Crystal Structure and Absolute Configuration of (1*R*,3*S*)-(−)-*trans*-1-Benzyl-3-methyl-1-phenylphospholanium Iodide. Steric Course of Base Hydrolysis.

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Abstract: The absolute configuration of the levorotatory form of *trans*-1-benzyl-3-methyl-1-phenylphospholanium iodide has been assigned based on both the results of independent refinement of both enantiomers and the correctness of the signs of Bijvoet differences. The compound crystallizes in the orthorhombic space group $P2_12_12_1$, with a = 9.598 (5) Å, b = 11.308 (4) Å, c = 16.733 (6) Å, and Z = 4. Friedel pairs were collected out to a maximum $2\theta_{\mathrm{MoK}\bar{\alpha}}$ of 55°. Refinement led to R = 0.032 and R_w = 0.038 for the correct configuration. In agreement with the predictions made using ^{1}H NMR spectroscopy and reactions of known stereochemistry, the methyl and benzyl groups have a trans configuration. The five-membered ring is in the envelope form with the methyl group at the point of the flap. A molecular mechanics approach on related ring methyl phospholanium salts indicates that the stereochemical course of alkaline cleavage is dependent on the direction of ring pucker which alters the steric encounter between the ring methyl and approaching hydroxide ion.

Introduction

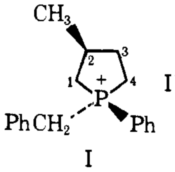
Studies by Marsi and co-workers[2] of the alkaline cleavage of chiral phospholanium salts show that product stereochemistry is a function of the nature of the departing group. For the examples cited in Table I, only retention of configuration is observed when benzyl is the departing group, Using a better leaving group, methoxy, a mixture of retention and inversion of configuration is obtained in the product phosphine oxides and the cis isomer gives the greater amount of inversion.

The inversion mechanism is considered to involve a direct displacement via a trigonal-bipyramidal transition state with the ring located diequatorially. For corresponding six membered ring containing phosphonium salts, ring strain for this placement is undoubtedly lower and 100% inversion of configuration takes place with methoxy as the leaving group.

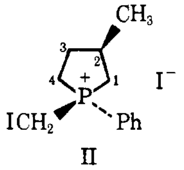
The retention mechanism is considered to proceed by way of apical attack leading to apical-equatorial ring placement followed by pseudorotation to bring the leaving group to an apical position.

It is of interest to model the alkaline cleavage reaction for the methoxy derivatives cited in Table I in order to ascertain possible reasons for the variation in retention and inversion found in the products. Marsi[2a] alluded to a greater steric effect between the ring methyl and attacking hydroxide ion as a possible cause of the reduced amount of inversion for the trans compared to the cis methoxyphospholanium derivatives.

We report the absolute configuration of *trans*-1-benzyl-3-methyl-1-phenylphospholanium iodide (I) determined by X-ray analysis on an optically pure sample[2g] kindly supplied by Professor Marsi (entry 1 of Table I). Earlier, the X-ray analysis of *cis*-1-iodomethyl-3-methyl-1-phenylphospholanium iodide (II) was reported.[3] With the knowledge of these structures, a molecular mechanics calculation is carried out to simulate the process of alkaline cleavage for the methoxy derivatives. The reaction coordinate obtained shows that the steric influence of the ring methyl depends on the type of ring puckering arrangement encountered in the inversion route.



I



II

Experimental Section

Space-Group Determination and Data Collection. An optically pure sample of *trans*-1-benzyl-3-methyl-1-phenylphospholanium iodide (I) having $[\alpha]^{22}_{\mathrm{D}}$ −2.14° [2g] was used for the X-ray diffraction analysis. A well-formed crystal shaped like a distorted truncated octahedron, which can be described as roughly spherical with a diameter of about 0.3 mm, was glued to the interior of a thin-walled glass capillary which was then sealed. Preliminary investigations using an Enraf-Nonius CAD 4 automated diffractometer and graphite monochromated Mo K$\bar{\alpha}$ radiation (fine focus tube, 45 kV, 20 mA, take-off angle = 3.1°, $\lambda K_{\alpha 1}$ = 0.709 30 Å, $\lambda K_{\alpha 2}$ = 0.713 59 Å) indicated orthorhombic (*mmm*) symmetry. From the observed extinctions $h00$, $h = 2n + 1$, $0k0$, $k = 2n + 1$, and $00l$, $l = 2n + 1$, the space group was uniquely determined as $P2_12_12_1$ (D_2^4—no. 19).[4] The lattice constants as determined by the least-squares refinement of the diffraction geometry for 25 reflections having 11.07° ≤ $\theta_{\mathrm{MoK}\bar{\alpha}}$ ≤ 15.30° and measured at an ambient laboratory temperature of 23 ± 2 °C are a = 9.598 (5) Å, b = 11.308 (4) Å, and c = 16.733 (6) Å. A unit-cell content of 4 molecules gives a calculated density of 1.449 g/cm^3 and a calculated volume of 22.7 Å^3 per nonhydrogen atom, both of which are in the range expected for such compounds. The assignment of Z = 4 was confirmed by all subsequent stages of solution and refinement.

Data were collected using the θ–2θ scan mode with a θ scan range of $(0.65 \pm 0.35 \tan\theta)°$ centered about the calculated Mo K$\bar{\alpha}$ peak position. The scan range was actually extended an extra 25% on either side of the aforementioned limits for the measurement of background radiation. The scan rates varied from 0.59 to 4.0°/min, the rate to be used for each reflection having been determined by a prescan. The intensity, I, for each reflection is then given by $I = (\mathrm{FF}/S)(P - 2(B1 + B2))$ where P are the counts accumulated during the peak scan, $B1$ and $B2$ are the left and right background counts, S is an integer which is inversely proportional to the scan rate, and FF is either unity or a multiplier to account for the occasional attenuation of the diffracted beam. The standard deviations in the intensities, σ_I, were computed as $\sigma_I{}^2 = (\mathrm{FF}^2/S^2)(P + 4(B1 + B2)) + 0.002I^2$.

A total of 4155 independent reflections having 2° ≤ $2\theta_{\mathrm{MoK}\bar{\alpha}}$ ≤ 55° were measured in both the regions $+h$, $+k$, $+l$ and $-h$, $-k$, $-l$. Five standard reflections, monitored after every 12 000 s of X-ray exposure time, gave no indication of crystal deterioration or loss of alignment. No corrections were made for absorption ($\mu_{\mathrm{MoK}\bar{\alpha}}$ = 1.86 mm^{-1}), and the intensities were reduced to relative amplitudes by means of standard Lorentz and polarization corrections, including corrections for the monochromator.

Solution and Refinement of the Structure. The solution and early stages of refinement were accomplished using only the $+h$, $+k$, $+l$ data with no corrections being applied for anomalous scattering. Initial coordinates for the I$^-$ ion were deduced from a Patterson synthesis, while initial coordinates for the 19 remaining independent nonhy-

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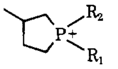
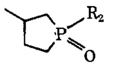
Table I. Product Distributions for Alkaline Cleavage of Phosphonium Salts[a]

		compd 		product 		
entry		R_1	R_2	retention[b]	inversion	ref
1	cis	CH_2Ph	Ph	100	0	2c,d,f
2	trans	CH_2Ph	Ph	100	0	
3	cis	OCH_3	Ph	42[c]	58	2a
4	trans	OCH_3	Ph	51[c]	49	

[a] Cis and trans refer to the orientation of R_2 and the ring methyl for entries 1 and 2. For entries 3 and 4, cis and trans refer to methoxy and ring methyl orientation. [b] Retention describes reactant–product geometry, cis–cis and trans–trans; inversion refers to cis–trans and trans–cis changes. [c] These percentages include 11% retained product by attack of hydroxide at carbon, as shown by ^{18}O labeling.[2a] The percentages for retention by attack of hydroxide at phosphorus consequently are 31 and 40% for these cis and trans methoxy derivatives, respectively.

Table II. A Comparison of the Signs of the Observed and Calculated ΔF_{Bij} for the Two Enantiomers of I

D[a]	no. of Bijvoet pairs meeting criteria[b]	no. of ΔF_{Bij} with correct sign[c]	enantiomer
4.0	33	33	I
	32	0	I*
2.0	98	94	I
	98	3	I*
1.5	140	132	I
	138	7	I*
1.0	224	205	I
	222	17	I*
0.5	397	344	I
	396	49	I*

[a] $(\Delta F_{Bij,calcd}{}^2/\sigma^2(F_0) > D$. [b] Since the two enantiomers were refined independently, the $\Delta F_{Bij,calcd}$ were not exactly the same for each, resulting in a different number of pairs meeting the criteria. [c] Correct sign indicates that $\Delta F_{Bij,obsd}$ and $\Delta F_{Bij,calcd}$ have the same sign.

Table III. Atomic Coordinates in Crystalline $(CH_3C_4H_7)$-$P(C_6H_5)(CH_2C_6H_5)I$[a]

atom type[b]	coordinates $10^4 x$	$10^4 y$	$10^4 z$
I	7237.7(4)	5203.3(3)	467.7(2)
P	5342(1)	3093(1)	3344(1)
C1	6348(5)	1756(5)	3462(3)
C2	7869(6)	2196(5)	3578(3)
C3	8032(6)	3231(6)	3011(3)
C4	6799(6)	4071(5)	3139(3)
CM	8925(7)	1197(8)	3442(4)
CP1	4127(4)	2981(4)	2535(2)
CP2	4356(6)	3569(5)	1818(3)
CP3	3429(7)	3415(6)	1191(3)
CP4	2263(7)	2694(5)	1278(3)
CP5	2027(7)	2141(5)	2001(3)
CP6	2956(5)	2266(4)	2631(2)
CB1	3505(4)	4529(4)	4188(2)
CB2	4039(6)	5674(5)	4206(3)
CB3	3150(7)	6650(5)	4136(3)
CB4	1736(8)	6463(7)	4070(3)
CB5	1193(6)	5363(8)	4062(3)
CB6	2074(6)	4381(6)	4131(3)
CB7	4455(5)	3460(4)	4265(3)

[a] Numbers in parentheses are estimated standard deviations in the last significant figure. [b] Atoms are labeled to agree with Figure 1.

drogen atoms were obtained by standard Fourier difference techniques. Unit-weighted full-matrix least-squares refinement[5] (anisotropic for I^-, isotropic for the rest) of the structural parameters for the 20 independent nonhydrogen atoms and a scale factor gave a conventional residual $R = \Sigma(|F_o| - |F_c|)/\Sigma|F_o|$ of 0.051 and a weighted residual $R_w = \{\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}^{1/2}$ of 0.060 for the 1192 reflections having $I \geq 2\sigma_I$ and $\sin\theta/\lambda \leq 0.52$. Anisotropic refinement then gave $R = 0.044$ and $R_w = 0.053$. A Fourier difference synthesis run at this stage gave geometrically reasonable initial coordinates for only one of the three methyl hydrogen atoms. Initial coordinates for the 21 remaining hydrogen atoms were then inferred from the required geometry of the molecule, using a C–H bond length of 0.98 Å. Attempts to refine the parameters for the hydrogen atoms at this and at later stages of refinement proved unsuccessful. Their positional parameters, however, were updated as refinement converged. Subsequent variable-weighted ($w^{1/2} = 2F_oLp/\sigma_I$) refinement including the hydrogen atoms as fixed isotropic scatterers, and applying dispersion corrections for all atoms except hydrogen, was based on all of the independent data (+++ and −−−, excluding the centric $0k\bar{l}$, $\bar{h}0l$, and $\bar{h}\bar{k}0$ reflections) and led to the final values of $R = 0.032$, $R_w = 0.038$, and GOF[6] = 1.112 for the 3421 reflections having $I \geq 2\sigma_I$ and $2° \leq 2\theta_{MoK\bar{\alpha}} \leq 55°$. During the final cycle of refinement the largest shift in any parameter was 0.004 times its estimated standard deviation. The only peaks of any consequence (1.072 and 0.980 e/Å^3) on a final Fourier difference synthesis were in the immediate vicinity of the I^- ion.

As a test of the correctness of the absolute configuration of the structure, I, parallel refinement for the inverse structure, I* ($x^* = 1 - x$, $y^* = 1 - y$, $z^* = 1 - z$), was accomplished. The refinement of I* converged with $R = 0.038$, $R_w = 0.046$, and GOF = 1.357, indicating that the original absolute configuration, I, is the correct one.[7]

To further test the correctness of the absolute configuration, we obtained the Bijvoet differences $F(hkl) - F(\bar{h}\bar{k}\bar{l})$, denoted as ΔF_{Bij}. It is well known that for the correct absolute configuration it is to be expected that the signs of ΔF_{Bij} observed and ΔF_{Bij} calculated will be the same. To compare the structures I and I* with respect to correctness of the signs of the Bijvoet differences, enantiomer-sensitive reflections were selected from the 3421 reflections having $I \geq 2\sigma_I$ by using the criteria $(\Delta F_{Bij,calcd})^2/\sigma^2(F_0) > D$,[8] where D was allowed to assume several values. The results, summarized in Table II, are most dramatically in agreement with the absolute configuration indicated by R_w and GOF.

Computations were done on a CDC Cyber-175 computer using LINEX, a modification of the Busing and Levy full-matrix least-squares program, ORFLS; Johnson's thermal ellipsoid plot program, ORTEP; the Oak Ridge Fortran function and error program, ORFFE; Zalkin's Fourier program, FORDAP; and several locally written programs.

Results and Discussion

Figure 1 shows the molecular geometry and atom labeling scheme for I. Atomic coordinates appear in Table III. Thermal parameters, fixed atom parameters, and bond parameters for hydrogen atoms are provided as supplementary material. Bond lengths and angles are listed in Table IV.

The five-membered ring is puckered as can be seen in the deviations from plane I in Table V. This distortion from planarity can best be described in terms of a folding along C1–C3 which brings C2 out of the plane of the four remaining ring atoms in a direction toward CB7. Atoms P, C1, C3, and C4 are coplanar to within ±0.07 Å (plane II, Table V), with C2 displaced 0.616 Å from this plane. The dihedral angle between planes II and III (Table V), which represents the extent of puckering, is 42.2°.

Variation in ring puckering is encountered in the related phospholanium iodides II[3] and III.[9] Using a common labeling scheme, the ring pucker atom in I and II is C2 but, as seen in Figure 2, puckering occurs in opposite directions relative to the phenyl group. In the case of III, having no ring substituents, the direction of ring puckering is the same as that in I.

Based on steric arguments, the difference in ring puckering in I and II seems reasonable. Location of the ring methyl substituent in II provides a lower steric interaction with the

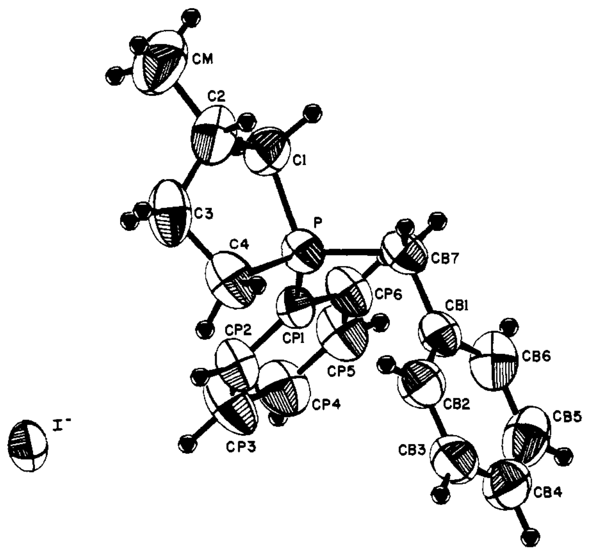


Figure 1. ORTEP plot of the salt $(CH_3C_4H_7)P^+(C_6H_5)(CH_2C_6H_5)I^-$ (I) with thermal ellipsoids at the 50% probability level for nonhydrogen atoms. Hydrogen atoms are represented by spheres of arbitrary radius.

Table IV. Bond Lengths and Angles for Nonhydrogen Atoms in $(CH_3C_4H_7)P(C_6H_5)(CH_2C_6H_5)I^a$

type^b	bond length, Å	type	bond length, Å
P-C1	1.805(6)	CB3-CB4	1.378(10)
P-C4	1.816(5)	CB4-CB5	1.349(10)
P-CP1	1.792(4)	CB5-CB6	1.400(9)
P-CB7	1.809(5)	CB6-CB1	1.387(7)
C1-C2	1.555(8)	CP1-CP2	1.388(6)
C2-C3	1.513(9)	CP2-CP3	1.386(8)
C3-C4	1.532(9)	CP3-CP4	1.392(8)
C2-CM	1.535(9)	CP4-CP5	1.380(7)
CB7-CB1	1.520(7)	CP5-CP6	1.389(7)
CB1-CB2	1.393(7)	CP6-CP1	1.393(6)
CB2-CB3	1.401(8)		

type	bond angle, deg	type	bond angle, deg
C1-P-C4	96.8(3)	CB6-CB1-CB2	118.5(5)
C1-P-CP1	111.8(2)	CB1-CB2-CB3	120.4(5)
C1-P-CB7	110.6(2)	CB2-CB3-CB4	119.1(6)
C4-P-CP1	113.6(2)	CB3-CB4-CB5	121.5(6)
C4-P-CB7	112.6(2)	CB4-CB5-CB6	119.8(5)
CP1-P-CB7	110.7(2)	CB5-CB6-CB1	120.6(6)
P-C1-C2	104.3(4)	P-CP1-CP2	121.1(4)
P-C4-C3	104.1(4)	P-CP1-CP6	118.6(3)
C4-C3-C2	108.2(4)	CP6-CP1-CP2	120.3(4)
C1-C2-C3	105.5(5)	CP1-CP2-CP3	119.4(5)
CM-C2-C1	111.4(5)	CP2-CP3-CP4	120.7(5)
CM-C2-C3	114.1(5)	CP3-CP4-CP5	119.3(5)
P-CB7-CB1	113.2(3)	CP4-CP5-CP6	120.9(6)
CB7-CB1-CB2	121.1(4)	CP5-CP6-CP1	119.3(5)
CB7-CB1-CB6	120.3(5)		

[a,b] See footnotes to Table III.

iodomethyl group relative to what it would be if the ring puckering were as in I. With the orientation of the ring methyl group as in I, the steric interaction between the methyl and phenyl groups would be larger if the puckering arrangement in II were retained. Most of the other bond parameters are very comparable among the three structures shown in Figure 2.

Using ^1H NMR spectroscopy and reactions of known stereochemistry, Marsi and co-workers[3] predicted the trans or cis configuration for a number of molecules, consistent with the X-ray structural results of II. The trans arrangement of the methyl and benzyl found for I agrees with these predictions. In addition to confirming these assignments, the present X-ray study provided the absolute stereochemistry of I. In agreement

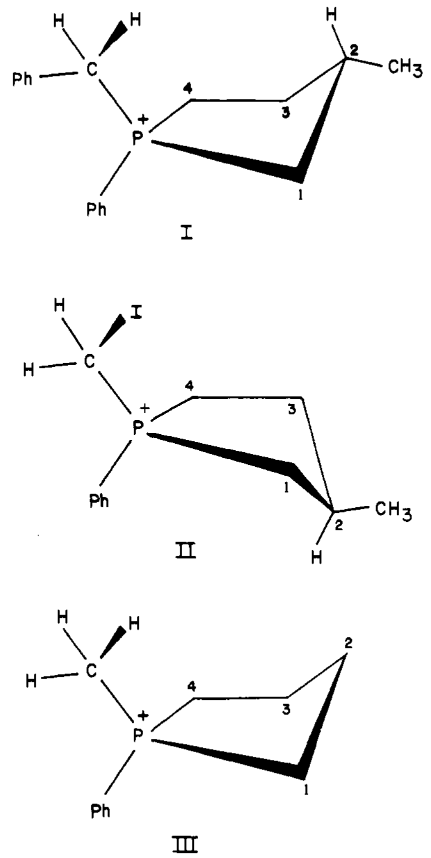


Figure 2. Ring conformations for *trans*-1-benzyl-3-methyl-1-phenylphospholanium iodide(I), *cis*-1-iodomethyl-3-methyl-1-phenylphospholanium iodide (II),[3] and methylphenylphospholanium iodide (III).[9] The atom labeling agrees with that given in Figure 1 rather than that provided by the compound names.

with the rules governing chiral derivatives, I is designated as (1*R*,3*S*)-(−)-*trans*-1-benzyl-3-methyl-1-phenylphospholanium iodide.

Molecular Mechanics Study of the Base Hydrolysis of *cis*- and *trans*-1-Methoxy-3-methyl-1-phenylphospholanium Salts. If the approach of an attacking nucleophile, e.g., a hydroxide ion, opposite the benzyl or iodomethyl groups of the cis and trans isomers of I and II (Figure 2) is considered, one might anticipate that the largest steric repulsion would occur for II between the attacking nucleophile and the cis ring methyl-phenyl orientation. In an attempt to probe steric effects more quantitatively, we employed the molecular mechanics approach outlined in the preceding article[10] to the related phospholanium salts having a methoxy group in place of the benzyl or iodomethyl as the departing group.

In accord with the above, the isomer containing the ring methyl cis to the leaving methoxy group undergoes alkaline cleavage with a greater amount of inversion of configuration relative to that for the trans isomer[2a] (cf. Table I). Since isomers of I are expected to offer little steric hindrance to the approach of an attacking hydroxide ion, the conformation of II was used to establish initial coordinates for the calculation. Even though we might expect both conformers of each isomer to exist in solution, product differentiation most likely results from nucleophilic attack on conformers containing the ring orientation shown for II (Figure 2). Therefore this conformation was chosen as a basis for the calculations.

The iodomethyl group was replaced by a methoxy group using known geometrical parameters. After minimization of the altered X-ray coordinates, the "reaction" was initiated by placing the OH^- ion 3.5 Å from the phosphorus atom, trans to the leaving methoxy group. All bond angles centered at

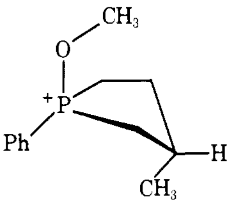
Table V. Deviations from Some Least-Squares Mean Planes in Å for I[a,b]

	I	II	III		IV		V
P	0.023	−0.066	(1.098)	CP1	−0.008	CB1	−0.012
C1	−0.143	0.050	0.0	CP2	0.010	CB2	0.009
C2	0.289	(0.616)	0.0	CP3	−0.002	CB3	−0.003
C3	−0.277	−0.060	0.0	CP4	−0.009	CB4	−0.001
C4	0.108	0.077	(1.110)	CP5	0.011	CB5	−0.002
CM	(−0.172)	(0.400)		CP6	−0.002	CB6	0.008
CB7	(1.551)	(1.322)		P	(−0.079)	CB7	(0.003)
CP1	(−1.394)	(−1.627)					

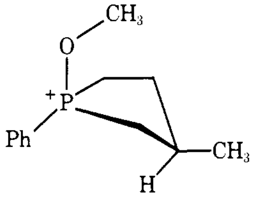
[a] Entries in parentheses are for atoms not included in the calculation of the plane. Atoms labeled to agree with Figure 1. [b] Selected dihedral angles (deg): II and III = 42.2, II and IV = 69.6, II and V = 18.7, I and IV = 60.4, I and V = 17.4.

phosphorus were given zero bending force constants. With a zero value for the P–OH stretching force constant, the OH^- ion is subject only to van der Waals interactions. Steric repulsions from substituents on phosphorus may force the OH^- ion to move further away. In subsequent steps along the reaction coordinate, the OH^- ion was allowed to move closer to phosphorus by decreasing the strainless bond length for the P–OH bond and assigning this bond an increasingly larger stretching force constant. Also in later steps, the CH_3O–P–OH angle was assigned a bending force constant of 1 mdyn·Å/rad^2 to assume an inline attack; i.e., it is felt that an apical orientation in the trigonal bipyramid that is forming represents the preferred configuration for the transition state.[11]

The interesting feature of the calculation, performed on the methoxy isomer conformations IV and V, is found in the initial steps. When the approach of the OH^- ion is unconstrained but placed 3.5 Å from the phosphorus atom, energy minimization shows that its approach is effectively blocked in IV by the cis orientation of the methyl and phenyl groups. The OH^- ion moves to an equilibrium position of 5.1 Å and the resultant strain energy is 26.4 kcal/mol. In this same step for isomer V, the equilibrium position of the OH^- ion is 3.2 Å with an energy of 19.7 kcal/mol.



IV-*trans*



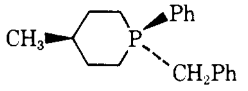
V-*cis*

In the second step, when the P–OH bond length is reduced to 3.00 Å and a small P–OH stretching force constant, k_s = 0.19 mdyn/Å, is imposed, the OH^- ion moves much closer to the phosphorus atom in isomer IV, 3.1 Å. However, it does not remain in line but is forced to the edge of the five-membered ring, more appropriate for cis attack rather than trans attack. In contrast, the phenyl group of isomer V, which already begins to rotate out of the way of the attacking OH^- ion, continues to do so. Here the OH^- ion remains essentially in line at 3.1 Å from the phosphorus atom.

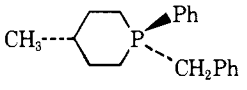
In order to constrain the OH^- ion to approach isomer IV in line, i.e., trans to the leaving methoxy group, the calculations were repeated with a small bending force constant k_θ = 0.2 mdyn·Å/rad^2 for the O–P–O angle. Other conditions remained as outlined for the second step. The geometry of IV became nearly in line with respect to attack by the OH^- ion but the strain energy rose by about 0.6 kcal/mol. The effect of this constraint on the geometry of isomer V was slight, producing an increase in strain energy of only 0.1 kcal/mol. If k_θ is progressively increased toward 1 mdyn·Å/rad^2, again little change in V is noted. However, use of the latter value for IV causes the ring puckering to change from the type shown in Figure 2 for II to I. As a result the strain energy drops to that near isomer V. Further calculations as the OH^- ion is brought even closer to the phosphorus atom show little difference in strain energy between the two isomers IV and V.

In summary it is concluded, in agreement with the initial suggestion by Marsi,[2a] that the decreased amount of inversion at phosphorus for *trans*-IV compared to *cis*-V is primarily a result of the relative positioning of the ring methyl group in IV which results in a steric interference to in-line attack by hydroxide ion. It appears that for the trans isomer IV edge attack (along the side of the ring) leading to a trigonal-bipyramidal transition state having the ring oriented apical-equatorially is a favored route. Of course these calculations are limited since we have not comparatively investigated the pseudorotational pathway involving square-pyramidal barrier states[11,12] leading to retention of configuration at phosphorus.

Compared to the base hydrolysis reactions of *cis*- and *trans*-1-phenyl-1-benzyl-4-methylphosphorinanium bromides VI, modeled in the preceding article,[10] where steric interference to in-line OH^- ion attack occurred in the transition state, steric interference in IV is encountered in the ground state. Hence, reaction leading to reduced inversion for the five-membered-ring compound IV appears to result from kinetic shielding, whereas a higher transition state barrier energy appears to cause the reduced amount of inversion in the corresponding trans six-membered-ring derivative VI-*trans*.



VI-*cis*



VI-*trans*

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Supplementary Material Available: A compilation of observed and calculated structure factor amplitudes, thermal parameters, fixed atom parameters, and bond parameters for hydrogen atoms for I (16 pages). Ordering information is given on any current masthead page.

References and Notes

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Transition-State Effects in the Divalent Metal Ion Catalysis of Acetal Hydrolysis

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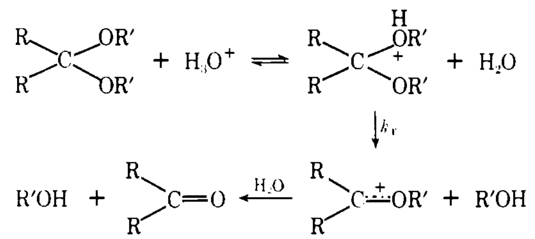
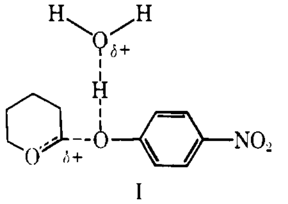
Abstract: The rates of hydrolysis of a series of substituted benzaldehyde methyl 8-quinolyl acetals have been determined in 50% dioxane–H_2O (v/v) at 30 °C. The reactions involve hydronium ion catalyzed hydrolysis of the neutral and protonated species. Hammett ρ values are −3.1 and −2.6, respectively. These acetals are also subject to general acid catalysis. Divalent metal ions (Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, and Zn^{2+}) exert a large catalytic effect even though binding to the reactant is very weak. For example, a 0.02 M concentration of Ni^{2+} (1000-fold excess) at pH 7.2 produces a 2×10^5 enhancement in k_{obsd} for hydrolysis of 3,4-dichlorobenzaldehyde methyl 8-quinolyl acetal, but there is no indication of saturation effects. The rate constants for metal ion catalysis of the hydrolysis of the substituted benzaldehyde methyl 8-quinolyl acetals vary with changing substituents in the same manner as those for the hydronium ion catalyzed reactions. At constant metal ion concentration k_{obsd} is pH independent at pH values above the pK_a of the quinoline nitrogen. Metal ion catalysis must be due to a transition-state effect in which the leaving group is stabilized. Incorporation of a second functional group which can chelate the metal ion, as in 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal, leads to strong binding to the reactant; i.e., saturation effects are observed at low metal ion concentrations (10^{-2}–10^{-3} M), but catalytic effects at >0.01 M metal ion concentration are slightly less than with the 8-quinolyl acetals where reactant binding is weak. This emphasizes the importance of transition-state binding in these reactions.

The mechanism of hydronium ion catalyzed hydrolysis of simple acetals has been well established as the classical A-1 mechanism (eq 1) in which there is preequilibrium protonation of the acetal followed by rate-determining breakdown of the conjugate acid to an alcohol and a resonance-stabilized carbonium ion.[2,3] In this mechanism protonation facilitates departure of the leaving group. In the light of eq 1, it might be expected that metal ions would also effectively catalyze the reactions if they could bind to the reactant. Apparently, simple acetals without metal ion coordinating functional groups are not subject to metal ion catalyzed hydrolysis. However, Clark and Hay[4] found that hydrolysis of 8-quinolyl β-D-glucopyranoside is catalyzed by metal ions. Binding to the substrate was found to be weak, and saturation effects could not be achieved.



(1)

General acid catalysis and partially rate-determining protonation by hydronium ion occur in cases where C–O bond breaking is facile,[5,6] owing to a good leaving group (a phenol) in combination with a moderately stable carbonium ion intermediate,[7-9] or to a highly stabilized carbonium ion when the leaving group is poor.[10,11] In those reactions, protonation and C–O bond breaking occur in a concerted manner, as, for example, in I.[5-7] A metal ion should participate similarly; i.e., its effect would be a transition-state effect. A transition-state effect in which the leaving group is stabilized has been regarded as a possibility in metal ion catalyzed ester and amide hydrolysis,[12-15] but evidence is lacking. In order to determine the effectiveness of metal ions in reactions in which C–O bond breaking is part of the rate-determining step, we have studied the hydrolysis of substituted benzaldehyde methyl 8-quinolyl acetals such as II, and, to determine the effects of strong metal ion binding to the reactant, the hydrolysis reactions of 3,4-dichlorobenzaldehyde 8-(2-carboxyquinolyl) methyl acetal (III) have been investigated. Mixed methyl phenyl acetals of substituted benzaldehydes have been shown to be subject to general acid catalysis in their hydrolysis reactions.[9,16]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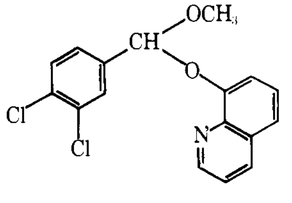
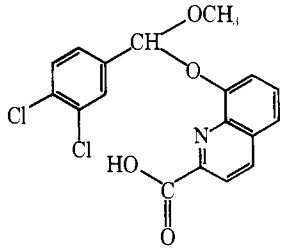

II


III

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