest of the solvent at a pressure of 0.5 mm Hg gave a rubber-like material, soluble in $CHCl_3$. Yield: 54.6 g (71.8%, calculated for $C_8H_{20}O_{12}P_4$).

Material C.--114 g (0.4 mole) P_4O_{10}, 148 g (208 ml, 2.0 mole) ether and 100 ml chloroform were refluxed with vigorous stirring for 25 hr. The mixture was filtered from the undissolved P_4O_{10} and from the filtrate the ether and chloroform removed by evaporation (at least at a pressure

of 0.5 mm Hg). A highly viscous oil was obtained. Yield: 120 g (69.4%, calculated for $C_8H_{20}O_{12}P_4$).

Material D.--156.8 g material A was dissolved in 120 ml $CHCl_3$ and 142.7 g (200 ml, 1.93 mole) ether was added. After 10 hr. reflux the chloroform and the excess of ether were evaporated. An oil was obtained which had the same refractive index, viscosity, and phosphorus n.m.r. spectrum as the material prepared as described in the next section.

Yield: 175 g.

Material D.--(new method for the preparation of "ethylmetaphosphate").

We summarize the procedure in the following flow diagram:

145 g (0.51 mole) P_4O_{10} + 300 ml $CHCl_3$ + 37.8 g (53 ml, 0.51 mole) ether

reflux ↓ 4 hr

add 37.8 g (53 ml, 0.51 mole) ether

reflux until most of the P_4O_{10} is dissolved ↓ 10-20 hr

add 35.6 g (50 ml, 0.48 mole) ether

reflux ↓ 2 hr

add 35.6 g (50 ml, 0.48 mole) ether

reflux ↓ 2 hr

add 57.0 g (80 ml, 0.77 mole) ether

reflux ↓ 8-15 hr

nearly clear solution

(We suppose that the small undissolved residue contains compounds resulting from impurities in the phosphorus pentoxide such as highly polymeric polyphosphoric acids.)

After filtration the $CHCl_3$ and the excess of ether were removed by evaporation under vacuum and the oil which resulted was freed of the solvent at 0.2 mm Hg. Yield: 218.0 g (99%, calculated for $C_8H_{20}O_{12}P_4$).

Analysis: Theoretical for $C_8H_{20}O_{12}P_4$ (432.16)

C, 22.24%; H, 4.66%; P, 28.67%

Found: C, 22.2% H, 4.7%; P, 28.3%

The $CHCl_3$ and the excess of ether can be reused after fractional distillation. If the polyphosphate ester is dissolved in $CHCl_3$ and precipitated by adding ether, the oil then obtained shows the same phosphorus n.m.r. spectrum as the original ester.

Material E.--15 g (0.035 mole) "ethylmetaphosphate" was dissolved in 15 ml $CHCl_3$. 20.6 g (29 ml, 0.28 mole)ether was added and the mixture was refluxed for 65 hr. After filtration and the removal of the ether and $CHCl_3$ under vacuum (final pressure at 0.5 mm Hg) a light fluid oil was obtained. Yield: 15 g.

The same procedure, but refluxing for 145 hr or 220 hr, led, respectively, to materials F and G.

N.M.R. Measurements.--All the phosphorus n.m.r. measurements were made with the Varian V-4300-C spectrometer operating at 24.6 megacycles/sec, in conjunction with an apparatus for "continuous averaging".[17]

(17) M. P. Klein a. G. W. Barton, Jr., Rev. of Sci. Instr. 34, 754 (1963).

The curves were cut out and weighed for quantitative analysis. The chemical shifts are identical to those published in earlier papers[6,7]: P_t = 16, P_m = 29, P_b = 42, compared to 85% phosphoric acid as external standard. The proton n.m.r. measurements were made with the Varian A-60 spectrometer.

Calculation of the ratio of the compounds II, III, IV or III, IV, V in the products from the ratio of the n.m.r. peaks of P_b, P_m, P_t

To illustrate the manner by which the relative amounts of the various components, in mole percent, were determined from the n.m.r. spectra, we give a sample calculation.

In mixture B, for example

$$P_m + P_t + P_b = \Sigma P_B$$

where P_i refers to the area under the i-th peak and is proportional to the number of P_i atoms.

Material B is composed of compounds III, IV, and V.

P_m occurs in III, IV, and V.

P_t occurs in IV and V.

P_b occurs in IV only.

In IV, $P_b = P_{tIV}$ and $P_{mIV} = P_{tIV} + P_b$

In V, $P_{tV} = P_{mV}$ and $P_{tV} = P_t - P_{tIV}$

Experimentally

$$\frac{P_b}{\Sigma P_B} = 9.8\% : \frac{P_m}{\Sigma P_B} = 78.7\% \text{ and } \frac{P_t}{\Sigma P_B} = 11.5\%$$

Therefore

$$IV = P_b + P_{tIV} + P_{mIV} = 9.8 + 9.8 + 19.6 = 39.2\%$$

$$V = 2(\Sigma P_t - P_{tIV}) = 2(11.5 - 9.8) = 3.4\%$$

$$III = \Sigma P_m - P_{mIV} - P_{mV} = 78.7 - 19.6 - 1.7 = 57.4\%$$

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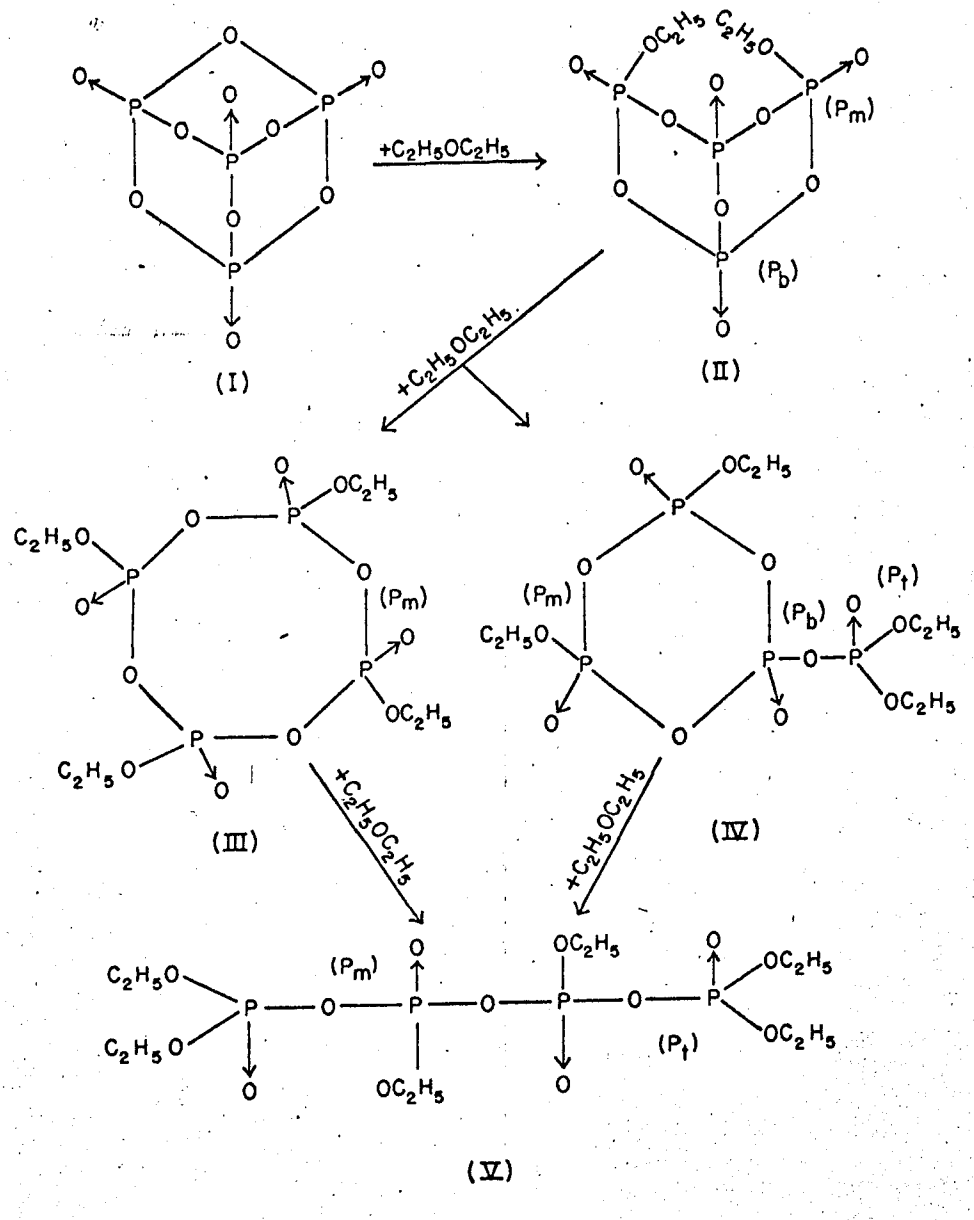

Fig. 1. Reaction of P_4O_{10} with diethylether.

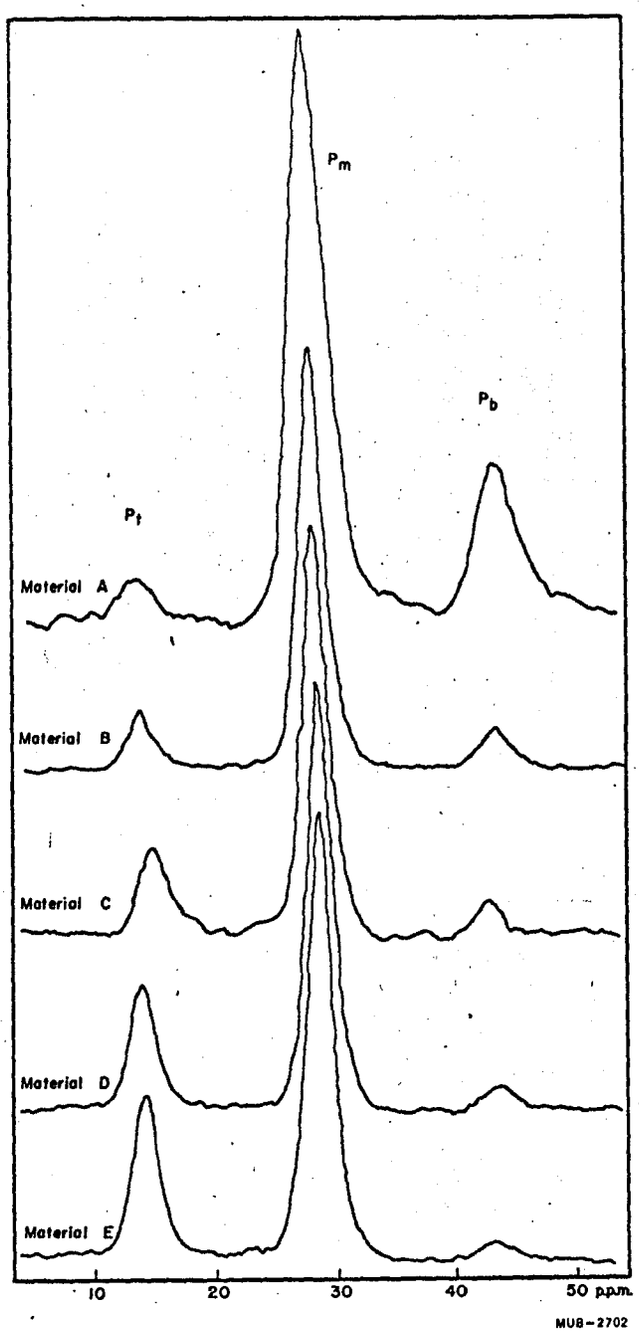

Fig. 2. Phosphorus n.m.r. spectra of different samples of "ethylmetaphosphate". The abscissa is the chemical shift in parts per million from 85% H_3PO_4.

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