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Stereoelectronic Effects on the Conformation and Kinetics of Nucleophilic Displacement Reactions in Epimeric Six-membered Ring Phosphonate Diesters

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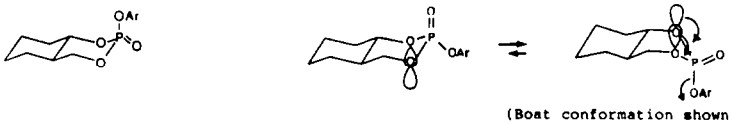
Abstract: Epimeric cyclic six-membered ring phosphonate phenyl esters, *cis-* and *trans*-2-phenoxy-2-oxo-*trans*-4,5-tetramethylene-1,2-oxaphosphorinane, *7a* and *7b* were synthesized and shown to exist in chair conformations for the phosphorinane ring. Configurational and conformational analyses of the esters were accomplished through analysis of the ^{1}H, ^{13}C, and ^{31}P NMR spectral data. Epimerization of the aryl phosphonate diesters *7a* and *7b* gave an equilibrium ratio of 89.5:10.5 (*trans:cis*), consistent with the ground state stereoelectronic or anomeric effect. Methanolysis in sodium methoxide proceeds with 100% inversion of configuration for both epimeric phenyl esters, consistent with placing the six-membered ring in a diequatorial position of a trigonal bipyramidal pentacovalent intermediate. The small difference in rate between the aryl ester epimers (the equatorial ester reacts faster by a factor of 5-8 fold) is consistent with this mechanism and the kinetic stereoelectronic effect.

INTRODUCTION:

The role of orbital orientation in organic and enzymatic reactions has been of considerable current interest[1-13] as well as controversy.[14,15] Deslongchamps and coworker[2,3] in studying tetracovalent carbon species have demonstrated selective cleavage of bonds which are antiperiplanar (app) to lone pair electrons on directly bonded oxygen and nitrogen atoms. Molecular orbital calculations have provided theoretical justification for these stereoelectronic effects in tetracovalent carbon, phosphorus and pentacovalent phosphorus species[6-13].

In contrast to the large body of experimental and theoretical work supporting the role of orbital orientation in carbon chemistry[1-3,7-11], limited experimental evidence yet exists to support this hypothesis in the reactions of organophosphorus compounds[16-20]. Attempts to experimentally confirm this effect in constrained six membered ring systems have been frustrated by conformational flexibility in these studies[21-23]. On the basis of NMR data, the axial aryloxy isomers of these six-membered ring phosphate esters have been shown to be in a chair conformation in which lone pairs on the ring oxygens are antiperiplanar to the exocyclic P-O bond. However, NMR, IR and x-ray data support the assignment of a twist-boat conformation for the "equatorial" epimers in which lone pairs on the ring oxygens can be antiperiplanar to the exocyclic pseudo-axial P-O ester bond only in this twist-boat conformation[21](a ground state anomeric, or stereoelectronic effect).



(Boat conformation shown)

This flexibility is not present in five-membered ring systems, and our laboratory's molecular orbital calculations[12] and experimental studies[18] supported a significant stereoelectronic effect in the hydrolysis of methyl ethylene phosphate. These claims were contested by Kluger and Thatcher[15]. However, most recently we have shown that the large increase in exocyclic cleavage observed by them, used to argue against the stereoelectronic effect, is due to an artifactual dimerization reaction.[16] By constraining a phosphate ester into the proper stereoelectronically favorable conformation, such as in a bicyclic phosphate triester, Gorenstein, Verkade, and co-workers[20] have confirmed significant rate enhancements possibly attributable to a stereoelectronic effect. Thus, this bicyclic phosphate triester hydrolyzes in base 5200 times faster than its acyclic analogue, triethyl phosphate.

Because of the structural flexibility in six-membered ring esters, both epimers (axial isomer in the chair conformation and "equatorial" isomer in a twist-boat conformation) can have lone pair electrons antiperiplanar to the exocyclic axial or pseudo-axial ester bonds. The twist-boat conformation represents a balance between the anomeric, ground state stereoelectronic effect which favors the axial orientation of the aryloxy group in a boat conformation

and 1,3-steric as well as eclipsing interactions which favor the chair conformation. However, reducing the anomeric effect and increasing the 1,3-steric and eclipsing interactions, we might expect to get a more rigid *trans*-decalin-type system with which both equatorial and axial isomers exist in the chair conformation.

One of the ways to accomplish this goal is to replace one of the ring oxygen atoms by a methylene group. Since one oxygen has been replaced by a carbon atom, the anomeric effect should become less significant and the two hydrogen atoms in the methylene group will increase the 1,3-steric and eclipsing interactions which will destabilize the twist-boat conformation. This will make it more difficult for the equatorial isomer to flip from its chair conformation to the twist-boat form. The effect of substitution of one of the ring oxygens by a methylene group on the ground state structure and energy, and reactivity of epimeric phosphonate esters is described.

EXPERIMENTAL SECTION:

General Methods

Chemicals were generally of highest purity. Baker analyzed 60-200 mesh silica gel was used for column chromatography after being activated at 130 °C overnight. Solvents and other liquid reagents were distilled before use. Melting points were taken on a Thomas Hoover apparatus and were uncorrected. HPLC was performed on a Spectra Physics high perfomance liquid chromatograph using a preparative C-18 reverse phase column.

^{1}H NMR spectra were recorded on Nicolet NT360 and Bruker WP-200 spectrometers with chemical shifts referenced to TMS. ^{31}P NMR spectra were recorded on a Bruker WP-80, WP-200 and Nicolet NT200, NT360 spectrometers at 32.4, 81, 81, 146 MHz respectively with 85% H_3PO_4 as external standard. ^{13}C NMR spectra were recorded on a Nicolet NT360 spectrometer at 90 MHz with chemical shifts referenced to TMS or $CDCl_3$. Mass spectra were obtained on an AEI MS 30 spectrometer. Infrared spectra were obtained on a Perkin-Elmer 521 or 700 spectrometer.

Diethyl *cis*-1,2-cyclohexanedicarboxylate (*1*) was prepared as previously described[24] from *cis*-1,2-cyclohexane dicarboxylic anhydride.

Diethyl *trans*-1,2-cyclohexanedicarboxylate (*2*) was prepared as previously described[24] from the *cis*-diester (*1*) by treatment with ethanolic sodium ethoxide. The ester was extracted with ether, then distilled under vacuum, to yield 105 g (86%) of *trans*-diester, b.p. 85-87 °C/0.25 mm (lit.[25]: 133-135 °C/9 mm).

Trans-1,2-bis(hydroxymethyl)cyclohexane (*3*) was prepared as previously[24] described by lithium alumium hydride reduction of diethyl *trans*-1,2- cyclohexanedicarboxylate (*2*), resulting in a viscous liquid (56.7 g, 91%) which crystallized, m.p. 56-57 °C. (lit.[24]: *cis* 42-43 °C; *trans* 57 °C).

Trans-1,2-bis(tosylmethyl)cyclohexane (*4*) was prepared as previously described[24] from *trans*-1,2-bis(hydroxymethyl)cyclohexane (*3*) and toluene-p-sulfonyl chloride in pyridine. The crude ditosylate was recrystallized from acetone-methanol to yield 127.1 g (74%) of stout needle crystals, m.p. 108-110 °C. (lit.[24]: *cis* 84-85 °C; *trans* 108 °C).

Trans-1,2-bis(iodomethyl)cyclohexane (*5*) was prepared as previously described[24] from the *trans*-ditosylate (*4*) in boiling acetone containing sodium iodide. The crude *trans*-1,2-bis(iodomethyl)cyclohexane was recrystallized from methanol as needles (57.0 g, 94%), m.p. 39-40°C (lit.[24] m.p. 39-40 °C).

Diisopropyl phenyl phosphite[26] (*6*)

(i) 12.0 g isopropanol (0.2 mole) in 30 mL anhydrous tetrahydrofuran was added slowly to a cooled, stirred solution of 4.6 g sodium (0.2 mole), 31.0 g triphenyl phosphite (0.1 mole) in 150 mL anhydrous tetrahydrofuran. The solution was then heated to reflux until all of the suspended sodium dissolved. After cooling, sodium phenoxide was filtered off, the ether was removed by rotatory evaporation. The crude phosphite was then distilled under vacuum to yield 15 g (62%) of diisopropyl phenyl phosphite (b.p. 65-68° C/0.2 mm; lit.[26] bp 117-118° C/10mm). The coupled ^{31}P NMR spectrum appears as a triplet (due to coupling to two isopropyl protons). ^{31}P NMR($CDCl_3$): 135.8 ppm.

(ii) Alternatively, 24.0 g isopropanol (0.4 mole) in 60 mL anhydrous ether was added slowly to a cooled, stirred solution of 27.4 g phosphorus trichloride (0.2 mole) and 60.7 g triethylamine (0.6 mole) (dried over sodium) in 600 mL anhydrous ether. After 1 hour, 18.8 g phenol (0.2 mole) in 50 mL anhydrous ether was slowly added. Diisopropyl phenyl phosphite was obtained by the same procedure as (i), yield 40 g (82.5%).

Cis- and *trans*-2-phenoxy-2-oxo-*trans*-4,5-tetramethylene-1,2-oxaphosphorinane (2-phenoxy-1-oxa-2-phospha-*trans*-decalin-2-one) (*7*).

A mixture of 18.2 g of *trans*-1,2-bis(iodomethyl)cyclohexane (0.05 mole), 12.1 g diisopropyl phenyl phosphite (0.05 mole) and 50 mL p-xylene was heated under nitrogen atomosphere with an oil bath at 180-190 °C overnight while isopropyl iodide and p-xylene was continuously removed.[27-30] After the reaction was completed, the phenyl phosphonate was purified by silica gel column chromatography, with diethyl ether solvent as eluent to yield an epimeric mixture of phosphonates (3.0 g, 26%).

Note: The *trans* epimer (the stereochemistry is defined by the 6-substituted ring carbon relative to the 2-phenoxy group) is also referred to as the axial (*7a*) epimer, assuming a chair conformation for the phosphorinane ring. The *cis* epimer (stereochemistry again defined by the 2 and 6-position substituents) is also referred as the "equatorial" (*7b*) epimer, assuming a chair conformation.

The *trans*, "axial" isomer (*7a*) was purified on a preparative reverse phase HPLC using 65/35 methanol/water at a flow rate of 3.00 mL/min. ^{31}P NMR (in $CDCl_3$): 24.35 ppm. m.p. 92-93 °C. ^{1}H NMR ($CDCl_3$): 7.1-7.4 ppm (m, 5H), 4.08-4.2 ppm (ddd, 1H), 3.88-3.98 ppm (td, 1H), 0.8-2.2 ppm (m, 12H). ^{13}C NMR ($CDCl_3$): 74.47 ppm (d, J=7.10 Hz), 40.923 ppm (d, J=4.63 Hz), 38.395 ppm (d, J=6.85 Hz), 34.822 ppm (d, J=18.67 Hz), 29.557 ppm (d, J=126.7 Hz), 26.846 ppm (s), 25.303 ppm (d, J=2.78 Hz), 25.045 ppm (s). IR (KBr cm^{-1}): 3057.6(w), 2928.2(s), 2856.7(w), 1591.5(m), 1489.2(s), 1325.3(m), 1273.2(s), 1234.6(m), 1205.7(s), 1024.3(s), 999.3(s), 929.8(s), 918.2(s), 906.7(s). Elemental analysis, $C_{14}H_{19}O_3P$, Calculated: C 63.15, H 7.19, P 11.63. Found: C 63.48, H 7.40, P 11.41.

The *cis*, "equatorial" isomer (*7b*) was purified on a silica gel column using 40/60 hexane/ether as solvent. ^{31}P NMR (in $CDCl_3$): 21.33 ppm. m.p. 108-110 °C. ^{1}H NMR ($CDCl_3$): 7.1-7.4 ppm (m, 5H), 4.05-4.2 ppm (m, 2H),

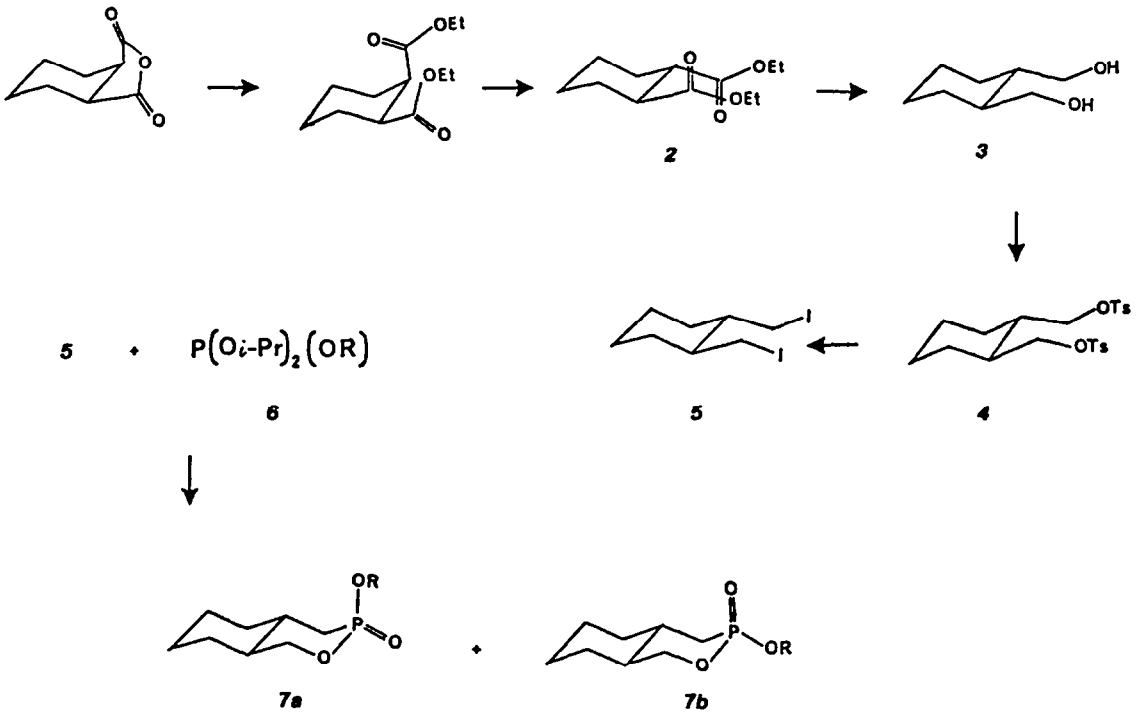
0.88-2.1 ppm (m, 12H). ^{13}C NMR ($CDCl_3$): 72.877 ppm (d, J~2 Hz), 41.721 ppm (d, J=3.85 Hz), 37.665 ppm (d, J~2 Hz), 35.147 ppm (d, J=19.23 Hz), 29.810 ppm (d, J=124.1 Hz), 26.873 ppm (s), 25.397 ppm (d, J~2 Hz), 25.162 ppm (s). IR (KBr cm^{-1}): 3060.1(w), 2930.2(s), 2858.9(m), 1591.5(m), 1489.2(s), 1450.7(w), 1321.4(w), 1267.4(s), 1232.7(m)1203.7(s), 1064.8(m), 1020.5(m), 999.3(s), 937.5(s), 846.(s). Elemental analysis, $C_{14}H_{19}O_3P$, Calculated: C 63.15, H 7.19, P 11.63. Found: C 63.27, H 7.44, P 11.83.

Kinetic Study

Kinetics of hydrolysis of the aromatic ester of the phosphonates were monitored at an absorption maximum at 290 nm on a Cary-210 UV-VIS spectrophotometer equipped with an automatic sample changer. The cells were maintained at a constant temperature by means of a thermostated cuvette holder. Time versus absorbance data was taken, and rate constants calculated on a PDP-11/03 computer interfaced to the spectrometer. The pseudo first-order rate constants were determined by an iterative nonlinear least-squares computer program[29]. Reactions were followed for at least 3 half lives. With this data the computer program would iteratively fit the rate constant, inital absorbance and final absorbance. The calculated and observed final absorbance generally agreed to within 5%.

All hydrolysis and transesterification reactions of the phosphonates gave good first-order kinetics. Duplicate runs generally agreed within 5%. Unless otherwise specified, hydrolyses were carried out in 50/50 dioxane/water at temperatures between 10 °C and 50 °C. Transesterification was carried out in dimethyl formamide at 10 °C.

Scheme I



RESULTS:

Synthesis

Synthesis of the phosphonate esters (7) is shown in Scheme I. The *trans*-fused decalin-type ring system can easily be separated from the *cis* isomer at the 1,2- bis(hydroxymethyl)cyclohexane step of the synthesis. Reaction of the di-iodide with phosphite followed by a cyclization in a Michaelis-Arbusov reaction has previously been used by Bergesen et al.[27-30] to synthesize various 1,2-oxaphosphorinanes with poor yield under neat reactions conditions. Following the same procedure, we failed to get any significant amounts of oxaphosphorinane. By raising the temperature and diluting the reactions mixture with an inert solvent, we obtained fair yields of products.

Configurational Analysis

The assignment of the equatorial and axial isomers of the phosphonate diesters 7 (R= Ph, Me), was based largely upon ^1H, ^{13}C and ^{31}P NMR spectra data. Of greatest utility was ^{31}P NMR because in all previous studies on epimeric esters of oxaphosphorinanes, the axial substituent has an upfield ^{31}P chemical shift [20,32-34]. Thus the 3.1 ppm upfield ^{31}P chemical shift for axial *7a* relative to equatorial *7b* in $CDCl_3$ strongly supports this assignment.

The 360 MHz ^1H NMR spectrum of the axial isomer, *7a*, shows a well resolved spectrum in the region of 3.8 ppm

to 4.3 ppm. These peaks represent the two protons of the methylene group which are next to the oxygen in the heterocyclic six-membered ring. Analysis of the coupling constants (Table I) shows that the downfield signals come from the equatorial proton and the upfield signals arise from the axial proton. Unfortunately, the same two protons in the equatorial isomer *7b* show a strong ABMY type coupling. The chemical shifts and coupling constants are difficult to obtain from this second order spectrum.

The proton noise decoupled ^{13}C NMR of both axial and equatorial isomers (*7a*, *7b*) proved valuable in confirming these assignments (Tables II and III). The carbon nuclei in the decalin-type system which are three or more bonds away from phosphorus atom are not very different from the phosphate triesters which our laboratory has studied previously[20]. Based on those spectra we can assign most of the carbons in the "decalin" ring system in *7a* and *7b*.

However, several peaks could not unambiguously be identified and in order to distinguish these peak we have used the attached proton test by SEFT (Spin Echo Fourier Transform). From this information and the large coupling constant between carbon 1 and phosphorus (one-bond coupling, $^1J_{PC}=120$ Hz) we were able to complete the peak assignment for all of the carbon nuclei and assignments are given in Table II.

Axial-Equatorial Epimerization

The equilibrium between the equatorial and axial isomers of the phenoxyphosphonate diesters as monitored by ^{31}P NMR using 0.05 M phosphonate diesters and 0.25 M phenoxide in 100% dimethylformamide at room temperature. The percentage axial epimer calculated is 89.5%.

Methanolysis Reaction

Methanolysis was carried out with 0.25 M sodium methoxide in methanol, and the reaction was followed by ^{31}P NMR. At the beginning of the reaction, there was no sign of the retention product. As the reaction proceeded to completion, some of the retention product began to appear. By carefully examining the rate of appearance of product, we believe that the retention product did not directly come from the methanolysis of phenyl phosphonate but came from subsequent isomerization of the initially formed inversion product by reaction with excess methoxide in the reaction mixture.

Alkaline Hydrolysis of Phosphonates

Both axial and equatorial isomers were hydrolyzed in 50% dioxane/water mixture with 0.1-0.5 M sodium hydroxide. The kinetic data demonstrated that the alkaline hydrolysis was first order in both phosphonate and sodium hydroxide concentration. The alkaline hydrolysis was also carried out at different temperatures (14°-43 °C) for both the equatorial and axial isomers. The second-order based catalyzed rate constants and calculated activation parameters are shown in Table IV.

DISCUSSION:

Configurational and Conformational Analysis

Configurational and conformational analysis of the phosphonate diesters is based upon the ^{31}P, ^1H and ^{13}C NMR spectral data.

^{31}P Chemical Shift Difference

As discussed previously, ^{31}P NMR chemical shifts are generally quite sensitive to P-O ester bond torsional angles[32-36]. The equatorial ester group is locked into a *trans* conformation relative to the endocyclic P-O ester bond, resulting in a downfield ^{31}P chemical shift compared to the *gauche* conformation such as in the axial isomers. Since axial esters are in the chair conformation, the chemical shift difference between epimers reflects the degree to which the equatorial esters are constrained to a chair conformation.[21,36] As the chemical shift difference between epimers increases, the equatorial epimer appears to be more constrained to the chair, rather than any twist-boat conformation.

^{31}P chemical shift differences among 1,2,3-dioxaphosphorinane esters in which the equatorial epimer is in ca. 50% twist-boat/50% chair conformation are 2.1~2.3 ppm in $CDCl_3$. For esters in which the equatorial epimer is in a 100% twist-boat conformation, the chemical shift difference is only 0.65 ppm.[21] For the phosphonate diester epimers, we observed a ^{31}P NMR chemical shift difference of 3.0 ppm. This suggests that the equatorial phosphonate diester exists largely in the chair conformation.

Vicinal P-H and H-H Coupling

As expected from the anomeric effect, the phenoxy group prefers the axial position of the six-membered ring which exists in the chair conformation. These are strongly supported by the coupling constants from Table I. The

equatorial proton shows a large coupling constant with phosphorus (22.8 Hz) due to the 180° dihedral angle in the H_2-C-O-P system (*trans*) and the axial proton shows a smaller coupling constant (2.0 Hz) because it is in a *gauche* conformation in the H_1-C-O-P system. However, the *gauche/trans* relationship is reversed between H1/H2 and H3, as shown in J_{13} (11.2 Hz) and J_{23} (4.1 Hz).

^{13}C Chemical Shifts

Table II shows the ^{13}C NMR chemical shifts of axial and equatorial phosphonate diesters. The chemical shifts are similar to those of related phosphate triesters except for carbons 2, 3 and 4.[21] The most notable difference appears at carbon 2 with a large upfield shift (~ 45 ppm) in the phosphonate due to the replacement of electronegative oxygen by carbon. This replacement also affects the chemical shifts of carbons 3 and 4 which show 1.4-2.5 ppm downfield shifts in the phosphonate with respect to the phosphate ester.

^{31}P-^{13}C Coupling Constants

Table III shows the ^{31}P-^{13}C coupling constants for both equatorial and axial isomers (absolute values only are reported). The one-bond coupling constant, $^1J_{P-C}$, of cyclohexylphosphonates are 135-144 Hz. It is smaller (15-20 Hz smaller in this case) when the phosphorus atom is incorporated into the ring. The $^1J_{P-C}$ of the axial isomer is 2.5 Hz larger than that of equatorial isomer, as found in six- membered ring phosphine oxides[37] and phosphines.[38,39]

Two-bond coupling constants (geminal coupling, ^2J) usually are small and frequently independent of stereochemistry, and are of little value in the structural assignments. However, some ^2J coupling constants do differ in isomeric pairs and for the few cases known it appears that orientation of exocyclic substituents has an effect.[40,41]

In the phosphonate isomeric pair, $^2J_{P-C}$ for carbons 2 and 8 show drastic differences between the equatorial and axial isomers. In the axial isomer both $^2J_{P-C}$ coupling constants (6.9 and 7.1 Hz for carbons 2 and 8, respectively) are larger than those in the equatorial isomer (although the splitting was observed, resolution was insufficient to obtain the coupling constants, estimated to be less than 2 Hz). It can be used as evidence to prove that the assignments from ^{31}P NMR chemical shifts are correct.

The $^2J_{P-C}$ coupling constants for carbons 2 and 8 in the axial isomers of phosphate triesters[21] are similar to those in the phosphonate diester. They appear to have the same chair conformations with those carbon nuclei *trans* to the P=O double bond. However, in the equatorial esters the geminal P-C coupling constants become more complicated. The chair conformation of the equatorial isomers would have geminal carbon nuclei *gauche* to the P=O double bond which would be expected to have smaller geminal P-C coupling constants.

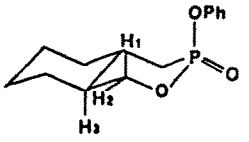
Since the equatorial phosphate esters will be an equilibrium mixture of the chair and twist-boat conformations and the twist-boat conformation will make geminal carbon nuclei no longer *gauche* to the P=O double bond, it will increase the coupling constants of carbon 2 and 8. Apparently, the greater the percentage twist-boat conformation in the equilibrium, the larger the geminal coupling constants. Our laboratory[21] has shown that different aryl phosphate triesters have the same $^2J_{P-C}$ in the axial isomers and different but smaller $^2J_{P-C}$ were observed in the equatorial esters. The geminal coupling constants among the equatorial phosphate esters consistently increase with the equilibrium proportion of the twist-boat conformation. Note that carbons 2 and 8 are eventually *trans* to the P=O double bond in a 100% twist-boat conformation which make $^2J_{P-C}$ the same in the *cis* and *trans* isomers.

Phosphorus also couples with remote carbons which are three or four bonds away. Vicinal P-C coupling constants, ^3J, are dependent on the dihedral angle which is similar to vicinal H-H coupling in the Karplus-type relationship. It has been shown that phosphonate[42-44] vicinal P-C coupling reaches a maximum at a dihedral angle of 180° and is at a minimum at 90°.

There are two vicinal coupling constants in the *trans*-fused decalin-type ring system. Carbon 3 which is antiperiplanar (dihedral angle 180°) to the phosphorus atom and carbon 7 which is *gauche* (dihedral angle 60°) have quite difference vicinal coupling constants in both axial and equatorial isomers. This *trans/gauche* relationship would be reversed if the conformation changes from a chair conformation to a twist-boat conformation. Thus, if more of the twist-boat form appears in equilibrium with the chair form the vicinal coupling constant of carbon 7 will increase and the ^3J of carbon 3 will decrease. This indeed has been shown for the phosphate triesters.[21]

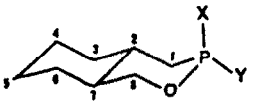
In the phosphonate diesters, the most notable difference compared to the phosphate triesters is the much larger vicinal coupling constant at carbon 3 (18-20 Hz). The large ^3J may result from a more rigid six-membered ring system in which the oxygen atom is replaced by carbon. With an oxygen atom in the ring the dihedral angle of the

Table I Selected ^1H NMR chemical shifts and coupling constants of axial phosphonate isomer *7a*



	δppm	J_{12}	J_{13},J_{23}	J_{1p},J_{2p}
H-1	3.93	11.1	11.2	2.0
H-2	4.1	11.1	4.1	22.8

Table II Selected ^{13}C NMR chemical shifts of phosphonates *7a* and *7b*.



axial : X=PhO, Y=O (7a)

equatorial : X=O, Y=PhO (7b)

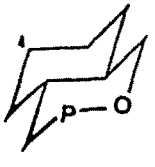
carbon #	1	2	3	4
axial	29.56	38.40	34.82	25.30
equ.	29.81	37.67	35.15	25.40

carbon #	5	6	7	8
axial	25.05	26.85	40.92	74.15
equ.	25.162	26.873	41.721	72.837

P-O-C_2-C_3 system was not exactly 180° and hence this could explain the smaller coupling constant. This was also shown in the vicinal P-H coupling, the maximum coupling constant for 180° is expected[36] to be 28 Hz and we only observed 24 Hz and 22 Hz in phosphate and phosphonate esters respectively.

Again, these two vicinal P-C coupling constants also support the chair conformation for both equatorial and axial isomers in the phosphonate diesters. The equatorial isomer has almost identical vicinal coupling constants as the axial isomer indicating the twist-boat form is not populated to any substantial extent.

For four-bond coupling, ^4J, through a saturated network, a planar W geometry has been shown to be most favorable for the H-H system[45], although many examples of resolvable non H-H W coupling are now known.[40,55] Carbon 4 in the *trans*-fused decalin system is the only one with a W coplanar geometry with respect to phosphorus as shown in the following:

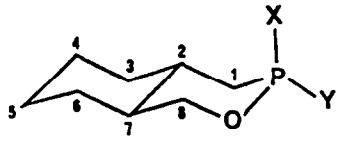


Thus, the only four-bond coupling shown is 2~2.5 Hz, occurring at carbon 4 for both epimers, again confirming the chair conformation for the phosphonate ring in both epimers.

Epimerization - Ground State Stereoelectronic Effect

The equilibration between *cis 7b* (equatorial) and *trans 7a* (axial) isomers again shows the axial preference of the polar substituent in the six-membered ring system. Because the lone pair of electrons on the endocyclic oxygen is antiperiplanar to the exocyclic P-O ester bond in the axial isomer while no app lone pairs to the exocyclic P-O ester bond in the equatorial isomer, the axial isomer is predicted to be more stable than the equatorial one.[1-3,12]

Table III ^{31}P-^{13}C coupling constants of phosphonate diesters *7a* and *7b* (absolute values only)



carbon #	1	2	3	4	7	8
axial	126.7	6.85	18.67	2.78	4.36	7.10
equatorial	124.1	~2	19.23	~2	3.85	~2

Table IV Second-order base catalyzed rate constants and activation parameters for phosphonates *7a* and *7b*.

	axial isomer	equatorial isomer
k_2^a	0.043	0.343
$\Delta H^{\ddagger}$	15.4	13.4
$\Delta S^{\ddagger}$	-21.2	-23.6
$\Delta G^{\ddagger}$	21.7	20.5
$\Delta\Delta G^{\ddagger}$	1.25	

[a] At 24.5 °C

With only one ring oxygen in the phosphonate system compared with two in the phosphate system, we expect a smaller anomeric effect in the phosphonates compared to the phosphates. This is confirmed by the free energy difference between epimers in the phosphonates and phosphates. Thus, the free energy difference between the epimer six-membered ring phosphate phenyl esters is 1.95 kcal/mol while the free energy difference between the phosphonate phenyl esters is only 1.24 kcal/mol.

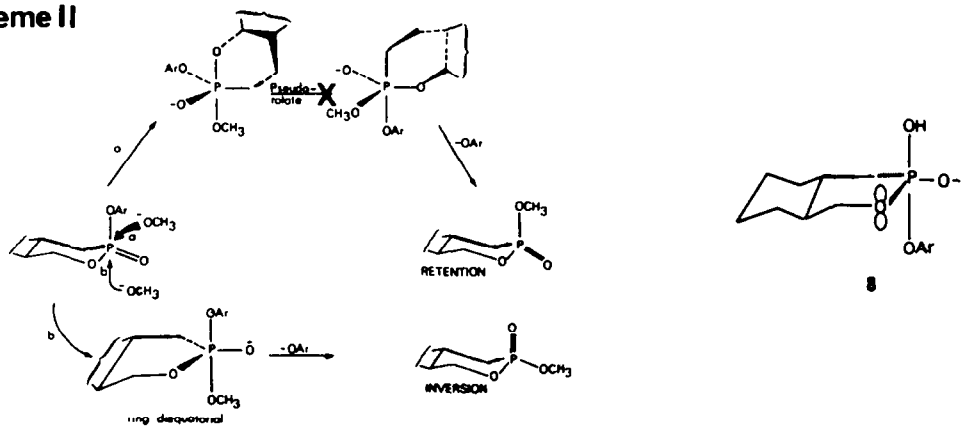
Stereochemistry of Methanolysis

If the methoxide ion attacks the phosphorus center from the backside relative to the phenoxy group, the resulting phosphorane will have the leaving group (phenoxide) and attacking group (OH) in axial positions of a trigonal bipyramid (tbp) and the six-membered ring will occupy a diequatorial position. The direct breakdown of this phosphorane will lead to the inversion product[47,48].

If the methoxide ion attacks the phosphorus center from the side opposite to the endocyclic P-O bond, the resulting phosphorane would have the six-membered ring spanning equatorial-axial positions and the leaving group will be in the equatorial position of the trigonal bipyramid. Because the leaving group must depart from the axial position, this phosphorane first pseudorotates before yielding the retention product[48].

In the phosphate triesters, the pentacovalent phosphorane was surrounded by five oxygen atoms which have a low energy barrier for pseudorotation[47-49]. The pentacovalent phosphorane which gives the inversion product has the most electronegative group (phenoxy) in its axial position of the tbp but suffers from ring strain because of the di-equatorial six-membered ring orientation[47-49] (120° O-P-O bond angle). On the other hand, the phosphorane which forms the retention product will likely have similar ring strain because the six-membered ring is in the axial-equatorial orientation (90° O-P-O bond angle), but now the most electronegative group is in the equatorial position of the tbp. Thus the ratio of inversion/retention products will vary depending on the electronegativity of leaving group. The better the leaving group, the more the inversion product. Indeed, this has been demonstrated in the methanolysis of phosphate triesters.[21] In the phosphonate diesters, one of the five oxygen atoms surrounding the phosphorus center is replaced by a carbon atom. Because of this replacement, pseudorotation of the phosphorane intermediate which gives the retention product is no longer favorable[48] (Scheme II).This pseudorotation must go

Scheme II



through a high energy pseudorotomer which has the carbon atom at an axial position of the tbp.[47-50] This high energy barrier for pseudorotation makes the retention product kinetically disfavored, hence leading to exclusive inversion product.

Relative Rates of Hydrolysis:

As shown in Table III, the difference in free energy of activation for the alkaline hydrolysis of epimeric phosphonate diesters was only 1.25 kcal/mol. (The equatorial isomer reacts faster than the axial isomer by a factor of only 5-8 times at various temperatures.) Although the ground state free energy difference of the reactants, ΔG_o, was obtained from the equilibrium constant between two isomers in DMF, and the free energy of activation was obtained from the rate of hydrolysis at a different temperature in dioxane/H_2O, solvent effects are not expected to greatly alter the values of ΔG_o and $\Delta G^{\ddagger}$).[21] Assuming that these assumptions are correct, the most notable observation is that both isomers have very similar free energies for their transition states. ($\Delta\Delta G^{\ddagger}$ ~0.05 kcal/mol). This suggests that both epimers have similar transition state geometries: likely a half-chair, di-equatorial ring trigonal bipyramid, *8*.

In the transition states for reaction of either isomer, the two lone-pair orbitals on the endocyclic oxygen can be treated as one sp^2 hybrid orbital and one pure p-orbital. The p-orbital on the endocyclic oxygen can most effectively overlap with the apical phosphorus p-orbital and both incoming nucleophile and leaving groups. This can avoid the difficulty of requiring a different orientation for the basal groups (producing app lone pair interactions) for different bond making and breaking transition states.[12]

Since the orientation of the lone pair on the endocyclic oxygen is the same for both apical ligands in the tbp, both axial and equatorial isomer transition states will be equally stabilized by a stereoelectronic orbital interaction. Therefore the relative hydrolysis rate of these two isomers can only reflect their ground state energy differences.

CONCLUSION:

^{31}P chemical shifts and P-C coupling constants have been used in configurational and conformational analysis of epimeric phosphonate esters. As in phosphate esters, axial phosphonate esters show ^{31}P chemical shifts upfield of equatorial esters. Large geminal P-C coupling constants in the axial isomer and small geminal coupling constants in the equatorial isomer provide strong support for the absence of any chair to twist boat ring flipping in the six-membered ring in the equatorial isomer of the phosphonates, which has previously been observed for cyclic phosphate triesters.

Other evidence confirms that the equatorial isomer is in the chair conformation and comes from the large vicinal P-C coupling at carbon 3 and the small vicinal P-C coupling at carbon 7.

Flipping from a chair conformation to a twist-boat conformation is restricted in the phosphonate diester system mainly because replacement of one of the ring oxygens with a methylene group reduces the anomeric effect and also adds some 1,3-steric and eclipsing interactions from the two hydrogen atoms in the substituted methylene group. The anomeric effect has been reduced by more than 0.5 kcal/mol by removing the ring oxygen as shown in the equilibration between the axial and equatorial isomers in the phosphonate diesters.

The six-membered ring cyclic phosphonates show different stereochemistries for methanolysis compared with the phosphate ester systems. The high energy barrier for pseudorotation presumably prevents the formation of retention product.

The small difference in the free energy of activation for alkaline hydrolysis of epimeric phosphonates is similar to their ground state free energy difference. Analysis of the free energy of activation for alkaline hydrolysis of both isomers indicates that both react through very similar (energetically and structurally) transition states. Because of the high energy barrier for pseudorotation, the transition states for reaction of either epimer is best described as a pentacovalent phosphorane with the six-membered ring spanning a di-equatorial position.

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