

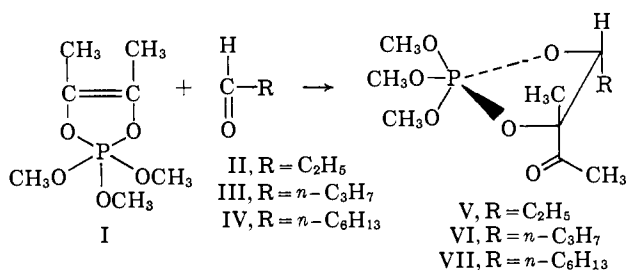
The Hydrolysis of Five-Membered Cyclic Oxyphosphoranes to Cyclic Phosphate Esters. P^{31} Nuclear Magnetic Resonance and Stereoisomerism at Phosphorus in Cyclic Phosphates^{1,2}

Fausto Ramirez,³ A. V. Patwardhan, N. B. Desai, and S. R. Heller

Contribution from the Department of Chemistry of the State University of New York at Stony Brook, Stony Brook, Long Island, New York. Received August 31, 1964

The biacetyl-aldehyde-trimethyl phosphite adducts (2,2,2-trimethoxy-4 β -methyl-4 α -acetyl-5 α -alkyl-1,3-dioxaphospholanes) undergo a very rapid and exothermic reaction with 1 mole of water and yield five-membered cyclic phospho triesters. Two diastereomers at phosphorus of the cyclic phosphates are formed; the coupling constant between the P^{31} and the ring proton in the n.m.r. spectrum differs by a factor of three in the isomers. P^{31} n.m.r. shifts are given for a number of five-membered cyclic phosphate esters (-15.2 to -11.8 p.p.m. vs. 85% H_3PO_4).

The previous paper in this series^{1b,2} described the reaction of the biacetyl-trimethyl phosphite 1:1 adduct, I, with simple aldehydes. This reaction gave only one of the two diastereomers which are possible for the cyclic oxyphosphorane structures, V, VI, and VII, with the acetyl group *cis* to the alkyl group, R.



This paper² is concerned with the partial hydrolysis of the oxyphosphoranes to five-membered cyclic phospho triesters, and with the P^{31} and H^1 n.m.r. spectra of the latter.

It was previously shown⁴ that the reaction of the 1:1 adduct I with a second molecule of biacetyl afforded two diastereomeric oxyphosphoranes, *meso* VIII and *racemic* IX, in an 80:20 proportion. These oxyphosphoranes reacted very rapidly with 1 mole equiv. of water and yielded the corresponding cyclic phospho triesters^{4b,c} X and XI.

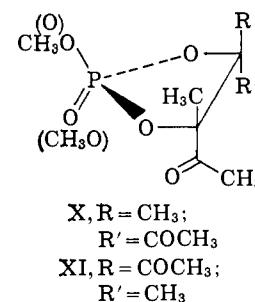
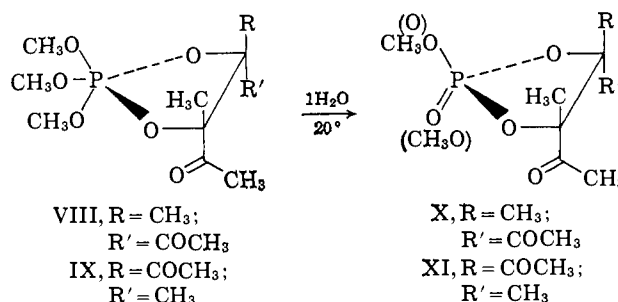
The *meso*-phosphate X is capable of existing in two diastereomeric forms which differ in the configuration

(1) (a) Organic Compounds with Pentavalent Phosphorus, Part XV. (b) Part XIV: F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 543 (1965).

(2) Presented on May 22, 1964 at the IUPAC Symposium on Organophosphorus Compounds, Heidelberg, Germany; cf. Abstracts, paper 44. Preliminary report: F. Ramirez, A. V. Patwardhan, N. B. Desai, N. Ramanathan, and C. V. Greco, *J. Am. Chem. Soc.*, **85**, 3056 (1963).

(3) This investigation was supported by Public Health Service Research Grant No. CA-04769-05 from the National Cancer Institute and by the National Science Foundation (G 19509).

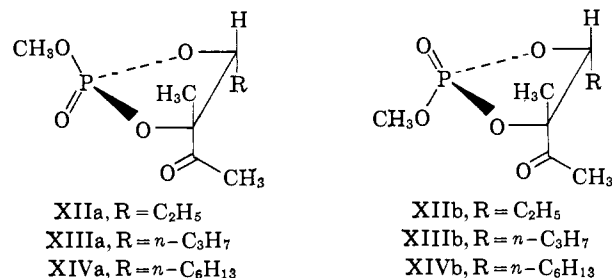
(4) (a) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 1317 (1962); (b) *ibid.*, **85**, 3465 (1963); (c) F. Ramirez, N. B. Desai, and N. Ramanathan, *ibid.*, **85**, 1874 (1963).



of the phosphorus atom. There is only one possible form of the racemic phosphate XI. The *meso*-phosphate which is obtained by slow crystallization from ether is stereochemically pure and undergoes a slow stereomutation at phosphorus in solution,^{4b,c} probably catalyzed by traces of methanol. The *cis-trans* isomerism in six-membered cyclic phosphonates has been observed by Wadsworth and Emmons.⁵ Verkade and King⁶ reported the P^{31} and H^1 n.m.r. of two polycyclic phosphates, with phosphorus in six-membered rings.

Results

The biacetyl-propionaldehyde-phosphite adduct (V) underwent a very rapid and exothermic reaction with 1 mole equiv. of water at 20° in benzene solution. A liquid, neutral phosphate ester, C₈H₁₅O₅P, was isolated in ca. 80% yield. The data given below show that this liquid is a mixture of two diastereomers at phosphorus, XIIa and XIIb, of DL-erythro-methyl (3-methylhexane-3,4-diol-2-one) cyclic phosphate.



The hydrolysis produced also some open-chain phosphate ester (less than 10%) which was not investigated further.

The infrared spectrum of the cyclic phosphate XII shows a strong carbonyl band at 5.85, a strong and sharp phosphoryl band at 7.70 and a double band at 9.43 and 9.57 μ due to POCH₃ stretching vibrations. There was no absorption due to OH groups.

(5) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **84**, 610 (1962).

(6) J. G. Verkade and R. W. King, *Inorg. Chem.*, **1**, 948 (1962).

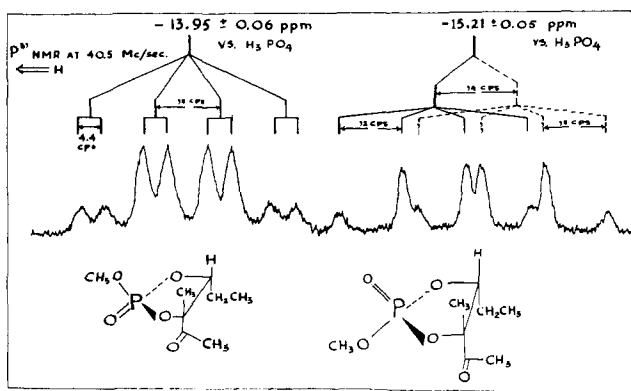


Figure 1.

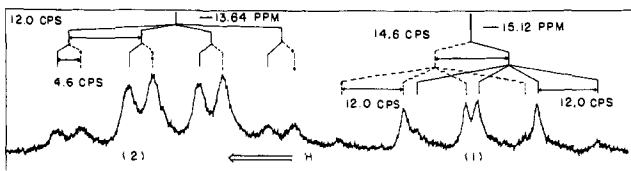
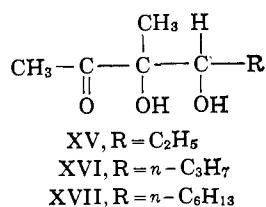


Figure 2. P^{31} n.m.r. spectrum of the cyclic phosphotriesters from the hydrolysis of the biacetyl-butylaldehyde-trimethyl phosphite adduct. Neat liquid; 40.5 Mc./sec. Signals 1 and 2 correspond to diastereomers at phosphorus.

The H^1 n.m.r. spectrum of XII shows clearly the presence of two diastereomers at phosphorus. The acetyl protons of the major isomer gave a singlet at 7.66 p.p.m. (τ); this isomer probably has configuration XIIa, with the acetyl *cis* to the phosphoryl oxygen, for reasons discussed below. The acetyl protons of the minor isomer, probably XIIb, gave a signal at τ 7.72. The ring methyl protons of XIIa were at τ 8.50, while those of XIIb were at 8.40. (For the complete spectrum see Experimental.)

The hydrolysis of the butylaldehyde adduct VI with 1 mole equiv. of water gave the two isomers at phosphorus of the cyclic phosphate (XIIIa + XIIIb), isolated in 92% yield. The heptanal adduct, VII, gave the corresponding cyclic phosphates, XIVa + XIVb.

The cyclic phosphate esters were converted to the phosphorus-free α,β -dihydroxy ketones XV, XVI, and XVII upon heating in water at pH *ca.* 5.0.



P^{31} N.m.r. Spectra^{8,9} of Five-Membered Cyclic Phosphates. The P^{31} spectrum of the biacetyl-proprionaldehyde-cyclic phosphate (XII) is reproduced in

(7) Reviewed in L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959: (a) p. 47; (b) p. 87.

(8) For leading references to work on spin-spin splittings of phosphorus resonance peaks, see R. A. Y. Jones and A. R. Katritzky, *Angew. Chem., Intern. Ed. Engl.*, **1**, 32 (1962).

(9) Leading references to P^{31} n.m.r. spectroscopy are given in ref. 8 and F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.*, **85**, 3252 (1963).

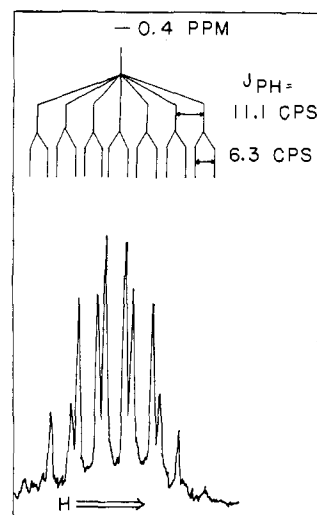
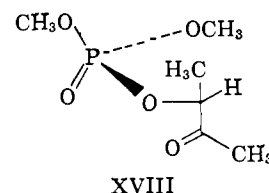


Figure 3. P^{31} n.m.r. spectrum of dimethyl phosphoacetoin (XVIII).

Figure 1. Clearly, there are two kinds of closely related phosphorus nuclei. The signal at high field, $\delta_{P^{31}} = -13.95$ p.p.m., results from: (1) a 12-c.p.s. coupling between the phosphorus and the methoxyl protons,⁸ as shown by the H^1 spectrum; (2) a 4.4-c.p.s. coupling between the phosphorus and the ring proton. The signal at low field, $\delta_{P^{31}} = -15.21$ p.p.m., arises from a 12-c.p.s. coupling as before, but now the coupling constant for the ring hydrogen has increased to 14 c.p.s.

The chemical shifts are at a significantly lower field than that of trimethyl phosphate, $\delta_{P^{31}} = -2.5$ p.p.m. Jones and Katritzky¹⁰ have reported $\delta_{P^{31}} = -17$ p.p.m. for ethyl ethylenephosphate.

The spectrum of the biacetyl-butylaldehyde-cyclic phosphate (XIII) shown in Figure 2 confirms the large differences in the coupling constants for the ring hydrogens and the phosphorus, as a function of configuration at phosphorus. These spectra should be



XVIII

compared with that of an open-chain α -ketol phosphate, dimethyl phosphoacetoin¹¹ (XVIII), Figure 3. The chemical shift in the latter, $\delta_{P^{31}} = -0.4$ p.p.m., is at higher field, and the coupling between the phosphorus and the methine hydrogen, 6.3 c.p.s., falls in between the two extremes found in the cyclic phosphates (4 and 14 c.p.s.).

Table I lists the chemical shifts of several five-membered cyclic phosphates. The two diastereomers at phosphorus in the *meso*-dibiacetyl phosphate,^{4b,c} Xa and Xb, gave very close signals. The crystalline

(10) R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.*, 4376 (1960).

(11) F. Ramirez, B. Hansen, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 4588 (1962). The H^1 n.m.r. of dimethyl phosphoacetoin (60 Mc./sec.) has a multiplet at τ 5.3 (methine- H^1); one doublet at τ 6.23 and another at 6.27, both $J_{HP} = 11.5$ c.p.s., due to the nonequivalent methoxyls; a singlet at τ 7.82 (CH_3CO) and a doublet at 8.66, $J_{HH} = 6.5$ c.p.s. (CH_3C).

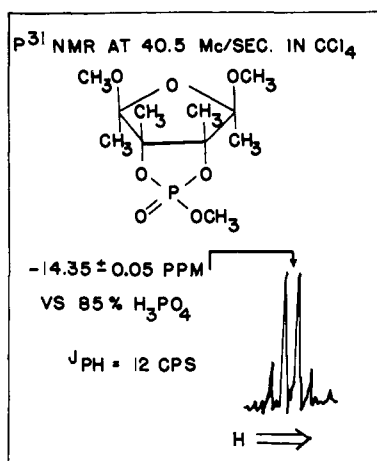


Figure 4.

phosphate XIX is derived from the biacetyl-methyl pyruvate-trimethyl phosphite adduct²; although two diastereomers at phosphorus are possible, only one signal was detectable in this sample.

Table I. P^{31} N.m.r. of the Cyclic Phosphotriesters

Formula	R	R'	$\delta_{P^{31}}$, p.p.m. ^{a,b}
XII	H	C ₂ H ₅	-13.9 ^c -15.2
XIII	H	<i>n</i> -C ₃ H ₇	-13.8 ^c -15.1
X	CH ₃	COCH ₃	-11.8 ^{d,e} -12.1
XI	COCH ₃	CH ₃	-13.0 ^d
XIX	CO ₂ CH ₃	CH ₂	-13.1 ^f

^a Chemical shifts in p.p.m. vs. 85% H₃PO₄ at 40.5 Mc./sec.; ± 0.1 p.p.m. unless otherwise specified. ^b (CH₃O)₃PO had -2.5 p.p.m.; dimethyl phosphoacetoin had -0.4 p.p.m. ^c Neat. ^d In CDCl₂. ^e In CH₃OH: -13.8 and -14.2 p.p.m. ^f In CH₂Cl₂.

Phosphates X, XI, and XIX gave P^{31} spectra with four lines, similar to that shown in Figure 4 for a furanose-2,3-cyclic phosphate.^{12,13}

Discussion

The phosphorus nucleus of the five-membered cyclic phosphates appears to be less shielded by electrons than that of the open-chain phosphates, since the chemical shifts are more negative in the former. This can, perhaps, be attributed to a steric inhibition of p-d π -bonding, *i.e.*, in the cyclic phosphates the unshared electrons of the oxygens contribute less to the bonding with the phosphorus. Covitz and Westheimer¹⁴ have

(12) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Am. Chem. Soc.*, **85**, 2681 (1963).

(13) For a discussion on nucleoside-2',3'-cyclic phosphates see: D. M. Brown and A. R. Todd, *J. Chem. Soc.*, 52 (1952); D. M. Brown, D. I. Magrath, and A. R. Todd, *ibid.*, 2708 (1952). Reviewed in H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961.

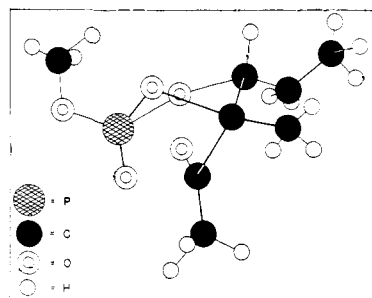


Figure 5. Model of a five-membered cyclic phosphotriester with the phosphoryl group (PO) *cis* to a ring acetyl group (COCH₃). Formula XIIa.

suggested that resistance of the ring to p-d double bonding between the ester oxygens and the phosphorus should result in lower stabilization for five-membered cyclic phosphates than for open-chain phosphates.

The cyclic phosphate X and the furanose-2,3-cyclic phosphate shown in Figure 4 react very rapidly with 1 mole of water with loss of methanol and formation of a cyclic phosphodiester.¹² It may well be that the large negative P^{31} chemical shifts and the fast hydrolysis to cyclic diesters are manifestations of the same fundamental property of these phosphates. Van Wazer¹⁵ has discussed π -bonding in various types of phosphorus compounds.

The available evidence does not permit a definitive configurational assignment to the isomers at phosphorus in the cyclic phosphates XII, XIII, and XIV. However, the isomer with the smaller coupling between the P^{31} and the ring proton, *i.e.*, the major isomer of Figure 1 ($\delta_{P^{31}} = -13$ p.p.m.), probably has the acetyl group *cis* to the phosphoryl oxygen. The ring of XII is probably not planar¹⁶; a model of XII was built with Cenco-Petersen scalar models, assuming a strong dipole-dipole interaction between the phosphoryl PO and the carbonyl CO (Figure 5). The resulting dihedral angle between the planes P-O-C and H-C-O in the ring POCH system was closer to 90° in this model than in the model of the isomer having the acetyl *trans* to the phosphoryl oxygen. This would be consistent with a smaller P^{31} -H¹ coupling for the *cis* isomer XIIa.^{6,7b} Furthermore, if the sulfonyl SO group in cyclic sulfites has a deshielding effect on protons of ring substituents,¹⁷ the phosphoryl PO group could also show a deshielding effect on similar protons; this would explain the relative positions of the acetyl protons (and of the methyl protons) in the isomers XIIa and XIIb, *i.e.*, acetyl of major

(14) (a) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 1773 (1963). (b) After this paper had been submitted (Aug. 31, 1964), G. M. Blackburn, J. S. Cohen, and A. Todd, *Tetrahedron Letters*, No. 39, 2873 (1964) (published Nov. 1964), reported the P^{31} chemical shifts of a number of five-membered cyclic phosphates taken at 16.5 Mc./sec. They attributed the relatively large negative shifts vs. 85% H₃PO₄ to a "diminution in the d π -p π double bond character of cyclic P-O bonds in the five-membered ring." See also F. Ramirez, O. P. Madan, A. V. Patwardhan, S. R. Heller and N. B. Desai, Abstracts of Papers, IUPAC Symposium on Organo-phosphorus Compounds, Heidelberg, Germany, May 20-22, 1964.

(15) J. R. Van Wazer, "The Phosphorus and its Compounds," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1958, p. 36, and references therein.

(16) (a) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **81**, 4915 (1959); (b) F. V. Brutcher, Jr., and W. Bauer, Jr., *ibid.*, **84**, 2233 (1962).

(17) J. G. Pritchard and P. C. Lauterbur, *ibid.*, **83**, 2105 (1961).

isomer at lower field and ring methyl of minor isomer at lower field.

The mechanism previously suggested¹² for the hydrolysis of the oxyphosphorane VIII to the cyclic phosphate X is applicable to the hydrolysis of the oxyphosphoranes V, VI, and VII to the cyclic phosphates XII, XIII, and XIV. In the former case, VIII \rightarrow X, it was shown that the oxygen-18 of labeled water became attached to the phosphate ester as the phosphoryl oxygen,¹² implying the substitution of a methoxy by a hydroxy group at the oxyphosphorane phosphorus.

Experimental

The preparation of the oxyphosphoranes V, VI, and VII, the instrumentation employed, and the method of calibration of the P³¹ n.m.r. spectra are given.^{1b} The analyses were performed by Schwarzkopf Micro-analytical Laboratories, Woodside, N. Y.

Hydrolysis of the Biacetyl-Propionaldehyde-Tri-methyl Phosphite Adduct (2,2,2-Trimethoxy-4 β -methyl-4 α -acetyl-5 α -ethyl-1,3-dioxaphospholane, V) with 1 Mole Equiv. of Water. Preparation of DL-erythro-Methyl (3-Methylhexane-3,4-diol-2-one) Cyclic Phosphate (XII). A solution of the adduct V (11.31 g.) in dry benzene (20 ml.) was treated with 0.76 ml. of water (1 mole equiv.) at 20°, under N₂, with stirring. An exothermic reaction was noted within 1 min.; the temperature rose to 43°. The solvent was removed at 45° (15 mm.), the last traces at 1 mm. The H¹ n.m.r. of the liquid residue showed the presence of cyclic phospho triester XII contaminated with ca. 10–15% of what may be the open-chain phospho triester (weak doublet at τ 6.25 and singlets at 7.75 and 8.72 in the H¹ n.m.r. of the crude ester).

The crude cyclic phosphate was distilled in a 12-in. spinning band column: (1) bath at 135°, b.p. <80° (0.2 mm.), 1 g.; (2) bath at 140°, b.p. 78–81° (0.2 mm.), 6.7 g., *n*^{25D} 1.4381; the yield of DL-erythro-methyl (3-methylhexane-3,4-diol-2-one) cyclic phosphate (XII) is 78%.

Anal. Calcd. for C₈H₁₅O₅P: C, 43.3; H, 6.8; P, 14.0. Found: C, 43.0; H, 7.0; P, 14.1.

The cyclic phosphate was very sensitive to moisture. The following properties were determined in a fresh sample.

The P³¹ n.m.r. spectrum (neat liquid) had an octet at -13.95 ± 0.06 and another octet at -15.21 ± 0.05 p.p.m. (Figure 5).

The infrared spectrum (in CCl₄) had bands at 5.85 (s), 6.86 (w), 7.06 (w), 7.38 (w), 7.70 (strong, sharp), 9.43 and 9.57 (very strong), and 10.1 (s) μ .

The H¹ n.m.r. spectrum (neat liquid) had a 1H¹ multiplet at τ 5.6; a 3H¹ doublet at τ 6.14, *J*_{HP} = 12.2 c.p.s., which can be resolved into two doublets separated by about 0.8 c.p.s.; a 3H¹ singlet at τ 7.66 and another at 7.72 (Δ = 3 c.p.s.); one singlet at τ 8.40 and another at 8.50 (Δ = 5 c.p.s.), which integrate as 5H¹ because they coincide with two methylene H; and a 3H¹ multiplet at τ 9.0.

Hydrolysis of the Cyclic Phosphate (XII) to DL-erythro-3-Methylhexane-3,4-diol-2-one (XV). The cyclic phosphate was dissolved in water. The solution was treated with 1 equiv. of sodium hydroxide, heated for 6 hr. at the boiling point, cooled, saturated with

NaCl, and extracted with chloroform. From the chloroform the liquid DL-erythro-3-methylhexane-3,4-diol-2-one (XV) was obtained in 60% yield. It was identified by comparison with an authentic sample.^{1b}

Hydrolysis of the Biacetyl-Butyraldehyde-Tri-methyl Phosphite Adduct (2,2,2-Trimethoxy-4 β -methyl-4 α -acetyl-5 α -n-propyl-1,3-dioxaphospholane, VI) with 1 Mole Equiv. of Water. Preparation of DL-erythro-Methyl (3-Methylheptane-3,4-diol-2-one) Cyclic Phosphate (XIII). A solution of the adduct VI (45.79 g.) in dry benzene (50 ml.) was treated with 2.92 ml. (1 mole equiv.) of water at 20°, under N₂, with stirring. An exothermic reaction occurred within 2 min.; the temperature rose to 55°. The solvent was removed at 40° (15 mm.), the last traces at 1 mm. The H¹ n.m.r. and the infrared spectra of the liquid residue showed the presence of cyclic phospho triester XIII contaminated with ca. 10% of what may be the open-chain phospho triester. The liquid was fractionated in a 12-in. spinning band column: (1) bath temperature 140°, b.p. <100° (1.5–0.5 mm.), 1 g.; (2) bath at 145°, b.p. 88–100° (0.5–0.2 mm.), 14.6 g., *n*^{25D} 1.4391; (3) bath at 145°, b.p. 84–88° (0.2–0.1 mm.), 16.33 g., *n*^{25D} 1.4402; (4) residue 4 g.

Fractions 2 and 3 had identical infrared and H¹ n.m.r. spectra; yield of DL-erythro-methyl (3-methylheptane-3,4-diol-2-one) cyclic phosphate (XIII) 92%.

Anal. Calcd. for C₉H₁₇O₅P: C, 45.8; H, 7.2; P, 13.1. Found: C, 45.6; H, 7.3; P, 13.3.

The cyclic phosphate was very sensitive to moisture. The properties given are of fresh samples protected against moisture. The P³¹ n.m.r. spectrum (neat liquid) had an octet at -13.84 ± 0.05 and another at -15.12 ± 0.05 p.p.m. (Figure 2).

The infrared spectrum (in CCl₄) had bands at 5.84 (s), 6.90 (w), 7.06 (w), 7.27 (w), 7.38 (m), 7.70 (strong, sharp), 9.52 (very strong, with weak shoulder at 9.66), and 10.2 (s) μ .

The H¹ n.m.r. spectrum (neat liquid) had a 1H¹ multiplet at τ 5.6; a 3H¹ doublet at τ 6.17, *J*_{HP} = 12.0 c.p.s., which can be resolved into two doublets, with the same coupling, separated by 0.8 c.p.s.; one 3H¹ singlet at τ 7.66 and the other at 7.71 (Δ = 3.0 c.p.s.); one singlet at τ 8.51, the other at 8.42 (Δ = 5.5 c.p.s.), which integrate as 7H¹ since they coincide with four methylene protons; and a 3H¹ multiplet at τ 9.0.

Hydrolysis of the Cyclic Phosphate (XIII) to DL-erythro-3-Methylheptane-3,4-diol-2-one (XVI). The cyclic phosphate (XIII, 82 mmoles) was mixed with water (40 ml.). Heat was evolved and the water became acidic (pH ca. 0.6). This solution was titrated with 1 N NaOH (ml., pH): 20, 1.0; 40, 1.4; 60, 1.9; 75, 2.6; and 82, 5.0. This solution was kept for 8 hr. at reflux, cooled, saturated with NaCl, and extracted with chloroform. From the chloroform solution, the liquid DL-erythro-3-methylheptane-3,4-diol-2-one (XVI) was isolated in 55% yield. It was characterized by comparison with an authentic sample.^{1b}

Hydrolysis of the Biacetyl-Heptanal-Trimethyl Phosphite Adduct (2,2,2-Trimethoxy-4 β -methyl-4 α -acetyl-5 α -n-hexyl-1,3-dioxaphospholane, VII) with 1 Mole Equiv. of Water. Preparation of DL-erythro-Methyl (3-Methyldecane-3,4-diol-2-one) Cyclic Phosphate (XIV). A

benzene solution of the adduct VII (3.913 g. in 15 ml.) was treated with 0.217 ml. of water (1 mole equiv.). An exothermic reaction occurred within 2 min. The solvent was removed at 40° (15 mm.; last traces at 0.2 mm). The H¹ n.m.r. spectrum (CCl₄) of the crude residue showed all the signals of the cyclic triester XIV and in addition two doublets (*J* = 11.2 c.p.s.) at τ 6.25 separated by 1.5 c.p.s. and a singlet at τ 7.78, which could be due to an open-chain phospho triester (<20%). This material was submitted to short-path distillation (bath 150–155°, 0.1 mm.). The cyclic phosphate XIV had b.p. 109–112° (0.1 mm.), *n*_D²⁵ 1.4441, yield 80%.

Anal. Calcd. for C₁₂H₂₃O₅P: C, 51.8; H, 8.3; P, 11.5. Found: C, 51.8; H, 8.6; P, 10.8.

The infrared spectrum (in CCl₄) had a strong carbonyl band at 5.80, a strong, sharp PO band at 7.68, and a very strong POCH₃ band at 5.90 μ . The H¹ n.m.r. spectrum (in CCl₄) had a 1H¹ multiplet at τ 5.8; one 3H¹ doublet at τ 6.19 and another at 6.21

(Δ = 1.3 c.p.s.), both with *J*_{HP} = 11.6 c.p.s.; one 3H¹ singlet at τ 7.70 and another at 7.77 (Δ = 4.2 c.p.s.); there was a singlet at τ 8.46 and another at 8.57 (Δ = 6 c.p.s.), a multiplet at 8.70 and a multiplet at 9.1; these four signals integrated as 16H¹. There was no trace of the signals due to the open-chain triester.

Hydrolysis of the Cyclic Phosphate XIV to DL-erythro-3-Methyldecane-3,4-diol-2-one (XVII). The cyclic phosphate XIV (25 g.) in water (40 ml.) was treated with 3.6 g. of NaOH. This solution, with pH ca. 5.1, was kept for 6 hr. at the boiling point, cooled, saturated with NaCl, and extracted with chloroform. Removal of the chloroform left 16 g. (90%) of DL-erythro-3-methyldecane-3,4-diol-2-one (XVII), identified by comparison with a sample previously described.^{1b}

Acknowledgment. We are grateful to Professor P. C. Lauterbur of this department for instruction and advise in n.m.r. spectroscopy.

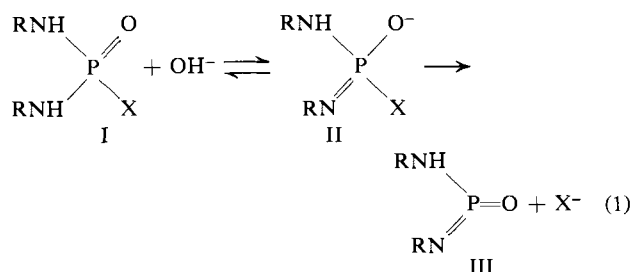
Mechanisms in the Hydrolysis of Phosphorodiamidic Chlorides¹

Patricia S. Traylor and F. H. Westheimer

Contribution from the James Bryant Conant Laboratory of Harvard University, Cambridge, Massachusetts. Received September 29, 1964

The hydrolyses of *N,N,N',N'*-tetramethylphosphorodiamidic chloride (TMPC) and of *N,N'*-dipropylphosphorodiamidic chloride (DPPC) with water under neutral or slightly acidic conditions proceed at comparable rates. Similarly, a number of nucleophiles, such as pyridine, react with the two phosphorodiamidic chlorides at comparable rates in bimolecular reactions. However, in alkaline solution, DPPC is hydrolyzed at least 4 million times faster than TMPC. These results are consistent with a special mechanism for the alkaline hydrolysis of DPPC which involves the formation of an anion of the phosphorodiamidate as an intermediate in the hydrolysis. The possible formation of a monomeric metaphosphate intermediate from the anion is discussed.

In 1956, Heath² discovered that the rates of alkaline hydrolysis of phosphorodiamidic fluorides vary enormously with structure, and explained these variations in rate as the result of steric effects to which phosphoramides (and phosphoric esters³) are especially sensitive. However, since all of the phosphorodiamidic fluorides and pyrophosphoramides which react rapidly with alkali contain at least one amide hydrogen, one of us suggested⁴ that the fast reactions proceed by way of an anion derived from the amidate:



Here X represents a leaving group (e.g., F), and III is an analog of the hypothetical monomeric metaphosphate ion,^{5–15} PO₃⁻. If III is formed, it would add water rapidly to yield a phosphorodiamidic acid similar to the ones isolated in this study. Considerable support

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