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The Effect of Added Salts on the Stereochemistry of Nucleophilic Displacements at Phosphorus in Phosphate Esters and Their Analogs

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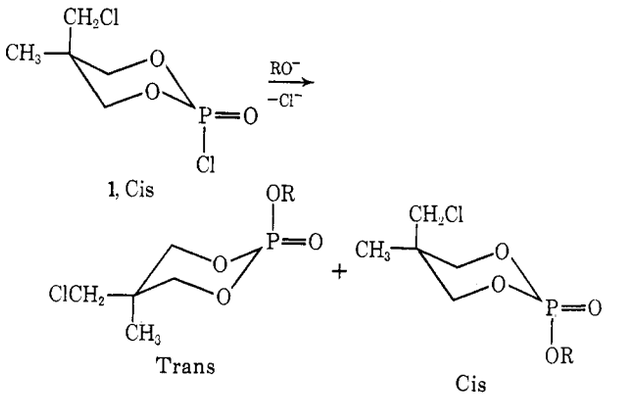
The stereochemistry of nucleophilic substitutions at phosphorus was studied by means of the 2-substituted 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system described previously. It has been observed that added salts dramatically influence the stereochemical outcome. The results are rationalized on the basis of a duality of mechanisms.

The mechanisms by which nucleophiles attack phosphorus leading to substitution have been studied extensively.[1] Both substitution by inversion and retention have been detected and pathways have been advanced to explain results. Because of their importance we are interested in phosphate esters and especially factors which effect the mechanism of substitution at the phosphorus atom. In this paper we report the effect of added cations on the inversion–retention ratio, an effect which may have broad implications not only with respect to phosphate esters and their role in biological systems[2] but with other classes of organophosphorus compounds as well.

In a previous publication[3] we outlined a procedure by which retention and/or inversion could be detected by merely observing the nmr spectra of products. Treatment of *cis*-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (**1**) with a nucleophile gives rise to substitution products whose configurations can be determined simply by observing the chemical shifts of hydrogen contained on groups at the 5 position. The structure of the phosphorochloridate **1** has been well established and the phosphoryl oxygen found to occupy an equatorial position in the cis and trans isomers. The latter was obtained by equilibration of **1**. Single-crystal X-ray analysis performed in our laboratories on the cis and trans phenyl esters (R = C_6H_5) have confirmed their structures.[4] Our data and that accumulated by others[5] gives reliable evidence that, in the case of cyclic phosphorinan esters, the phosphoryl oxygen prefers an equatorial position. The two geometrical isomers show a marked lack of conformational mobility owing to strong preference of groups at phosphorus for axial or equatorial positions. Thus the isomers can be detected *via* nmr, for the hydrogens of an axial chloromethyl group are shifted downfield from those of an equatorial chloromethyl group owing to deshielding by the ring oxygens. Likewise, the methyl hydrogens when axial as in the trans isomers are shifted downfield relative to those of an equatorial methyl group found in the cis isomers.



By means of our diagnostic tool, which eliminates those ambiguities usually associated with optically active substrates, we have followed the course of substitution at phosphorus. Starting with the phosphorochloridate **1**, we find, as outlined in our previous

(1) A. I. Kirby and S. G. Warren, "The Organic Chemistry at Phosphorus," Elsevier, Amsterdam, 1967, Chapter 10; W. E. McEwen, "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Wiley, New York, N. Y., 1965; R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapter 8; M. J. Gallagher and I. D. Jenkins in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1968.

(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, Chapter 5.

(3) W. S. Wadsworth, Jr., S. Larsen, and H. L. Horten, *J. Org. Chem.*, **38**, 256 (1973).

(4) R. E. Wagner, W. Jensen, W. S. Wadsworth, Jr., and Q. Johnson, presented at the 8th Midwest Regional Meeting of the American Chemical Society, Columbia, Mo., 1972.

(5) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971).

publication,[3] that the retention–inversion ratio is influenced by the basicity of the nucleophile with retention favored by increased basicity. We have also noted pronounced solvent effects (Table I), and have

TABLE I

PERCENTAGE OF CIS AND TRANS ISOMERS OBTAINED BY TREATING PHOSPHOROCHLORIDATE 1 WITH SODIUM PHENOXIDE IN VARIOUS SOLVENTS[a]

Solvent	Trans (inversion)	Cis (retention)
Benzene	14.3	85.7
Chloroform	14.3	85.7
Dioxane	33.4	66.6
Tetrahydrofuran	50.0	50.0
Acetonitrile	52.0	48.0
Acetone	69.2	30.8
Dimethylformamide	83.4	16.6

[a] All spectra were obtained in $CDCl_3$ by means of a Varian A-60A spectrometer using TMS as an external standard.

now determined that the change in isomer ratio with solvent is a function of the solubility of the salt produced as by-product. The amount of trans isomer increases as the solubility of the salt increases. In all cases the ratio of isomers formed is kinetically controlled, for the individual isomers are stable under the reaction conditions and indeed no isomerization was observed, except where noted, even under drastic conditions.

The influence of salt was determined by carrying out the substitutions in a solvent to which salt was added. Thus in acetonitrile saturated with sodium chloride a change in the ratio was observed with an increase in the product of inversion (Table II). The effect was much

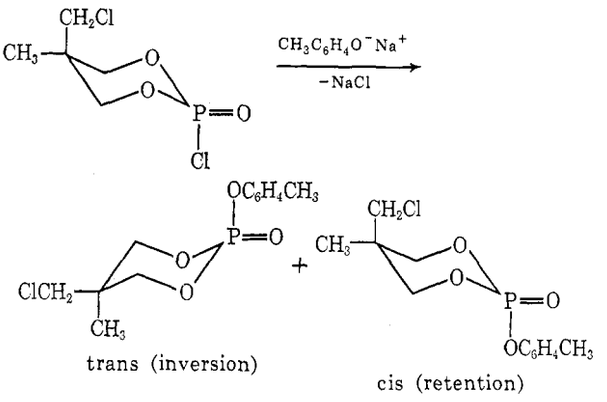
TABLE II

ADDITION OF SODIUM *p*-METHYLPHENOXIDE TO PHOSPHOROCHLORIDATE 1. EFFECT OF ADDED SALTS ON THE INVERSION–RETENTION RATIO

Solvent	% trans (inversion)	% cis (retention)
CH_3CN	46.5	53.5
CH_3CN[a]	55.8	44.2
CH_3CN + saturated NaCl	65.8	34.2
CH_3CN[a] + 1 equiv $(CH_3)_4N^+Cl^-$	88.8	11.2
CH_3CN + 1 equiv $LiClO_4$	12.2	87.8
$HCN(CH_3)_2$[a]	80.2	19.8
$HCN(CH_3)_2$[a] + 1 equiv $(CH_3)_4N^+Cl^-$	95.2	4.8
$HCN(CH_3)_2$[a] + 1 equiv $LiClO_4$	47.4	52.6
Benzene	10.0	90.0

[a] Inverse addition. The phosphorochloridate added to salt solutions.

more pronounced with added tetramethylammonium chloride, for here the added salt and sodium *p*-methylphenoxide precipitated sodium chloride to give acetonitrile-soluble tetramethylammonium *p*-methylphenoxide. Added lithium perchlorate had an effect opposite to that which might be expected. The added perchlorate evidently does not ionize appreciably in acetonitrile and its effect was to reduce the solubility



of the sodium ion, thereby diverting the substitution to predominantly retention. When the order of addition was reversed, the chloridate added to a solution of sodium *p*-methylphenoxide, the amount of inversion increased. The result is not unexpected, for it again reflects the ability of the sodium ion to enhance the inversion mechanism.

Sodium *p*-methylphenoxide was found owing to its better stability and greater ease in product purification to be a more favorable reactant then sodium phenoxide. In all cases lack of solubility of added salts hindered attempts at obtaining meaningful quantitative results. Dimethyl sulfoxide was not a suitable solvent, for it readily reacts with phosphorochloridates.[6]

Solvents, especially those capable of solvating cations, had a pronounced effect on the ability of added salts to divert the substitution to inversion. In ethanol, for example (Table III), in which cations are capable of

TABLE III

ADDITION OF PHOSPHOROCHLORIDATE 1 TO SODIUM *p*-METHYLPHENOXIDE DISSOLVED IN ETHANOL. EFFECT OF ADDED SALT ON ISOMER RATIOS

Solvent	% trans (inversion)	% cis (retention)
CH_3CH_2OH	37.0	63.0
CH_3CH_2OH + saturated NaCl	37.5	62.5
CH_3CH_2OH + 1 equiv $(CH_3)_4N^+Cl^-$	85.2	14.8
CH_3CH_2OH + 1 equiv $LiClO_4$	21.3	78.7
CH_3CH_2OH + 1 equiv LiCl	27.3	72.7

being solvated, inversion is less pronounced than with acetonitrile. The effect of added sodium chloride was much less pronounced even though more soluble in the medium. Again, the addition of tetramethylammonium chloride had a pronounced effect which indicates that the tetramethylammonium ion is particularly effective, owing perhaps to relatively less solvation. In order to reduce the possibility of reaction of the phosphorochloridate with solvent, the chloridate was added to the sodium *p*-methylphenoxide–ethanol mixtures.

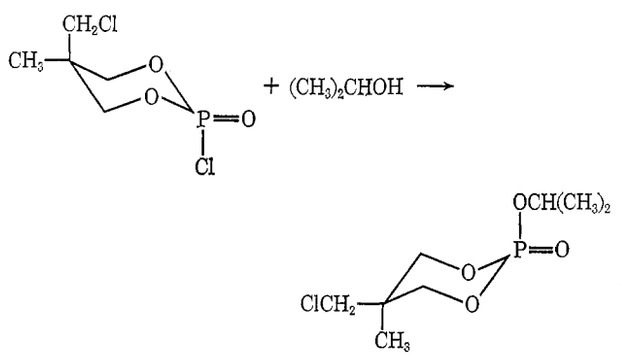
The ratio of isomers obtained upon methanolysis of the phosphorochloridate was also effected by added salts. In the absence of added salt the inversion–retention (trans/cis) was 3:2. Addition of 1 equiv of $NaHCO_3$ to the solvent before addition of the phosphorochloridate increased the ratio to 3:1, whereas silver nitrate led to complete inversion. The ratios are

(6) M. A. Ruveda, E. N. Zerba, and E. M. DeMoutier Aldao, *Tetrahedron*, **28**, 5011 (1972).

based on the nmr spectra[3] of distilled products. The methanolysis could also be conveniently followed *via* nmr by using deuterated solvent. By means of this technique, tetramethylammonium ion gave essentially complete inversion with an overall rate approximately twice that without the added salt. The change in isomer ratio and rate is more striking when it is realized that, although a saturated solution of the salt was employed, tetramethylammonium chloride is only sparingly soluble in methanol. Based on the nmr spectrum less than 0.1 equiv of salt was in solution. In comparison to the observed change in stereochemistry, the variation in rate appears to be surprisingly small.

The methanolysis study was complicated not only by lack of solubility of added salt but by a side reaction which is concurrent with solvolysis of the phosphorochloridate. The methyl esters once formed react with methanol especially under acidic conditions to produce by C–O bond scission dimethyl ether and the acid 2-hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (**3**). Unfortunately, the chemical shifts of hydrogen on groups at the 5 position of the acid coincide with those of the starting phosphorochloridate. Equilibration of the initially formed isomer mixtures by acid-catalyzed trans methanolysis also occurs but is extremely slow, requiring over 2 months for the final 2.5:1 cis/trans equilibrium ratio to be reached.

2-Propanolysis of the phosphorochloridate gave only a single isomer, the trans, *via* inversion. Apparently attack by retention is unfavorable owing to steric hindrance. The axial ring hydrogens hinder attack from the side opposite the phosphoryl oxygen (see Discussion section). That steric hindrance is important was evident by comparison of the inversion–retention ratio, 1.26:1, obtained by treatment of the phosphorochloridate with sodium *p*-methylphenoxide, with that obtained under identical conditions with the more bulky sodium 2,6-dimethylphenoxide, 3.55:1.



Data obtained with the phosphorochloridate prompted us to look at substrates with a leaving group other than chloride ion. Owing to its ease of formation, stability, and ease of substitution we selected *trans*-2-*p*-nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan[3] (**2**). As with the phosphorochloridate, the ratio of isomers obtained by treating the *p*-nitrophenyl ester with sodium *p*-methylphenoxide varied with the solvent and was influenced by added salt (Table IV).

The *p*-nitrophenyl ester **2** was of further interest. As with other esters and the phosphorochloridate it gave no indication of isomerization when heated in a variety of polar solvents, *i.e.*, formic acid, nitrobenzene, or acetonitrile. Unlike the phosphorochloridate, which isomerizes readily in dimethylformamide, it also gave no indication of isomerization when a dimethylformamide solution was heated. In the case of phosphorochloridates, dimethylformamide has been found to act as a nucleophile.[7] Evidently the *p*-nitrophenoxide ion is not a good enough leaving group for substitution by the solvent to occur.

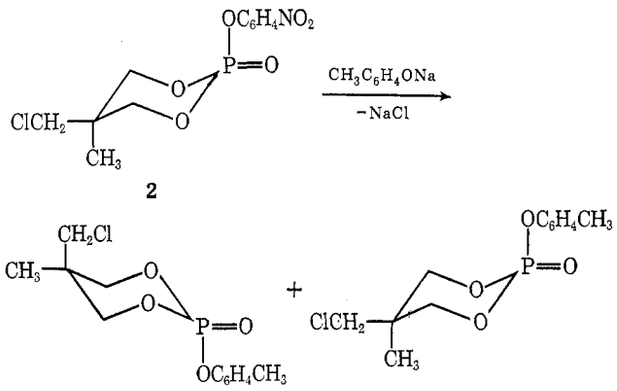


TABLE IV

PERCENTAGE OF CIS AND TRANS ISOMERS OBTAINED BY ADDITION OF *trans*-2-*p*-NITROPHENOXY-5-CHLOROMETHYL-5-METHYL-2-OXO-1,3,2-DIOXAPHOSPHORINAN (**2**) TO SODIUM *p*-METHYLPHENOXIDE. SOLVENT AND SALT EFFECTS

Solvent	% cis (inversion)	% trans (retention)
CH_3CN	44.5	55.5
CH_3CN + 1 equiv $(CH_3)_4N^+Cl^-$	86.0	14.0
$HCN(CH_3)_2$ (O)	74.5	25.5

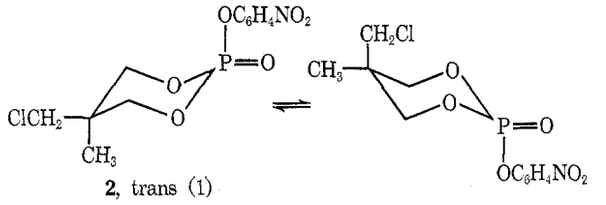
Addition of a small amount of sodium *p*-nitrophenoxide to a solution of the ester does, however, owing to ester exchange, cause isomerization with the rate dependent upon the polarity of the medium. Thus in acetonitrile isomerization was incomplete after a solution containing added sodium *p*-nitrophenoxide which was only slightly soluble had stood at room temperature for 4 days. When dimethylformamide was employed an identical mixture of ester and sodium *p*-nitrophenoxide required less than 10 min to reach equilibrium. The large difference in rate may reflect the increased solubility of the sodium *p*-nitrophenoxide in the latter solvent and in turn the greater influence of the sodium ion.

The effect of added salts other than sodium *p*-nitrophenoxide is also striking. Whereas no isomerization of the ester is observed even in refluxing dimethylformamide, it is observed upon warming a dimethylformamide solution containing tetramethylammonium chloride. Upon heating, the solution slowly turns yellow owing to liberated *p*-nitrophenoxide ion with the color fading upon cooling. The added salt appears to increase the electrophilicity of the phosphorus atom, enabling the weak nucleophile, dimethylformamide, to displace the *p*-nitrophenoxide ion which reattacks upon cooling with both inversion and retention to give an equilibrium-controlled ratio of isomers. The other phenyl esters described in this paper, which contain a poorer leaving group, do not equilibrate in dimethyl-

(7) F. Cramer and M. Winter, *Ber.*, **94**, 989 (1961).

formamide upon the addition of a common ion or upon heating solutions containing added tetramethylammonium chloride.

The final equilibrium mixture of isomers obtained upon addition of sodium *p*-nitrophenoxide to the *p*-nitrophenyl ester is thermodynamically controlled and reflects the preference of the chloromethyl group for an axial position possibly owing to dipole interaction between the group and ring oxygens.[8] An identical ratio was obtained upon equilibration of the cis phosphorochloridate **1** by dissolving a sample in dimethylform-



2, trans (1) cis (2.5)

amide.[3] In the latter case where the solvent acts as a nucleophile equilibrium was reached without added chloride ion or other salts within 15 min. The ability of the trans *p*-nitrophenyl ester in the presence of added *p*-nitrophenoxide ion and cis phosphorochloridate to equilibrate in dimethylformamide may render the isomer ratios obtained upon substitution less valid when this solvent is employed. It should be pointed out, however, that the increased tendency for inversion in dimethylformamide owing to salt solubility is firmly established.

In contrast to dimethylformamide, when dissolved in nonnucleophilic solvents, **1**, **2**, and **4** can be recovered unchanged and under the reaction conditions do not undergo isomerization in the presence of inert salts. Also, when a twofold excess of **2** was added to sodium *p*-methylphenoxide in acetonitrile and the unreacted starting material isolated shortly after substitution was complete (within 15 min), the recovered reactant contained only the starting trans isomer. When inert solvents are employed the starting materials do not undergo isomerization prior to substitution.

Phosphorylation by pyrophosphates has been found to be metal catalyzed.[9,10] It was of interest, therefore, to determine if added cations could have the same influence on the mechanism of substitution with pyrophosphates as substrates as they have with phosphorochloridates and reactive phosphate esters. The pyrophosphate **4** was best prepared by refluxing a chloroform solution of **3** with thionyl chloride. The product was probably a mixture of the three possible isomers which unfortunately defied separation into its components. The two phosphorinan rings of different configurations were not of equal concentration in the mixture. That with the chloromethyl group equatorial predominated over that with the chloromethyl group axial by a 2:1 ratio. We have assumed that, as in the case of the esters, the preference is for the phosphoryl oxygen to be equatorial. Our assumption is based on the ratio of isomeric phosphoramidates obtained by treatment of an acetonitrile solution of the pyrophosphate with piperidine. It has been shown previously[3] that substitution by amines under these conditions proceeds, at least with phosphorochloridates, entirely by inversion. The fact that the combined yield of product was over 90% and that the cis predominated over the trans would indicate our assignment of the configuration at phosphorus to be correct. If the phosphoryl oxygens in the pyrophosphate were axial, the ratio of products should be reversed. The fact that the ratio of cis to trans phosphoramidates is greater than two would indicate that attack by inversion at that phosphorus atom whose phosphorinan ring contains a chloromethyl group equatorial is more facile than attack at that phosphorus atom whose phosphorinan ring has an axial chloromethyl group. By means of X-ray analysis we have shown that the phosphoramidates, unlike the phosphorochloridate and phosphate esters, have the phosphoryl oxygen axial.[11] The reason for the preference of an amido group for an equatorial position, a phenomenon which has also been observed by others,[12] is not certain.

Treatment of the pyrophosphate with sodium *p*-methylphenoxide gave a mixture of the two possible isomers in a ratio which is solvent dependent and which is influenced by added salt (Table V). As the polarity

TABLE V

TREATMENT OF PYROPHOSPHATE 4 WITH SODIUM *p*-METHYLPHENOXIDE

Solvent	% cis	% trans
CH_3CN	70.9	29.1
CH_3CN + 1 equiv $(CH_3)_4N^+Cl^-$	83.0	17.0
Benzene	66.6	33.3

of the medium increases the cis to trans product ratio increases. In benzene, where retention would be expected to predominate, the ratio is unexpectedly large, which may reflect the fact that, while inversion favors attack at that ring containing an equatorial chloromethyl group, attack by retention is favored at that ring having an axial chloromethyl group. It is also possible, of course, that owing to steric hindrance by the relatively large leaving group, inversion is more favorable in this case than with the phosphorochloridate or phosphate esters. At any rate, the trend toward increased inversion with added salt is apparent.

The pyrophosphate is completely stable in all solvents studied with the exception of dimethylformamide. In the latter solvent the pyrophosphate slowly equilibrates upon heating to give a new mixture of pyrophosphates in which the ratio of chloromethyl groups axial to equatorial has a final ratio of 2.5:1. The "tail wagging" can easily be followed by nmr and as with the phosphorochloridate must be a consequence of the ability of dimethylformamide to act as a nucleophile. The equilibrium ratio is identical with that obtained with the phosphorochloridate and again reflects the relative thermodynamic stability of the two ring configurations. In the presence of 0.1 equiv of tetramethylammonium chloride the rate of attainment of

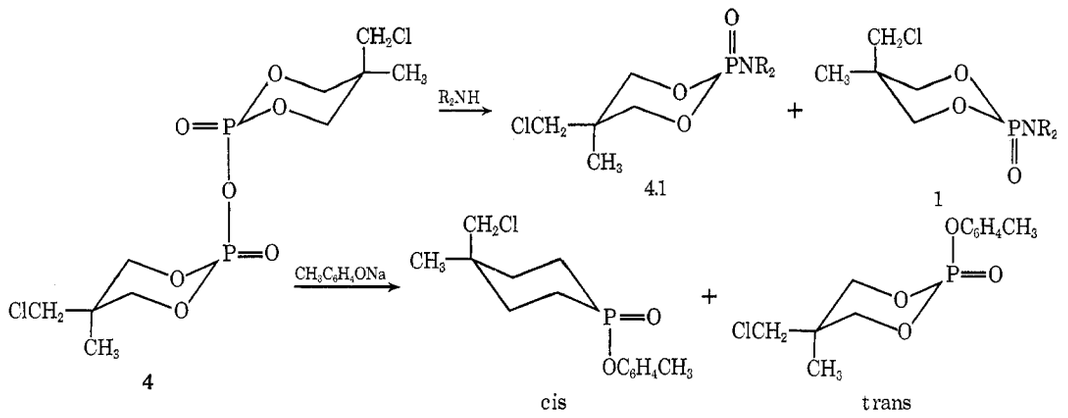
(8) The preference of the chloromethyl group to be axial has been reported for an analogous 2-methoxy phosphite: D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970).

(9) M. Tetas and J. M. Lowenstein, *Biochemistry*, **2**, 350 (1963).

(10) W. P. Jeneks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 112.

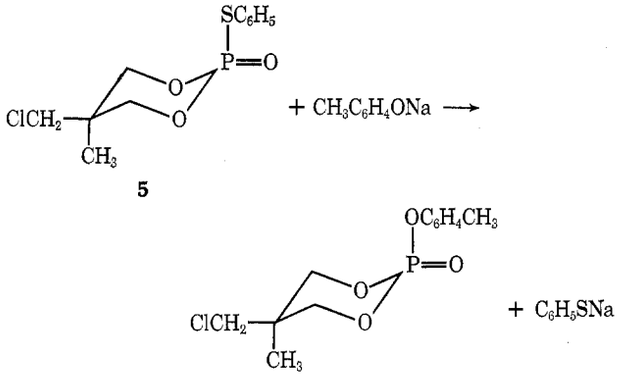
(11) R. E. Wagner, W. Jensen, W. S. Wadsworth, Jr., and Q. Johnson, *Acta Crystallogr.*, in press.

(12) J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, **94**, 8224 (1972).



equilibrium was nearly twice that without the added salt.

In the case of a phosphorothiolate whose configuration is known, substitution of a mercaptide group proceeds entirely by retention. Treatment of *trans*-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (**5**)[3] with either sodium *p*-methyl-



phenoxide or sodium phenoxide gave only the single isomer, the trans. Addition of 1 equiv of $(CH_3)_4N^+Cl^-$ to the reaction mixtures prior to addition of the sodium salt did not change the course of substitution.

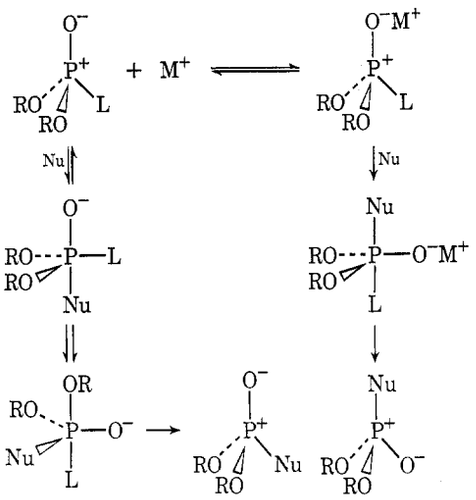
Discussion

In accordance with conclusions drawn by others[13,14] on related systems, there is no evidence that substitutions at phosphorus in phosphates occur by anything but by an associative mechanism. In support of this conclusion, the cis phosphorochloridate does not in the absence of added chloride ion undergo isomerization when dissolved in polar solvents such as nitrobenzene, trifluoroacetic acid, etc., and the solutions were heated. As stated earlier, dimethylformamide and also pyridine are exceptions but here evidence indicates that the solvents are acting as nucleophiles. Methanolysis in the presence of silver ion leads only to the inverted ester, whereas, if a phosphoryl cation were an intermediate, one might expect a mixture with perhaps a 2.5:1 ratio of isomers.[15]

It is probable that cations complex with phosphates through the phosphoryl oxygen.[16] Treatment of the phosphorochloridate **1** with $AlCl_3$ in ether gave a viscous precipitate. The precipitate, when dissolved in acetonitrile and the solution treated with piperidine, gave only a single isomer, the trans phosphoramidate. The latter is also obtained by inversion from the starting phosphorochloridate without added $AlCl_3$. Thus treatment of cis phosphorochloridate with $AlCl_3$ did not cause isomerization, which might have been expected if the $AlCl_3$ had complexed with the chloride ion.

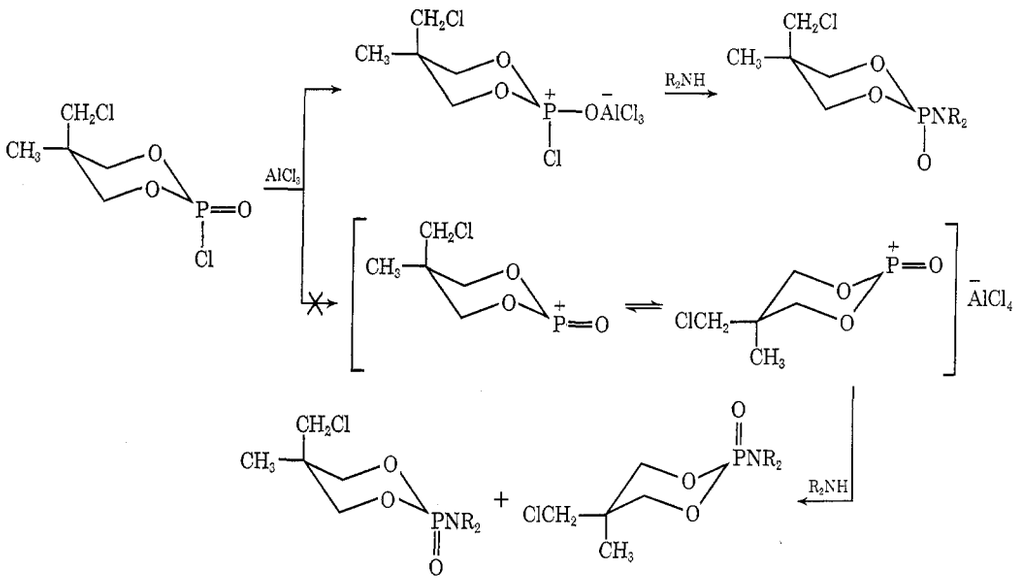
A change in stereochemistry with added salts would suggest two separate mechanisms for substitution, one for retention and one for inversion (Scheme I). If the

SCHEME I



influence of extraneous cations could be completely eliminated, it appears from our data that substitution would perhaps proceed entirely by retention, whereas, if complex formation were complete, substitution might be entirely by inversion. In the presence of a cation an equilibrium may be established which is dependent upon the concentration of the cation and the strength of the complex. The equilibrium will also be influenced by solvation effects. In accordance with the "polarity rule,"[17,18] a charged nucleophile would be expected to attack the uncomplexed phosphate from a side opposite the phosphoryl oxygen, a position of minimum electron density. Pentacoordinated intermediates in the trigonal bipyramid form are well estab-

(13) P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, **93**, 6924 (1971).
(14) E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 3591 (1962).
(15) Our original assumption that a phosphoryl cation may be involved was based on impure phosphorochloridate and has proven to be false: W. S. Wadsworth, Jr., and H. L. Horten, *J. Amer. Chem. Soc.*, **92**, 3785 (1970).
(16) D. E. C. Corbridge, "Topics in Phosphorus Chemistry," Vol. 3, M. Grayson and E. J. Griffith, Ed., Wiley, New York, N. Y., 1966, p 297.
(17) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).
(18) F. Ramirez and I. Ugi in "Advances in Physical Organic Chemistry," Vol. 9, V. Gold, Ed., Academic Press, New York, N. Y., 1971.



lished as intermediates in phosphorus substitutions.[19,20] Nucleophiles are assumed to enter and leaving groups depart from apical positions. The trigonal bipyramid would undergo a pseudorotation which leads to substitution by retention.

As a result of complex formation, the positive charge on phosphorus is increased owing to the reduction in backbonding by oxygen lone-pair electrons with d orbitals of phosphorus. One would, therefore, expect an increase in the rate of substitution as a result of complex formation. Nucleophiles may attack the complex with direct displacement in an SN2 fashion without the formation of an intermediate, a situation which would lead directly to inversion. There has been some dispute[21-23] as to whether substitutions involve a pentacoordinated intermediate, and it may well be that inversion does not.

With our duality of mechanism scheme, the ability of added cations to shift substitution to the inversion pathway is obvious.[24] The greater ability of more basic nucleophiles to substitute by retention in contrast to less basic ones is also explained. The results merely reflect a difference in rate of attack at the two species in equilibrium. The energy of activation for attack by a weakly basic nucleophile would be greater at the uncomplexed phosphate than at phosphorus in which the phosphoryl oxygen is complexed. With more basic nucleophiles, which form strong bonds to phosphorus, the difference in activation energies would be diminished.

It is apparent that the mode of substitution is also dependent upon the leaving group. This would be expected if the inversion mechanism proceeded by direct displacement. The percentage of inversion should vary with the leaving group, especially if the third step in the retention pathway was not rate determining. Recent kinetic evidence[25] has shown that in the decomposition of suspected pentacoordinated intermediates the departure of the leaving group is rate determining in those cases involving a poor leaving group such as isopropoxide ion, whereas formation of the intermediate becomes the slow step in cases which involve a good leaving group such as phenoxide ion. Under identical conditions the percentage of inversion is greater for the phosphorochloridate than for the *p*-nitrophenyl ester, both of which contain a good leaving group. We believe this to be evidence that inversion proceeds by a one-step mechanism.

Why substitution of a mercaptide ion proceeds only by retention,[26] even in the presence of added salts, is more difficult to rationalize. Certainly, only the mechanism which involves the formation of an intermediate must be operative. Backbonding between sulfur and phosphorus is less than between oxygen and phosphorus and thus the phosphorus atom in phosphorothiolates has more positive character than that in phosphates.[27] In consequence, with respect to phosphorothiolates, backbonding between the phosphoryl oxygen and phosphorus atom might be increased to the extent that complex formation is inhibited.[28]

Unlike charged nucleophiles, neutral nucleophiles such as piperidine and other amines react with the cis phosphorochloridate to give phosphoramidates almost exclusively by inversion. This is the case even under conditions where the effect of the by-product, a quaternary salt, should be at a minimum. Thus, when substitutions are carried out at low temperatures in hexane, only a trace of that phosphoramidate which results from retention is observed. From our previous work both isomers have been obtained in pure form and their spectra are well defined. To account for predominant inversion even without the influence of added salt, one needs to consider the transition state. The charge on the phosphoryl oxygen is partially neutralized as is the charge on nitrogen which would result in a lowering of

(19) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).
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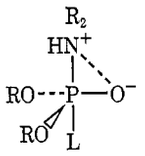
the energy of activation. If substitution by inversion were a three-step process with a trigonal bipyramid



intermediate, attack could as easily be from two other planes of the starting tetrahedron also with neutralization of charges. Such attack would result in retention. Since inversion is almost exclusive, it would again appear that the leaving group departs as the entering group approaches from the back-side and no intermediate is involved.

Since methanolysis proceeds in the absence of a cation predominantly but not exclusively by inversion, we may assume a transition state similar to that postulated for the amines. Charge stabilization, however, may be less, thereby allowing a greater percentage of retention.

Our results and especially the effect of added salts on the stereochemical pathway serves to point up the complexity of nucleophilic substitutions at phosphorus. The interpretation of our results is not a simple matter and should be accepted only as a starting point for further investigations.

Experimental Section

The nmr spectra and procedures for the preparation of the phosphorochloridate 1, phosphate esters, acid, and amides have been published previously.[3] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. A typical preparation of a phosphate ester applicable to a study of salt effects is given.

2-*p*-Methylphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.—Phosphorochloridate 1, 2.18 g (0.01 mol), and tetramethylammonium chloride, 1.09 g (0.01 mol), were added to 20 ml of acetonitrile. Sodium *p*-methylphenoxide, 1.30 g (0.01 mol), was added and the solution was stirred at room temperature for 24 hr. The mixture was diluted with 100 ml of water and filtered. The product, 2.85 g (98.2% yield), was dried and its nmr spectrum was recorded. The product could be recrystallized from hexane without a change in isomer ratio.

Yields were consistently over 95% and no isomerization of isomer mixtures was noted under the procedures of work-up.

For those cases in which a water-immiscible solvent was employed, the solvent was removed under reduced pressure before addition of the water.

Pyrophosphate 4.—2-Hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 5.0 g (0.025 mol), and 10.0 g of thionyl chloride were added to 75 ml of chloroform. The mixture was refluxed for 48 hr and solvent was removed under reduced pressure. The residue was recrystallized from toluene, 4.55 g (95% yield).

Anal. Calcd for $C_{10}H_{18}Cl_2O_7P_2$: C, 31.41; H, 4.71; Cl, 18.32; P, 16.23. Found: C, 31.28; H, 4.69; Cl, 18.59; P, 15.99.

Partial separation of isomers could be accomplished by fractional crystallization from carbon tetrachloride, but pure isomers could not be obtained by this or by chromatographic methods. The mixture of pyrophosphates was equilibrated by heating a dimethylformamide-d_7 solution at 55°. The variation in peak heights was followed by nmr until heating produced no further change.

Phosphoramidates from Pyrophosphate 4.—Piperidine, 0.34 g (0.004 mol), was added to an acetonitrile solution of pyrophosphate, 0.76 g (0.002 mol). The solution was stirred at room temperature for 24 hr, during which time the amine salt of the acid by-product precipitated. The filtrate was diluted with 50 ml of water, the mixture was filtered, and the product was dried to give a mixture of isomeric phosphoramidates, 0.36 g (70% yield). The nmr spectrum of the product was identical with that of an authentic mixture.[3]

The pyrophosphate was treated with sodium *p*-methylphenoxide with and without added salt in a similar fashion to give isomeric mixtures of known esters.

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Registry No.—**1**, 28097-07-6; **2**, 36912-38-6; **4**, 36914-95-1; sodium phenoxide, 139-02-6; sodium *p*-methylphenoxide, 1121-70-6; *trans*-2-*p*-methylphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-34-2; *cis*-*p*-methylphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-33-1.