Isomeric Five-Membered Ring Phosphites and Phosphates[1]

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Abstract: A variety of ring- and phosphorus-substituted five-membered ring phosphites have been prepared. These materials exist as mixtures of *cis* and *trans* isomers which can be separated by glpc. The phosphites can be oxidized stereospecifically with nitrogen tetroxide to give mixtures of *cis* and *trans* phosphates which are also separable by glpc. The ^{1}H and ^{31}P nmr spectra of these materials are reported. The ^{1}H nmr spectra shows that the isomer present in the smallest amount in the phosphite mixtures has its ring alkyl group absorptions at lower fields than the most abundant isomer. The corresponding phosphates show much smaller differences in chemical shifts between the alkyl groups. It is suggested that the greater downfield shift of the alkyl group in the least stable phosphites is due to deshielding by the OR group on phosphorus which is *cis* to the alkyl group. Oxidation to the phosphates put oxygens *cis* to alkyl groups in both isomeric phosphates and thus deshielding occurs in either isomer. The thermodynamic equilibrium mixture of the two phosphites, **4**, is 87:13. Oxidation yields the same mixture of phosphates, **12**. Partial hydrolysis changes the ratio of phosphates to 61:39. This ratio does not change on further hydrolysis. These results favor a *trans* relationship of the ring alkyl groups and the OCH_3 attached to phosphorus. Oxidation places an oxygen *cis* to the ring alkyl groups and thus in the phosphates steric interactions are more nearly equal than they are in the phosphites. Molecular models also support the configurational assignments. Isomeric six-membered ring phosphates are hydrolyzed without conversion into each other.

The chemistry of five-membered ring phosphates has received intensive study because of their biological interest.[2] One of the most fascinating aspects of their chemistry is the very high rate of hydrolysis which they exhibit relative to open chain phosphates and phosphates with larger rings. It has been suggested that five-membered ring containing cyclic phosphates hydrolyze by formation of a pentasubstituted intermediate. The major piece of evidence for this postulation has been the finding that oxygen-18 is incorporated into recovered phosphate during the course of hydrolysis. Such incorporation has not been observed in acyclic phosphates and phosphates containing six-membered rings.

Recently Goldwhite[3,4] has shown that five-membered ring phosphites are configurationally stable as are a wide variety of other five-membered ring phosphorus compounds.[5] Similar conclusions have also been reached concerning six-membered ring phosphites.[6,7]

It was the purpose of this work to prepare a variety of five-membered ring phosphites, to examine the ratio of isomers obtained as a function of structural change, to convert them into the corresponding phosphates, and to study the course of the hydrolysis of selected phosphates. The results of these studies have confirmed that five-membered ring phosphates hydrolyze by a unique mechanism and they have allowed tentative assignment of configuration to the phosphites and phosphates.

Results

Important spectral data for the series of phosphites and phosphates, **1–15**, which were studied are collected in Table I. The methods of preparation, yields, physical properties, and analyses are collected in Table II.

Table I. ^{1}H and ^{31}P Nmr Spectral Data

Compd no.	Compound	^{31}P[a]	^{1}H CCH$_3$[b]	J_{HH}	Isomer, %
1	Methylethylene methyl	−139	1.26	6	62
	phosphite	−142	1.40	6	38
2	Methylethylene	−139	1.24	6	67
	isopropyl phosphite	−142	1.36	6	33
3	*t*-Butylethylene methyl	−134	0.88[c]		77
	phosphite	−142	0.94		23
4	*meso*-1,2-Dimethyl-	−135	1.10		87
	ethylene methyl	−150	1.22		13
	phosphite				
5	*dl*-1,2-Dimethylethylene	−140	1.22	6	
	methyl phosphite		1.29	6	
6	Tetramethylethylene	−147	1.18		
	methyl phosphite		1.30		
7	1,1-Dimethylethylene	−145	1.27		
	methyl phosphite		1.46		
8	Trimethylethylene		1.08		
	methyl phosphite	−137	1.37		88
		−150	1.21	6	12
9	Methylethylene methyl	−16	1.40	7	61
	phosphate				39
10	Methylethylene	−14	1.35	6	39
	isopropyl phosphate		1.38	6	61
11	*t*-Butylethylene methyl	−16	0.95[c]		77
	phosphate				23
12	*meso*-1,2-Dimethylethyl-	−15	1.30		86
	ene methyl phosphate	−17			14
13	*dl*-1,2-Dimethylethylene	−14	1.37	6	
	methyl phosphate		1.39	6	
14	Tetramethylethylene		1.34		
	methyl phosphate		1.42		

[a] Chemical shifts relative to 85% H_3PO_4 in parts per million. [b] Chemical shifts relative to TMS. [c] Hydrogens of *t*-butyl group.

In those phosphites in which the possibility for *cis–trans* isomerism exists it has been found, compounds **1–4**, and **8**. It manifests itself in a regular trend in change of proportion of isomers as the substitution on the ring becomes increasingly heavy. For example compound **1**, with a single methyl group, has a ratio of isomers of 62:38 whereas **3**, with a single *t*-butyl group, has a ratio of 77:23. Substitution of two *cis*-methyl

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[2] (a) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); (b) D. B. Boyd, *J. Am. Chem. Soc.*, **91**, 1200 (1969).

[3] H. Goldwhite, *Chem. Ind.* (London), 494 (1964).

[4] B. Fontal and H. Goldwhite, *Tetrahedron*, **22**, 3275 (1966).

[5] D. Gagnaire, J. B. Robert, J. Verrier, and R. Wolf, *Bull. Soc. Chim. France*, 3719 (1966).

[6] D. Z. Denney and D. B. Denney, *J. Am. Chem. Soc.*, **88**, 1830 (1966).

[7] G. Aksnes, R. Eriksen, and K. Mellingen, *Acta. Chem. Scand.*, **21**, 1028 (1967).

Table II. Phosphite and Phosphate Properties

Compd	Preparation[a]	Yield, %	Mp or bp (mm), °C	Calcd		Found	
				C	H	C	H
1	A	23	53–59 (23)	35.25	6.62	35.15	6.87
	C		(lit.[b] 60 (25))				
2	C	40	35–38 (2)				
3	B	60	38–44 (2)				
4	A	20	70–72 (15)	40.01[c]	7.33	40.29	7.40
	B	58					
5	A		62–64 (18)				
6	A						
	B	75	33 (3)				
7	C	35	54 (20)	40.01	7.39	40.12	7.30
8	C	51	69 (16)	43.90	7.98	44.17	8.01
9	HgO	28	76–82 (0.005)	31.58	5.92	31.90	6.24
	N_2O_4	50					
10	N_2O_4	50	109–111 (1.25)	40.00	7.22	40.27	7.36
11	N_2O_4	61	45–60 (0.02[d])	43.30	7.73	43.52	7.67
12	N_2O_4	82	84 (0.35)	36.14[c]	6.63	36.32	6.59
13	HgO		62–64 (0.65)				
14	HgO		101–103				

[a] The methods of preparation of phosphites are as follows: A, transesterification; B, $(RO)_2PCl + R'OH +$ base; C, glycol + $(RO)PCl_2$ + 2base. [b] H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950). [c] Analysis on mixture of *meso*- and *dl*-phosphite and -phosphate. [d] Evaporative distillation.

groups, **4**, changes the ratio to 87:13. The compound **8**, with three methyl groups, shows essentially the same ratio as **4**. Substitution of an isopropoxy group for the methoxy group, compound **2**, has a very small effect on the ratio of isomers.

It is believed that these mixtures of isomers are essentially the thermodynamic equilibrium mixtures in all of the cases reported here. Attempts to prepare mixtures with different ratios by methods which have been successful with six-membered ring phosphites[6,7] have always yielded essentially the same ratio of isomers.

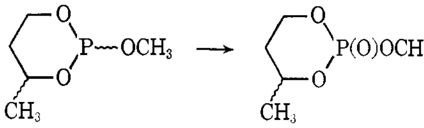
The ^{31}P nmr spectra of the phosphites are typical of those found for compounds of this structure. In all cases the least stable isomer absorbs at lower fields than the most stable isomer and the difference in chemical shift becomes larger as the equilibrium shifts toward one isomer of the pair. The chemical shift of the major isomers remain relatively constant and it is the least stable substance whose chemical shift changes. The chemical shifts of phosphorus nuclei of the phosphates are essentially the same and only with the compounds **12** and **15** could separate absorptions be resolved.

The ^1H nmr spectra show that the ring substituents, *i.e.*, CH_3's or $(CH_3)_3C$– have different chemical shifts in the different isomers. In all cases the least stable isomer has its substituents more deshielded than the most stable isomer. Conversion of the phosphites into the phosphates results in a downward shift of the absorption of the substituent on that phosphate derived from the most stable phosphite. The chemical shift of the substituent on the phosphate derived from the least stable phosphite tends to move much less and thus the absorptions come together.

The 86:14 mixture of phosphates **12** obtained by oxidation of **4** was subjected to hydrolysis with a limited amount of water, 11.4 mole %, in tetrahydrofuran. After 5 days at room temperature the phosphates were recovered and analyzed. The isomer ratio was found to be 66:34. This material was hydrolyzed to near completeness. Analysis of the small amount of remaining phosphate showed that the ratio was 62:38. A sample of **12**, ratio of isomers 88:12, was hydrolyzed to 93% completion at which time the isomer ratio was 60:40.

Incomplete hydrolysis of a mixture of isomers of **11**, 72:28, yielded after 3 days at room temperature recovered phosphate whose ratio of isomers was 60:40.

The six-membered ring phosphates, **17**, were prepared by mercuric oxide oxidation of **16** which consisted of



16 **17**

two isomers in a ratio of 95:5. Mercuric oxide oxidation was not stereospecific and the two isomers were formed in a ratio of 2:5. These isomers were separated by fractional distillation. Hydrolyses of each isomer were conducted at 50.5 and 75° in the presence of base and at 100° under initially neutral conditions. Isolation of phosphates under all of these conditions showed that there was no isomerization of one into the other. One isomer hydrolyzes *ca.* four times faster than the other.

Discussion

It is believed that the ratio of isomers obtained for the various phosphites is quite close to or the same as the thermodynamic equilibrium mixture. Oxidation of the phosphites with nitrogen tetroxide is a stereospecific process and it undoubtedly proceeds with retention of configuration about the phosphorus atom. This conclusion is based on the finding that bicyclic phosphites with phosphorus at the bridgehead are smoothly oxidized by this reagent to give the corresponding phosphates.[8] This is a reaction which involves retention of configuration. Ozone also oxidizes **4** stereospecifically to give the same ratio of isomers as is found with nitrogen tetroxide. Oxidation of bicyclic phosphites by ozone also gives the bicyclic phosphates.[9] It would be very peculiar indeed if both of these reagents

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(8) D. B. Denney and S. Varga, *Tetrahedron Lett.*, 4935 (1966).
(9) S. Schutzbank, unpublished results.

oxidized the five-membered ring phosphites by inversion mechanisms and still oxidized the bicyclic phosphites facily by a retention mechanism. It is on this basis that it is concluded that all of the oxidations involve retention.

There is no reason for believing that the mixture of phosphates obtained by the stereospecific oxidations is the thermodynamic equilibrium mixture. In fact the hydrolysis studies suggest that this is not the case. Westheimer[2a] has discussed in detail the mechanism of hydrolysis of five-membered ring phosphates. His basic conclusion is that the process is stepwise and that a pentasubstituted intermediate is formed which can undergo pseudorotation, revert to starting material, and decompose to products. The results reported here strongly support this mechanistic scheme.

If the two isomers of **12** were hydrolyzing at different rates without the intervention of a common intermediate, *i.e.*, the pentasubstituted compound, then the relative amounts of each isomer should change throughout the course of the hydrolysis; this is not the case. Initially the ratio of isomers changes but it soon reaches what appears to be the thermodynamic equilibrium value. The results with **11** although not as extensive are in agreement with this concept. During his discussion of the role pseudorotation plays in the hydrolysis of five-membered ring phosphates, Westheimer suggested that pseudorotation which leads to the isomer in which the five-membered ring occupies two equatorial positions, *i.e.*, O–P–O bond angle is 120° is an inhibited process because of the introduction of strain into the ring system. It is important to note that the results reported here do not provide a test of this hypothesis. It is possible to convert one phosphate into the other *via* a pseudorotating intermediate without performing a pseudorotation in which the rings lie in equatorial positions. This is true for these cases because two of the groups, OH, bonded to phosphorus are identical.[10]

That hydrolysis of the six-membered ring phosphates proceeds without interconversion of the isomers is in complete agreement with earlier work which has indicated that a pseudorotating pentasubstituted intermediate is not formed during the hydrolyses.[11]

The change in the ratio of isomers that is found as the degree of substitution is changed on the five-membered ring phosphites is in accord with increasing steric crowding as the ring becomes more highly substituted. A conventional assignment of structure would be that the most stable isomer, in the pairs, has the groups *trans* to each other. This assignment presupposes that the OR group which is attached to phosphorus is larger than the lone pair. The lone pair is in an orbital which is close to 3s and thus this argument does not seem unreasonable.[12]

The ^{1}H nmr data also support this structural assignment. It is clear that the relationship of a ring-substituted alkyl group and the POR group has a definite effect on the chemical shift of the hydrogens of the alkyl group. It is also important to note that the most abundant isomer has a more highly shielded alkyl group than does the least stable isomer. Pritchard and Lauterbur[13] have investigated the structures of five-membered ring sulfites by nmr spectroscopy. These substances also exist as *cis–trans* isomers and the same kind of shielding–deshielding effects of the ring alkyl substituents were found with these substances as have now been found with the phosphites. Pritchard and Lauterbur assigned structures to the sulfites on the basis of calculations of the effect of the S=O bond on the ring hydrogens. The POR bonding system undoubtedly uses different orbitals so a direct comparison cannot be made. It is important to note though that conversion of the phosphites to the phosphates results in a general deshielding of the ring alkyl substituent in the most stable isomer with little or no change in the chemical shift of the ring alkyl substituent of the least stable isomer. These results are entirely consistent with the assignment of configuration which was made on the basis of steric considerations. Deshielding of the hydrogens on the ring alkyl substituents by a *cis* P–O group is not unreasonable. Conversion of the phosphites to the phosphates places such a group *cis* to every ring alkyl substituent and their hydrogens then have very similar chemical shifts.

The final ratio of isomers obtained after hydrolysis of **12** shows that there is a smaller difference in energy between the two isomers of the phosphates then there is between the isomeric phosphites. Introduction of the oxygen in converting the phosphite into the phosphate changes the steric environment around phosphorus such that there is now a very similar environment for either a *cis* or *trans* alkyl group and thus the energy of the isomers becomes very similar. Clearly a final assignment of configuration will require a definitive proof such as is offered by an X-ray study; however, it is believed that the present data are sufficient to allow further stereochemical studies with a reasonable degree of confidence. It should be noted that Ramirez and coworkers have isolated geometric isomers of five-membered ring phosphates and have also made tentative assignments of structure on the basis of nmr data.[14]

Experimental Section

All proton nmr spectra were obtained with a Varian A-60 nmr spectrometer. The spectra were recorded on solutions in carbon tetrachloride using tetramethylsilane (0 ppm) as an internal standard. All ^{31}P nmr spectra were recorded with a Varian HA-100 nmr spectrometer operating at 40.5 MHz. The chemical shifts in parts per million are relative to 85% phosphoric acid as an external standard. Glpc analyses of the phosphites were performed on an F & M Model 700 using an $^1/_8$ in. × 50 ft "Hi-Pak" silicone gum rubber column at 100–130° and *ca.* 90 lbs pressure of helium. The isomeric phosphates were analyzed on the same instrument but with a $^1/_8$ in. × 16 ft column with 5% GE-XE60 column at 180° unless otherwise noted.

Preparation of Phosphites by Transesterification. A mixture of equimolar quantities of the appropriate glycol and a trialkyl phosphite was heated gradually to 110° (bath). The alcohol was allowed to distil as it formed. After distillation of the alcohol ceased, the residual oil was distilled at reduced pressure. The properties of the phosphites are collected in Table II.

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(10) For discussions of the role of pseudorotation in interconverting isomers or racemizing pentasubstituted compounds, see (a) J. D. Dunitz and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, 7, 725 (1968); (b) P. C. Lauterbur and F. Ramirez, *J. Am. Chem. Soc.*, **90**, 6722 (1968).

(11) P. W. C. Barnard, C. A. Bunton, D. R. Llewellyn, C. A. Vernon, and V. A. Welch, *J. Chem. Soc.*, 2670 (1961).

(12) A. J. Kirby and S. T. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., New York, N. Y., 1967, Chapter 1.

(13) J. G. Pritchard and P. C. Lauterbur, *J. Am. Chem. Soc.*, **83**, 2105 (1961).

(14) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *ibid.*, **87**, 549 (1965), and references cited therein.

Preparation of Phosphorochloridites. To a stirred solution of the appropriate glycol (1 mol) and N,N-dimethylaniline (2 mol) at 5° in ether was added dropwise phosphorus trichloride (1 mol) in ether. After stirring for 16 hr, the ether solution was separated from the amine hydrochloride by forcing it through a filter stick under a positive pressure of nitrogen. The ether solution was distilled to give a residual oil which was distilled at reduced pressure. The phosphorochloridites were used as obtained. Their nmr spectra were in agreement with the expected structures.

Preparation of Phosphites from Phosphorochloridites. To a stirred solution of equimolar quantities of the appropriate alcohol and N,N-dimethylaniline in ether at 5° was added dropwise the phosphorochloridite in ether. The reaction mixture was stirred for 16 hr and then the ether was separated from the precipitated amine hydrochloride by use of a filter stick. The excess ether was removed by distillation and the residual oil was distilled at reduced pressure. The properties of the phosphites prepared by this method are collected in Table II.

Isopropoxydichlorophosphine. To 137 g (1.0 mol) of phosphorus trichloride stirred and cooled to $-10°$ was added carefully 60 g (1 mol) of purified isopropyl alcohol. The mixture was stirred until it appeared that no more hydrogen chloride was being evolved. Distillation afforded a constant-boiling fraction, bp 56° (58 mm). The nmr spectrum had a doublet at 1.34 (J = 7 Hz) and a multiplet at 4.97. The ratio of areas was 6:1.

Reaction of Isopropoxydichlorophosphine with 1,2-Propanediol. To a stirred solution of 15.2 g (0.2 mol) of 1,2-propanediol and 48.4 g (0.4 mol) of N,N-dimethylaniline in 250 ml of ether at 5° was added dropwise 32.2 g (0.2 mol) of isopropoxydichlorophosphine in 50 ml of ether. The reaction mixture was stirred overnight, filtered with a filter stick, and the ether was distilled. The residue was distilled to give 13 g (40%) of product.

Preparation of Phosphates. A. Mercuric Oxide Oxidation. A solution of the phosphite in benzene was added to a cooled stirred suspension of a 25% molar excess of yellow mercuric oxide in benzene. The mixture was stirred for a minimum of 4 hr. The mixture was filtered and the excess solvent was removed by distillation. The residual oil was analyzed by glpc and distilled.

B. Nitrogen Dioxide Oxidation. To a solution of the phosphite in methylene chloride at $-78°$ there was added dropwise and with stirring a 10% solution of nitrogen dioxide in methylene chloride. The reaction was considered complete when a green-brown color persisted. The solvent was removed by distillation at atmospheric pressure and the residue was distilled at reduced pressure.

The oxidation was also carried out by bubbling dry nitrogen through liquid nitrogen dioxide. This gas stream was then passed through the neat phosphite which was maintained at 0°. A light yellow color indicated that the reaction was complete. The reaction mixture was allowed to stand overnight at room temperature and then distilled at reduced pressure.

Methyl-1-methylpropylene Phosphate. To 59.2 g (0.274 mol) of yellow mercuric oxide suspended in 75 ml of benzene was added with stirring and cooling a mixture (95:5) of 26.4 g (0.176 mol) of the phosphites. The mixture was stirred overnight at room temperature, filtered, and the benzene was evaporated at reduced pressure. Glpc analysis of the residue indicated that two major components were present in the ratio 2:5. The reaction mixture was distilled under reduced pressure. The total volatiles were fractionated through a 3-ft spinning band column at 0.1 mm to give 12 fractions. The third fraction, bp 80°, was essentially the component with the shorter retention time and fractions 7–9, bp 94–95°, contained the isomer with the higher retention time.[15]

Hydrolysis of the Isomeric Six-Membered Ring Phosphates. The phosphates were hydrolyzed in dilute base at 75.5 and 50.5°. They were also hydrolyzed in initially neutral media at 100°. The progress of the reactions was followed by titration with acid or base, respectively. After titration the phosphates were extracted with chloroform which was evaporated and the residue was analyzed by glpc. In no case was isomerization detected.

Hydrolysis of Methyl *cis*-1,4-Dimethylethylene Phosphates. The isomeric phosphites were prepared by transesterification of a mixture of *meso*-2,3-butanediol and *dl*-2,3-butanediol with trimethyl phosphite. The two *meso*-phosphites were separated from the *dl*-phosphite by distillation through a spinning-band column. Oxidation of the *meso*-phosphites with nitrogen tetroxide gave the isomeric phosphates in the ratio of 87:13 as determined by glpc. The mixed phosphates, 3.195 g (0.0192 mol), were dissolved in 10 ml of tetrahydrofuran containing 0.0394 g (0.00219 mol) of water. After 5 days at room temperature the solvent was distilled and the residue was evaporatively distilled to give 2.196 g (69%) of recovered phosphates whose ratio was shown to be 66:34 by glpc.

Hydrolysis of 0.2830 g (0.001705 mol) of the phosphates, 66:34, in 5 ml of tetrahydrofuran containing 0.0255 g (0.001417 mol) of water was followed by glpc analysis over 6 days. The ratio of phosphates changed slightly over the first 112 min but after that it remained constant within the limits of analysis at 62:38.

This experiment was repeated with 0.2640 g (0.00159 mol) of phosphates (88:12) in 5 ml of tetrahydrofuran containing 0.0274 g (0.00152 mol) of water. The ratio of phosphates after 5 min was 81:19, after 90 min 72:28, after 27 hr 60:40, and after 4 days 61:39.

Hydrolysis of Methyl *t*-Butylethylene Phosphates. The phosphates, 72:28, 0.4044 g (0.00208 mol), were dissolved in 2.5 ml of tetrahydrofuran. Water, 0.006 g (0.000333 mol), was added. After standing at room temperature for 3 days the ratio of phosphates was 60:40.

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[15] These isomers have been obtained by stereospecific oxidation of the two phosphites. The properties of the pairs of isomers obtained by the two methods are identical.