to warm to room temperature slowly. The spectral data were as follows: IR (thin film) 1250 cm^{-1} (P=O); ^{31}P NMR ($CDCl_3$) δ +22.3; ^{13}C NMR ($CDCl_3$) δ 26.4 (d, ring CH_2CH_2OP, J_{CCOP} = 4.9 Hz), 27.9 (d, side chain CH_2CH_2NP, J_{CCNP} = 1.9 Hz), 30.8 (s, $CH_2SC_6H_5$), 47.2 (s, side chain CH_2NP), 47.6 (d, ring CH_2NP, J_{CNP} = 1.9 Hz), 69.7 (s, CH_2OP), plus resonances in the range δ 125-135 (aromatic carbons); ^1H NMR ($CDCl_3$) δ 1.36-2.51 (m, 4 H), 2.70-3.79 (m, 6 H), 3.96-4.60 (m, 2 H), 7.26-8.06 (m, 10 H). Attempts to purify this material by molecular distillation failed.

Reaction of 4 with Dithiete (16). To a solution of 0.99 g (7.5 mmol) of **4** in 2 mL of methylene chloride, cooled to -78 °C and under a nitrogen atmosphere, was added 1.71 g (8.0 mmol) of freshly distilled dithiete (**16**) dissolved in 2 mL of methylene chloride. After stirring at this temperature for 1 h the reaction mixture was allowed to warm to room temperature. After the volatiles were removed at reduced pressure, there remained a red-brown oil which could not be purified and had to be stored in solution to prevent its decomposition: ^{31}P NMR (CD_2Cl_2) δ +20.9; ^{13}C NMR ($CDCl_3$) δ 48.7 (d, J_{CNP} = 7.5 Hz), 65.8 (s), 121.3 (d of q, J_{CF} = 275.4, J_{CCSP} = 16.1 Hz), 125 (m); ^1H NMR (CH_2Cl_2) δ 3.33 (d of t, J_{HCNP} = 17.0, J_{HCCH} = 6.4 Hz), 4.22 (d of t, J_{HCOP} = 16.0, J_{HCCH} = 6.4 Hz); ^{19}F NMR ($CDCl_3$, 25 °C) δ -60.5 (d, J_{FCCSP} = 2.1 Hz); (-32 °C) δ -58 to -61 (very broad mound); (-65 °C) δ -58.8 (d, J_{FCCSP} = 10.6 Hz), -61.0 (d, J_{FCCSP} = 10.0 Hz).

Reaction of 4 with Ethane 1,2-Bis(benzenesulfenate). To a solution of 0.39 g (2.97 mmol) of **4** in 1 mL of methylene chloride, cooled to -78 °C and under argon, was added 0.83 g (3 mmol) of ethane 1,2-bis(benzenesulfenate) dissolved in 1 mL of methylene chloride. After stirring for 1 h at this temperature the reaction mixture was allowed to warm to room temperature, slowly. After removal of the solvent, at reduced pressure, the residual oil was triturated with pentane. Further purification was not possible because of the thermal instability of the product: ^{31}P NMR (CD_2Cl_2) δ -6.0; ^{13}C NMR (CD_2Cl_2, 25 °C) δ 45.1 (d, J_{CNP} = 11.3 Hz), 61.4 (d, NCH_2CH_2OP, J_{COP} = 5.1 Hz), 61.4 (d, OCH_2CH_2OP, J_{COP} = 3.5 Hz); (-45 °C) δ 44.8 (d, J_{CNP} = 11.0 Hz), 61.4 (d, NCH_2CH_2OP, J_{COP} = 4 Hz); (-70 °C) δ 44.7 (d, J_{CNP} = 11.0 Hz), 59.5 (d, OCH_2CH_2OP, J_{COP} = 3 Hz), 61.4 (d, NCH_2CH_2OP, J_{COP} = 4 Hz), 63.3 (s, OCH_2CH_2OP); ^1H NMR (CD_2Cl_2) δ 2.93 (d of t, J_{HCNP} = 15, J_{HCCH} = 6.1 Hz, 4 H), 3.80 (d, OCH_2CH_2OP, J_{HCOP} = 13.8 Hz, 4 H), 3.84 (d of t, NCH_2CH_2OP, J_{HCOP} = 13.5, J_{HCCH} = 6.1 Hz, 4 H).

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Stereoelectronic Effects in the Reactions of Epimeric 2-Aryloxy-2-oxy-1,3,2-dioxaphosphorinanes and Oxazaphosphorinanes

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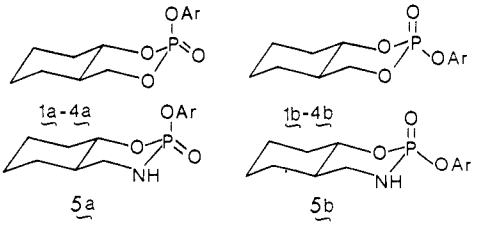
Abstract: Configurational and conformational analysis of isomeric 2-aryloxy-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinane (**1-4**) (ArO = *p*-methoxyphenoxy, *p*-nitrophenoxy, phenoxy, and 2,4-dinitrophenoxy) and isomeric 2-*p*-nitrophenoxy-2-oxo-*trans*-5,6-tetramethylene-1,3,2-oxazaphosphorinane (5) is presented. Based upon ^1H NMR coupling data and ^{31}P and ^{13}C NMR and IR spectra the axial aryloxy isomers of **1-5** of these *trans*-decalin-type six-membered-ring phosphorinanes are in chair conformations. However, NMR and IR data support the assignment of a twist-boat conformation for "equatorial" isomers of the 2,4-dinitrophenoxy ester **4b** and the *p*-nitrophenoxy ester of **5b**. Mixed chair and twist-boat conformations are found for the other aryloxy esters **1b-3b**. The axial isomers **1a-5a** are 1.5-2 kcal/mol lower in energy and hydrolyze in base 4-17 times slower than their epimers. Only the twist-boat isomers of 2,4-dinitrophenoxy ester **4b** and the *p*-nitrophenoxy ester **5b** react with 100% inversion of configuration with methoxide. All other compounds react with 4-83% inversion of configuration. Speculations on the stereoelectronic effects in these reactions are considered.

Introduction

Deslongchamps[2] and more recently Kirby[3] have established that the orientation of lone pairs controls the decomposition of tetrahedral carbon species. In this stereoelectronic theory cleavage of specific bonds is facilitated by antiperiplanar (app) lone pairs on directly bonded oxygen or nitrogen atoms. Lehn and Wipff[4] and Gorenstein et al.[5-9] have proposed that similar stereoelectronic effects control the hydrolysis of phosphate esters. These predictions were based upon molecular-orbital calculations and obviously require experimental confirmation. In this paper we report on the reactions of the epimeric pairs of 2-aryloxy-2-oxy-1,3,2-dioxaphosphorinanes **1a,b-4a,b** and 1,3,2-oxazaphosphorinanes **5a,b**, designed to test this theory.



The present combination of conformational analysis and kinetic, stereochemical, and equilibration studies of the epimeric pairs of dioxaphosphorinanes and oxazaphosphorinanes has provided the most detailed definition to date of the associative mechanism of reaction at phosphorus. Unfortunately for the test of the stereoelectronic theory it is now recognized that low-energy twist-boat

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conformations exist in equilibrium with the chair forms even in these *trans*-decalin-type systems.[10] (See also related twist structures in ref 11–13.) This unusual conformational flexibility has essentially precluded any kinetic analysis in this system of the stereoelectronic control of reaction at phosphorus. As shown in the present study and in the work of Kirby on the hydrolysis of cyclic acetals,[3b] the absence of any large kinetic acceleration expected from the stereoelectronic theory does not necessarily denigrate its potential importance.

Experimental Section

^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker WP-80 spectrometer at 80, 20.1, and 32.4 MHz, respectively, or ^1H NMR on a 60-MHz Varian T-60 spectrometer. Chemical shifts in parts per million for ^1H NMR spectra are referenced to internal Me_4Si and for ^{31}P NMR spectra are referenced to external 85% H_3PO_4. Infrared spectra were obtained on a Perkin-Elmer 521 or 700 spectrometer. Mass spectra (70 eV) were obtained on an AEI MS 30 spectrometer. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Gas chromatography was performed on a Hewlett-Packard 5830A instrument equipped with a 15% DEGS on Anachrom AB $^1/_8$ in. × 6 ft column, using the thermal conductivity detector.

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. Triethylamine, phosphoryl chloride, and methylene chloride were distilled before use. Other solvents were dried over 4 Å molecular sieves (Grace Chemical Co.). Doubly distilled water and dioxane purified by treatment with acid and nitrogen bubbling, then base, and finally by distillation from sodium[14] were used for kinetics.

***trans*-2-Hydroxymethyl-1-cyclohexanol (9)** was prepared from cyclohexene and paraformaldehyde according to precedure B of Blomquist and Wolinsky.[15]

2-*p*-Nitrophenoxy-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinanes (2-*p*-Nitrophenoxy-1,3-dioxa-2-phospha-*trans*-decalin-2-one) (3a,b). The preparation and separation have been described previously.[10]

2-*p*-Nitrophenoxy-2-oxo-*trans*-5,6-tetramethylene-1,3,2-oxazaphosphorinane (2-*p*-Nitrophenoxy-1,3-oxaza-2-phospha-*trans*-decalin-2-one) (5a,b). This preparation has previously been described.[10]

2-Chloro-2-oxo-5,6-tetramethylene-1,3,2-dioxaphosphorinane (10). A solution of 7.82 g (51 mmol) of phosphorus oxychloride in 25 mL of ether was added dropwise to a solution of 6.5 g (50 mmol) of diol **9** in 25 mL of ether at 0 °C under an argon atmosphere.

The reaction mixture was stirred for an additional 1 h and filtered, and the ether was removed on a rotary evaporator. The product was stored at 5 °C under argon until ready for use. Only one of the two possible epimers was obtained. The chloro substituent is believed to be axial by the strong similarity of the 4.0–4.8 ppm part of the ^1H NMR to that of the other axial isomers.

^1H NMR ($CDCl_3$): δ 0.8–2.2 (m, 9 H, ring), 3.82–4.64 (m, 3 H). ^{31}P NMR ($CDCl_3$): δ −4.75. IR ($CDCl_3$): 2922 (m), 2844 (w), 1458 (w), 1442 (w), 1374 (m), 1368 (s), 1360 (s), 1212 (w), 1164 (w), 1104 (w), 1092 (w), 1066 (m), 1053 (m), 1032 (s), 992 (m), 972 (m), 952 (m) cm^{-1}.

2-(2,4-Dinitrophenoxy)-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinane [2-(2,4-Dinitrophenoxy)-1,3-dioxa-2-phospha-*trans*-decalin-2-one] (4a,b). A solution of 4.21 g (20 mmol) of the phosphorochloridate **10** in 50 mL of dry toluene was heated to ca. 90 °C. Dried sodium 2,4-dinitrophenoxide (4.12 g, 20 mmol) was rapidly added and the solution stirred for 4 min. The solution was filtered immediately to remove NaCl and concentrated on a rotary evaporator. With this reaction time a slight excess of the equatorial isomer could be formed. A longer reaction time will give 97% of the axial compound. The isomers were separated on a silica gel column using ethyl acetate or ether as eluent. (Note that if any water remains on the column it will hydrolyze the esters. This occurred on the first two trials but separation was achieved thereafter.) The axial isomer, **4a**, was recrystallized three times from acetonitrile, mp 127–130 °C, and the equatorial isomer, **4b**, from toluene, mp 110–113 °C. IR ($CDCl_3$) **4a**: 3106 (w), 2936 (m), 2858 (w), 1608 (s), 1537 (s), 1486 (m), 1455 (w), 1351 (s), 1321 (s), 1314 (s), 1273 (s), 1218 (w), 1168 (m), 1135 (w), 1067 (m), 1056 (m), 1035 (s), 995 (m), 978 (m), 965 (m), 952 (m), 935 (s) cm^{-1}. **4b** ($CDCl_3$): 3106 (w), 2934 (m), 2857 (m), 1608 (s), 1535 (s), 1485 (m), 1452 (m), 1347 (s), 1320 (s), 1300 (s), 1272 (s), 1252 (w), 1214 (w), 1159 (w), 1140 (w), 1065 (s), 1053 (m), 1033 (m), 1004 (m), 959 (m), 931 (s) cm^{-1}. ^1H NMR ($CDCl_3$) **4a**: δ 1.01–2.28 (m, 9 H, ring), 4.14–4.64 (m, 3 H, H1,2,4), 8.02–8.84 (m, 3 H, aromatic). **4b**: δ 1.20–2.17 (m, 9 H, ring) 4.14–4.52 (m, 3 H, H-1,2,4), 7.92–8.82 (m, 3 H, aromatic).

Anal. Calcd for $C_{13}H_{15}N_2O_8P$: C, 43.59; H, 4.22; N, 7.82; P, 8.65. Found for **4a**: C, 43.49; H, 4.17; N, 7.89; P, 8.58. Found for **4b**: C, 43.58, H, 4.23; N, 7.63; P, 8.69.

2-*p*-Methoxyphenoxy-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinane (2-*p*-Methoxyphenoxy-1,3-dioxa-2-phospha-*trans*-decalin-2-one) (1a,b). To a 90 °C solution of 10.5 g (50 mmol) of the phosphorochloridate **10** in 50 mL of dry toluene was added 7.3 g (50 mmol) of sodium *p*-methoxyphenoxide. The mixture was stirred for 5 min. Half the solution was taken, the salts were filtered off, and the solvent was removed on a rotary evaporator yielding the equatorial isomer. The remaining half of the solution was heated until the equatorial isomer isomerized to the axial (followed by TLC); then it was also filtered and concentrated. The isomers were purified by column chromatography in ether with the axial isomer eluting first. **1a** crystallized from ether (mp 142–144 °C) and **1b** recrystallized from ether (mp 111–114 °C).

IR ($CDCl_3$) **1a**: 2930 (m), 2858 (w), 1505 (s), 1454 (s), 1317 (m), 1298 (s), 1250 (w), 1204 (s), 1166 (w), 1106 (w), 1069 (m), 1056 (w), 1037 (s), 975 (m), 962 (s), 945 (s), 900 m cm^{-1}. **1b** ($CDCl_3$): 2925 (m), 2852 (w), 1505 (s), 1454 (w), 1317 (w), 1275 (s), 1252 (w), 1204 (s), 1096 (w), 1067 (w), 1030 (s), 978 (m), 950 (m), 895 (m) cm^{-1}. ^1H NMR ($CDCl_3$) **1a**: δ 0.72–2.44 (m, 9 H, ring), 3.80 (s, 3 H, OCH_3), 3.92–4.61 (m, 3 H, H-1,2,4), 6.86 (d, J = 10 Hz, aromatic), 7.20 (d, J = 8 Hz, aromatic). **1b**: δ 0.70–2.44 (m, 9 H, ring), 3.80 (s, 3 H, OCH_3), 3.93–4.64 (m, 3 H, H-1,2,4), 6.82 (d, J = 9 Hz, aromatic), 7.19 (d, J = 10 Hz, aromatic). MS: molecular ion at m/e 298.

2-Phenoxy-2-oxo-*trans*-5,6-tetramethylene-1,3,2-dioxaphosphorinane (2-Phenoxy-1,3-dioxa-2-phospha-*trans*-decalin-2-one) (2a,b). A solution of 5.2 g (40 mmol) of diol **9** and 11.4 mL of triethylamine in 50 mL of CH_2Cl_2 was added dropwise to a solution of 10.0 g (47 mmol) of phenylphosphorodichloridate in 80 mL of CH_2Cl_2 at 0 °C under an argon atmosphere. The reaction mixture was stirred for an additional hour, washed four times with 150 mL of water, and dried over $CaCl_2$. The solution was filtered and concentrated on a rotary evaporator. The esters were separated on a silica gel column with chloroform eluent. The axial isomer, **2a**, came off first followed by the equatorial isomer **2b**. Isomer **2a** was recrystallized from acetonitrile (mp 157–159 °C) and isomer **2b** from toluene (mp 65–68 °C).

IR ($CDCl_3$) **2a**: 2938 (m), 2856 (w), 1596 (w), 1490 (m), 1453 (w), 1319 (m), 1303 (s), 1213 (m), 1168 (m), 1137 (w), 1107 (w), 1097 (w), 1067 (m), 1056 (m), 1036 (s), 1027 (s), 996 (w), 975 (m), 960 (m), 940 (s) cm^{-1}. **2b** ($CDCl_3$): 2930 (m), 2856 (w), 1596 (w), 1490 (m), 1453 (w), 1319 (w), 1276 (s), 1213 (m), 1168 (w), 1139 (w), 1106 (w), 1096 (w), 1066 (m), 1056 (w), 1038 (m), 1026 (s), 1012 (w), 976 (m), 952 (m) cm^{-1}. ^1H NMR ($CDCl_3$) **2a**: δ 0.86–2.16 (m, 9 H, ring), 3.97–4.49 (m, 3 H, H-1,2,4), 7.28 (m, 5 H, aromatic). **2b** ($CDCl_3$): 0.85–2.15 (m, 9 H, ring), 4.07–4.50 (m, 3 H, H-1,2,4), 7.30 (m, 5 H, aromatic). MS: molecular ion at m/e 268.

Anal. Calcd for $C_{13}H_{17}O_4P$: C, 58.21; H, 6.39; P, 11.55. Found for **2a**: C, 58.36; H, 6.44; P, 11.23. Found for **2b**: C, 58.21; H, 6.49; P, 11.28.

Kinetic Studies. Kinetic measurements were carried out on a Cary 16 UV-visible spectrophotometer equipped with an automatic sample changer. The cells were maintained at a constant temperature by means of a thermostated cuvette holder. Time vs. absorbance data were fed directly to a PDP 11/03 computer. The pseudo-first-order rate constants, k_{obsd}, were determined by an interative, nonlinear least-squares computer program.[16] Occasionally the computer-generated rate constant was checked against the slope of a ln $(A_\infty - A_t)$ vs. time plot. Reactions were followed for at least 3 half-lives. With these data the computer program would iteratively fit the rate constant, initial, A_0, and final, A_∞, absorbance. The calculated and observed A_∞ generally agreed to within ±1%.

Reactions were followed by measuring the rate of appearance of the particular phenoxide at its absorbance maximum. In a few cases confirmatory runs were carried out by following the disappearance of the triester. All the hydroxide reactions on the triesters gave good first-order kinetics. Duplicate runs generally agreed within ±3%. Unless otherwise specified, kinetic runs were carried out in 30% dioxane/water (v/v) at

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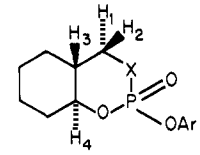
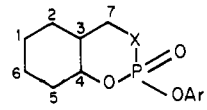
Table I. Selected ^1H and ^{31}P NMR Spectral Parameters for 1a,b–5a,b



compd	chemical shifts			coupling constants						
	δH_1	δH_2	δ_{31P}	J_{12}	J_{13}	J_{23}	J_{1P}	J_{2P}	J_{3P}	J_{4P}
1a[b]	4.13	4.22	−12.56	−10.8	11.1	4.6	0	24.4	0.0	1.0
2a[b]	4.13	4.23	−13.03	−10.8	11.1	4.6	0	24.4	0.0	1.0
3a[b]	4.22	4.35	−13.89	−10.8	11.4	4.4	1.0	24.6	0.0	~0
4a[b]	4.34	4.38	−14.93	−10.5	11.0	4.6	0.5	24.9	0.0	~0
5a[c]	3.02	3.22	−2.59	−12.4	10.7	4.4	2.0	27.9	0.0	~0
1b[b]	4.29	4.33	−10.20	−10.7	11.0	5.0	5.5	18.5	0.0	2.0
2b[b]	4.29	4.33	−10.65	−10.7	11.0	5.0	5.5	18.5	0.0	2.0
3b[b]	4.27	4.36	−11.76	−10.8	12.5	5.0	5.5	18.0	0.0	2.0
4b[b]	4.24	4.49	−14.24	−10.5	10.5	5.2	10.9	11.4	0.0	~0
5b[c]	3.02	3.30	−2.84	−11.0	11.1	5.5	13.6	8.8	0.0	11.5

[a] X = O, 1a,b–4a,b; X = NH, 5a,b. [b] In $CDCl_3$. [c] In acetone-d_6.

Table II. Selected ^{13}C NMR Parameters for 1a,b–5a,b



carbon	^{13}C chemical shifts[a] (^{13}C-^{31}P coupling constants)[b]									
	1a	**2a**	**3a**	**4a**	**5a**	**1b**	**2b**	**3b**	**4b**	**5b**
6	24.05	23.99	23.79	23.92	24.84	23.94	23.92	23.85	23.87	24.53
	(2.44)	(2.44)	(2.65)	(2.44)	(2.44)	(2.44)	(2.45)	(1.95)	(2.45)	(2.92)
1	24.41	24.41	24.12	24.22	25.45	24.35	24.35	24.24	24.17	25.36
2	25.39	25.32	25.13	25.20		25.87	25.87	25.90	26.36	
5	32.55	32.55	32.29	32.44	33.98	32.76	32.76	32.75	32.70	34.17
	(9.76)	(9.76)	(8.84)	(9.77)	(8.55)	(8.54)	(8.54)	(7.82)	(6.10)	(6.84)
3	41.05	41.08	40.82	40.96	42.48	40.68	40.62	40.50	39.35	39.30
	(4.98)	(6.11)	(6.20)	(6.10)	(6.10)	(7.32)	(7.32)	(8.78)	(12.21)	(12.70)
7	73.23	73.30	73.65	74.21	47.43	72.66	72.72	73.19	74.39	47.08
	(7.33)	(7.32)	(7.96)	(7.32)	(2.44)	(6.10)	(6.10)	(6.84)	(7.32)	(0.0)
4	83.80	83.75	84.31	85.02	85.02	82.53	82.65	83.42	85.02	83.66
	(7.32)	(7.32)	(7.07)	(7.33)	(7.33)	(4.88)	(4.89)	(5.86)	(7.33)	(7.82)

[a] ^{13}C chemical shifts in parts per million from Me_4Si ($CDCl_3$, 1a,b–4a,b; acetone-d_6, 5a,b). [b] In hertz.

70.7 °C and ionic strength 1.0 maintained with KCl.

Product Studies. The sodium methoxide attack on the esters was followed by ^{31}P NMR. The concentration of the starting triester was 0.05 M and the concentration of $NaOCH_3$ in CH_3OH was either 0.2 or 0.025 M. The amount of axial/equatorial methoxy ester formed was extrapolated back to zero time. Initially only the axial or equatorial methoxy esters were formed but, if the reaction was followed longer, two ring-opened compounds were observed from further attack of methoxide on the methyl esters. Also only with the 2,4-dinitrophenyl esters the cyclic phosphate anion was formed in about 40% yield. This was assumed to result from methoxide attack at the aromatic carbon of the 2,4-DNP. This was confirmed by isolating the methyl ether of 2,4-dinitrophenol and confirming its identity by ^1H NMR and by GC with the known ether.

The hydrolysis followed by ^{31}P NMR was done in 75% dioxane/water with the concentration of hydroxide 0.1 M and triesters **2a** and **4a** of 0.05 M. No ring-opened products were detected.

Equilibrations were done in 100% DMF with 0.1 M sodium aryloxide and 0.05 M axial triester and separately with the equatorial triester. Both isomers yielded the same equilibrium ratio within the experimental error. Peak integrations were obtained from the Bruker WP-80 spectral printout and confirmed by electronic integration.

Conformational analysis for the phosphorinanes was based largely on the coupling constants in Table I, as described in ref 10. The spectral parameters were obtained by iterative fitting of the ^1H NMR spectra and coupled ^{31}P NMR spectra, using the Bruker Laocoon-type program NMRCAL. The following equations were used in calculating the percent twist-boat conformation:

$$P_{TB} + P_C = 1 \quad (1)$$

$$J^{2P}_{obsd} = J^{2P}_{TB}(P_{TB}) + J^{2P}_{c}(P_c) \quad (2)$$

Table III. ^{31}P NMR Chemical Shift Difference and Percent Twist-Boat

solvent	^{31}P NMR Chemical Shift Difference[a]				
	1b–1a	2b–2a	3b–3a	4b–4a	5b–5a
$CDCl_3$	2.36	2.38	2.13	0.69	−0.25[d]
CH_3OH	1.30	1.27	1.08	0.51	−0.06[d]
	% Twist-Boat				
solvent	1b	2b	3b	4b	5b
$CDCl_3$[b]	50	49	56	100	100[d]
$CDCl_3$[c]	46	46	50	100	
CH_3OH[b]	77	78	84	100	100

[a] ppm, 25 °C. [b] Calculated via shift difference. [c] Calculated via eq 1 and 2. [d] Acetone-d_6.

where J^{2P}_{obsd} is the observed coupling constant for H_2 and phosphorus in Table I. J^{2P}_{c} and J^{2P}_{TB} are the H_2–phosphorus coupling constants for pure chair and twist-boat, respectively. P_{TB} and P_c are fractions of twist-boat and chair conformation, respectively. The J^{2P}_{c} value for the axial ester (assumed 100% chair) was assumed to be the same for the chair equatorial ester. J^{2P}_{TB} is given the value of 11.4 Hz based upon J_{2P} (=11.4 Hz) for **4b** and J_{4P} (=11.5 Hz) for **5b**, which are both believed to be 100% twist-boat. In methanol solution the percent twist-boat was calculated from the difference in chemical shifts in Table III. If the ^{31}P chemical shifts of the **1b–5b** twist-boats (with pseudoaxial ester groups) are assumed to be the same as those of the **1a–5a** chairs (also with axial ester groups), then the total ^{31}P chemical shift difference between the chair forms of the axial and equatorial esters would be 4.0 ppm (using the

Table IV. IR Phosphoryl Stretching Frequencies for 1a,b-5a,b

	a isomer[a]	b isomer[a]	$\Delta\nu$[a]
1	1298	1275	23
2	1303	1276	27
3	1312	1290	22
4	1314	1300	14
5	1272	1258	14

[a] cm^{-1}, $CDCl_3$.

observed ^{31}P chemical shift for **1b–3b** which are 50% boat). This 4.0-ppm difference was used to calculate the percent twist-boat in CH_3OH seen in Table III.

Results and Discussion

Conformational Analysis. Configurational and conformational analysis for epimeric pairs **1a,b–5a,b** is based upon ^{31}P chemical shifts,[17-22] $^3J_{HCOP}$ coupling constants,[23,24] and P=O stretching frequencies[20,21,25] as previously described.[10]

All of the axial isomers, **1a–5a**, are in a chair conformation[10] based upon the single large $^3J_{2P}$ coupling constant (≥24.4 Hz) and small $^3J_{1P}$ and $^3J_{4P}$ coupling constants (~0 Hz) as seen in Table I. Epimer **5b** was shown earlier to be in an unusual twist-boat conformation, **6**, again based upon spectral analysis (see also ref 11–13). Compound **4b** is also in a twist-boat conformation, although a slightly different twist form than **5b** since in the ^{31}P proton coupled NMR spectrum **5b** is a quartet and **4b** is a triplet (J_{4P} is 11.5 Hz in **5b** but ~0 Hz in **4b**, Table I).[26] This is clearly in contrast to the doublet found in the ^{31}P proton coupled spectra for all chair conformations, **1a–5a**. Compounds **1b**, **2b**, and **3b** have intermediate $^3J_{1P}$ and $^3J_{2P}$ coupling constants which indicate that they are mixtures of chair and twist-boat conformations. The precentage of twist-boat conformations was calculated with the ^3J coupling constant data and eq 1 and 2 and the ^{31}P chemical shift data (Experimental Section). As shown in Table III, switching from chloroform to more polar CH_3OH increases the twist-boat population from 50 to about 80% for these compounds. The solvent dependence to the chemical-shift difference between epimers further argues against the previous conclusion that **3b** or **4b** exists in a single flattened chair conformation.[10]

The infrared spectra of these compounds also supports the twist-boat/chair equilibrium for **1b**, **2b**, and **3b** and twist-boat conformation for **4b** and **5b**. Generally the IR stretch of an axial phosphoryl bond is 20–30 cm^{-1} smaller than that of an equational P=O bond.[10,20,21,25] The difference in the phosphoryl stretching frequency is much smaller between epimeric pairs **4a/4b** and **5a/5b** (14 cm^{-1}) than between epimeric pairs **1a/1b**, **2a/2b**, and **3a/3b**. This is to be expected since as **4b** or **5b** flips into a boat conformation the aryloxy substituent becomes pseudoaxial and the phosphoryl oxygen becomes equatorial. Thus in both chair **4a** and **5a** and twist-boat **4b** and **5b** the P=O bond is equatorial or pseudoequatorial (and hence has similar P=O stretching). In addition the phosphoryl IR signals for **1b**, **2b**, and **3b** are much broader than the peaks for **1a**, **2a**, and **3a**. This suggests that the P=O stretching signal is a partially overlapping superposition of an axial P=O bond stretch (from the chair conformation for **1b–3b**) and an equatorial P=O bond stretch (from the twist-boat conformation for **1b–3b**).

Table V. Summary of Hydrolysis, Equilibration, and Stereochemistry of Reaction for Phosphorinanes **1–5**

		1	2	3	4	5
Ar =		*p*-MeOPh	Ph	PNP	2,4-DNP	PNP
hydrolysis:						
$\Delta(\Delta G^{\ddagger})$, kcal/mol		1.08	1.17	1.47	1.44	0.75
A,B $\xrightarrow[OH^-]{}$		(1.37)			(1.67)	
70 °C, 30% dioxane[a]						
equilibration:						
$\Delta(\Delta G_0)$, kcal/mol						
A $\rightleftharpoons$ B, ArO^-		1.81	1.73	1.95	1.85	1.45
					(1.85)[b]	
100% DMF, 30 °C						
stereochemistry:						
% inversion	B:	9	4	73	100	100
A,B $\xrightarrow[CH_3O^-]{}$	A:	28	24	17	83	67
25 °C, $HOCH_3$						

[a] Values in parentheses at 25 °C. [b] In 75% dioxane/water, 30 °C.

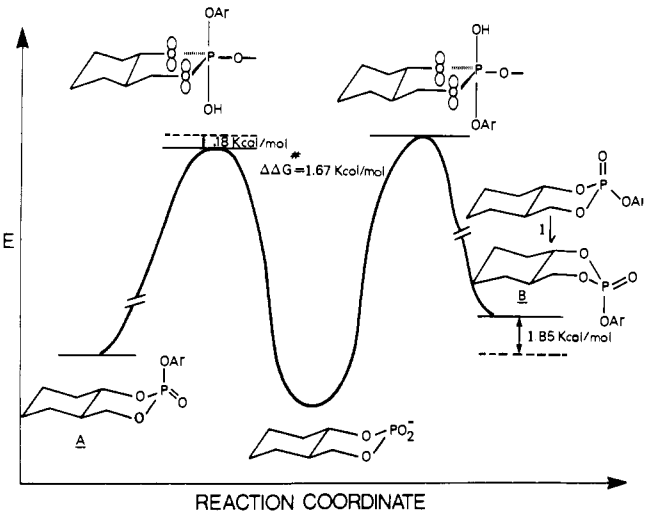


Figure 1. Reaction diagram for hydrolysis of epimeric phosphorinanes.

The ^{13}C NMR spectra are also consistent with the above conformational analysis (Table II). In flipping from a chair to a boat the $C_5–C_4–O–P$ torsional angle changes from trans to gauche. In **1a–4a** the carbon–phosphorus coupling constant $^3J_{5P}$ is 8.8–9.8 Hz (trans) while in **4b** $^3J_{5P}$ is 6.1 Hz (gauche). In **1b–3b** $^3J_{5P}$ is intermediate (7.8–8.5 Hz), consistent with the rapid equilibration between chair and boat conformations.

Three-bond coupling to carbon 3 (via $C_3–C_4–O–P$ or $C_3–C_7–O–P$) is small (5–6.2 Hz) in **1a–4a** since in the chair conformation C_3C_4OP and C_3C_7OP torsional angles are gauche (note the similarity between $^3J_{5P}$ in boat **4b** and $^3J_{3P}$ in chair **1a–4a**: ~6 Hz). In one of the twist-boat forms C_3C_4OP or C_3C_7OP torsional angles are more trans-like and in **4b** $^3J_{3P}$ is very large, 12.2 Hz. In **1b–3b**, $^3J_{3P}$ is 7.3–8.8 Hz, indicating both trans and gauche coupling patterns.

Equilibrium and Relative Rates of Hydrolysis. As shown in Table V, the difference in the free energy of activation for the hydroxide-catalyzed hydrolysis for the epimeric pairs **1a,b–5a,b** only varies from 0.75 to 1.47 kcal/mol at 70 °C in 30% dioxane. Isomer **b** thus always reacts *faster* by a factor of only 3–9 (22 for **4b** at 30 °C), which is in the *opposite* direction than required by the stereoelectronic theory. However, analysis of the ^{31}P NMR

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(26) The quartet would arise in **5b** from the aryloxy substituent flipping pseudoaxial to make ~120° bond angles with H1, H2, and H4 so that $J_{1P} \approx J_{2P} \approx J_{4P} \approx 11$ Hz. The triplet would arise from flipping the ring oxygen rather than phosphorus. This still puts the aryloxy group pseudoaxial but the boat is much more twisted.

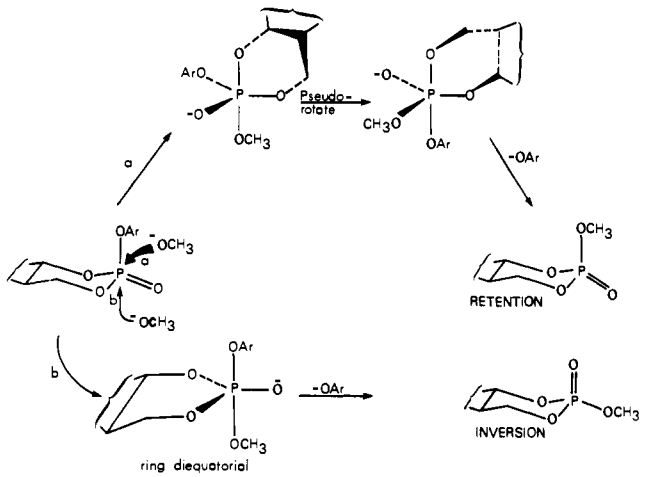
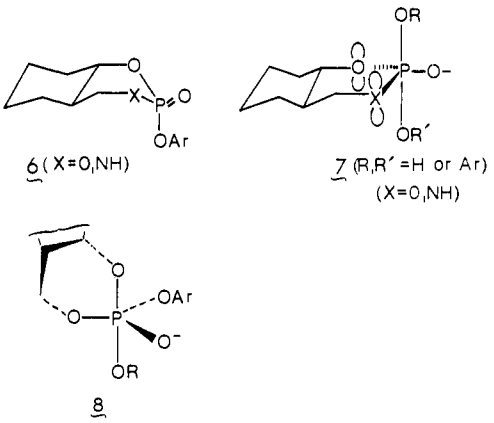


Figure 2. Reaction paths for methanolysis of axial phosphorinane esters.

spectra of the phosphorinanes after equilibration with the appropriate aryloxide in 100% DMF, 30 °C, shows that the **b** isomers are 1.45 (for **4b**) to 1.95 (for **3b**) kcal/mol higher in energy than the corresponding axial isomers (Table V). This result is consistent with the expected anomeric effect[27,28] at phosphorus.[17-19] It also provides an explanation for the unusual stabilization of the twist-boat conformation for the **b** isomers. Thus by flipping from the chair conformation to the twist-boat conformation **6** the chair equatorial ester bond in **4b** and **5b** moves into a pseudoaxial position. This conformation represents a balance between the anomeric effect favoring the axial orientation in the twist-boat and the 1,3-steric and eclipsing interactions favoring the chair conformation. The faster hydrolysis for the **b** isomers can now be entirely explained by ground-state destabilization. (Although reaction conditions are different for equilibration and hydrolysis, solvent effects are not expected to greatly alter the $\Delta\Delta G^\circ$ and $\Delta\Delta G^\ddagger$ values in Table V.)[29] In fact as shown in Figure 1 the difference in the transition-state energies for the hydrolysis of the 2,4-DNP epimers is less than 0.2 kcal/mol.[29] This suggests that both epimers of **1** have similar transition-state geometries: likely a half-chair, diequatorial ring trigonal bipyramid **7**. The p orbitals on the endocyclic oxygens can most effectively overlap with the apical phosphorus p orbital and both incoming nucleophile and leaving groups, and it avoids the difficulty of requiring a different orientation for the basal groups (producing app lone pair interactions) for different bond-making and -breaking transition states.[7-9]

Stereochemistry of Displacement. The observed 100% inversion for **4b** in the methoxide displacement reaction (analyzed via ^{31}P NMR of methoxyphosphorinane products) supports the above model for the transition state. However, epimer **4a** goes with 83% inversion, and thus a second pathway for reaction is also occurring as shown in Figure 2. Observation of retention of configuration for a reaction at phosphorus has been interpreted in terms of a mechanism (path b, Figure 2) involving formation of a trigonal-bipyramidal intermediate **8** with attacking and leaving groups in apical and equatorial sites.[30,32] Pseudorotation[31] then allows the equatorial aryloxy group to leave from the preferred apical position. In fact except for **3b** all of the other aryloxy esters of the dioxaphosphorinanes react with predominant retention of configuration. This is consistent with the relative apicophilicities



of the aryl esters since the more electronegative oxygen (of 2,4-DNP and PNP relative to a ring oxygen) will prefer an apical site in **7**.[30-33] The complete inversion observed for the **4b** epimer could be a steric effect since the boat conformation is much more open for backside attack than is the axial chair conformation.

The strong apicophilicities of these aryl esters must provide sufficient energy to overcome the diequatorial ring strain in **7**. The preferred 120° O–P–O bond angle in the basal sites must in turn stabilize the half-chair conformation for the six-membered ring. The similarity in rate for the two epimers is consistent with the suggestion that both react via a similar late transition state **7** involving substantial ring strain in the half-chair. Since retention competes with inversion the transition state with the six-membered ring spanning apical and equatorial sites (**8**) is also similar in energy to **7**. While **7** is stereoelectronically preferred to a transition state **8** with an apical/equatorial ring, the two nonring basal oxygens can still provide two app lone pairs to the translating apical bond,[2] thus avoiding a violation of the stereoelectronic rule.

Finally, the 100% inversion of configuration for methoxide displacement in the oxazaphosphorinane **5b** and predominant (67%) inversion in the axial epimer **5a** suggest that these compounds react via a similar $S_N2(P)$ associative mechanism as the dioxaphosphorinanes **1–4**. Stereochemical and rate-acceleration arguments have previously been used to show that phosphoramidates can also react in strong base via a dissociative $S_N1(P)$ monomeric metaphosphoramidate mechanism.[30,34] This $S_N1(P)$ mechanism would likely not be important in the hydrolysis reaction as well. The slightly faster rate of hydrolysis for **5b** relative to **5a** (Table V) also must then be due to ground-state destabilization in **5b**. The transition states for hydrolysis of **5a** and **5b** must be of similar energy and likely are related to the half-chair, diequatorial ring trigonal bipyramid **7**.[35]

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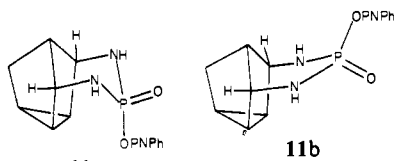

11a **11b**