Isolation of Hydrogenated Products of 1b. After treatment of the solution of **1b** in EtOAc with Pt, the resulting mixture was separated by means of column chromatography to afford **2b** mp 58–59 °C (lit.[7] mp 59 °C); **5b** n^{25}_D 1.478 (lit.[7] 1.4797); **3b** n^{25}_D 1.518, ^{1}H NMR δ 3.4 (1 H, m; lit.[24] 3.55); **6b** n^{25}_D 1.476 (lit.[7] mp 1.477); and **4b** n^{25}_D 1.516; ^{1}H NMR δ 3.0 (1 H, m; lit.[24] 3.3).

Separation of Hydrogenated Mixture of 1c. The resulting mixture was submitted on an alumina column with hexane to be seperated into a mixture of **5c** and **6c**, pure **2c**, and a mixture of **3c** and **4c**. **2c**: n^{25}_D 1.518 (lit.[25] 1.5233); ^{1}H NMR δ 1.21–1.29 (1 H, m, ax-H_4), 1.31–1.45 (4 H, m), 1.71–1.73 (1 H, m, eq-H_4), 1.81–1.86 (4 H, m), 2.45 (1 H, tt, J = 3.2 and 10.8 Hz), 2.31 (3 H, s), 7.08 (4 H, s).

Each cis/trans mixture was separated by preparative HPLC using a column (20-mm i.d., 30 cm) containing Merck LiChroprep RP-18 with acetonitrile as mobile phase. **5c**: n^{25}_D 1.476; ^{1}H NMR δ 0.88 (3 H, d, J = 7.0 Hz). **6c**: n^{25}_D 1.472; ^{1}H NMR δ 0.83 (3 H, d, J = 6.6 Hz). **3c**: n^{25}_D 1.515; ^{1}H NMR[26] δ 1.02 (3 H, d, J = 7.1 Hz). **4c**: n^{25}_D 1.507; ^{1}H NMR[26] δ 0.93 (3 H, d, J = 6.6 Hz).

Isolation of the Hydrogenated Products of 11. The resulting mixture was chromatographed on silica gel with hexane to give **8**, **7**, **12** (n^{25}_D 1.528; lit.[7] 1.5175), **16** (n^{25}_D 1.478), **14** (n^{25}_D 1.518), **15** (n^{25}_D 1.480), **13** (n^{25}_D 1.520), and 3-phenylcyclohexanone (2,4-dinitrophenylhydrazone (mp 178–180 °C, dec; lit.[27] mp 182–186 °C) in this order.

Acknowledgment. Toshikatsu Funahara and Tooru Kawata provided helpful technical assistance as graduation theses for which we thank them. M.M. greatly appreciates the helpful advice of Professor Ronald G. Harvey, Ben May Laboratory for Cancer Institute, University of Chicago.

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(25) Burwell, R. L., Jr.; Archer, S. *J. Am. Chem. Soc.* **1942**, *64*, 1032.
(26) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.
(27) Woods, G. W.; Tucker, I. W. *J. Am. Chem. Soc.* **1948**, *70*, 2174.

Acid-Catalyzed Solvolysis of Highly Reactive Phosphoramidates: A Stereochemical Study

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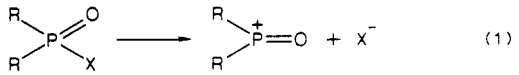
Two 2-substituted-5-(chloromethyl)-1,3,2-dioxaphosphorinanes have been prepared in which the 2-substituent is either imidazole or benzimidazole. The two phosphoramidates in which the 2-substituent is axial have opposite configurations as determined by NMR and solvolysis studies. Acid-catalyzed methanolysis in both cases is extremely rapid and proceeds by 100% inversion. However, with weak nucleophiles or a nucleophile kept in low concentration, an intermediate is formed which has enough lifetime to allow at least partial equilibration about the phosphorus atom. Although a completely free phosphacylium ion is unlikely, with aromatic solvents a similar product ratio from both isomers which may reflect a common intermediate is approached.

In the area of organophosphates and their analogues, there has been and continues to be speculation that analogous to carbon chemistry a continuum exists between dissociative and associative mechanisms. Indeed, the possibility of a process proceeding dissociatively via a phosphacylium ion analogous to an acylium ion has intrigued a number of research groups (eq 1).[1a-c] Most speculation

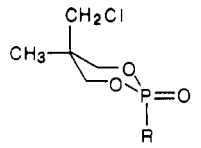


(1)

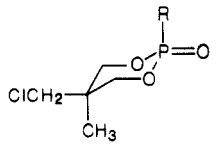
rests on kinetic data, whereas the meager stereochemical data available has led to rejection of a unimolecular dissociation leading to a discrete intermediate.[1a] If definite proof of a dissociative process based on stereochemical arguments could be illustrated, it would have implications beyond its immediate sphere for it would lend credence to the possible role of metaphosphate generated, among other ways, by the dissociation of mono- and dianions of phosphate monoesters, an area of intense study.[2a-h] This paper outlines our efforts to provide a reasonable mechanism, based on stereochemical principles, for the solvolysis of a highly reactive phosphoramidate.

The 2-substituted-5-(chloromethyl)-5-methyl-1,3,2-dioxaphosphorinane system, which we have described in a

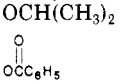
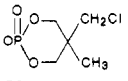
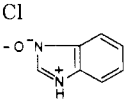
Table I. Chemical Shifts of 2-Substituted 5-(Chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes[a,b]



cis



trans

R	CH_3	CH_2Cl	CH_3	CH_2Cl
OCH_3	0.92	3.78	1.24	3.48
$OCH(CH_3)_2$	1.00	3.80	1.20	3.55
	0.97	3.75	1.36	3.45
	1.03	3.77	1.41	3.42
Cl	1.10	3.90	1.40	3.46
	0.91	3.90		
OH	1.03	3.80		

[a] A number of other compounds as well as complete spectra can be found elsewhere.[3b] [b] In parts per million downfield from internal Me_4Si in $CDCl_3$.

(1) (a) Michalski, J.; Radziejewski, Cz.; Skryzpczynski, Z.; Dabkowski, W. *J. Am. Chem. Soc.* **1980**, *102*, 7976. (b) Tyssee, D. A.; Hakke, P. Ibid. **1973**, *95*, 8066. (c) Haake, P.; Ossip, P. S. *J. Am. Chem. Soc.* **1971**, *93*, 6919.
(2) (a) See, for a summary: Westheimer, F. J. *Chem. Rev.* **1981**, *81*, 313. (b) Calvo, K. C.; Rozzell, J. D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1983**, *105*, 1693. (c) Bourne, N.; Williams, A. Ibid. **1984**, *106*, 7591. (d) Skoog, M. T.; Jencks, W. P. Ibid. **1984**, *106*, 7597. (e) Ramirez, F.; Marecek, J. F.; Shrishailam, S. Y. Ibid. **1982**, *104*, 1345. (f) Ramirez, F.; Marecek, J. F. *Tetrahedron* **1980**, *36*, 3151. (g) Ramirez, F.; Marecek, J. F.; Shrishailam, S. Y. *Tetrahedron Lett.* **1982**, *23*, 1515. (h) Ramirez, F.; Marecek, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 1460.

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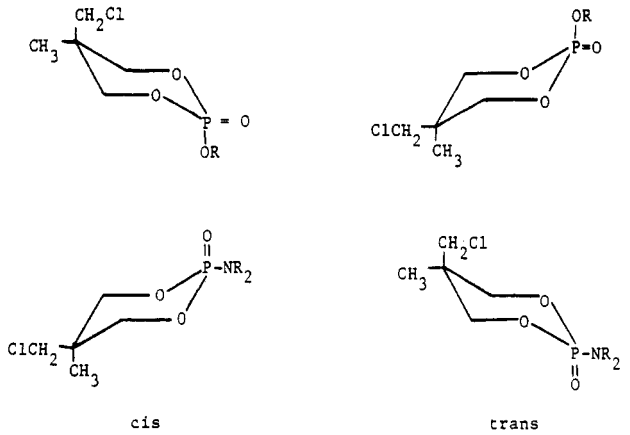
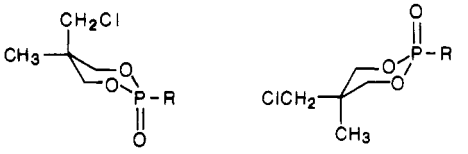


Figure 1.

Table II. Chemical Shifts of 2-Amino-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes[a,b]



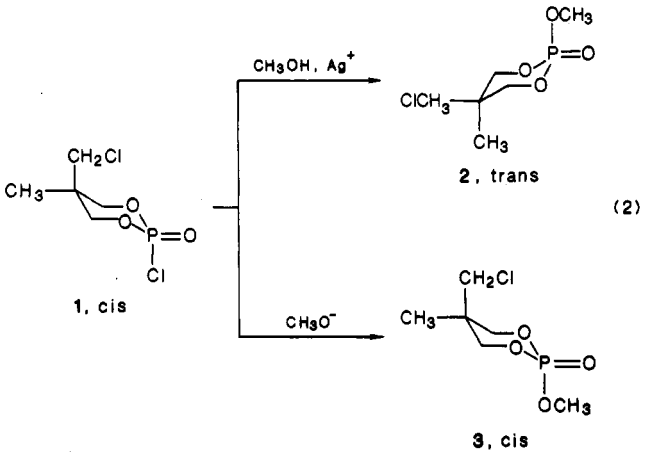
R	CH_3	CH_2Cl	CH_3	CH_2Cl
NC_5H_{11}	0.98	3.83	1.28	3.60
$N(CH_3)_2$	0.91	3.75		
$NHCH_2C_6H_5$	0.90	3.62		
NH_2	0.94	3.90		
$NHNH_2$	1.00	3.90	0.91[1b]	3.77

[a] A number of other compounds as well as complete spectra can be found elsewhere.[3b] [b] In parts per million downfield from internal Me_4Si in $CDCl_3$.

number of publications, has advantages over acyclic phosphates.[3a-e] Not only are the compounds, especially if only one geometrical isomer is present, highly crystalline but, equally as important, they are conformationally immobile. In the case of the ester, the phosphoryl oxygen requires an equatorial position, while in most cases the same group is axial in the phosphoramidates (Figure 1).[3b,4a,b] Simple chemical shift differences between the axial and equatorial 5-methyl and 5-(chloromethyl) hydrogens can be used to verify which geometrical isomer is present in solution. When either group is axial, hydrogen absorption is shifted downfield relative to hydrogens on equatorial groups (Tables I and II). Thus, optically active substrates are not required for stereochemical studies. We have synthesized numerous 2-substituted phosphorinanes of this type and have recently outlined those mechanisms by which these cyclic phosphates and their analogues undergo solvolysis, none of which could be described as proceeding via ionization prior to nucleophilic attack.[5a,b] It has been recognized, on the other hand, that certain phosphinamides, those in which the leaving group is stabilized by inductive and resonance effects, tend, via kinetic evidence, to solvolyze under acidic conditions by a mechanism with dissociative character.[6] Phosphonamides are believed to hydrolyze by an associative mechanism, whereas phosphoramidates have received scant attention.[7a-c] Ramirez and co-workers have shown that a cyclic enediol *N*-phosphorylimidazole undergoes rapid displacement of the imidazole function in the presence of alcohols to produce cyclic triesters.[8a,b] In none of these cases has the stereochemistry of the displacements been determined. As the imidazole moiety under solvolytic conditions departs more rapidly than any other reported leaving group, we felt that via the phosphorinane system it might be possible to detect a dissociative process. At the least, any unusual stereochemical consequences of solvolysis would be of interest and lead to a better understanding of the mechanism of solvolysis of very reactive phosphate systems.

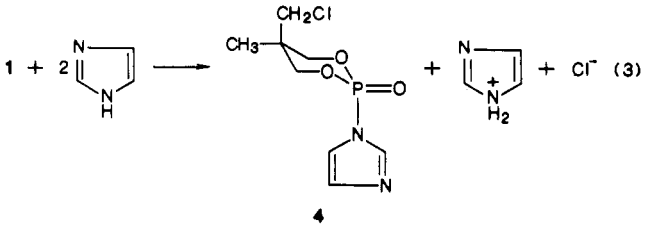
Synthesis and Reactivity

As we have shown previously, displacement of the 2-substituent from a phosphorinane system under neutral or acidic conditions proceeds by inversion. Under basic conditions retention is the sole route.[3b] Inversion most likely proceeds by a direct S_N2 displacement, while retention results from attack by a charged nucleophile at a position opposite phosphoryl oxygen to give a trigonal bipyramidal intermediate. For example, upon methanolysis under neutral conditions, chloride ion is displaced from a phosphorochloridate (1) by inversion but solely by retention by methoxide ion (eq 2).



(2)

The phosphochloridate (1) was used to prepare a single isomer of a *N*-phosphorylimidazole, a procedure previously used to prepare *N*-phosphorylated amines (eq 3). The



position of the groups at the five position, chloromethyl axial, methyl equatorial, is via NMR unquestionable. The

(3) (a) Wadsworth, W. S., Jr. *J. Org. Chem.* **1967**, *32*, 1603. (b) Wadsworth, W. S., Jr.; Larsen, S.; Horton, H. L. *J. Org. Chem.* **1973**, *38*, 256. (c) Wadsworth, W. S., Jr. *J. Org. Chem.* **1973**, *38*, 2921. (d) Wadsworth, W. S., Jr.; Tsay, Y. G. *J. Org. Chem.* **1974**, *39*, 984. (e) Bauman, M.; Wadsworth, W. S., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 6388.

(4) (a) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1984**, *106*, 2353 and references cited therein. (b) Stec, W. J.; Okruszek, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1828 and references cited therein.

(5) (a) Wadsworth, W. G.; Wadsworth, W. S., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 1631. (b) Wadsworth, W. S., Jr. *Ind. Eng. Chem. Prod. Res. Dev.* **1984**, *23*, 625.

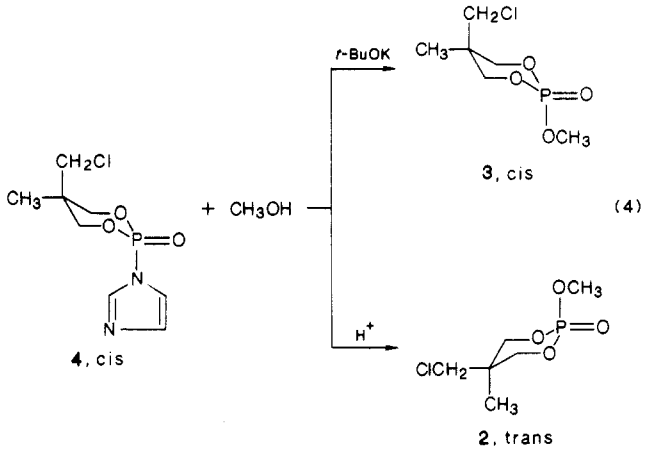
(6) Tyssee, D. A.; Bausher, L. P.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8066.

(7) (a) Allen, G. W.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8080. (b) Rahil, J.; Haake, P. Ibid. **1981**, *103*, 1723. (c) Koizumi, T.; Kobayashi, Y.; Yoshii, E. *Heterocycles* **1978**, *9*, 1723.

(8) (a) Ramirez, F.; Okazaki, H.; Marecek, J. F. *Tetrahedron Lett.* **1977**, *34*, 2927. (b) Ramirez, F.; Marecek, J. F.; Okazaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 5310.

position of the imidazoyl moiety is, however, in the first analysis uncertain. If substitution proceeds via retention and the imidazoyl group is axial, as shown, the conformation around phosphorus is different than that of other phosphoramidates in this class in which the amino moiety is normally equatorial (Table II). If the structure given for **4** is correct, displacement of the chloride ion must have proceeded by retention, and the imidazole anion, not the free base, most likely is the reacting species.

Our structure, **4**, although unusual, is based on solvolysis studies and comparison of those results with results obtained upon methanolysis of the chloridate **1** and other reactive species whose structures are unquestionable.[5a] Treatment of **4** with methoxide ion gives very rapidly, too fast to follow under normal conditions, the cis methyl ester, conditions which in all cases lead to retention. Under acidic conditions where prior protonation of the leaving group must be involved, methanolysis by neutral solvent yields exclusively the trans methyl ester, in all cases studied an inversion process (eq 4).[7b,9a-d] The methyl



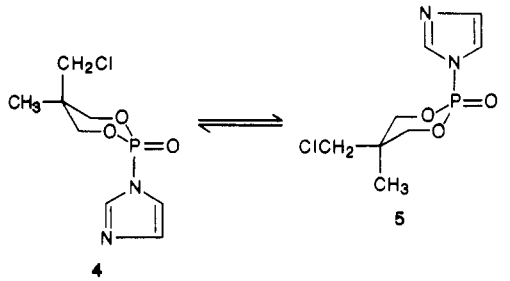
(4)

esters are stable under reaction conditions, and their structures are fully confirmed.[3b] From comparison of these results with those of other reactive systems of known geometry, the structure of **4** is written with a fair degree of certainty. Imidazole is certainly different than alkyl amines, and the anomeric effects that are invoked to explain an equatorial 2-amino group must be lacking in the imidazole system.[4a]

N-Phosphorylimidazole **4** undergoes acid-catalyzed methanolysis at an unusually rapid rate, which is not surprising considering the leaving group. The high reactivity might allow under correct conditions solvolysis to proceed via a dissociative process.

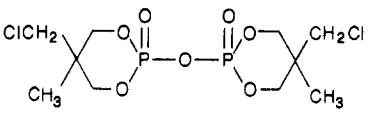
Addition of **4** to methanol without added base gives substitution via exclusive retention. As with acid-catalyzed methanolysis protonation of the potential leaving group must first occur followed by attack by the newly formed methoxide ion. Methoxide ion is also formed by protonation of imidazole, the byproduct of solvolysis. Indeed, in an independent experiment we find that added imidazole is a sufficient base to catalyze the methanolysis of phosphorochloridate (**1**) by retention. Solvolysis of **4** by isopropyl alcohol is slow enough to be followed, and in this case both the known and fully characterized cis and trans isopropyl esters are formed in approximately equal amounts. Again, protonation of the potential leaving group must precede attack by both the isopropoxide anion and isopropyl alcohol. In this case, competition between the anion and alcohol exists due to the lower nucleophilicity of the isopropoxide anion compared to the methoxide ion.

Yields of the *N*-phosphoroylimidazole **4** are drastically reduced upon recrystallization from benzene. Isomerization takes place slowly in warm benzene and, due to its lower solubility, only the cis isomer precipitates from solution (eq 5).



(5)

The isomerization can be followed simply by observing the slow formation of a new peak, 16.5 Hz downfield from that due to the 5-methyl hydrogens of **4**. The latter peak slowly decreases as isomerization proceeds. The new peak is assigned to the axial 5-methyl hydrogens of the trans isomer **5**. Although the ratio is dependent upon solvent and the 2-substituent, the final cis/trans ratio, 1.6/1, is typical for the phosphorinane system and, as usual, the more thermodynamically stable isomer with the chloromethyl group axial predominates at equilibrium. Similarly, while a freshly prepared $CDCl_3$ solution of the cis isomer shows the absence of trans isomer, when the solution stands over a number of hours, isomerization is again complete, a process easily followed with a sample held in the NMR probe. While it would be tempting to assign isomerization to a unimolecular phosphous–nitrogen bond cleavage, in all cases, even though extraordinary measures were taken to exclude moisture, the slow rise of peaks due to 5-methyl hydrogen absorption assigned to pyrophosphate **6** and imidazole, both products of hydrolysis,

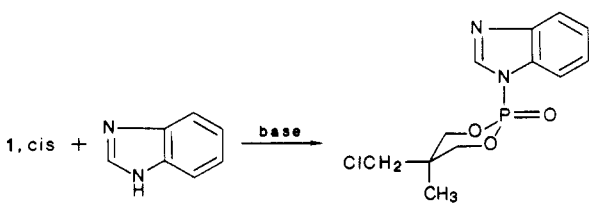


6

were noted. The rate of isomerization parallels the intensity of these peaks and is likely promoted by the free base. Indeed, as confirmed by an independent experiment, added imidazole does catalyze isomerization.

To determine by stereochemical means whether a dissociative process can operate, it is imperative that not only pure cis isomer be available but also the trans isomer. Although numerous attempts were made to prepare the pure trans isomer **5**, its sensitivity toward hydrolysis and isomerization voided our attempts at isomer separation by standard techniques.

Benzimidazole, although a stronger acid than imidazole, has a weaker conjugate base and appears to substitute for chloride ion by at least partial inversion (eq 6). Although

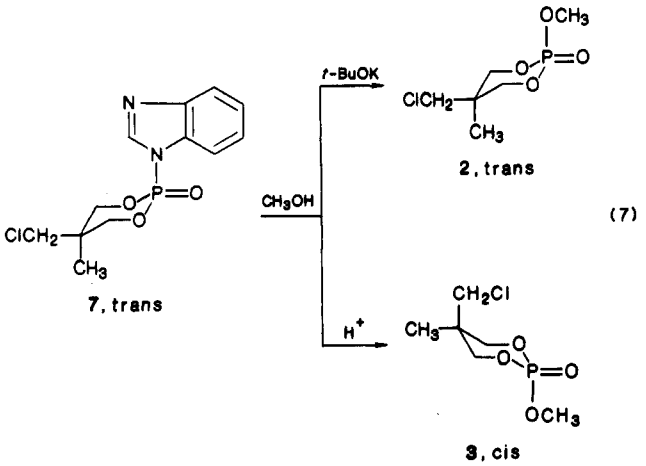


(6)

the yield is not high, fortunately, it is the trans isomer that is least soluble and crystallizes in essentially pure form

(9) (a) Koizumi, T.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8073. (b) Mizrahi, V.; Modro, T. A. *J. Org. Chem.* **1983**, *48*, 3030. (c) Modro, T. A.; Graham, D. H. Ibid. **1981**, *46*, 1923. (d) Kobayashi, Y.; Koizumi, T.; Yoshi, E. *Chem. Pharm. Bull.* **1979**, *27*, 1641.

from the reaction medium, benzene. Again, the configuration and conformation were established by NMR and solvolysis studies (eq 7). Typically, the trans isomer 7 has



(7)

its 5-methyl hydrogen absorption, δ 1.21, shifted down field and its 5-(chloromethyl) hydrogen absorption, δ 3.64, shifted upfield relative to the cis isomer, δ 1.03 and 3.87, respectively.[10] The aromatic proton absorption is typical of that of the benzimidazole moiety and consists of three multiplets which can be used as a diagnostic tool for phosphorus–nitrogen bond cleavage. The salt obtained by allowing the trans isomer 7 to stand even in a closed container (an inert atmosphere is required to prevent hydrolysis) has its single 5-methyl hydrogen absorption upfield, δ 0.96, and shows an increase in the spread between aromatic multiplets relative to those found for the reactant. Isomerization again occurs upon melting, although unlike 4 it does not occur when the pure isomer is dissolved in chloroform or benzene.

Also, unlike 4, methanolysis of 7 without added base is slow enough to be followed. A sample dissolved in CD_3OD requires, at 35 °C, over 48 h for complete reaction to occur, and instead of a single isomer, as is obtained with added base, a cis/trans methyl ester isomer ratio of 1.3/1 is obtained. As with solvolysis of 4 by isopropyl alcohol, neutral solvent competes with alkoxide ion for the protonated substrate. The relatively slow rate and lack of specificity can be attributed to the lower basicity of benzimidazole compared to imidazole. The concentration of both the protonated substrate and alkoxide ion would be less in the case of 7 than with 4.

As pointed out, acid-catalyzed methanolysis of both 4 and 7 with inversion is, within our limits of measurement, instantaneous. The leaving group most likely is imidazole and benzimidazole, respectively, due to protonation prior to attack by neutral solvent. To further point out the enhanced reactivity of these systems over simple phosphoramidates, a number of experiments were conducted. A benzene solution of either 4 or 7 reacts exothermically with trifluoroacetic acid to produce an immediate precipitate of pyrophosphate 6, a reaction similar to that reported previously.[11] A reasonable mechanism can be drawn by assuming that trifluoroacetate anion, which probably is a weak nucleophile in an aprotic solvent, attacks the phosphorus atom after initial protonation of the substrate. A similar result, pyrophosphate formation, is obtained when isopropyl alcohol is used in place of benzene. No isopropyl ester is produced. Trifluoroacetate anion is a better nucleophile than isopropyl alcohol, a result which is opposite to that obtained with methyl alcohol where the ester is formed rapidly by inversion and is the only product.

As determined by NMR measurements and comparison with an authentic sample, pyrophosphate also arises when either 4 or 7 is dissolved in D_2SO_4 and the solution warmed. The formation of pyrophosphate may be a consequence of reaction of protonated substrate with bisulfate ion or water generated through self-ionization of the sulfuric acid. At any rate, we do not observe peaks that could be assigned to an unknown intermediate.

From these experiments it appears certain that, although a very reactive species with enhanced electrophilicity is produced by protonation of either 4 or 7, there is no evidence of a free phosphacylium ion intermediate. First, if such an ion has a finite lifetime, we would expect from acid-catalyzed methanolysis of either reactant a product ratio that reflects thermodynamic conditions. In all experiments where equilibrium is established, that isomer with the chloromethyl group axial predominates over that with the group equatorial by better than a 1.5/1 ratio. As seen, acid-catalyzed methanolysis proceeds with complete inversion even in the case of 4, where the least thermodynamically stable trans methyl ester, 2, is produced exclusively. Second, although methanolysis catalyzed by trifluoroacetic acid is rapid and produces methyl ester in essentially quantitative yield, solvolysis by isopropyl alcohol is unsuccessful. If a phosphacylium ion were produced, it would be expected to react with isopropyl alcohol to produce at least some ester. It should be mentioned at this point that solvolysis by isopropyl alcohol catalyzed by sulfuric acid, in which case a good competing nucleophile is evidently absent, does in the case of 4 give isopropyl ester. The yield is low due to concurrent pyrophosphate formation.

Solvolysis

If either 4 or 7 is to undergo substitution by a dissociative process, it would appear that acid catalysis should be employed under conditions in which its conjugate base is weak and in low concentration. The phosphacylium ion, under such circumstances, might then have enough lifetime to undergo conformational changes and produce a mixture of geometrical isomers, the ultimate being the same ratio of isomers produced from each starting material, the thermodynamically controlled ratio. To approach this limit, we need a weak nucleophile, one that does not give products which can undergo secondary reactions as does trifluoroacetate ion, and an aprotic solvent, one that can stabilize a positive charge by solvation.

With respect to the nucleophile, fluoride ion, a hard base, is a poor nucleophile and a likely candidate.[12] Treatment of a methanolic solution of 7 with tetrafluoroboric acid (TFBA) gives in addition to the expected methyl ester by inversion a small impurity as noted from extraneous peaks in the NMR spectrum of the product. A repeat of the reaction using chloroform as solvent gives an essentially quantitative yield of *cis*-2-fluoro-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane identical in every respect to an authentic sample.[13] The fluoride ion which is formed from BF_4^- is under the reaction conditions kept in low concentration. In chloroform, inversion is the only mode of substitution and thus parallels our methanolysis studies. The peaks observed as an impurity

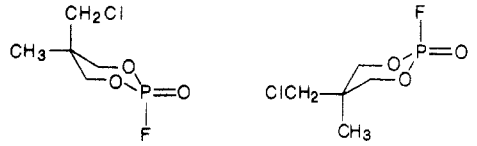
(10) Chemical shifts are reported relative to tetramethylsilane used as an internal standard.

(11) Dabkowski, W.; Michalski, J.; Radziejewski, C.; Skryzpczynski, Z. *Chem. Ber.* **1982**, 1636.

(12) Huheey, J. E. *Inorganic Chemistry*, 3rd ed.; Harper & Row: New Nork, 1983; p 316.

(13) Corriu, R. J. P.; Dutheil, J. P.; Lanneau, G. F.; Ould-Kaka, S.; *Tetrahedron Lett.* **1979**, *35*, 2889.

Table III. Treatment of *cis*-*N*-Phosphorylimidazole 4 with TFBA



cis trans

solvent	retention,[a] %	inversion, %
$CHCl_3$	22	78
isopropyl alcohol	22	78
CH_3CN	40	60
benzene	61	39
anisole	64	36

Treatment of *trans*-*N*-Phosphorylbenzimidazole 7 with TFBA

solvent	inversion, %	retention, %
$CHCl_3$	100	0
isopropyl alcohol	77	23
CH_3CN	77	23
benzene	76	24

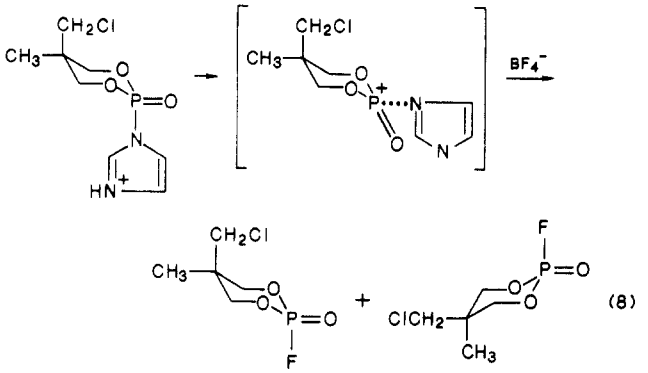
[a] Average of three runs, all of which did not vary over a few percent.

in methanolysis catalyzed by TFBA matched those of the authentic phosphorofluoridate.

In other solvent systems, solvents which might best solvate a positive ion, stereochemical results are quite different (Table III). Even with chloroform in the case of 4, retention does occur. Some equilibration to give the more thermodynamically stable isomer is apparent. Acetonitrile is more effective, although inversion still predominates. Recently, the isomerization of metaphosphate, an intermediate in a presumed dissociation process, has been reported to occur by use of acetonitrile as solvent, whereas inversion only is noted in less polar solvents.[14] As in the case reported and noted by the authors, acetonitrile may form a complex with the intermediate, in our case a phosphacylium ion, which by solvent exchange leads to partial equilibration. Our results obtained with benzene as solvent are surprising. No products that might arise from electrophilic aromatic substitution are observed. The electrophilic intermediate whether at first completely free of leaving group or not could form a complex with benzene, a π-complex, which would increase its lifetime and allow for equilibration. With benzene as solvent we are approaching a thermodynamically controlled product ratio, for the ratio of phosphorofluoridate isomers is not nearly as dependent upon the configuration of the starting material as in other solvents. It should be emphasized that by means of independent experiments the phosphorofluoridates, as is the case with the methyl esters, do not isomerize under reaction conditions. The equilibrium must occur during a stage of the substitution process (eq 8). As pointed out earlier, reactants isomerize at a much slower rate than substitution, which within our experimental parameters is instantaneous.

The effectiveness of benzene to cause at least partial equilibration is demonstrated further by the results obtained from the acid-catalyzed methanolysis of 4 in a benzene–methanol solvent mixture. Instead of the methyl ester produced by 100% inversion as in pure methanol, a 20% methanol–benzene mixture gives 34% of the retention product.

(14) Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 6126.



(8)

Although results might, as is often the case, be explained by various pseudorotational permutations, it is doubtful that there would be much, if any, relief in ring strain if the phosphorinane ring were to span equatorial and axial positions.[15] Also, such permutations, which require a series of trigonal bipyramidal intermediates do not, in this case conform to the observed rapid rate of the inversion process. There is also no ring opening followed by ring closing in these experiments. Where ring opening is observed, it can easily be followed by NMR.[5a] We are left with an explanation that presumes a process in which the nucleophile attacks late in the reaction pathway and in some cases late enough so that partial equilibration of an intermediate with positive character can occur.[16] It should be pointed out that, although we are fairly confident of our structural assignments for 4 and 7, the above conclusions are not predicated on the structures being known with absolute certainty, only that they have opposite configurations, which is beyond question.

Experimental Section

All reagents were of analytical grade or purified before use. ^1H NMR spectra were recorded on a Perkin-Elmer R12B spectrometer at 35 °C by using Me_4Si as an internal standard. ^1H NMR spectra of the methyl esters 2 and 3 and of chloridate 1 have been published.[3b,e] Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, 37921.

***cis*-*N*-Phosphorylimidazole 4.** Imidazole (2.72 g, 0.04 mol) was added to benzene (50 mL) and the slurry brought to reflux with stirring. In order to ensure anhydrous conditions, benzene (10 mL) was removed by distillation and phosphorochloridate (4.36 g, 0.02 mol) was added all at once to the benzene slurry held at 60 °C. The mixture was immediately filtered through glass wool and the filtrate stripped under reduced pressure, 30 mmHg at 25 °C. The white crystalline residue was recrystallized from freshly distilled benzene and dried under reduced pressure without heating (3.3 g, 66%). Anal. Calcd for $C_5H_{12}ClN_2O_3P$: C, 38.40; H, 4.80; N, 11.20. Found: C, 38.31; H, 4.75; N, 11.14. To keep isomerization to a minimum, prolonged heating of a benzene solution must be avoided. As measured by ^1H NMR, it requires about 48 h for cis isomer dissolved in C_6D_6 to become completely isomerized (62% cis, 38% trans) at 60 °C.

If during recrystallization the hot benzene solution is passed through filter paper, the benzene solution is allowed to stand exposed to the atmosphere, or dried glassware is not used, an insoluble oil separates from solution. The oil slowly solidifies and is separated by filtration and recrystallized (CH_3CN). Anal. Calcd for $C_5H_{14}ClN_2O_4P$: C, 35.95; H, 5.22; N, 10.44. Found: C, 35.86; H, 5.38; N, 10.39.

Solvolysis of *cis*-*N*-Phosphorylimidazole 4. After a sample of the phosphorylated imidazole was dissolved in methanol, solvent was immediately removed under reduced pressure. The residue

(15) Westheimer, F. J. *Acc. Chem. Res.* **1968**, *1*, 70.

(16) A preassociation mechanism has been invoked by others to explain comparable results: (a) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345. (b) Buchwald, S. L.; Knowles, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6601. (c) Buchwald, S. L.; Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4911. (d) Calvo, K. C. *J. Am. Chem. Soc.* **1975**, *107*, 3690.

was taken up in CH_2Cl_2, and the solution was washed with dilute HCl, dried over $MgSO_4$, and stripped under reduced pressure. A residue whose ^1H NMR spectrum was identical with that of authentic cis methyl ester **3** was obtained. A second sample placed in methanol-d_4 and the spectrum taken immediately upon dissolving showed complete transformation to the cis methyl ester.

In a separate experiment, *N*-phosphorylimidazole (0.25 g, 0.001 mol) was dissolved in 10 mL of 0.1 M TFAA in CH_3OH, excess solvent immediately removed under reduced pressure, and the viscous residue taken up in CH_2Cl_2. The solution was washed with dilute KOH and dried over $MgSO_4$, and the solvent was removed to give a residue which crystallized on standing and whose spectrum was identical with that of authentic trans methyl ester **2** (92%). An identical result was obtained when *p*-toluenesulfonic acid was used in place of TFAA.

In a third experiment, a sample of reactant was dissolved in isopropyl alcohol and the solution allowed to stand at room temperature for 1 week. Solvent was removed under reduced pressure to give nearly a quantitative yield of cis and trans isopropyl esters as determined by the ^1H NMR of the mixture and comparison with authentic samples.[5a] Interruption before the time period gave mixtures containing reactant. A sample of reactant added to 0.1 M TFAA in isopropyl alcohol produced an immediate precipitate of pyrophosphate **6**.

***trans*-*N*-Phosphorylbenzimidazole 7.** A solution of benzimidazole (2.36 g, 0.02 mol) in 50 mL of benzene was brought to reflux and 10 mL of solvent removed by distillation. The mixture was cooled to 50 °C, triethylamine (6.06 g, 0.06 mol) and phosphorochloridate **1** (4.36 g, 0.02 mol) were added, the latter all at once, and the mixture was stirred for $^1/_2$ hour. The hot mixture was filtered through glass wool and solvent removed under reduced pressure (30 mmHg 50 °C). The crystalline residue was recrystallized twice from a small quantity of freshly distilled benzene to give a white crystalline solid (2.0 g, 33%). Anal. Calcd for $C_{12}H_{14}N_2O_3PCl$: C, 48.00; H, 4.66; N, 9.33. Found: C, 47.82; H, 4.66; N, 9.23. ^1H NMR ($CDCl_3$) shows 5-methyl hydrogen (axial) and 5-(chloromethyl) hydrogen (equatorial) peaks due to trans isomer only. A sample dissolved in C_6D_6 or $CDCl_3$ showed no indication of isomerization.

A sample of the product, **7**, was heated to 120 °C, whereupon melting was complete. The ^1H NMR spectrum of the melt ($CDCl_3$) showed the reactant had isomerized, 55% cis, 45% trans, without decomposition.

Methanolysis of *trans*-*N*-Phosphorylbenzimidazole 7. Uncatalyzed methanolysis was carried out precisely as described for the *N*-phosphorylimidazole analogue except that the solution was allowed to stand for 70 h at room temperature (a sample dissolved in CD_3OD had taken 48 h for complete conversion to a mixture of isomeric methyl esters without concurrent isomerization as determined by following changes in the ^1H NMR spectrum of the solution with time). Upon workup of the methanolic solution, a mixture of methyl esters, 56% **3** and 44% **2**, was obtained as determined by comparison of the spectrum of the mixture with that of authentic isomers.

In a separate experiment, *trans*-*N*-phosphorylbenzimidazole (0.3 g, 0.01 mol) was dissolved in 0.1 M TFAA in CH_3OH. The solution was worked up as described previously for the acid-catalyzed methanolysis of **4** to give a nearly quantitative yield of the cis methyl ester **3** as a crystalline solid. There was no trace of **2**, the trans ester, in the product.

TFAA Solvolysis of *trans*-*N*-Phosphorylbenzimidazole 7. To *trans*-*N*-phosphorylbenzimidazole (0.3 g, 0.001 mol) was added 2 mL of anhydrous TFAA. The ^1H NMR spectrum of the mixture indicated that P–N bond cleavage had taken place instantaneously as determined by a change in the chemical shifts of aromatic protons. The viscous mixture when taken up in ether gave a white crystalline solid which was recovered by filtration, washed with water, and dried (0.1 g, 52%). The yield is reduced by partial hydrolysis during the water wash. The ^1H NMR and IR spectra of the product were identical with those of an authentic sample of pyrophosphate **6** (69% 5-CH_3 equatorial, 31% 5-CH_3 axial).

An identical procedure was carried out with *cis*-*N*-phosphorylimidazole **4**. The initial solid was washed with a small quantity of cold water to give a 72% yield of product whose spectra were identical with that of authentic pyrophosphate (43% 5-CH_3 equatorial, 57% 5-CH_3 axial).

Dropwise addition of TFAA to a benzene solution of either **7** or **4** gave an immediate separation of a viscous oil. Separation of layers by decantation and treatment of the bottom oily layer with anhydrous ether caused the oil to solidify. The IR and ^1H NMR spectra of the water-soluble solid were identical with those of authentic TFAA salts of benzimidazole or imidazole, respectively. In each case, upon removal of solvent from the benzene layer, a residue was obtained which when washed with a small quantity of cold water gave a crystalline product whose spectra were identical with that of pyrophosphate **6**.

2-Fluoro-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane. To *cis*-*N*-phosphorylimidazole **4** (0.25 g, 0.001 mol) dissolved in 10 mL of solvent (see Table III) was added dropwise HBF_4 etherate (Aldrich Chemical Co.) until exotherm ceased. Solvent was removed under pressure. The residue was dissolved in 20 mL of CH_2Cl_2, the solution was washed with dilute KOH and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The ^1H NMR spectrum of the single isomer obtained with chloroform as solvent is identical with that of an authentic sample.[13] In the case of other solvent systems, isomer ratios are obtained by the integration of peaks due to 5-methyl hydrogen absorption.

A similar procedure was employed in the treatment of **7** with HBF_4 etherate.

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