were determined by peak matching at 10 000 resolution, 10% valley definition. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and Galbraith Laboratories, Inc., Knoxville, TN. All C, H, N analyses not reported here were acceptable (±0.3%) and can be found with other physical data in the supplementary material.[7] The 6-(1-alkylhydrazino)isocytosines (**2a–c**) were prepared as described previously.[1]

Cyclizations to 6-Amino-1,4-dihydro-8*H*-pyrimido[6,1-*c*][1,2,4]triazin-8-ones (5a–e) The appropriate α-halo ketone was added all at once to a stirred mixture of (alkylhydrazino)-isocytosine **2** and solvent at room temperature in the proportion of 0.009 75 mol in 100 mL. An exception to this proportion was the preparation of **4d** (0.009 75 mol in 130 mL). At the end of the reaction time, the acidic solution or mixture was brought to pH 8–9 with 10% (w/w) aqueous NaOH equimolar with the α-halo ketone used. The mixture was concentrated under vacuum to a solid residue that was stirred with water,[8] collected by filtration, washed with a little fresh reaction solvent, dried at 70 °C in a vacuum oven, and recrystallized. A specific example is described below for the preparation of **5a**.

6-Amino-1,3-dimethyl-1,4-dihydro-8*H*-pyrimido[6,1-*c*]-[1,2,4]triazin-8-one (5a). To a stirred mixture of 1.60 g (0.009 75 mol) of 6-(1-methylhydrazino)isocytosine hemihydrate (**2a**) and 100 mL of water was added all at once 1.80 g (0.0131 mol) of bromoacetone. After 3 h the mixture was adjusted to pH 8–9 with 5.30 g of 10% (w/w) aqueous NaOH and was then concentrated under vacuum to dryness. The residue was stirred for 10 min with 15 mL of water, and a light gray solid was collected by filtration, washed with water (2 × 5 mL), and dried under vacuum at 70 °C to yield 1.414 g. A 0.500-g sample of this solid was recrystallized from 2-propanol to give 0.418 g of light green, fine crystals: mp 280–288 °C dec; NMR (CF_3COOH) δ 2.22 (s, 3 H), 3.55 (s, 3 H), 4.60 (s, 2 H), 5.60 (s, 1 H), 8.3 (br s, 2 H); UV λ_{max} (CH_3OH) 253.5 nm (sh, ε 4700), 300 (13 700), 312.5 (sh, 9700); mass spectrum (175 °C), *m/e* 193 (M, 91%), 178 (10), 152 (3), 151 (M − CH_2N_2, 27), 150 (27), 149 (2), 136 (16), 82 (100). The following selected accurate masses were determined: 151.0741 ($C_7H_9N_3O$), 150.0668 ($C_7H_8N_3O$), 136.0508 ($C_6H_6N_3O$). Anal. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.58; H, 5.77; N, 36.15.

Hydrolysis of Ester 5e. 6-Amino-3-carboxy-1,4-dihydro-1-methyl-8*H*-pyrimido[6,1-*c*][1,2,4]triazin-8-one (5f). A mixture of 0.108 g (0.000 378 mol) of crude **5e**[9] in 3 mL of water was stirred while 10% (w/w) aqueous NaOH was added until pH 11–12 was reached. The resulting solution was allowed to stand, and solid slowly precipitated. After 22 min the mixture was brought to pH 5 with glacial acetic acid. Precipitated solid was collected by filtration, washed with 0.5 mL of water, and dried under vacuum at 70 °C to yield 0.089 g of pale yellow solid. Recrystallization of this solid from water afforded 0.046 g (53%) of off-white solid: mp >300 °C; NMR (CF_3COOH) δ 3.69 (s, 3 H), 4.90 (s, 2 H), 5.80 (s, 1 H), 8.4 (br s, 2 H); UV λ_{max} (0.1 N NaOH) 330 nm (ε 16 100). Anal. Calcd for $C_8H_9N_5O_3 \cdot 0.4H_2O$: C, 41.70; H, 4.29; N, 30.40. Found: C, 41.57; H, 4.00; N, 30.37.

7-Amino-3-methylpyrimido[4,5-*c*]pyridazin-5(6*H*)-one (7).[10] To a stirred mixture of 2.00 g (0.0142 mol) of 6-hydrazinoisocytosine (**6**) in 140 mL of water was added all at once 2.57 g (0.0188 mol) of bromoacetone. After 1 h the mixture was adjusted to pH 8–9 with 7.53 g of 10% (w/w) aqueous NaOH (0.0188 mol) and was concentrated under vacuum to a solid that was stirred for 20 min with 20 mL of water, collected by filtration, rinsed with 5 mL of ethanol, and dried under vacuum at 70 °C to yield 2.01 g of a very crude product.[11]

A 1.00-g sample of solid was suspended in 3 L of boiling methanol. Some undissolved solid was removed by filtration. The filtrate was concentrated by boiling to 500 mL whereupon a solid began to precipitate. The mixture was allowed to cool slowly to room temperature and was refrigerated overnight. Solid was collected by filtration, washed with 10 mL of methanol, and dried under vacuum at 70 °C to yield 0.302 g. Three recrystallizations of this solid from water afforded 0.103 g of a brown solid: mp >300 °C; NMR (CF_3COOH) δ 3.13 (s, 3 H), 8.99 (s, 1 H); UV λ_{max} (0.1 N NaOH) 252 nm (ε 21 600), 270 (sh, 7700), 362 (4200); mass spectrum (300 °C), *m/e* 177 (M, 100%), 149 (18), 148 (3), 136 (M − CHN_2 and M − CH_3CN, 1), 133 (10), 132 (5), 122 (13), 121 (7), 120 (5), 109 (7), 107 (12). The following selected accurate masses were determined: 136.0517 ($C_6H_6N_3O$), 136.0388 ($C_5H_4N_4O$). Anal. Calcd for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53; O, 9.03. Found: C, 47.73; H, 3.70; N, 39.50; O, 9.25.

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Registry No. 2a, 67873-21-6; **2b**, 67873-24-9; **2c**, 67873-25-0; **5a**, 74467-08-6; **5b**, 74467-09-7; **5c**, 74467-10-0; **5d**, 74467-11-1; **5e**, 74467-12-2; **5f**, 74467-13-3; **6**, 6298-85-7; **7**, 74482-47-6; 1-bromo-2-propanone, 598-31-2; 3-chloro-2-oxopropanal 1-oxime, 14337-41-8; 3-bromo-2-oxopropanoic acid ethyl ester, 70-23-5.

Supplementary Material Available: Full data available include the microanalyses, UV data, and NMR data on compounds **5b–e** and mass spectral data on **5d** and **5e** (5 pages). Ordering information is given on any current masthead page.

(7) See paragraph on supplementary material at end of paper.
(8) A minimum of water should be used in order to maximize the yield of crude product.
(9) Shown by microanalysis to be a 1.9 hydrate.
(10) V. L. Styles in our laboratory also prepared this compound by a preferred procedure from 6-hydrazinoisocytosine and pyruvaldehyde in refluxing water.
(11) No pyrimidotriazine was indicated by NMR or UV data.

Methanolysis of a Phosphate Triester: A Change in Mechanism with Acidity

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In previous publications, we have pointed out the utility of the 2-substituted-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system in determining stereochemistry of substitutions at phosphorus in phosphate triesters.[1] We reported that for aprotic media, substitutions at phosphorus occur by both inversion and retention, with the former favored by good leaving groups, i.e., Cl^-, while retention is favored by nucleophiles which can backbond to phosphorus, i.e., RO^-. Retention can be made the only pathway by employing conditions under which the attacking nucleophile is highly associated with its counterion.[2]

Our initial success has dictated employment of the same system in protic media, specifically acid-catalyzed methanolysis. Due to ease of handling and lack of side reactions,[3] we selected the 2-(*p*-nitrophenyl) esters as model substrates. As pointed out in previous publications, the cyclic esters strongly prefer that conformation with the phosphoryl oxygen equatorial.[1,4] As a consequence, and

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(3) An insignificant amount of ring-opened methyl ester is also obtained which becomes a problem only in those cases where a poor leaving group, i.e., phenol, is employed.
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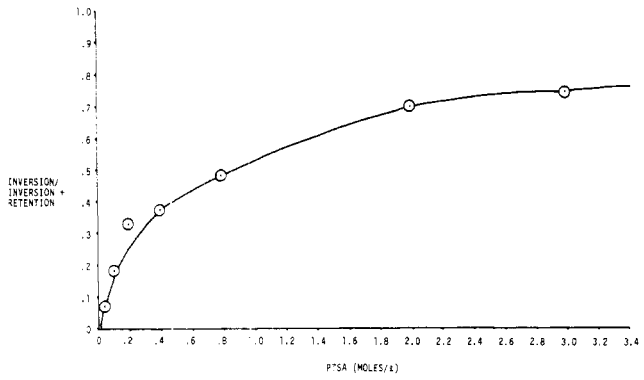
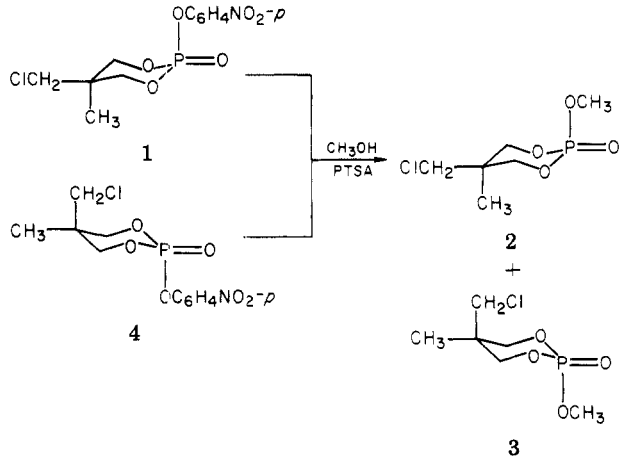


Figure 1. Methanolysis of 4. Change in isomer ratio with acid concentration.

as explained in detail previously, isomer ratios can be measured by merely analyzing ^1H NMR spectra of product mixtures.

Methanolic solutions of the *trans*-*p*-nitrophenyl ester 1 were refluxed in the presence of *p*-toluenesulfonic acid (PTSA). In the absence of catalyst substitution does not

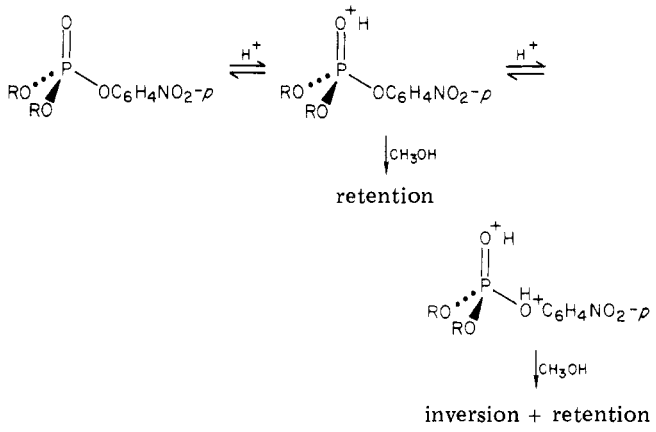


occur. Isolation and characterization of unreacted starting material prior to complete reaction indicated a lack of isomerization. Pure methyl ester isomers do not undergo isomerization and are completely recovered after prolonged reflux under the strongest acid conditions employed. We conclude that the product ratios are proportional to rate of product formation and are not equilibrium ratios.

We find methanolysis to be first order in ester disappearance but not first order in acid; for 0.1 M trans ester, k = 0.1 h^{-1} at 0.1 M PTSA but only 0.15 h^{-1} at 0.2 M PTSA. Of significance is the change in isomer ratio with acid concentration (Figure 1). Although the isomer ratios were obtained after reactions were complete, they did not, within detectable limits, vary significantly during methanolysis.

We have shown that cis esters are thermodynamically more stable than the trans.[1] The increase in inversion to give the more stable methyl ester **3** might be the consequence of a dissociative mechanism at high acid concentrations. A mechanism in which the ring is opened followed by closure to the more stable isomer might also be envisioned. Although results are independent of the anion employed, at high PTSA concentrations, an equilibrium mixture of sulfonyl phosphates might form which undergoes methanolysis via retention thereby leading to the predominance of the cis methyl ester. These possibilities are invalid for treatment of *cis*-*p*-nitrophenyl ester 4, which, under conditions similar to those used for the trans ester, also shows an increase in inversion product as the

Scheme I[a]



[a] Rings are omitted for simplicity.

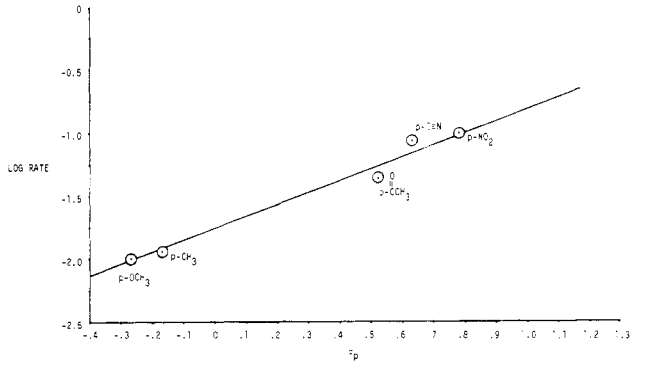


Figure 2. Hammett plot of methanolysis of para-substituted trans phenyl esters catalyzed by 0.1 M PTSA.

acid concentration is increased. The percent of trans methyl ester **2**, the least thermodynamically stable isomer, increases from 26% at 0.1 M PTSA, k = 0.04 h^{-1}, to 55% at 0.8 M PTSA, k = 0.08 h^{-1}.

The results are best explained by assuming a change in mechanism from predominate retention at low acid concentration to predominate inversion at high acid concentration. Phosphoryl oxygen is the most basic site and would be expected to be protonated initially. At high acid concentrations, a diprotonated species might be involved with the second proton, residing in part on the oxygen which is eventually involved in P–O bond breaking (Scheme I). Protonation of ring oxygen is inconsequential (rings are not cleaved by an acid-catalyzed mechanism) but may account in part for the lack of first-order dependency in acid.

The increase in inversion with acid concentration may be accounted for by the formation, as a result of the second protonation, of a superior leaving group. Whereas inversion might simply involve a backside displacement via an S_N2 process, retention is more difficult to describe. Although we favor, as a result of our work in aprotic solvents, formation of a square planar intermediate,[2] apical attack opposite the protonated phosphoryl oxygen followed by ligand scrambling either directly or via pseudorotation cannot be ruled out. Other options may also be available.

Although the intermediate involved in the retention process is unknown, its formation is apparently rate determining. A satisfactory Hammett plot is obtained at low acid concentration if σ_p values are used, ρ = 0.95 (Figure 2). The 2-phenylphosphorinans follow first-order kinetics with respect to the rate of disappearance of starting material, regardless of the fate of the reactant. In those cases where poor leaving groups are employed, *p*-OCH_3 and

p-CH_3, ring opening competes to give dimethyl 2-(chloromethyl)-2-methyl-3-hydroxypropyl phosphate. The latter has been synthesized independently (see Experimental Section). Apparently, at low acid concentration, retention and ring opening involve a similar or common intermediate.

Systems analogous to the p-nitrophenyl esters have received some attention. Thus, the *trans*-2-phenylthio ester, $k = 0.9\ h^{-1}$ for a solution 0.1 M in ester and acid, gives after complete reaction 18% inversion, while a solution 0.1 M in ester and 0.8 M in acid, $k = 1.4\ h^{-1}$, gives 52% inversion. The 2,4-dinitrophenyl ester analogous to **4** yields, at low acid concentrations, only the methyl ester formed by retention, **3**, while at high acid concentrations inversion reaches a maximum of only 5%. The results in this latter case may reflect the very low basicity of the oxygen adjacent to phosphorus in the leaving group and its inability to undergo protonation.

It is reported that the acid-catalyzed hydrolysis of phosphinamides proceeds by inversion.[5] Similarly, we find the acid-catalyzed methanolysis of a 2-benzylamido analogue of **1** to give 85% inversion product, even at a low acid concentration, 0.1 M. In this instance the nitrogen atom must be a more basic site than phosphoryl oxygen and is perhaps protonated first.

Experimental Section

^1H NMR spectra were recorded on a Perkin-Elmer R-12B spectrophotometer and chemical shifts, reported in parts per million, measured relative to an internal tetramethylsilane standard with $CDCl_3$ as solvent. The ^1H NMR spectra of the methyl esters **2** and **3** have been published. Isomer ratios were obtained by integration of peaks due to 5-methyl hydrogens, cis methyl ester 0.958 and trans methyl ester 1.258. ^{13}C NMR spectra were recorded on a JEOL FX-100 spectrometer and the ^{31}P NMR spectra on an NT-150 spectrometer.

Materials. The preparation and properties of the 2-substituted-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinans have been reported in a prior publication.[1] Methanol was distilled before use and PTSA·H_2O dried under reduced pressure. All glassware was washed with distilled water and carefully dried before use.

Dimethyl 2-(Chloromethyl)-2-methyl-3-hydroxypropyl Phosphate. 2-Methyl-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (1.07 g, 0.005 mol) and potassium *tert*-butoxide (1.12 g, 0.01 mol) were dissolved in 25 mL of methanol. The mixture was allowed to stand for 48 h and then added to 150 mL of water. The solution was extracted with two 20-mL portions of methylene chloride and the combined extracts were dried over $MgSO_4$. After filtration, solvent was removed under reduced pressure and the residue was distilled, bp 130 °C (1.0 mm), 0.95 g (77.2%).

Anal. Calcd for $C_7H_6ClO_5P$: C, 34.15; H, 6.50; Cl, 14.23. Found: C, 34.32; H, 6.60; Cl, 14.17. The 2-methyl hydrogens and carbon absorbed as follows: ^1H NMR 1.03 (3 H); ^{13}C NMR 16.988; ^{31}P NMR (85% H_3PO_4 external standard) 2.23. All other peaks in the ^1H NMR and ^{13}C NMR spectra were easily assigned to the proposed structure.

Methanolysis of *trans*-2-(*p*-Nitrophenyl)-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinan. A methanolic solution of PTSA·H_2O (0.1 M) was added to the trans p-nitrophenyl ester **1** (0.32 g, 0.001 mol) to give a total volume of 10 mL. The solution was gently refluxed for 24 h and then diluted after cooling with 20 mL of CH_2Cl_2. The solution was washed well with two 100-mL portions of 0.1 M KOH and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The NMR of the residue was taken without further purification. Peaks due to 5-methyl hydrogens of the reactant (1.358 ppm) and aromatic protons are completely absent.

An identical spectrum was obtained after rewashing a CH_2Cl_2 solution of the residue with aqueous KOH, drying, and removal of solvent. The workup procedure had no effect on product ratios. Other data reported in this article were obtained in an identical manner. The reactant and its concentration as well as the concentration of acid and reflux times were varied.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. The ^{13}C and ^{31}P NMR spectra were supplied by the Colorado State University Regional NMR Center, supported by the National Science Foundation Grant No. CHE 78-18581.

Registry No. 1, 36912-37-5; 2, 28097-12-3; 3, 36912-27-3; 4, 36912-38-6; dimethyl (2-chloromethyl)-2-methyl-3-hydroxypropyl-phosphate, 74465-69-3; 2-methyl-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 74465-70-6.

Ring-Closure Reactions. 17.[1] Kinetics of Formation of Meta- and Paracyclophane Diethers

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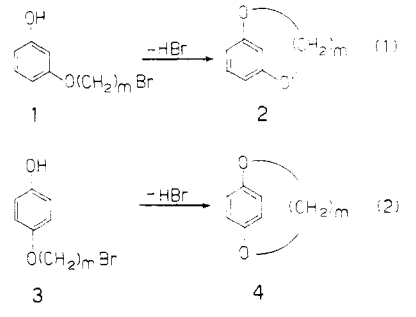
The [n]cyclophanes are a stereochemically interesting group of compounds in which an aromatic moiety is incorporated into a ring structure by means of nonadjacent positions connected by a cyclic side chain of n atoms. Their distinguishing feature is that a substantial strain energy is expected to develop as n gets sufficiently small.[2] Qualitative evidence for this derives, for instance, from the increasing synthetic difficulties encountered when the cyclophane ring size becomes smaller.[3]

Our continuous interest in the quantitative aspects of intramolecular reactions, as well as the aim at providing an insight into the energetics of formation of cyclophane systems, led us to extend our previous investigation[4] on the kinetics of formation of meta- and paracyclophane diethers by intramolecular Williamson synthesis (eq 1 and 2). Since, as shown by Allinger's force-field calculations,[5]



the amount of strain energy of the smaller cyclophanes is such as to seriously discourage any effort to study the kinetics of formation of these rings, the present study is restricted to medium-sized cyclophane systems. We report the results of such an investigation, including the kinetics of formation of compounds **2**, m = 8, 9, 10, and 12, and

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