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Stereoelectronic Effects in the Conformation and Hydrolysis of Epimeric(4aα, 8aβ)-Hexahydrobenzo-2-(p-Nitrophenoxy)-2-Oxo-1,3,2λ^5 Dioxaphosphorinanes and 4aα-methyl-8aβ-Pentahydrobenzo-2-(p-Nitrophenoxy)-2-Oxo-1,3,2λ^5-Dioxaphosphorinanes

Kazunari Taira[a], Kofen Lai[a], and David G. Gorenstein*[a,b]

Contribution from the Departments of Chemistry

[a]University of Illinois at Chicago, Chicago, Illinois 60680

[b]Address correspondence to author at Purdue University, West Lafayette, Indiana 47907

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Abstract - The epimeric (4aα, 8aβ)-hexahydrobenzo-2-(p-nitrophenoxy)-2-oxo-1,3,2λ^5-dioxaphosphorinanes 1a, 1b (axial and pseudo-equatorial p-nitrophenoxy group) and 4aα-methyl-8aβ-pentahydrobenzo-2-(p-nitrophenoxy)-2-oxo-1,3,2λ^5-dioxaphosphorinanes 2a, 2b (axial and equatorial p-nitrophenoxy group) were hydrolyzed in 12% methanol/water. For axial isomers 1a and 2a, the methyl group at the trans-ring junction did not affect the rate of hydrolysis. The methyl substitution of the equatorial isomer 2b, on the other hand, decreased the hydrolysis rate by 30% as compared to 1b. For both epimers, the equatorial compounds (as viewed in a chair conformation) hydrolyzed faster than the corresponding axial isomer. These results are consistent with the idea that the axial isomers react via a chair conformation and the equatorial isomer 1b reacts via a twist-boat conformation with the leaving group in a pseudo-axial position.

Introduction

The role of orbital orientation in organic and enzymatic reactions has been of considerable current interest.[1-10] Deslongchamps and coworkers[2] in studying tetracovalent carbon series have demonstrated selective cleavage of bonds which are trans-antiperiplanar (app) to lone pairs on directly bonded oxygen and nitrogen atoms. Molecular orbital calculations have provided theoretical justification for these stereoelectronic effects in tetracovalent carbon and phosphorus species and pentacovalent phosphoranes.[5-11] Thus, as has been shown in molecular calculations on the X_1-Y-X_2 (X = O,N; Y = P,C) structural fragments, the X_1-Y bond is strengthened (as indicated by an increase in the Mulliken overlap population) while the Y-X_2 bond is weakened when the X_1 atom lone pair is app to the Y-X_2 bond (Structure A, Figure 1).

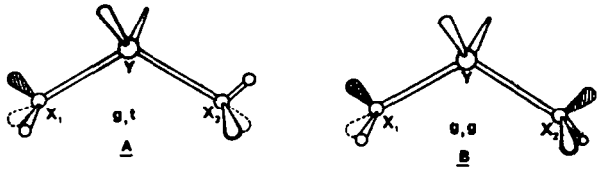
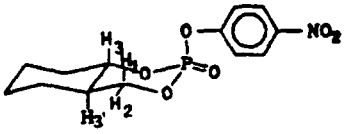


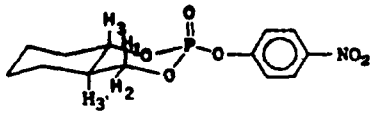
Fig. 1

Molecular orbital calculations on phosphate esters (Figure 1, X_1, X_2 = OCH_3, Y = PO_2^-) and tetrahedral carbon intermediates (Figure 1, X_1 = NH_2, X_2 = OH, Y = CHOH) have thus provided support for the stereoelectronic effect.[6,8-10] Lehn[5,6] and Pople[7] and co-workers have shown similar differences in related systems.

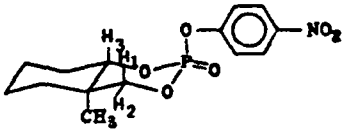
In contrast to the large body of experimental and theoretical work supporting the role of orbital orientation (the stereoelectronic effect) in carbon chemistry,[1,2,6,7] little experimental evidence yet exists to support this hypothesis in the reactions of organophosphorus compounds.[12] The available direct experimental evidence was obtained by examining the hydrolysis rates and modes of cleavage of cyclic five-membered ring organophosphorus compounds.[12] However, attempts to experimentally confirm this effect in unstrained ring systems have been frustrated by conformational flexibility in the relatively unconstrained six-membered ring cyclic phosphate ester systems earlier studied.[13] On the basis of earlier ^{1}H NMR coupling data and ^{31}P and ^{13}C NMR data, the axial aryloxy isomers of these six-membered ring phosphorinanes 1a are in chair conformations, in which lone pairs on the ring oxygens are antiperiplanar (app) to the exocyclic P-O bond. However, NMR and IR data support the assignment of a twist-boat conformation for the epimer 1b, in which lone pairs on the ring oxygens can be antiperiplanar (app) to the exocyclic P-O ester bond only in this twist-boat conformation.[13] In these conformations, in which the lone pairs are app to the electronegative aryloxy group, the anomeric (ground-state stereoelectronic) effects are optimal. Since 1b has been shown to exist in a twist-boat conformation,[13b] we have methylated it at the trans-ring junction carbon in order to attempt to restrict the chair-twist boat ring-flipping. Additionally, we report that 2b (ring methylated 1b) hydrolyzes more slowly than 1b, although the effect is not large, and both 1a and 2a hydrolyze at identical rate. The results are consistent with our previous interpretation that the isomer 1b reacts via a twist-boat conformation.[13]



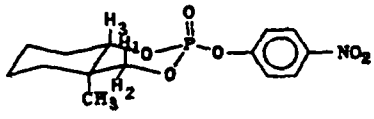
1a



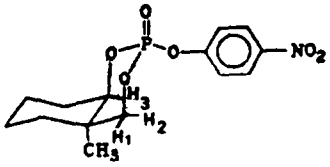
1b



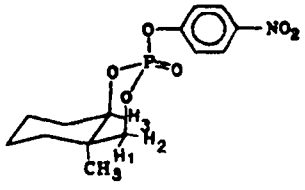
2a



2b



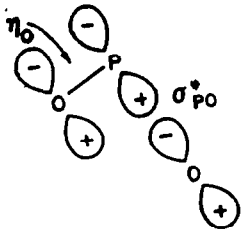
3a



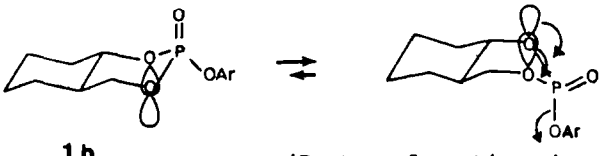
3b

Results and Discussion

The stereoelectronic effect in the hydrolysis of phosphate esters is attributed to n_O <--> σ^*_{P-O} orbital mixing (n_O, oxygen lone pair; σ^*_{P-O}, P-O antibonding orbital) which will facilitate P-O ester bond cleavage (or its formation).[1,5,8-13] This orbital overlap requires that the lone pair orbital on oxygen should be app to the attacking or leaving group.



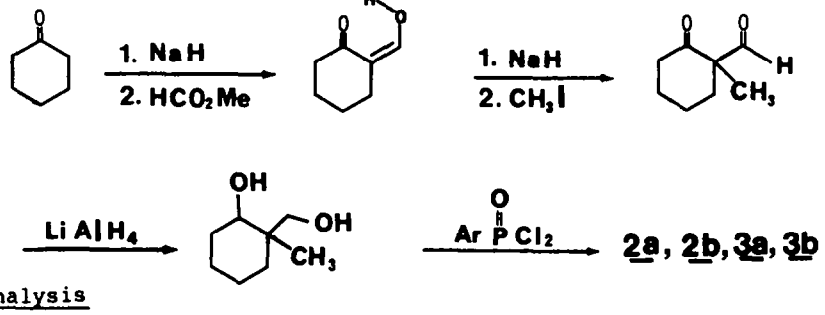
As a test of the stereoelectronic effect, attempts have been made to utilize six-membered ring systems.[1,13-15] Unfortunately it is now recognized that low-energy twist-boat conformations exist in equilibrium with the chair forms even in the trans-decalin-type systems.[13-17] The hydrolysis of 1a, 1b and related compounds could be explained by the ground-state stereoelectronic effect.[13] Although 1a was in a chair conformation for the phosphorinane ring, 1b preferred to be in a twist-boat conformation (again all references to ring conformations refer only to the phosphorinane ring moiety) where two lone pair electrons on the ring oxygens are antiperiplanar (app) to the electron-withdrawing p-nitrophenoxy group.[13]



1b (Boat conformation shown)

In order to minimize the conformational flexibility (chair to twist-boat conformational isomerization) of the phosphorinane ring, the ring-junction methylated esters 2 and 3 were synthesized as shown in Scheme 1.

Scheme 1.



Conformational Analysis

Configurational and conformational analysis of the phosphorinane esters 2 and 3 is based upon ^{31}P and ^{1}H chemical shifts, $^{3}J_{HCOP}$ coupling constants, and P=O stretching frequencies as previously described.[13,16-26]

Thus, as previously demonstrated[13,18] ^{31}P NMR chemical shifts are dependent on P-O ester torsional angles. The "equatorial" ester group (as viewed in a chair conformational) in 1b or 2b is locked into a trans conformation (COPO(R) dihedral angle of 180°) relative to the endocyclic P-O ester bond, resulting in

a 4-5 ppm downfield ^{31}P chemical shift compared to gauche esters (dihedral angle COPO(R) of 60°) such as 1a and 2a.[13,18-20] Since axial esters such as 1a and 2a are in chair conformations, the ^{31}P chemical shift difference between epimers (1a/1b or 2a/2b) approximately reflects the relative proportion of twist boat and chair conformers for the equatorial esters: the greater the chemical shift difference between epimers up to a maximum of 4-5 ppm, the greater is the proportion of pure chair conformations with the ester group in an equatorial position (trans conformation). Although the ^{31}P chemical shift difference between 1a and 1b is 2.1 ppm in $CDCl_3$, it is 4.5 ppm for 2a/2b under the identical conditions, indicating that 2b is essentially in a pure chair-equatorial conformation while 1b is in ca. 50% twist-boat (with pseudo-axial ester)/50% chair-equatorial conformation.[13]

This conclusion is also supported by the equilibration results. At 30°C in DMF, 1b is 1.95 kcal/mol higher in energy than 1a. However, this energy difference is greater in the case of the 2a/2b pair: 2b is 2.3 kcal/mol higher in energy than 2a. As discussed earlier, 1b prefers to be in a twist-boat conformation because of the ground state (anomeric) stereoelectronic effect compensating for the torsional strain in the twist-boat conformations. Since this ring-flipping to form twist-boat conformation is sterically more destabilizing in the case of 2b, with very unfavorable boat bowsprit interactions between the C(4) ring-junction methyl group and P(2), it is higher in energy than 1b.

Further support for these conclusions are provided by the coupled ^{31}P and ^{1}H NMR spectra of 1a/b and 2a/b. The coupled ^{31}P spectrum for 1a is a pseudo-doublet, because in the chair conformation, only H(2) has the H(2)COP dihedral angle of ca. 180° showing the largest coupling of $J_{H(2)P}$ = 24.6 Hz.[13,18-26] On the other hand, the dihedral angles between phosphorus and H(1), H(3'), and H(3) are ca. 60° showing very small couplings ($J_{H(1)P} \approx J_{H(3')P} \approx J_{H(3)P} \approx$ 0-1Hz).[13a,b,16-26] In contrast, the coupled ^{31}P spectrum of 1b is a pseudo-triplet since in the twist-boat conformation the dihedral angle between P and H(2) decreases from 180° and the angle between P and H(1) increases from 60° (in a pure boat conformation the dihedral angles H(1)COP and H(2)COP are ca. 120°, with $J_{H(1)P} \sim J_{H(2)P} \sim$ 10-12 Hz[13,16,17]). The coupled ^{31}P signal of 2a is a doublet ($J_{H(2)P}$ = 23.8 Hz) and thus 2a is also in a chair conformation. In contrast to 1b, the coupled ^{31}P signal for 2b is a doublet with identical coupling constant as 2a ($J_{H(2)P}$ = 23.8 Hz), and thus 2b must also be in a chair conformation. Analysis of the ^{1}H NMR spectral data of 1a, 1b, 2a, and 2b (Table I)

Table I. NMR Data for 1a, 1b, 2a, and 2b in $CDCl_3$.

Compd.	Chemical Shifts (ppm)			Coupling Constants (Hz)						
	δH_1	δH_2	$\delta^{31}P$	J_{12}	$J_{13'}$	$J_{23'}$	J_{1P}	J_{2P}	$J_{3'P}$	J_{3P}
1a	4.22	4.35	-13.89	-10.8	11.4	4.4	1.0	24.6	0.0	~0
1b	4.24	4.49	-11.76	-10.5	10.5	5.2	10.9	11.4	0.0	~0
2a	4.15	4.10	-14.2	-9.8	-	-	~0	23.8	-	~0
2b	4.30	3.94	-9.7	-10.6	-	-	~0	23.8	-	~0

confirms these conclusions. Note particularly for 2b that the ^{1}H chemical shift of H(1) is strongly deshielded (δ~4.30 ppm) relative to H(2) (δ~3.94 ppm). In the chair conformation for 2b the P=O group is axial and is expected to deshield the axial H(1) proton.[22c] In contrast in 1b the H(2) proton is slightly deshielded relative to H(1) (4.49 ppm vs. 4.24 ppm), consistent with the mixture of chair and twist forms for this ester. Incidentally, the coupling pattern of the conformationally flexible 3b differs from those of 1a, 1b, 2a, and 2b. The pseudo-quartet in the coupled ^{31}P spectrum indicates that the phosphorus couples with all three protons, H(1), H(2), and H(3), with coupling constants of ca. 10.3-12.3 Hz.

Hydrolysis Rates and the Stereoelectronic Effect.

It was earlier suggested that the faster rate of hydroxide-catalyzed hydrolysis for the "equatorial" epimer 1b was due to ground state destabilization in this epimer relative to 1a.[13] Equilibration of the epimeric triesters established that the 1b epimer was 1.9 kcal/mol destabilized relative to the 1a epimer, which is close to the difference in free energies of activation (Table II and ref 13b).

Table II. Summary of Hydrolysis and Equilibrium of Phosphorinane Esters.

Compd.	$\Delta\Delta G_0$(kcal/mol)[a]	k_{obs} x 10^5(sec^{-1})[d]	$\Delta\Delta G^{\neq}$(Kcal/mol)[e]
1a	0	9.53	
			1.27
1b	1.95[b]	78.3	
2a	0	9.62	
			1.06
2b	2.3[c]	56.0	
3b		27.5	

[a]in 100% DMF at 30° C for equilibration of a and b epimers; relative energies.

[b]relative to 1a

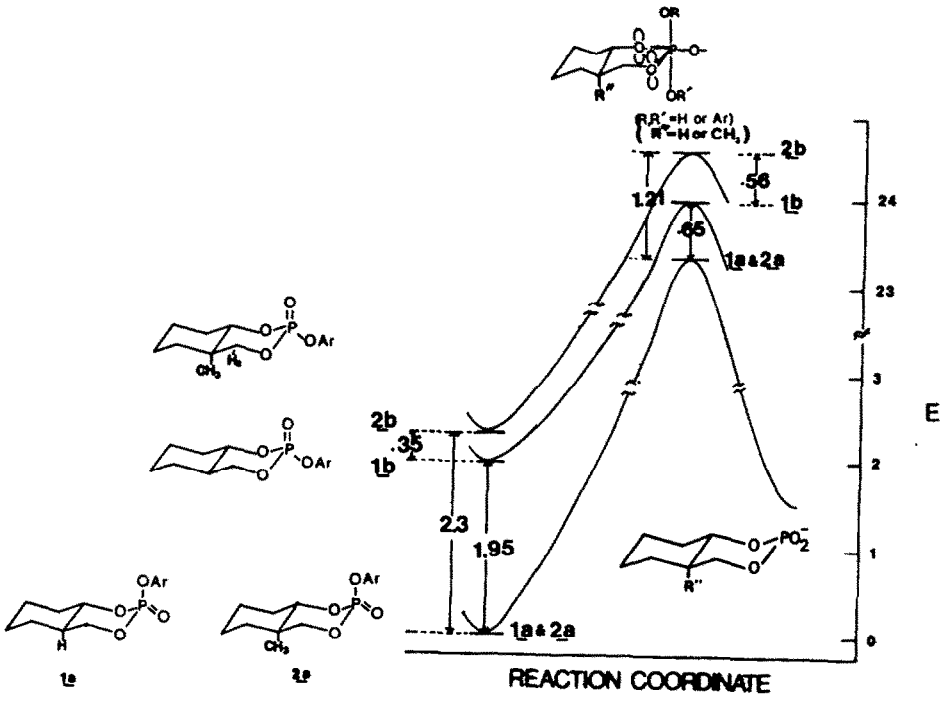
[c]relative to 2a

[d]in 12% methanol/water at pH 12 at 30.0° C

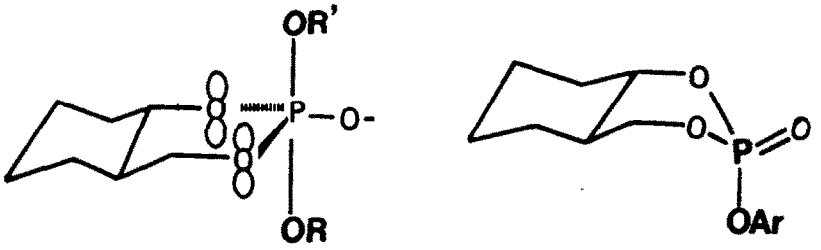
[e]difference in free energies of activation ($\Delta G^{\neq}$) between epimers b and a.

In fact as shown in Figure 2, the difference in the transition-state energies for the hydrolysis for the 1 a/b is 0.65 kcal/mol.(Although reaction conditions are different for equilibration and hydrolysis, solvent effects are not expected to greatly alter the $\Delta\Delta G_0$ and $\Delta\Delta G^{\neq}$ values in Table II. As demonstrated earlier[13b] these values would likely be altered by <0.2 kcal/mol.) This suggested that both epimers of 1 have similar transition-state geometries in their hydrolysis reaction: likely half-chair, diequatorial ring trigonal-

Figure 2. Reaction diagram for hydrolysis of phosphorinanes.



bipyramid 4. The p orbitals on the endocyclic oxygens can most effectively overlap with the phosphorus apical p orbital and both incoming nucleophile and



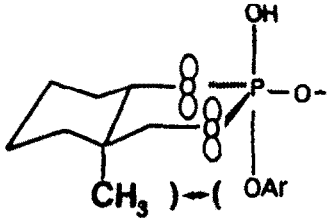
4 (R,R' = H or Ar) 5 (BOAT)

(Several Twist Boat Structures Possible)

leaving groups. The unusual conformational freedom of 1b with low energy twist-boat structures 5 effectively prevented a direct test of the stereoelectronic theory: in both epimers 1a and 1b (assuming twist structure 5 for 1b) the ring oxygen (or nitrogen) lone pairs are antiperiplanar to OAr leaving group. Previous molecular orbital calculations[8,9] suggested that the magnitude of the rate acceleration expected from any stereoelectronic effect would depend upon whether the lone pairs were app to the translating bond in the rate-determining step. If nucleophilic attach was rate determining, then the optimal stereoelectronic conformation for facilitating bond making is quite different from that facilitating bond breaking. The lone pairs must be app to the leaving group in the bond-breaking step but app to the attacking group in the bond-making step. The attractiveness of transition-state 4 is that this problem is eliminated, since the lone pairs nicely overlap with both groups.

Assuming that both 1a and 2a have identical relative ground state energies because of identical stereoelectronic effects, a reaction diagram for hydrolysis of the four phosphorinanes is drawn in Figure 2. Kinetic parameters for the hydrolysis and equilibration reactions are given in Table II. As can be seen from Figure 2 and Table II, 2b, despite its higher ground state energy than 1b, hydrolyzes slower than 1b and both 1a and 2a hydrolyze at identical rates within experimental error. These results are consistent with our previous conclusion that 1b reacts via a twist-boat conformation[13]: since both 1a and 2a have identical chair conformations differing only in the presence of the distal methyl group at the ring junction, and identical stereoelectronic effects throughout the reaction, they react at very similar rates.

In contrast, the transition state for the hydroxide catalyzed hydrolysis of 2b is 1.21 kcal/mol higher energy than that for 2a and is even 0.56 kcal/mol higher energy than the transition state for hydrolysis of 1b (Figure 2). Again, this is consistent with the hypothesis that the stereoelectronically favored transition state has ring-diequatorial structure 4, since the methyl group at the ring junction will be destabilizing by sterically interacting with the leaving p-nitrophenoxy-group:



Conclusions.

In conclusion the methylation of 1b provided a more rigid chair-equatorial compound 2b that was confirmed by the fact that the ^{31}P signal of 2b was 4.5 ppm downfield of 2a and 2b was 2.3 kcal/mol higher energy than 2a. These results are expected from the ground state stereoelectronic effect, with the conformation representing a balance between the ground state stereoelectronic (anomeric) effect favoring the axial orientation in the twist-boat and the 1,3-steric and eclipsing interactions favoring the chair conformation. Compound 1b hydrolyzed slightly faster than 2b suggesting that the more flexible 1b had a better orbital orientation with respect to the leaving OAr group at the transition state as expected from the kinetic stereoelectronic effects. Finally 1a, with a chair conformation to begin with, was not influenced by the methylation.

Experimental Section

General

^{1}H and ^{31}P NMR spectra were recorded on a Bruker WP-80 spectrometer at 81.02 and 32.4 MHz, respectively, or ^{1}H NMR on a 60 MHz Varian T-60 spectrometer or Bruker WP-200SY spectrometer at 200 MHz. Chemical shifts in parts per million for ^{1}H NMR spectra are referenced to Me_4Si and for ^{31}P spectra are referenced to 85% H_3PO_4. Positive chemical shifts are to low field. IR spectra were obtained on a Perkin-Elmer 727B spectrometer. Mass spectra were obtained on a Hewlett-Packard 5985 Gas-chromatograph-Mass-Spectrometer. Kinetic measurements were carried out on a Cary 210 UV-visible spectrometer equipped with an automatic sample changer. Gas chromatography was performed on a Hewlett-Packard 5830A instrument equipped with a 15% DEGS (diethylene glycol suclinate) on Anachrom AB 1/8 in. x 6 ft column, using a thermal conductivity detector. Melting points were obtained on a Thomas Hoover apparatus and are uncorrected. Chemicals were generally of high purity. Baker analyzed 60-200 mesh silica gel was used for column chromatography after being activated.

2-Hydroxymethylenecyclohexanone.

This compound was prepared from cyclohexanone and methyl formate as described in ref. 27.

2-Formyl-2-methylcyclohexanone.

To a mixture of 16.0 g (0.660 mol) of 99% sodium hydride and 500 mL of DMSO, which had been stirred for 30 m, was added dropwise 68.0 g (0.540 mol) of 2-hydroxymethylenecyclohexanone over a period of 20 m with stirring. The mixture was stirred for 1 h, then 115 g (0.810 mol) of methyl iodide was added and the stirring was continued at rt overnight. After an addition of ca. 1300 mL of aqueous saturated NaCl solution, products were extracted with ether. A crude oil was separated into four fractions by vacuum distillation (there was no constant boiling temperature). G.C. analyses showed that the third fraction (13 g, collected between 54-64 °C (1.4-2.0 mm)) contained 24% impurity and the fourth fraction (25 g, collected between 64-68 °C (1.4-2.0 mm)) was the desired 2-formyl-2-methylcyclohexanone. (Both fractions were independently reduced to 2-methyl-2-hydroxymethyl cyclohexanol.) This synthesis was not successful when benzene was used as the solvent in place of DMSO.

2-Methyl-2-hydroxymethylcyclohexanol.

In order to avoid rapid reflux, 25.0 g (0.179 mol) of 2-formyl-2-methylcyclohexanone (fourth fraction) was added, over a period of 1.5 h, to a mixture of 10 g (0.25 mol) of 95% $LiAlH_4$ and 400 mL of anhydrous ether. The mixture was stirred at rt overnight, and water followed by 6N HCl was added to this mixture. A crude oil (23.5 g) was obtained after extraction with ether, washing with aq. sat. NaCl, drying over anh. $MgSO_4$, and concentration. The third fraction of 2-formyl-2-methyl-cyclohexanone (76% purity, 13 g) was also reduced as described above (½ scale) to give 11.0 g of a crude oil. Although, according to G.C. analyses, the latter crude oil ketone fraction contained slightly more impurities, both crude oil products were combined and vacuum distilled into four fractions (I:40-50, II: 50-60, III: 60-70, IV: 70-90 °C (0.2 mm)). Since the last fraction (IV, 25.7 g) still contained some impurities (G.C.), it was further vacuum distilled at 82-83 °C (0.2 mm) to obtain a mixture of cis and trans 2-methyl-2-hydroxymethylcyclohexanol. ^1H NMR ($CDCl_3$): δ (s, -OH, 2H), 3.42 (s, CH_2OH, 2H), 1.1-1.9 (br m, CH, 8H), 1.0 (s, CH_3, 3H). IR (thin film): 3.0 μm (s, br), 3.42 (s), 3.5 (s), 6.98 (s), 9.8 (s).

(4aα, 8aβ)-Hexahydrobenzo-2β-(p-nitrophenoxy)-2α-oxo-1,3,2λ^5-dioxaphosphorinane, (1a); (4aα, 8aβ)-Hexahydrobenzo-2α-(p-nitrophenoxy)-2β-oxo-1,3,2λ^5-dioxaphosphorinane, (1b).

The preparation and separation have been described previously.[13]
4aα-Methyl-8aβ-pentahydrobenzo-2β-(p-nitrophenoxy)-2α-oxo-1,3,2λ^5-dioxaphosphorinane, (2a); 4aα-Methyl-8aβ-pentahydrobenzo-2α-(p-nitrophenoxy)-2β-oxo-1,3,2λ^5-dioxaphosphorinane, (2b); 4aα-Methyl-8aα-pentahydrobenzo-2α-(p-nitrophenoxy)-2β-oxo-1,3,2λ^5-dioxaphosphorinane, (3a); 4aα-Methyl-8aα--pentahydrobenzo-2β-(p-nitrophenoxy)-2α-oxo-1,3,2λ^5-dioxaphosphorinane, (3b).

A solution of 2-methyl-2-hydroxymethylcyclohexanol (11.3 g, 78.9 mmol) and triethylamine (16.0 g, 158 mmol) in CH_2Cl_2 (40 mL) was added dropwise over a period of 1 h to a solution of p-nitrophenyl phosphorodichloridate (20.0 g, 78.1 mmol) in CH_2Cl_2 (200 mL) at 0 °C. The stirring was continued overnight (12 h) at rt. The reaction mixture was washed with 100 mL of water four times, dried over anhydrous $MgSO_4$, and concentrated under vacuum to give 22 g of crude products which showed mainly two spots on TLC (silica, ether). This crude product was easily separated into two fractions by a silica-gel column with ethyl ether as the eluting solvent.

^1H NMR of the first fraction showed two methyl peaks at δ0.94 ppm (later confirmed as 3a) and at 1.27 ppm (later confirmed as 2a). ^1H NMR of the second fraction also showed two methyl peaks at 1.14 ppm (3b) and at 1.03 ppm (2b), indicating that each fraction consisted of two isomers. This was confirmed by ^{31}P NMR since the first fraction consisted of two peaks at δ -13.9 ppm (41%, later identified as 3a) and at -14.2 ppm (59%, later identified as 2a). The second fraction showed ^{31}P signals at -9.7 ppm (59%, later identified as 2b) and at -12.9 ppm (41%, later identified as 3b).

Observations such as (a) the axial isomers travel faster than equatorial isomers on a silica-gel column with ether and (b) ^{31}P chemical shifts of axial isomers are upfield of those for equatorial isomers, are consistent with our previous conclusions.[13] ^{31}P NMR integration ratios and ^{1}H NMR methyl integration ratios indicate that, upon reduction of 2-formyl-2-methylcyclohexanone with $LiAlH_4$, 59% of trans-diol (2-methyl-2-hydroxymethylcyclohexanol) and 41% of cis-diol have been produced.

Pure 2a was obtained by fractional recrystallization of the first silica gel fraction from ether. Mp: 135.5-136.0 °C. ^{31}P NMR ($CDCl_3$): δ -14.2 ppm. ^{1}H NMR ($CDCl_3$): δ8.27, 8.23, 7.45, 7.40 (dd, Ar, 4H), 4.36-3.89 (m, $H_{1,2,3}$, 3H), 2.1-0.9 (broad, ring CH, 8H), 1.27 ppm (S, $-CH_3$, 3H). MS (70 eV): molecular ion at m/e 327.1 (13.6% base abundance). Anal. Calcd for $C_{14}H_{18}NO_6P$: C, 51.38; H, 5.54; O, 29.33; P, 9.46. Found: C, 51.14; H, 5.76; P, 9.21.

Pure 3b was obtained by fractional recrystallization of the second silca gel fraction from ether. Mp: 165.5-166.0 °C. ^{31}P NMR ($CDCl_3$): δ -12.9 ppm. ^{1}H NMR ($CDCl_3$): δ 8.28, 8.23, 7.42, 7.38 (dd, Ar, 4H), 4.62-4.05 cm, $H_{1,2,3}$, 3H), 2.1-1.1 (broad, ring CH, 8H), 1.13 ppm (s, $-CH_3$, 3H). MS (70 eV): molecular ion at m/e 327.1 (7.67% base abundance). Anal. Found: C, 51.18; H, 5.66; P, 9.66.

Pure 2b was separated from 3b by preparative reverse phase (C_{18}) HPLC with 50% acetonitrile in water. Mp: 129.5-130.5 °C. ^{31}P NMR ($CDCl_3$): δ -9.7 ppm. ^{1}H NMR ($CDCl_3$): δ 8.27, 8.23, 7.41, 7.37 (dd, Ar, 4H), 4.62-3.81 (m, $H_{1,2,3}$, 3H), 2.1-0.9 (broad, ring CH, 8H), 1.03 ppm (s, $-CH_3$, 3H). MS (70 eV): molecular ion at m/e 327.1 (17.66%). Anal. Found: C, 51.17; H, 5.58; P, 9.46.

Since 3a did not separate from 2a under the identical or similar HPLC conditions as described above, no further attempt was made to isolate conformationally flexible 3a.

Equilibration (2a ⇌ 2b).

Each isomer (0.0245 mmol) was mixed with excess sodium p-nitrophenoxide (0.280 mmol) in 0.3 mL of dry DMF and heated at 52 °C for 19 h, then kept at 30 °C for 30 h. The epimer 2a yielded 2.4% of 2b (97.6% of 2a remaining unchanged) based upon ^{31}P NMR integration. Most of 2b (98.4%) was converted to 2a, leaving only 1.6% of 2b. Based upon the ^{31}P NMR integration method, the equilibrium concentration of axial (2a) and equatorial (2b) isomers at 30 °C are ca. 98% and 2% respectively. These results indicate that the axial isomer 2a is about 2.3 kcal/mol more stable than the equatorial epimer 2b at 30 °C in DMF.

Most (97.9%) of the isomer 3b was also converted to 3a, leaving only 2.1% of 3b, also indicating that the axial isomer 3a is about 2.3 kcal/mol more stable than the equatorial epimer 3b at 30 °C in DMF.

1a has been shown[13b] to be 1.95 kcal/mol more stable than its epimer 1b.

Kinetics Studies.

Kinetic measurements were carried out on a Cary 210 UV-visible spectrophotometer equipped with an automatic sample changer and thermostated cuvette holder. All the substrates were dissolved in dry, peroxide free dioxane (3.91 mM) and stored in a freezer. For each kinetic run 10λ of 3.91 mM substrate in dioxane was added to a cuvette, containing a 3.0 mL solution of 0.01 N NaOH, 1.0 N NaCl and 12% methanol in H_2O which had been kept in the thermostated holder at least for 30 min at 30.0 °C. All the reactions were followed for at least 3 half-lives by measuring the rate of appearance of the p-nitrophenoxide or p-nitrophenol at 400 nm. For each substrate kinetic measurements were repeated four times giving good first-order kinetics and all runs agreed within ±2%.

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