obscured; MS (DCI positive ion) m/e 1952 (M^+, 100%), 1866 (empty **7**, 50%); MS (DCI negative ion) m/e 1952 (M^-, 100%). Anal. Calcd for $C_{117}H_{142}S_4O_{17}$ (dried at 150 °C, 10^{-5} Torr, 6 h): C, 71.97; H, 7.54; S, 6.57; O, 13.93. Found: C, 71.91; H, 7.67; S, 6.49; O, 13.74; sum, 99.81.

Carceplex 4 ($H{\cdot}CH_3CH_2OH$). Cesium carbonate (1.2 g, 3.5 mmol) was dissolved in 100 mL of ethanol and 200 mL of benzene at reflux. Tetrathiol **21** (0.35 g, 0.35 mmol) and tetrachloride **19** (0.35 g, 0.35 mmol) in 100 mL of benzene were added dropwise over 24 h via a constant-rate addition funnel to the mixture stirred at reflux. The mixture was refluxed for an additional 24 h, and the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$–H_2O, and the organic layer was concentrated under reduced pressure. Chromatography of the residue on silica gel with 50% pentane in $CHCl_3$ as the mobile phase gave 0.13 g (20%) of **4**: ^1H NMR (360 MHz, $CDCl_3$) δ −3.33 (t, 1 H, CH_3CH_2OH), −1.18 (t, 3 H, CH_3CH_2OH), 0.59 (m, 2 H, CH_3CH_2OH), 0.91 (t, 24 H, CH_3), 1.34 (m, 48 H, $CH_2CH_2CH_2$), 2.18 (m, 16 H, CH_2 α to methine), 3.86 (s, 16 H, $(CH_2)_2S$), 4.47 (d, 8 H, inner OCH_2), 4.71 (t, 8 H, methine), 5.87 (d, 8 H, outer OCH_2), 7.03 (s, 8 H, ArH); MS (DCI positive ion) m/e 1913 ($M + H^+$, 100%), 1866 (empty **4**, 20%); MS (DCI negative ion) m/e 1912 (M^-, 100%), 1866 (empty **4**, 30%). Anal. Calcd for $C_{114}H_{142}S_4O_{17}$ (dried at 150 °C, 10^{-5} Torr, 6 h): C, 71.59; H, 7.48; S, 6.69; O, 14.22. Found: C, 71.97; H, 7.12; S, 6.46; O, 14.45; sum 100.02%.

Carceplex 5 ($H{\cdot}(CH_3)_2NCHO$). Rubidium carbonate (1.2 g, 4.5 mmol) was dissolved in 200 mL of degassed $(CH_3)_2NCHO$ at 80 °C. Tetrathiol **21** (0.35 g, 0.35 mmol) and tetrachloride **19** (0.35 g, 0.35 mmol) in 200 mL of $(CH_3)_2NCHO$ were added dropwise over 24 h via a constant-rate addition funnel. The mixture was stirred for an additional 24 h, and the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$–H_2O, and the organic layer was concentrated under reduced pressure. Chromatography of the residue on silica gel with 50% pentane in $CHCl_3$ yielded 0.14 g (20%) of **5**: ^1H NMR (360 MHz, $CDCl_3$) δ −0.33 (s, 3 H, CH_3NCH_3CHO), −0.10 (s, 3 H, CH_3NCH_3CHO), 0.89 (t, 24 H, CH_3), 1.32 (m, 48 H, $CH_2CH_2CH_2$), 2.18 (m, 16 H, CH_2 alpha to methine), 3.85 (s, 16 H, $(CH_2)_2S$), 4.47 (d, 8 H, inner OCH_2), 4.87 (t, 8 H, methine), 5.78 (s, 1 H, $(CH_3)_2NCHO$), 5.87 (d, 8 H, outer OCH_2), 7.03 (s, 8 H, ArH); MS (DCI positive ion) m/e 1939 (M^+, 100%), 1866 (empty **5**, 45%); MS (DCI negative ion) m/e 1939 (M^-, 100%), 1867 (empty **5**, 30%). Anal. Calcd for $C_{115}H_{143}NS_4O_{17}$ (dried at 150 °C, 10^{-5} Torr, 6 h): C, 71.22; H, 7.43; N, 0.72; S, 6.60; O, 14.03. Found: C, 71.41; H, 7.08; N, 0.92; S, 6.58; O, 14.24; sum 100.24.

Carceplex 1 ($H{\cdot}CH_3OH{\cdot}HOCH_3$). Rubidium carbonate (1.0 g, 4.3 mmol) was dissolved in 200 mL of methanol and 100 mL of benzene at reflux. Tetrathiol **20** (0.35 g, 0.35 mmol) and tetrachloride **18** (0.35 g, 0.35 mmol) in 100 mL of benzene were added dropwise to the stirred refluxing mixture over 24 h via a constant-rate addition funnel. The mixture was refluxed for an additional 24 h, and the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$–H_2O, and the organic layer was concentrated under reduced pressure. Chromatography of the residue on silica gel with 50% pentane in $CHCl_3$ as the mobile phase yielded 0.17 g (22%) of **1**: ^1H NMR (360 MHz, $CDCl_3$) δ −0.75 (d, 6 H, CH_3OH), −0.72 (d, 2 H, CH_3OH), 2.50–2.75 (m, 32 H, CH_2CH_2), 3.86 (s, 16 H, CH_2SH), 4.45 (d, 8 H, inner OCH_2), 4.75 (t, 8 H, methine), 5.96 (d, 8 H, outer OCH_2), 7.11–7.35 (m, 48 H, ArH); MS (DCI positive ion) m/e 2203 ($M + H^+$, 100%), 2171 ($M + H^+ - CH_3OH$, 75%), 2139 (empty **1** + H^+, 20%); MS (DCI negative ion) m/e 2202 (M^-, 100%), 2170 ($M^- - CH_3OH$, <10%), 2139 (empty carcerand, 20%). Anal. Calcd for $C_{138}H_{128}S_4O_{18}$ (dried at 150 °C, 10^{-5} Torr, 6 h): C, 75.24; H, 5.85; S, 5.83; O, 13.07. Found: C, 75.01; H, 5.97; S, 5.88; O, 13.13; sum, 99.99.

Carceplex 3 ($H{\cdot}CH_3CN$). Rubidium carbonate (1.0 g, 4.3 mmol) was dissolved in 200 mL of acetonitrile and 100 mL of benzene at reflux. Tetrathiol **21** (0.35 g, 0.35 mmol) and tetrachloride **19** (0.35 g, 0.35 mmol) in 100 mL of benzene were added dropwise over 24 h via a constant-rate addition funnel. The mixture was refluxed for an additional 24 h, and the solvent was evaporated in vacuo. The residue was extracted with $CHCl_3$–H_2O, and the organic layer was concentrated under reduced pressure. Chromatography of the residue on silica gel with 50% pentane in $CHCl_3$ yielded a mixture of **3** ($H{\cdot}CH_3CN$) and **2** ($H{\cdot}CH_3CN{\cdot}NCCH_3$) in 1:1.2 proportions, respectively, by proton counting of $H{\cdot}CH_3CN$ at δ −1.64 due to **3** and $H{\cdot}CH_3CN{\cdot}NCCH_3$ at δ −2.15 due to **2** (^1H NMR spectra in $CDCl_3$ at 25 °C). The mixture was dissolved in toluene and refluxed for 72 h during which time the 1:2 complex was converted to 0.19 g (25%) of the 1:1 carceplex (**3**) that was characterized: ^1H NMR (360 MHz, $CDCl_3$) δ −1.64 (s, 3 H CH_3CN), 2.50–2.75 (m, 32 H, CH_2CH_2), 3.86 (s, 16 H, $(CH_2)_2SH$), 4.45 (d, 8 H, inner OCH_2), 4.75 (t, 8 H, methine), 5.96 (d, 8 H, outer OCH_2), 7.11–7.35 (m, 48 H, ArH); MS (DCI positive ion) m/e 2180 ($M + H^+$, 100%) 2139 ($M + H^+ - CH_3CN$, 50%); MS (DCI negative ion) m/e 2179 (M^-, 50%), 2139 ($M^- + H - CH_3CN$, 50%). Anal. Calcd for $C_{138}H_{123}NS_4O_{16}$ (dried at 150 °C, 10^{-5} Torr, 6 h): C, 76.06; H, 5.69; N, 0.64; S, 5.87; O, 11.74. Found: C, 75.92; H, 5.88; N, 0.61; S, 5.72; O, 11.62; sum, 99.75.

Rates of Decomplexation of 2 To Give 3. A 3-mmol solution of **2** was prepared by dissolving the carceplex in tetrachloroethane-d_2. Samples of this solution were placed in NMR tubes, and the tubes were immersed in a thermostated oil bath (±1 °C) at 353 and 363 K. Spectra (^1H NMR) were recorded at 298 K. A series of 7–10 spectra were obtained over a 40-h period. The kinetic data at 373 and 383 K were derived from a series of spectra taken over 15- and 6-h periods, respectively. The experiments at 373 and 383 K were performed on a Bruker AM 500-MHz spectrometer equipped with a variable-temperature probe regulated to within ±1 °C of the desired temperature. The probe temperature was calibrated with an ethylene glycol standard. Spectra at 373 and 383 K were obtained via an automated data acquisition program, which recorded spectra at prescribed time intervals. The relative concentrations ([**2**]:[**3**]) in all experiments were calculated from the integrals of the distinct singlets unique to each species.

Use of ^{17}O NMR in a Stereochemical Study of the Alkaline Hydrolysis of Cyclic Six-Membered 2-Aryl Phosphates

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Abstract: The alkaline hydrolysis of the title compounds **1–5** (Chart II) with $^{17}OH^-$ has been studied. The labeled cyclic phosphate salts produced by hydrolysis of **1–5** were converted to a mixture of the corresponding methyl esters **9** (Scheme III) by treatment with diazomethane. The resulting mixture was analyzed by ^{31}P NMR or GC for the epimeric OCH_3 ratio and by ^{17}O NMR for the ^{17}O axial to equatorial ratio in the $P{=}^{17}O$ moiety. Nucleophilic displacement of ArO^- by $^{17}OH^-$ at phosphorus is nonstereospecific. The results can be rationalized by postulating that the direct displacement process involving inversion competes with pseudorotation of pentacoordinate intermediates involving retention.

Several years ago, we described[1] the use of ^{17}O NMR as a tool in the assignment of configuration of cyclic phosphates. In conformationally locked systems (Chart I) the axial phosphoryl oxygen nucleus is shifted downfield from the equatorial one by

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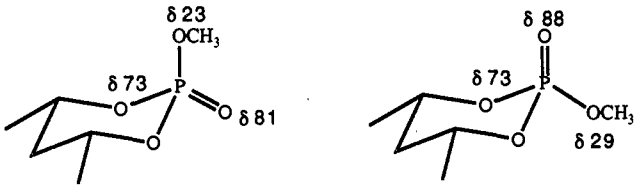
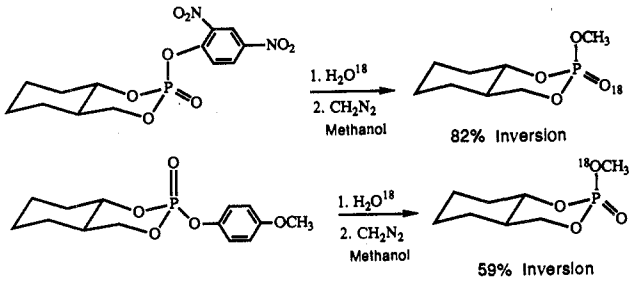
Chart I



Scheme I



~7 ppm, whereas axial OCH_3 in the ester oxygen resonates upfield of the equatorial OCH_3 as expected.[2]

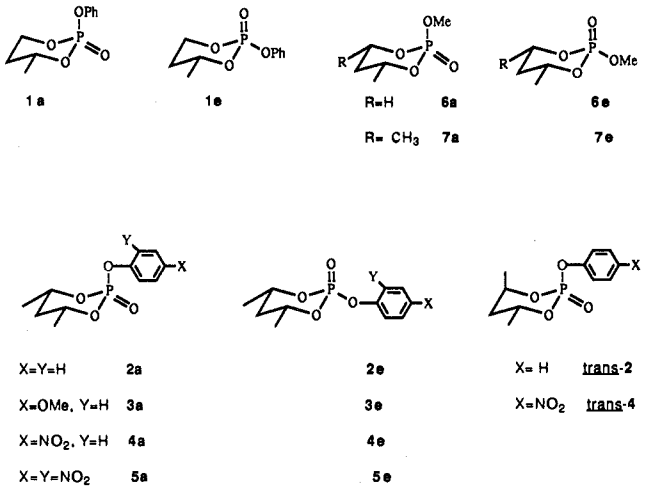
In view of the availability of high-field NMR instruments,[3] lack of reproducibility of spectroscopic parameters in ^{17}O NMR and lack of sensitivity[4] are no longer a handicap in such determinations. This fact and the well-known role of cyclic phosphates in biological functions as exemplified by cAMP (adenosine 5′-monophosphate) and cGMP (guanosine monophosphate), which are mediators of cell metabolism,[5] prompted us to study the stereochemistry of the hydrolysis of such phosphate esters using ^{17}O NMR spectroscopy.

The stereochemistry of hydrolysis of cyclic *trans*-decalin phosphates by $H_2{}^{18}O$ had previously been examined (Scheme I) by use of isotopically (^{18}O) shifted ^{31}P satellites as a probe to analyze the products.[6a] Only a preliminary report involving the two compounds shown in Scheme I has been published,[6a] though a more extensive study involving transesterification of these aryl esters with methoxide is available.[6b,c]

The results depicted in Scheme I suggest that the substituent in the aromatic ring may modify the mechanism of the reaction. However, the fact that an axial ester was used in one case and an equatorial one in the other complicates the interpretation.

In this report, we present ^{17}O NMR results of the basic hydrolysis of anancomeric 2-(aryloxy)-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinanes (**2**–**5**) (Chart II) with $H_2{}^{17}O$.[1b] The aryloxy (OAr) entity was varied by use of nitro or methoxy substituents to assess the importance of stereoelectronic effects in the reaction. Also, results for the hydrolysis of the anancomeric *cis*-**2** esters were compared with those for the potentially conformationally heterogeneous lower homologue **1**.[7]

Chart II[a]



[a] Cis/trans nomenclature is used in this work to denote the disposition of the methyl groups at $C_{4,6}$ of the phosphate ring; axial/equatorial (**a**/**e**) to denote the disposition of the OAr group.

Experimental Section

Materials and Chromatography. Phenyl dichlorophosphate, *p*-nitrophenyl phosphorodichloridate, and ethylene glycol dimethyl ether were purchased from Aldrich and used as received. Triethylamine was distilled before use. Hydrolysis was conducted with water containing ^{17}O, 15% (CIL) containing a similar amount of ^{18}O isotope. GC was performed on a 6-ft (30% SE 30/Chromosorb P) column at 190 °C. Thus, for example, peaks of 3.12- and 2.44-min retention time corresponded to the epimeric axial and equatorial OMe compounds (**7a**,**7b**), as shown by calibration with authentic samples.[8] Melting points are uncorrected.

Spectral Analyses. ^1H NMR spectra were recorded at 250 MHz and carbon-13 and phosphorus-31 spectra at 62.9 MHz and 101.26 MHz, respectively. ^{31}P shifts are reported in δ upfield (−) from external 85% H_3PO_4. ^{17}O NMR spectra were obtained by use of a Bruker MSL 360 wide-bore spectrometer operating at 48.82 MHz in FT mode, without lock. The irradiating frequency was placed in the middle of the spectrum in the "quadrature detection" method for improving the signal to noise ratio,[3] and a spin-echo pulse sequence was used (94–100-ms delay). The spectral width was 20–40 kHz with 1000–4000 data points, 20–60-ms acquisition time, and 200-μs acquisition delay. Samples of natural ^{17}O abundance were 0.5–1.0 M solutions and labeled ^{17}O-containing mixtures were 0.05–0.1 M, both in solvent toluene (distilled from CaH_2) in 10-mm tubes, heated at 100 °C. Tap water was used as external reference at the same temperature.

Syntheses. Cyclic phosphates **1**[9,6b] and **2**[9,6b] were synthesized according to literature procedure with use of phenyl dichlorophosphate and the corresponding diols. Products were purified by flash column chromatography[10] (elution with 40/60 *n*-hexanes/ethyl acetate) and characterized by ^1H, ^{13}C, and ^{31}P NMR spectra, which were identical, within experimental limits, with published values.

2-(*p*-Nitrophenoxy)-2-oxo-4,6-dimethyl-1,3,2λ^5)-dioxaphosphorinane (4). A solution of 6.25 g (60 mmol) of a mixture of *meso*- and *d,l*-2,4-pentanediol and 17.1 mL of triethylamine in 75 mL of CH_2Cl_2 was added dropwise to a solution of 17.92 g (70 mmol) of *p*-nitrophenyl phosphorodichloridate in 120 mL of CH_2Cl_2 at 0 °C under argon. The mixture was stirred at room temperature overnight, washed three times with 300 mL of water, and dried over $CaCl_2$. It was then filtered and the solvent removed in a rotary evaporator; crude yield 13.65 g (79.4%). Flash column chromatographic separation (elution with 50/50 *n*-hexanes/ethyl acetate) of 8.0 g of crude product afforded axial **4a** (2.38 g, 29.8%) as colorless crystals (mp 124–125 °C, from *n*-hexanes), which was eluted first, followed by *trans*-**4** (3.30 g, 41.3%; mp 88–89 °C) and equatorial **4e** (1.78 g, 22.3%; colorless prism; mp 78–79 °C (from *n*-hexanes)).

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4a: IR (KBr) 2991 (w), 2937 (w), 1593 (m), 1520 (m), 1489 (m), 1344 (s), 1308 (s), 1236 (s), 1084 (m), 987 (s), 921 (s) cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) δ 1.44 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.7 Hz, 6 H, CH_3's at C_4 and C_6), 1.83 (~dt, J_{gem} = 14.7 Hz, J_{anti} = 11.1 Hz, 1 H, H_5 ax.), 1.95 (dq, J_{gem} = 14.5 Hz, J_{gauche} = 2.6 Hz, 1 H, H_5 eq), 4.73 (m, 2 H, $H_{4,6}$), 7.43 (~d, J = 9.2 Hz, 2 H, H_{arom}), 8.24 (~d, J = 9.3 Hz, 2 H, H_{arom}).

***trans*-4**: IR (KBr) 3124 (w), 2985 (w), 2937 (w), 1617 (m), 1593 (m), 1520 (s), 1490 (m), 1351 (s), 1308 (s), 1284 (s), 1223 (s), 1168 (w), 1114 (m), 1084 (s), 981 (s), 909 (s) cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) δ 1.49 (dd, J_{HCCH} = 6.3 Hz, J_{HCCOP} = 2.4 Hz, 3 H, eq CH_3 at C_4 or C_6), 1.53 (d, J_{HCCH} = 7.4 Hz, 3 H, ax. CH_3 at C_4 or C_6), 1.89 (dm, J_{gem} = 14.5 Hz, 1 H, H_5 eq), 1.92 (m, 1 H, H_5 ax.), 4.91 (m, 2 H, $H_{4,6}$), 7.40 (dd, J = 9.2 Hz, J = 0.7 Hz, 2 H, H_{arom}), 8.25 (~d, J = 9.0 Hz, 2 H, H_{arom}).

4e: IR (KBr) 3119 (w), 2985 (m), 2937 (w), 2913 (w), 1617 (m), 1593 (m), 1514 (s), 1490 (m), 1393 (m), 1351 (s), 1278 (s), 1241 (m), 1235 (m), 1169 (m), 1108 (m), 1078 (m), 993 (s), 963 (s), 933 (s), 902 (m) cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) δ 1.42 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.3 Hz, 6 H, CH_3's at C_4 and C_6), 1.80 (dt, J_{gem} = 14.7 Hz, J_{anti} = 11.3 Hz, 1 H, H_5 ax.), 1.95 (dq, J_{gem} = 14.7 Hz, J_{gauche} = 2.7 Hz, 1 H, H_5 eq), 4.82 (m, 2 H, $H_{4,6}$), 7.37 (dd J = 8.2 Hz, J = 1.0 Hz, 2 H, H_{arom}), 8.23 (d, J = 8.8 Hz, 2 H, H_{arom}).

Anal. Calcd for $C_{11}H_{14}NO_6P$: C, 45.98; H, 4.92. Found: **4a**, C, 46.06; H, 5.09; *trans*-**4**, C, 46.16; H, 5.00; **4e**, C, 46.04, H, 4.94.

2-Chloro-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane. This compound was prepared by reaction between *meso*-2,4-pentanediol[11] and phosphorus oxychloride following a procedure described previously.[12]

2-(*p*-Methoxyphenoxy)-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane (3a, 3e). Solid sodium *p*-methoxyphenoxide[13] (3.17 g, 21.7 mmol) was added in portions to a solution of 4 g (21.7 mmol) of crude 2-chloro-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane in 20 mL of dry toluene at 90 °C. After the reaction mixture was stirred for 10 min, the precipitated NaCl was filtered and the filtrate concentrated to leave a residue that contained **3a**/**3e** in a proportion of ca. 2/1.[14] Flash chromatography (elution with 70/30 *n*-hexanes/ethyl acetate) resulted in 2.47 g (42%) of a white solid, axial **3a**, obtained as tiny needles after recrystallization from *n*-hexanes (mp 77–78 °C), and a yellow liquid, equatorial **3e** (1.62 g, 27.5%).

3a: IR (KBr) 2985 (w), 2925 (w), 2834 (w), 1508 (m), 1387 (w), 1308 (m), 1290 (m), 1205 (m), 981 (s) cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) δ 1.41 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.6 Hz, 6 H, CH_3's at C_4 and C_6), 1.82 (m, 2 H, H_5), 3.76 (s, 3 H, OCH_3), 4.67 (m, J_{gauche} = 2.8 Hz, 2 H, $H_{4,6}$), 6.65 (d, J = 9.0 Hz, 2 H, H_{arom}), 7.16 (d, J = 9.2 Hz, 2 H, H_{arom}). Anal. Calcd for $C_{12}H_{17}O_5P$: C, 52.93; H, 6.30. Found: C, 52.76; H, 6.40.

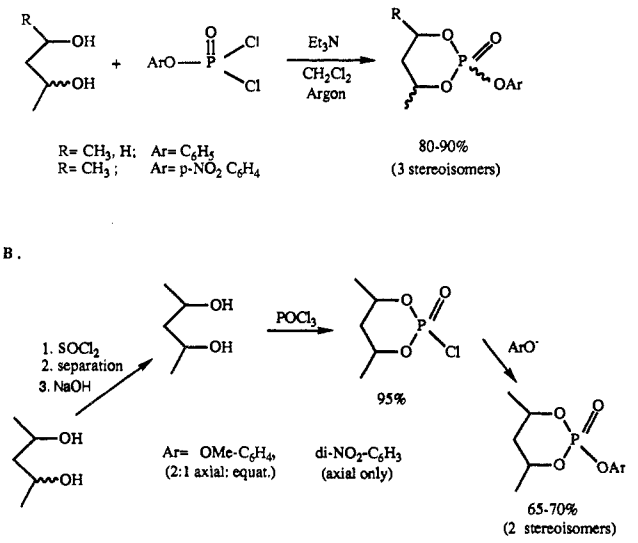
3e: IR (neat) 2985 (m), 2937 (m), 1508 (s), 1448 (m), 1381 (m), 1351 (w), 1284 (w), 1254 (s), 1205 (s), 1096 (s), 999 (s) cm^{-1}. ^1H NMR (250 MHz) ($CDCl_3$) δ 1.36 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.3 HZ, 1 H, H_5 ax.), 1.61 (dt, J_{gem} = 14.6 Hz, J_{anti} = 11.4 Hz, 1 H, H_5 ax.), 1.84 (dq, J_{gauche} = 2.5 Hz, J_{gem} = 14.6 Hz, 1 H, H_5 eq), 3.77 (s, 3 H, OCH_3), 4.74 (m, 2 H, $H_{4,6}$), 6.80 (~d, J = 8.9 Hz, 2 H, H_{arom}), 7.12 (~dd, J = 9.1 Hz, J = 2.5 Hz, 2 H, H_{arom}). MS *m/e* 272 (M^+).

2-(2,4-Dinitrophenoxy)-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane (5a). Solid sodium 2,4-dinitrophenoxide[13] (4.5 g, 21.7 mmol) was added in one portion to a solution of 4.0 g (21.7 mmol) of crude 2-chloro-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane in dry toluene at 90 °C, and the reaction mixture was stirred for an additional 5 min, filtered, and concentrated. The residue was separated by flash column chromatography (eluent: 50/50 *n*-hexanes/ethyl acetate), and the portions obtained were separately washed three times (each) with a cold 10% sodium carbonate solution (to remove the 2,4-dinitrophenol and the 2-hydroxy-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane formed through partial hydrolysis of the products during elution), extracted with diethyl ether, and concentrated. Recrystallization of the first portion afforded pale yellow crystals (mp 129–130 °C (from petroleum ether), 2.16 g 30.1%) of axial **5a**. Isomer **5b** was not obtained.[15]

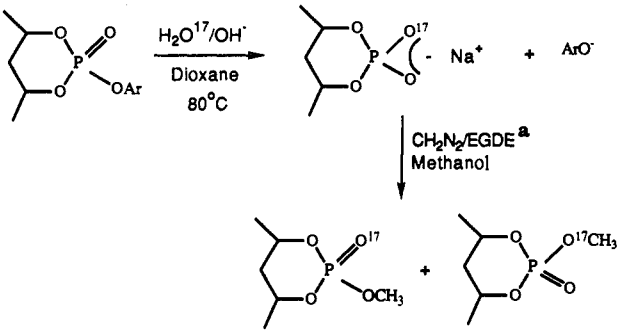
5a: IR (KBr) 3100 (w), 2991 (w), 2943 (w), 1611 (m), 1538 (s), 1478 (w), 1393 (w), 1344 (s), 1308 (s), 1266 (m), 1175 (w), 1078 (m), 1066 9m), 1011 (m), 993 (s) cm^{-1}. ^1H (250 MHz) ($CDCl_3$) δ 1.45 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.8 Hz), 6 H, CH_3's at C_4 and C_6), 1.86 (dt, J_{gem} = 14.8 Hz, J_{anti} = 10.9 Hz, 1 H, H_5 ax.), 1.99 (dq, J_{gem} = 14.8 Hz, J_{gauche} = 2.6 Hz, 1 H, H_5 eq), 4.85 (m, 2 H, $H_{4,6}$), 8.13 (dd, J = 9.2 Hz, J = 0.8 Hz, 1 H, H_{arom}), 8.47 (dd, J = 9.3 Hz, J = 2.8 Hz, 1 H, H_{arom}), 8.82 (dd, J = 2.75 Hz, J = 1.2 Hz, 1 H, H_{arom}). Anal. Calcd for $C_{11}H_{13}N_2O_8P$: C, 39.75; H, 3.95. Found: C, 40.16; H, 4.11.

Phosphate Hydrolysis and Esterification.[16] To a solution of 0.44 mmol of phosphate ester (**1**–**5**) in 3.5 mL of 1,4-dioxane was added 1.0 mL of 15% $H_2{}^{17}O$ and 60 mg (1.5 mmol) of NaOH. The mixture was stirred in a stoppered flask at 80 °C for 10–14 h.[17] The mixture of $H_2{}^{17}O$/dioxane was removed (and recovered) by sublimation (actually distillation in a sublimation apparatus with the distillate being frozen out on a cold finger) at atmospheric pressure. Water (4 mL) was added to the residue followed by concentrated aqueous HCl to acidify the solution to pH 2. Extraction of the solution with use of methylene chloride led to removal of the ArOH formed. Sodium hydroxide was added to the inorganic layer to reach a pH of 6–8,[18] and water was again removed by sublimation. The resultant salt was diluted with 5.0 mL of methanol, filtered, and cooled at 0 °C. A freshly prepared solution of diazomethane[19,20] was added rapidly to the methanol solution, which was

Scheme II



Scheme III



[a] Ethylene glycol dimethyl ether.

(11) *meso*-Pentanediol was obtained from a commercial ~1:1 mixture of meso + *d,l* alcohols following the procedure described by: Pritchard, J. G.; Vollmer, R. L. *J. Org. Chem.* **1963**, *28*, 1545. (Cyclic sulfites were separated in a Kontes spinning band column at 15 mmHg.)

(12) (a) See ref 1. (b) Edmundson, R. S. *Tetrahedron* **1965**, *21*, 2379.

(13) The sodium phenoxide salt was prepared by the addition of NaOH to a suspension of the parent phenol and water at room temperature. The reaction is complete when a solution is formed; the water is then removed in a rotary evaporator and the salt dried in a drying pistol.

(14) A longer reaction time led to a substantial amount of a side product, which was identified by ^{31}P (δ –21.9), ^{13}C (δ 21.87 (CH_3)C, 40.18 (C_5) 77.64 ($C_{4,6}$)), and ^1H NMR (δ 1.42 (dt, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 1.3 Hz, 12 H, CH_3's at C_4 and C_6), 1.75 (dt, J_{gem} = 14.7 Hz, J_{anti} = 11.1 Hz, 2 H, H_5 ax.), 1.85 (dm, J_{gem} = 2.7 Hz, 2 H, H_5 eq), 4.90 (m, 4 H, $H_{4,6}$)) spectroscopy as the dimeric pyrophosphate, i.e., anhydride of 2-hydroxy-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane; mp 182–184 °C. Anal. Calcd for $C_{10}H_{20}O_7P_2$: C, 38.21, H, 6.42. Found: C, 38.41; H, 6.42.

(15) Equatorial dinitrophosphorinane was not obtained even at –10 °C in THF with use of lithium phenoxide salt.

(16) A similar procedure was used in the hydrolysis of analogous phosphate esters.[6a]

(17) A reaction time of 65 h was required for the hydrolysis of *cis*-**3**.

(18) The yield in methylation reactions of the salt was increased with the pH (20 → 53%). However, pH >8 also resulted in a large amount of by-products.

Table I. Chemical Shifts in ^{17}O NMR Spectra[a] of 2-Aryl Phosphates in Toluene at 100 °C

compd	O_1	O_3	P=O	OAr	OMe	NO_2
1a	51.6	76.8	91.5 (161)	102.4		
1e	50.0	73.7	97.0 (162)	110.8		
2a	74.7	74.7	90.6 (165)	103.4		
2e	74.0	74.0	97.3 (162)	111.0		
trans-**2**			97.8 (163)	112.7		
3a	74.2[b]	74.2[b]	90.0[b] (164)	96.5[b]	42.9[b]	
3e	74.6[b]	74.6[b]	96.4[b] (158)	103.3[b]	44.4[b]	
4a	79.7	79.7	91.5 (166)	116.0		578.0
4e	77.7	77.7	99.3 (168)	117.9		579.0
trans-**4**	75.3	75.3	100.2 (159)	111.3		578.5
5a	73.4	73.4	94.3 (168)	106.4		581.2[c]
						616.0

[a] The spectra were recorded with a "line broadening" of 50 or 100 Hz. Chemical shift (ppm) relative to external H_2O at 100 °C. In parentheses, $J(^{31}P/^{17}O)$ (Hz). [b] Spectra recorded on a Varian Instrument operating at 54.21 MHz. [c] Upfield signal ascribed to ($C4-NO_2$) group.

stirred for 2 h at 0 °C and then at room temperature overnight. Either the solvent and the excess of diazomethane were removed at reduced pressure and the residue dissolved in chloroform, filtered, and concentrated, or the residue was washed two times with 5.0 mL of water (each), extracted with chloroform, dried with sodium sulfate, filtered, and concentrated.

Results and Discussion

Synthesis of the phosphates was performed by two general pathways (Scheme II, parts A and B).

Compounds **1–5** were hydrolyzed with dioxane–$H_2{}^{17}O$/NaOH (Scheme III). Since the results (vide infra) were independent of the reaction time, it was concluded that the reaction outcome was kinetically controlled. Because of the difficulty in analyzing the resulting isotopomer mixture as a salt in aqueous solution,[21] the salts were transformed to the corresponding triesters **9** by reaction with diazomethane in methanol.[1b] The methylation reaction was not stereospecific under these conditions;[22] hence, epimeric mixtures of different composition of labeled compounds were obtained depending on the exact esterification conditions used. The epimer ratio (equatorial/axial OCH_3) was determined by either ^{31}P NMR or GC (and checked by ^1H NMR).

^{17}O NMR and Conformation. Natural-abundance ^{17}O spectra of the phosphates (**1–5**) (Table I) indicated substantial differences in the signal positions between epimeric compounds, in accord with earlier work.[1] The P=O resonance is at 90–94 ppm in equatorial ^{17}O compounds and at 96–100 ppm in axial ones; it is characterized by a small bandwidth (1.0 ppm) that allows $^{17}O/^{31}P$ coupling constant measurements with acceptable reproducibility. The axial ^{17}O nucleus in the P–OAr moiety resonates upfield of the equatorial. Ring oxygens of 4,6-dimethyl-substituted compounds resonate at 73–80 ppm, the β_e and β_a effects of the P–OAr usually being small, as previously observed.[1a] Both ring and ArO oxygen signals are broad, and $^{31}P/^{17}O$ coupling is not well resolved.

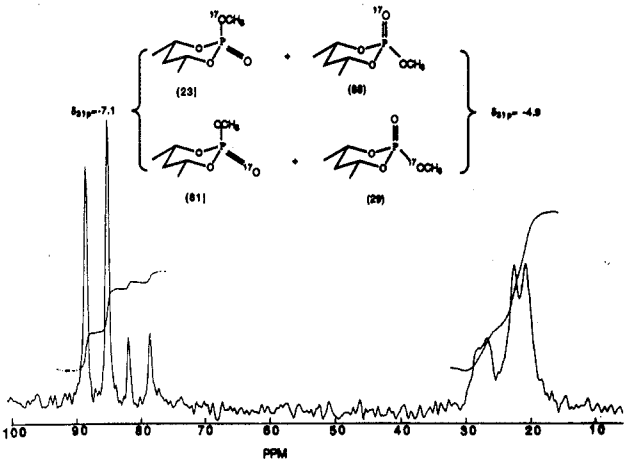


Figure 1. ^{17}O NMR 48.82-MHz spectrum and ^{31}P NMR data of the epimeric labeled mixture of 2-methoxy-2-oxo-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphorinane (**9**) from the hydrolysis of phosphate **2a**.

Scheme IV

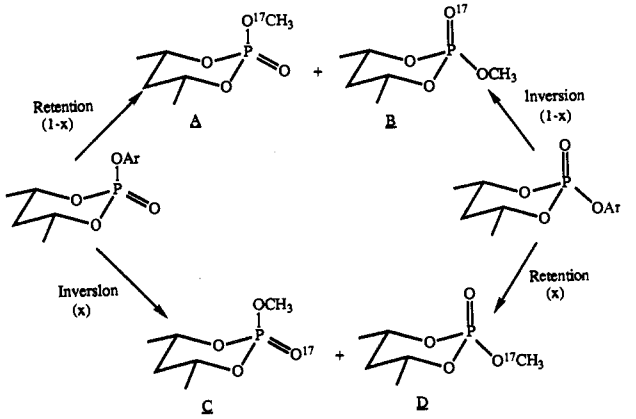


Table II. Stereochemistry in the Hydrolysis of Aryl Phosphate Esters

compd	*a/e*	*S*	retention/inversion[a]
1a	0.69	4.73	0.77/0.23 (0.82/0.18)
1e	2.44	0.33	0.55/0.45 (0.60/0.40)
2a[b]	0.65	4.00	0.72/0.28 (0.76/0.24)
2e	0.69	1.27	0.53/0.47 (0.56/0.44)
3a	0.88	2.67	0.70/0.30 (0.70/0.30)
3e	0.99	0.65	0.61/0.39 (0.57/0.43)
4a	0.77	1.00	0.44/0.56 (0.46/0.54)
4e	6.12	0.21	0.44/0.56 (0.31/0.69)
5a	*c*	*c*	*c*
5e	*d*	*d*	*d*

[a] The unparenthesized results are ±0.06 because of the accuracy limit of the ^{17}O signal integration. Unparenthesized values are based on GC or ^{31}P and P=^{17}O analysis; vide supra. Values in parentheses were calculated by integration of P=^{17}O and P—$^{17}OCH_3$ signals in the NMR spectra and are believed to be less accurate. [b] Hydrolysis of this compound over a longer reaction time (48 h) gave the same result. No change in the configuration of the remaining starting material was found after 8 h of reaction. [c] Here $^{17}OH^-$ largely attacks the aromatic ring rather than phosphorus, leading to formation of a major amount of $Ar^{17}OH$ detected by ^{17}O NMR of the recovered phenol.[26] [d] Not determined.

Analysis of contributions of twist or boat conformations[24] existing along with chair conformations in solution would have been of interest in this study, but no evidence for or against the existence of such conformational equilibria is manifest from the ^{17}O NMR spectra.

Stereochemistry of Hydrolysis of Phosphates (1–5). Reaction of compounds **1–5** with $^{17}OH^-$ will give phosphodiester salts with

(19) Diazomethane was synthesized from 3.3 g of nitrosomethylurea (warning! this substance is a carcinogen), following the procedure in: Blatt, A. *Organic Syntheses*; Wiley: New York, 1942; Collect. Vol. II, p 461. (Thus, by use of 10 mL of 50% aqueous KOH and 20 mL of ethylene glycol dimethyl ether at 0 °C, 0.63 mol of diazomethane was obtained for each mole of nitrosomethylurea and checked by titration with benzoic acid; see ref 20.) The diazomethane solution was stored over KOH pellets for 1 h at −78 °C and decanted (twice) before use.

(20) Hong, A. P.; Lee, J.-B.; Verkade, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 6547.

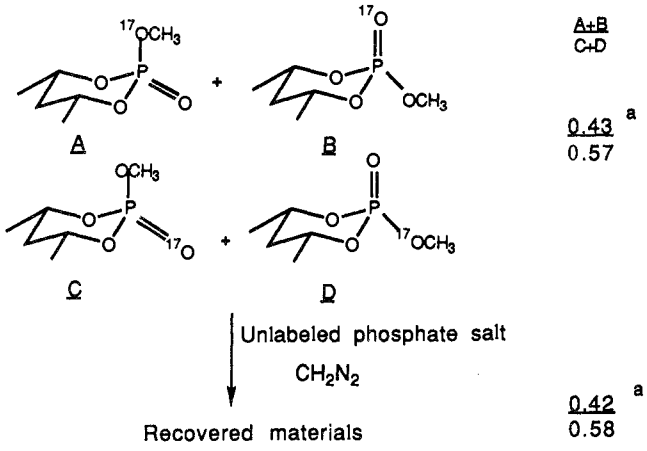
(21) Gerlt, J. A.; Demou, P. C.; Mehdi, S. *J. Am. Chem. Soc.* **1982**, *104*, 2848.

(22) Methylation of salts with diazomethane[23] in methanol is quite sensitive to the presence of water in the salt (Verkade, J. G. Personal communication). Epimer ratios near 1 were found when the salt was not rigorously dried (this work; see, however, refs 6a and 20).

(23) The methylation reaction of phosphate salts with MeI is not stereoselective either, resulting in epimeric mixtures. See for example: Jarvest, R. L.; Lowe, G.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1980**, 1142.

(24) Yu, J. H.; Sopchik, A. E.; Arif, A. M.; Bentrude, W. G. *J. Org. Chem.* **1990**, *55*, 3444 and references cited therein.

Scheme V



[a] By integration of P=O[17] and P—O[17]CH_3 signals.

axial or equatorial $=^{17}O$, depending on the configuration of the starting material and on whether the hydrolysis proceeds with retention or inversion of configuration. However, since the salts were methylated in nonstereospecific fashion, four compounds are ultimately obtained, as shown in Scheme IV.

Product stereochemistry can, in principle, be analyzed by measuring the axial/equatorial $P=^{17}O$ and $P—^{17}OCH_3$ area ratios in the ^{17}O NMR spectra of the labeled products (see Figure 1). However, area measurement of the ^{17}OMe ether signals introduces substantial errors caused by the broadening and poor resolution of these signals. The ratio of products of the nucleophilic displacement ($^{17}OH^-/ArO^-$) at phosphorus was therefore calculated with the OMe epimer ratio (s) obtained by ^{31}P NMR or GC (vide supra) by means of eq i.[25]

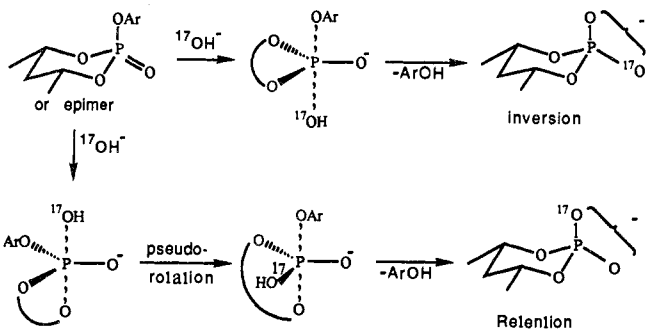
$$\frac{1-x}{x} = S\frac{a}{e} \qquad \text{(i)}$$

Here, S is the ratio of axial to equatorial $P=^{17}O$ measured by NMR and a/e is the ratio of epimeric esters (axial to equatorial OMe) measured by ^{31}P NMR or GC. In the case of the axial ester starting material, x is the percent inversion whereas for equatorial starting material it is the percent retention.[25] The stereochemical results are summarized in Table II.

As is shown in Table II, retention/inversion ratios in hydrolyses of phosphates vary from 1/1 to slightly more than 3/1. This result can be explained either by postulating that two processes, involving inversion and retention of configuration, respectively, are in competition with each other through a mechanism involving pentacoordinated intermediates of similar energy[27] (see the following text) or, improbably, as a result of epimerization during the methylation reaction.

In order to eliminate the latter possibility, the following control experiment was carried out: a mixture of labeled methyl esters was allowed to react with diazomethane in the presence of a similar amount of unlabeled phosphate salt. The ratio $x/(1-x)$ calculated from ^{17}O analysis ($^{17}OCH_3$ and $^{17}O=$) of the new labeled mixture obtained was very close to the initial ratio. This control experiment eliminates epimerization during the methylation reaction as a possible explanation of the results (Scheme V).

Scheme VI



Analogous stereochemistry is observed in hydrolysis of phosphates **1a–2a** and **1e–2e**. Thus, it appears that the conformation population in **1a** and **1e** is close to that in the presumably anancomeric (completely conformationally biased) systems, **2a** and **2e**, as expected from the large conformational energy (2.9 kcal/mol) of a methyl group at C(4) in a 1,3-dioxane.[28]

Interpretation and Conclusion

Alkaline hydrolysis of the six-membered cyclic aryl phosphates studied is not highly stereospecific. For the parent phenoxy and *p*-methoxyphenoxy compounds, retention of configuration predominates similarly as reported by Gorenstein et al.[6b] for the related transesterification reaction (but in contrast to results reported for hydrolysis of the bicyclic *p*-methoxyphenoxy compound[6a]) somewhat less so with the equatorial than with the axial esters. The *p*-nitrophenoxy compound is hydrolyzed with slight predominant inversion, but less so than reported for the bicyclic dinitrophenoxy analogue studied by Gorenstein et al.[6a]

The results can be rationalized by postulating that the direct displacement process with inversion competes with pseudorotation of pentacoordinate intermediates leading to retention (Scheme VI, cf. refs 6b, 29, 30).

Retention of configuration is observed when the incoming hydroxyl group enters the apical position of a bipyramidal pentacovalent phosphorus intermediate and the opposite apical position is occupied, not by the leaving group aryloxy but by one or other of the oxygen atoms of the ring. Since the ring is too stable to break,[31] no reaction takes place until a pseudorotation occurs that places the leaving group in the apical position from where it departs with overall retention of configuration. This process competes with a direct displacement (either via an unfavorably disposed pentagonal-bipyramidal intermediate or via a corresponding transition state without formation of an intermediate) that involves configurational inversion[32] (Scheme VI, top). The latter process (direct displacement) proceeds better with a good leaving group (*p*-nitrophenoxy) than with a poor one (phenoxy or *p*-methoxyphenoxy); thus, there is more inversion with the nitrophenoxy leaving group. As the portion of direct displacement increases (PhO < MeOPhO < O_2NPhO), inversion of configuration increases in the axial more than in the equatorial aryl ester. This may imply that the S_N2P reaction proceeds more readily by

(25) The equation may be derived as follows, with use of Scheme IV: starting with axial ester, the mole fraction of material ($A + B$) with axial ^{17}O (retention) is $1 - x$ and that ($C + D$) with equatorial ^{17}O (inversion) is x. Taking into account the partition ratio a/e on esterification, $A = (1-x)a/(e+a)$; $B = (1-x)e/(e+a)$; $C = xa/(e+a)$; $D = xe/(e+a)$. By definition $S = B/C = (1-x)e/xa$; hence $(1-x)/x = Sa/e$. When one starts with equatorial ester, the same scheme applies provided x (leading to $C + D$) refers to retention and $1 - x$ (leading to A + B) refers to inversion.

(26) This result contrasts with the behavior of a similar dinitrophenyl phosphate in which the hydrolysis led to complete P–O aryl cleavage.[6a]

(27) (a) Corriu, R. J. P. *Phosphorus and Sulfur*; **1986**, *27*, 1. (b) Marsi, K. L. *J. Org. Chem.* **1975**, *40*, 1779. (c) Maryanoff, B. E.; Hutchins, R. O.; Marianoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.

(28) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444. The results do not, however, rule out possible contributions of boat conformations to both **1e** and **2e**, cf. ref 24.

(29) (a) For an extensive discussion of the mechanisms of nucleophilic substitution in phosphate esters, see: Thatcher, G. R. J.; Kluger, R. *Adv. Phys. Org. Chem.* **1984**, *25*, 99. (b) For a recent kinetic study of transesterification of triaryl phosphates with phenoxide nucleophiles, see: Ba-Saif, S. A.; Waring, M. A.; Williams, A. *J. Am. Chem. Soc.* **1990**, *112*, 8115.

(30) This assumes that the six-membered ring preferentially spans apical-equatorial rather than diequatorial positions. This assumption has been made elsewhere,[32] although it has also been pointed out[29a] that there is not much difference in strain between the two alternatives. Although pseudorotation can, in principle, continue past the first ligand exchange shown in Scheme VI (bottom), it appears[32b] that once the leaving group is rotated into the apical position, it departs and no further pseudorotation occurs.

(31) However, minor amounts of ring-cleaved products might have escaped detection because of possible high water solubility.

(32) (a) Deiters, J. P.; Holmes, R. R.; Holmes, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 7672. (b) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059.

equatorial approach of $^{17}OH^-$ in the axial ester than by axial approach in the equatorial ester, presumably for steric reasons. No simple correlation was found between results for different axial and equatorial leaving groups; however, for a poor leaving group (OC_6H_5, OC_6H_4OMe-*p*) the spread of the retention/inversion ratio between axial and equatorial isomers is greater than for a better leaving group ($OC_6H_4NO_2$-*p*). The stereochemical outcome of these reactions is quite different from that in the hydrolysis of the six-membered ring in cAMP that proceeds with inversion at phosphorus[33] presumably because one of the oxygen atoms of the ring is always in the apical position[24] needed for the leaving group.

Acknowledgment. This work was supported by NSF Grant CHE-8703060. B.G. is thankful to CONACYT, Mexico, for a postdoctoral fellowship. We are grateful to Dr. David L. Harris for training in the use of NMR instruments and to Mr. Thomas Powers for his help in recording some of the oxygen-17 spectra on the 400-MHz Varian instrument.

(33) Mehdi, S.; Coderre, J. A.; Gerlt, J. A. *Tetrahedron* **1983**, *39*, 3483.

Investigations on Transition-State Geometry in the Aldol Condensation

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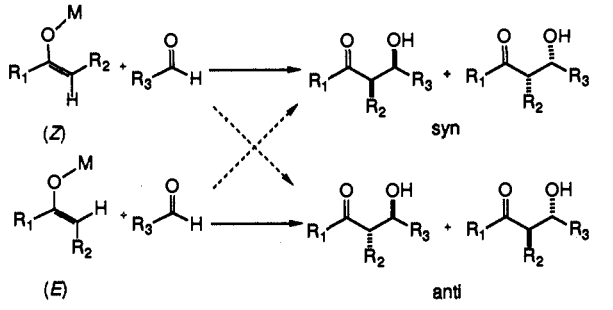
Abstract: Model compounds **1** and **2** have been studied to elucidate the relative orientation of enolate and carbonyl moieties in the aldol reaction. The syntheses of these compounds have been achieved from a common precursor derived from fragmentation of adamantane. Models of the limiting transition structures reveal that the cyclization must proceed through either a synclinal or antiperiplanar orientation of the aldehyde with respect to the enolate. Cyclizations of **1** were unexpectedly sluggish due to slow deprotonation of the tertiary center. The cyclization of **2** was very rapid and was studied as a function of enolate type (metal counterion), base type, solvent, and additive. The reactions of metal enolates showed an increasing preference for the syn product **5** with increasing cation coordinating ability ($K^+ < Na^+ < Li^+ < MgBr^+$). Attempted cyclization via boron and stannous enolates failed. The type of base and the choice of solvent had negligible effects on the selectivity. However, in the presence of strong cation-complexing agents, the model showed a strong preference for reaction via an antiperiplanar orientation of reactants giving the anti product **6** with high selectivity. The origin of the selectivities and the implication for enolate and transition structures are discussed.

Introduction and Background

The aldol reaction has developed into one of the most powerful and selective carbon–carbon bond forming reactions in synthetic organic chemistry.[1] Motivated by an interest in the total synthesis of polypropionate- and polyacetate-derived natural products such as macrolide and polyether antibiotics,[2] many research groups have developed methods that allow for stereoselective construction of β-hydroxy carbonyl compounds.[3] The efforts of Evans,[4] Masamune,[5] Mukaiyama,[6] Paterson,[7] Corey,[8] and others[9] in developing

Scheme I



a strategy based on chiral auxiliaries and additives have allowed the synthesis of each of the four possible aldol products in virtually enantiomerically pure form (Scheme I).[9,7]

The underlying factors responsible for controlling the stereoselectivity in the aldol condensation have also been the subject of numerous investigations.[1,10–12] The aldol reaction succeeds

(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley Interscience: New York, 1983; Vol. 13, p 1. (b) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; Vol. 5B, p 177. (c) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2. (d) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(2) (a) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982. (b) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, 1984. (c) Paterson, I.; Mansury, M. M. *Tetrahedron* **1985**, *41*, 3569.

(3) (a) Heathcock, C. H. *Science* **1981**, *214*, 395. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (d) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (e) Chow, H.-F.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 604.

(4) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(5) (a) Masamune, S.; Sato, T.; Kim, B.-M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(6) Mukaiyama, T.; Kobayashi, S.; Sano, T. *Tetrahedron* **1990**, *46*, 4653 and references to earlier work.

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