kinetics from the transient observed in the PhH/Cl• system. On the other hand, if only the <330- and 490-nm bands are found at the earliest times, it would be proof that the spectrum must be attributed to the CCH.

A second crucial test would result from examination of the C_6H_6/Cl• system in the picosecond regime with high arene concentrations, in a manner similar to what was done in the iodine atom studies.[25,26] This might help answer questions regarding simultaneous or sequential appearance of the <330- and 490-nm bands and provide a rate constant for formation of the chlorine atom/benzene π-complex which would be applicable where the Cl atom is generated in contact with benzene molecules.

The existence of Br atom or I atom π-complexes with arenes appears well documented.[47] We have provided evidence which suggests that the complex formed between a Cl atom and a benzene molecule is the 6-chlorocyclohexadienyl radical. For fluorine, the spectroscopic evidence is solely for the 6-fluorocyclohexadienyl radical.[38] There appears to be a gradation from relatively weak interactions, i.e., I• and arene (best viewed as a π-complex), to stronger covalent interactions (best viewed as a 6-halocyclohexadienyl radical or σ-complex) in the series I → F. This transition from the π- to σ-complex should be accompanied by (1) an alteration of angle between the carbon–halogen bond and the plane of the benzene ring (from 90° when X = I to 120° when X = F) and (2) a decrease in the C–X bond length. We bring this hypothesis to the attention of theoreticians.

Registry No. DMB, 79-29-8; MA, 108-31-6; CCH, 67542-83-0; PhH, 71-43-2; D_2, 7782-39-0; (*E*)-ClCH=CHCl, 156-60-5; Cl_2C=CHCl, 79-01-6; Cl_2C=CCl_2, 127-18-4; pentane, 109-66-0; 2,4-dimethylpentane, 108-08-7; cyclohexane, 110-82-7; neopentane, 463-82-1; propane, 74-98-6.

Supplementary Material Available: Quantitation of the effects of variations in [DMB], [PhH], and [T] and a table of least-squares analysis of data (9 pages). Ordering information is given on any current masthead page.

Stereoelectronic Effects in the Hydrolysis of Bicyclic and Acyclic Phosphates and Phosphorothionates

Tahsin Fanni,[1a] Kazunari Taira,[1a] David G. Gorenstein,*[1a] Ramamoorthy Vaidyanathaswamy,[1b] and John G. Verkade*[1b]

Contribution from the Department of Chemistry, University of Illinois at Chicago, Box 4348, Chicago, Illinois 60680, and Gilman Hall, Department of Chemistry, Iowa State University, Ames, Iowa 50011. *Received December 27, 1984. Revised Manuscript Received January 27, 1986. Revised Manuscript Received June 9, 1986*

Abstract: The bicyclic phosphate $OP(OCH_2)_3CCH_3$ (**1**) hydrolyzes 5.2×10^3 times faster than the acyclic compound $OP(OCH_2CH_3)_3$ at pH 14. At the same pH the bicyclic phosphorothionate $SP(OCH_2)_3CCH_3$ (**2**) hydrolyzes 8.1×10^2 times faster than the acyclic compound $SP(OCH_2CH_3)_3$. Part of this rate enhancement is attributed to a stereoelectronic factor since compounds **1** and **2** have two lone pairs antiperiplanar (app) to the breaking P–O bond, while in order to place two lone pairs app to the breaking P–O bond in the acyclic compounds, the molecule must be constrained to an appropriate conformation which is disfavored entropically. The anion $^-O_2P(OCH_2)_2CCH_3(CH_2OH)$ (**3**), which is the base hydrolysis product of **1**, was identified by ^1H, ^{13}C, and ^{31}P NMR spectroscopy. Its derivatives $HO_2P(OCH_2)_2CCH_3(CH_2OH)$ (**4**), the diastereomeric ester $MeO_2P(OCH_2)_2CCH_3(CH_2OH)$ (**5a,b**), and the diastereomeric ether–ester $MeO_2P(OCH_2)_2CCH_3(CH_2OCH_3)$ (**6a,b**) were isolated and characterized by ^1H and ^{13}C NMR and by mass spectroscopies. The anion $^-O(S)P(OCH_2)_2CCH_3(CH_2OH)$ (**7**), which is the base hydrolysis product of **2**, is shown to be a single isomer by the ^1H NMR spectrum of its neutral ester derivative, $CH_3S(O)P(OCH_2)_2CCH_3(CH_2OH)$, obtained via methylation of the acid **8** with diazomethane. The 2-oxo and 5-methyl substituents of **7** are cis to one another as is strongly suggested by the structural determination of the acid derivative **8** of **7** by X-ray means. These results are consistent with apical OH^- attack on phosphorus followed by apical departure of an alkoxy oxygen.

In one of our laboratories it was shown through ab initio molecular orbital calculations[2-8] and experimentally[9-14] that kinetic stereoelectronic effects[15-19] may play important roles in the reactions of organophosphorus compounds. In phosphate esters, these stereoelectronic effects involve facilitating the cleavage of

(1) (a) University of Illinois at Chicago. Address correspondence to D. G.G.: Chemistry Department, Purdue University, West Lafayette, Indiana 47907. (b) Iowa State University.

(2) Taira, K.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 7825.

(3) Gorenstein, D. G.; Findley, J. B.; Luxon, B. A.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 3473.

(4) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B.; Momii, R. *J. Am. Chem. Soc.* **1977**, *99*, 4170.

(5) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 8048.

(6) Gorenstein, D. G.; Luxon, B. A.; Goldfield, E. M. *J. Am. Chem. Soc.* **1980**, *102*, 1757.

(7) Gorenstein, D. G.; Rowell, R.; Taira, K. *ACS Symp. Ser.* **1981**, *No. 171*, 69.

(8) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5869.

(9) (a) Taira, K.; Gorenstein, D. G. *Tetrahedron* **1984**, *40*, 3215. (b) Taira, K.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1982**, *104*, 6130.

(10) Taira, K.; Lai, K.; Gorenstein, D. G. *Tetrahedron* **1986**, *42*, 229.

(11) Taira, K.; Fanni, T.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1521.

(12) Taira, K.; Fanni, T.; Gorenstein, D. G. *J. Org. Chem.* **1984**, *49*, 4531.

(13) Yang, J.-C.; Gorenstein, D. G. *Tetrahedron Lett.* **1984**, *41*, 4627.

(14) Taira, K.; Mock, W. L.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 7831.

(15) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983; pp 1-149.

(16) (a) Deslongchamps, P.; Taillerfer, R. J. *Can. J. Chem.* **1975**, *53*, 3029 and references cited therein. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

(17) Lehn, J. M.; Wipff, G. *J. Chem. Soc., Chem. Commun.* **1975**, 800.

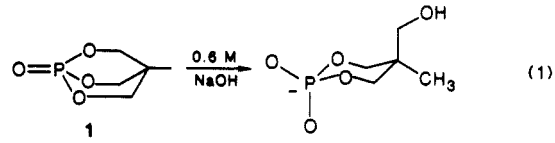
(18) (a) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 4048. (b) Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498. (c) Lehn, J. M.; Wipff, G. *Helv. Chim. Acta* **1978**, *61*, 1274.

(19) (a) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371; (b) Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* **1972**, *25*, 117.

0002-7863/86/1508-6311$01.50/0

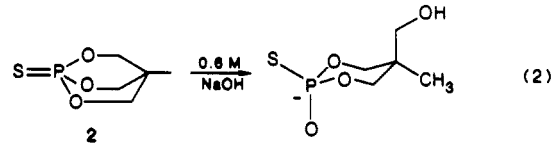
a P–O or a P–N bond by antiperiplanar (app) interaction with oxygen or nitrogen electron pairs. Calculations have suggested that orientation of a lone pair antiperiplanar (app) to a scissile bond can lower the energy of the transition state by as much as 11 kcal/mol relative to a corresponding transition state without an app lone pair.[5,8] The stereoelectronic effect in the hydrolysis of phosphate esters is believed to be due to n_o (oxygen lone pairs) $\leftrightarrow \sigma^*_{P-O}$ (P–O antibonding orbital) orbital mixing which facilitates P–O bond cleavage or formation.

Phosphate esters undergo marked changes in the rate of hydrolysis upon inclusion of the phosphorus atom into a monocyclic or bridgehead bicyclic system.[9-14] The rate of hydrolysis of the strained five-membered ring cyclic phosphates such as methyl ethylene phosphate and ethylene phosphate is 10^6 to 10^8 times that of their acyclic analogues, trimethyl phosphate and dimethyl phosphate, respectively.[20] However, the energy released from a strained cyclic ester in going to a "strain free" cyclic phosphorane transition state is insufficient to explain the total lowering of activation energy. We have shown[9-12] that part of this rate enhancement is probably due to the stereoelectronic effect. In this article we present an example of rate enhancement in bicyclic phosphate **1** and phosphorothionate, **2**, compared to their acyclic



(1)

1 **3**



(2)

2 **7**

analogues triethyl phosphate and triethyl phosphorothionate, respectively.

$$(EtO)_3P{=}O \xrightarrow[NaOH]{0.6\ M} (EtO)_2PO_2^- + EtOH$$

$$(EtO)_3P{=}S \xrightarrow[NaOH]{0.6\ M} (EtO)_2P(O)S^- + EtOH$$

Part of this rate enhancement is suggested to be due to the stereoelectronic effect.

Experimental Section

^1H NMR spectra were recorded on 60-MHz Varian T-60 or Varian EM-360 NMR spectrometers or on a Nicolet NT-300 300-MHz spectrometer. ^{31}P NMR spectra were recorded on a Bruker WP-80 spectrometer at 32.4 MHz or on a Bruker WM-300 spectrometer at 121.51 MHz. ^{13}C NMR spectra were recorded on an IBM WP-200 SY spectrometer at 50.3 MHz or on a Nicolet NT-300 spectrometer at 75.46 MHz. Chemical shifts in parts per million for ^1H and ^{13}C NMR spectra are referenced to internal Me_4Si or acetone and for ^{31}P spectra are referenced to external 85% H_3PO_4 with positive values downfield from the reference. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

The bicyclic phosphate **1**, the bicyclic phosphorothionate **2**, and triethyl phosphorothionate were prepared as described previously.[21] Compound **2** was also prepared by the route reported for $SP(OCH_2)_3C$-*t*-Bu from the corresponding phosphite ester.[22] Triethyl phosphate was purchased from Aldrich and used without further purification.

Hydrolysis in Strong Alkali. Bicyclic Phosphate 1. In 0.5 mL of dry dioxane was dissolved 3.18 mg (0.0194 mmol) of **1**, 0.4 mL of 0.6 M NaOH in D_2O was added, and the reaction was monitored by ^{31}P NMR at 31 °C. The hydrolysis was completed in ca. 10 min.

Triethyl Phosphate. In 0.5 mL of dry dioxane was dissolved 4.00 mg (0.0220 mmol) of triethyl phosphate, 0.4 mL of 0.6 M NaOH in D_2O was added, and the reaction was monitored by ^{31}P NMR at 31 °C.

Bicyclic Phosphorothionate 2. In 0.5 mL of dry dioxane was dissolved 3.240 mg of **2** (0.0180 mmol), 0.4 mL of 0.6 M NaOH in D_2O was added, and the reaction was monitored by ^{31}P NMR at 31 °C.

Triethyl Phosphorothionate. In 0.5 mL of dry dioxane was dissolved 3.50 mg (0.0177 mmol) of triethyl phosphorothionate, 0.4 mL of 0.6 M NaOH in D_2O was added, and the reaction was monitored by ^{31}P NMR at 31 °C. In all cases the reactions followed good first-order kinetics over at least 2 half-lives and were repeated at least twice, and calculated rate constants agreed within ±10%. The hydrolysis of the acyclic compounds is known to go by complete P–O bond cleavage, and the rate constants were reported earlier.[23]

Product Analysis of Hydrolysis of 1 and 2. $^-O_2P(OCH_2)_2CCH_3(CH_2OH)$ (3). The bicyclic phosphate **1** gives upon hydrolysis the monocyclic phosphate anion **3** (^{31}P NMR −3.2 ppm; ^{13}C NMR (CD_3OD/Me_4Si) 80.50 d (2 ring CH_2, ^2J(POC) = 5 Hz), 64.75 s (CH_2OH), 35.4 d (CC_4, ^3J(POCC) = 3.8 Hz), 12.30 s (CH_3)).

$HO_2P(OCH_2)_2CCH_3(CH_2OH)$ (4). Bicyclic phosphate **1** (820 mg, 5.00 mmol) was dissolved in 100 mL of dioxane, and 100 mL of 0.6 M NaOH were added. After being stirred for 2 h at room temperature the solution was neutralized to pH 7 with HCl and evaporated to about 5 mL. Addition of 20 mL of ethanol and filtration of the precipitated NaCl was followed by evaporation to dryness. The residue was dissolved in 5 mL of water, and the solution was passed through 20 g of Dowex 50-8-W ion exchange resin in the acid form. The 80 mL of solution collected was evaporated to dryness, and the product **4** was obtained in nearly quantitative yield (^1H NMR (acetone-d_6) 4.22 dd (OCH(eq), ^3J(POCH) = 15.3, ^2J(HCH) = 11.3), 4.05 dd (OCH(ax), ^3J(POCH) = 9.7, ^2J(HCH) = 11.1), 3.56 s (CH_2OH), 0.92 s (CH_3); ^{13}C NMR (D_2O/Me_2CO) 72.64 d (ring CH_2, ^2J(POC) = 2.9), 62.18 s (CH_2OH), 36.15 s (CC_4), 14.54 s (CH_3); *m/e* 183 (M + 1) base peak 99 $P(OH)_4^+$); high-resolution MS calcd 183.0422, found 183.0422).

$CH_3O_2P(OCH_2)_2CCH_3(CH_2OH)$ (5a,b) and $CH_3O_2P(OCH_2)_2CCH_3(CH_2OCH_3)$ (6a,b). Reaction of 0.183 g (1.00 mmol) of **4** with excess diazomethane (0.5 g) for 2 h at room temperature in 10 mL of ether gave upon evaporation of the solvent an oily residue which was eluted from silica gel with 10% acetone in benzene. The slower moving compound (55% by weight) was an approximately 50/50 mixture of **5a,b** (^1H NMR ($CDCl_3$) 4.30 dd (OCH(ax), ^3J(POCH) = 6.1, ^2J(HCH) = 11.0), 4.10 dd (OCH(eq), ^3J(POCH) = 21.6, ^2J(HCH) = 11.0), 3.90 m (2 ring CH_2), 3.70 d (2 CH_3O), 3.63 s (CH_2OH), 3.33 d (CH_2OH, *J* = 3.9), 1.06 s (CH_3), 0.75 s (CH_3); ^{13}C NMR ($CDCl_3$/Me_4Si) 74.12 d (ring CH_2, ^2J(POC) = 5.3), 72.77 d (ring CH_2, ^2J(POC) = 6.7), 63.28 s (CH_2OH), 61.61 s (CH_2OH), 52.96 d (CH_3O, ^2J(POC) = 5.7), 52.82 d (CH_3O, ^2J(POC) = 6.2), 36.41 d (CC_4, ^3J(POCC) = 5.3), 35.99 d (CC_4, ^3J(POCC) = 6.7), 16.34 s (CCH_3), 14.43 s (CCH_3); *m/e* 197 (M + 1) base peak 113 ($CH_3OP(OH)_3^+$)).

The faster moving component (45% by weight) was an approximately 50/50 mixture of **6ab** (^1H ($CDCl_3$) 4.37 dd (OCH(ax), ^3J(POCH) = 4.9, ^2J(HCH) = 11), 4.17 dd (OCH(eq), ^3J(POCH) = 21.5, ^2J(HCH) = 11), 4.00 m (2 ring CH_2), 3.82 d (2 CH_3OP, ^3J(POCH) = 11.1), 3.51 s (CH_2OH), 3.39 s (CH_3OC), 3.31 s (CH_3OC), 3.19 s (CH_2OH), 1.19 s (CH_3C), 0.86 s (CH_3C); *m/e* 211 (M + 1) base peak 113 $CH_3OP(OH)_3^+$)).

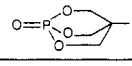
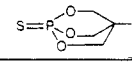
$^-O(S)P(OCH_2)_2CCH_3(CH_2OH)$ (7). The hydrolysis of the bicyclic phosphorothionate **2** gives the monocyclic phosphorothionate anion **7** (^{31}P NMR 52.4; ^{13}C NMR (CD_3OD) 73.36 d (2 ring CH_2, ^2J(POC) = 6 Hz), 65.7 s (CH_2OH), 38.55 d (CC_4, ^3J(POCC) = 5 Hz), 17.9 s (CCH_3)).

$HO(S)P(OCH_2)_2CCH_3(CH_2OH)$ (8). A 100-mg sample of **2** (0.556 mmol) was stirred at room temperature with 12 mL of 0.6 M NaOH and 15 mL of dioxane for 24 h. The solution was neutralized with dilute HCl to pH 6 whereupon water and dioxane were removed at room temperature under vacuum. The residue was taken up in absolute ethanol and filtered to remove sodium chloride. The filtrate was concentrated to obtain a white solid which was dissolved in a minimum amount of acetone and filtered. The filtrate on evaporation provided a single isomer of the corresponding acid **8** (*m/e* 198, (calcd 198), base peak (145) $SP(OH)_2(OH_2)^+$; high resolution MS (M + 1) calcd 199.0194, found 199.0182) as revealed by a single peak in the ^{31}P NMR spectrum (acetone-d_6, 54.0 ppm) and the single set of peaks in the ^{13}C NMR spectrum ((acetone-d_6) 72.4 d (2 ring CH_2, ^2J(POC) = 7.2), 62.9 s (CH_2OH), 37.1 d (CC_4, ^3J(POCC) = 4.4), 15.9 s (CCH_3)).

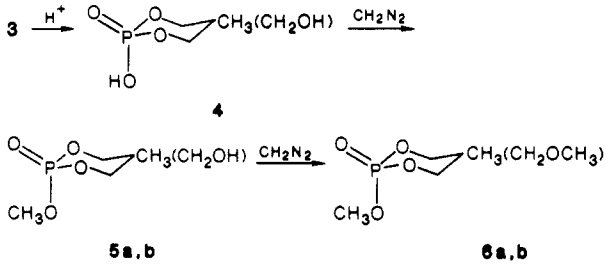
The product from one preparation of **8** was recrystallized from acetone/chloroform (1/1) to afford crystals suitable for X-ray analysis.[24]

(20) Gerlt, J. A.; Westheimer, F. H.; Sturtevant, J. M. *J. Biol. Chem.* **1975**, *250*, 5059.
(21) Verkade, J. G.; Reynolds, L. T. *J. Org. Chem.* **1960**, *25*, 663.
(22) Milbrath, D. S.; Engel, J. L.; Verkade, J. G.; Casida, J. E. *Toxicol. Appl. Pharmacol.* **1979**, *47*, 287.
(23) Cox, J. R.; Ramsay, O. B. *Chem. Rev.* **1964**, *64*, 317.
(24) Vaidyanathaswamy, R.; Benson, J.; Jacobson, R. A.; Verkade, J. G., to be published.

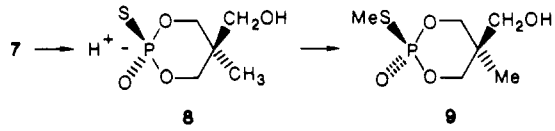
Table I. Observed Pseudo-First-Order Rate Constants for Hydrolysis of **1**, **2**, $(EtO)_3P{=}O$, and $(EtO)_3P{=}S$ in 0.6 M NaOH, 55% Dioxane/45% D_2O at 31 °C

		$(EtO)_3P{=}O$		$(EtO)_3P{=}S$
$k_{obsd} \times 10^{-3}$ s^{-1}	7.5	0.00149	0.097	0.00012

Scheme I



Scheme II



Crystal parameters, bond distances and angles, thermal and positional parameters, as well as details of the refinement can be obtained as Supplementary Material to this paper.

$CH_3S(O)P(OCH_2)_2CCH_3(CH_2OH)$ (9). The product from a second preparation of **8** was reacted with excess CH_2N_2 analogously to the preparation of **5a,b** and **6a,b**. The only product was the corresponding *S*-methyl ester **9** (TLC on silica gel with 10% acetone in benzene revealed only one spot; *m/e* 212 (calcd 212) base peak 129, $MeSP(OH)_3^+$; ^1H NMR ($CDCl_3$) 1.21 s (CCH_3), 2.35 d (SCH_3, ^3J(PSCH) = 15.3), 3.49 s (CH_2OH), 4.05 dd (2 OCH(eq), ^3J(POCH) = 21.6, ^2J(HCH) = 11 Hz), 4.44 dd (2 OCH(ax), ^3J(POCH) = 6, ^2J(HCH) = 11); ^{13}C NMR ($CDCl_3$) 11.23 d (SCH_3, ^2J(PSC) = 4.5), 17.73 s (CCH_3), 37.64 d (CC_4, ^3J(POCC) = 7.4), 64.87 s (CH_2OH), 74.68 d (ring CH_2, ^2J(POC) = 7.0)).

Results and Discussion

The pseudo-first-order rate constants for the hydrolyses were monitored by following the loss of the ^{31}P signal for the starting material as well as the appearance of the product signal. The rate of hydrolysis of the bicyclic phosphate **1** as shown in Table I is 5.2×10^3 times that of the acyclic phosphate while the rate of hydrolysis of the bicyclic phosphorothionate **2** is 8.1×10^2 times that of the acyclic phosphorothionate. Aksnes and Bergesen[25] possibly briefly report a similar rate acceleration for the bicyclic phosphate ester **1**. (This assumes that compound X in Table 1 of ref 26 is incorrectly drawn and is actually the same as our compound **1**.) The ^{13}C and ^{31}P NMR spectra of the hydrolysis products **3** and **7** are consistent with the structures shown and also with the existence of one isomer of **7**. Confirmatory evidence for the structure of **3** was obtained from the characterization of the isolated acid **4**, the methyl ester **5a,b**, and of the methyl ester–ether **6a,b** in Scheme I. Although the stereochemistries of the diastereomeric **5a,b** and **6a,b** cannot be unequivocably assigned, the spectral data are consistent with cis–trans isomerism of the P=O and CCH_3 groups. The conformations of these diastereomers are probably strongly influenced by the strong tendency of the P=O group to be equatorial in phosphate esters.[26] Evidence for a single isomer of **7** stems from the single ^{31}P NMR peak and the single set of ^{13}C NMR peaks for the entire organic reaction product **8** obtained upon acidification of **7** and also from the single TLC spot and the single sets of peaks in the ^1H and ^{13}C NMR spectra

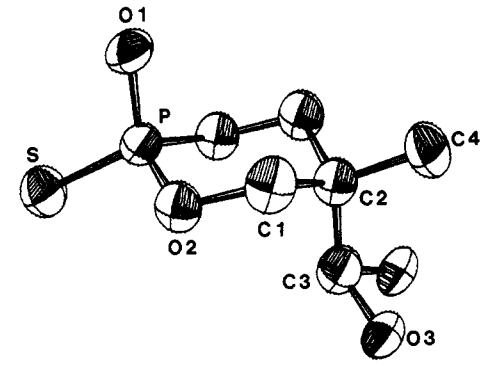
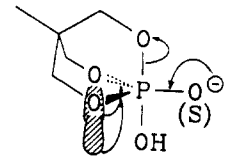


Figure 1. ORTEP drawing of **8**. Only the non-hydrogen atoms are shown. Two O3 atoms are shown because of the disorder of this atom about the molecular mirror plane.[25]

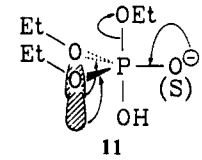
of the *S*-methyl ester **9** (Scheme II). The stereochemistry of **7** was determined by obtaining the crystal and molecular structure of the corresponding acid **8**. In the ORTEP drawing of **8** in Figure 1 the cis relationship of the thio and hydroxymethyl groups can be seen.

The rate enhancement in methyl and ethyl ethylene phosphates compared to their acyclic analogues was explained[12,20,27] *partially* by the release of ring strain in going to a "strain-free" cyclic phosphorane transition state. However, in the case of the bicyclic phosphate or bicyclic phosphorothionate the lowering of the activation energy in going to the bicyclic phosphorane transition state cannot be totally ascribed to release of ring strain, because it is not favored over the ground state owing to the placement of one of the six membered rings in two equatorial positions as well as two six-membered rings in an unfavorable apical/equatorial position of the trigonal bipyramidal transition state.



10

As can be seen from structure **10** each of the two equatorial endocyclic oxygens have lone electron pairs which are approximately app to the breaking apical P–O bond, and this is suggested to be mainly responsible for the increased rate of cleavage of this bond relative to its acyclic analogues, triethyl phosphate and phosphorothionate. In these acyclic compounds, freezing of one conformation is required to place two lone pairs app to the breaking P–O bond, **11**. This conformational restriction will be entropically disfavored.[3-5]



11

Conclusion

The results of the hydrolyses reactions suggest that the reactivity differences between the bicyclic phosphate and phosphorothionate and their acyclic counterparts can be accounted for by stereoelectronic effects in the transition states/intermediates. The results of the structural investigations are consistent with stereospecificity in the hydrolysis of **2**.

Acknowledgment. Support by NSF (Chem 83K0098 and CHE-8315313) and DOD (ARO-K-0098) is greatly appreciated. We thank Professor William Mock for his helpful discussions.

(25) Aksnes, G.; Bergesen, K. *Acta Chem. Scand.* **1966**, *20*, 2508.
(26) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.
(27) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70.

Registry No. 1, 1449-89-4; **2**, 3196-56-3; **3**, 103731-66-4; **4**, 103731-67-5; **5a**, 103731-68-6; **5b**, 103731-69-7; **6a**, 103731-70-0; **6b**, 103731-71-1; **7**, 103731-72-2; **8**, 103731-73-3; **9**, 103731-74-4; triethyl phosphate, 78-40-0; triethyl phosphorothionate, 36061-67-3.

Supplementary Material Available: Tables of data for the X-ray crystal and molecular structure, final positional parameters, bond distances and angles, and final thermal parameters for HO(S)-$P(OCH_2)_2CCH_3(CH_2OH)$ (**8**) (5 pages); table of structure factors (1 page). Ordering information is given on any current masthead page.

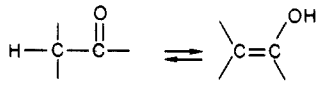
Generation of Simple Enols in Aqueous Solution from Alkali Metal Enolates. Some Chemistry of Isobutyraldehyde Enol

Y. Chiang, A. J. Kresge,* and P. A. Walsh

Contribution from the Department of Chemistry, University of Toronto, Scarborough College, Scarborough, Ontario M1C 1A4, Canada. *Received March 18, 1986*

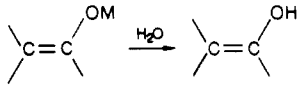
Abstract: The enol isomer of isobutyraldehyde was generated in aqueous solution by reaction of its lithium and potassium enolates with water and of the trimethylsilyl enol ether with fluoride ion, and rates of ketonization of the enol were measured in HCl, DCl (in D_2O), and NaOH solutions and in $CNCH_2CO_2H$, HCO_2H, CH_3CO_2H, $CH_2ClPO_3H^-$, and $H_2PO_4^-$ buffers. Rates of enolization of isobutyraldehyde were also determined, by iodine scavenging, in $HClO_4$ and NaOH solutions. The reaction rates in HCl and NaOH give two independent estimates of the keto–enol equilibrium constant for isobutyraldehyde in aqueous solution at 25 °C, which are in good agreement with each other and whose average is $K_E = (1.37 \pm 0.09) \times 10^{-4}$, $pK_E = 3.86 \pm 0.03$. The ketonization rates in NaOH solution also provide an estimate of the acidity constant of isobutyraldehyde enol ionizing as an oxygen acid, $K_a^E = (2.37 \pm 0.14) \times 10^{-12}$ M, $pK_a^E = 11.63 \pm 0.03$, which, when combined with K_E, gives the acidity constant of the keto form of isobutyraldehyde ionizing as a carbon acid, $K_a^K = (3.23 \pm 0.29) \times 10^{-16}$ M, $pK_a^K = 15.49 \pm 0.04$. The ketonization reaction in buffer solutions shows both general-acid and general-base catalysis, consistent with two parallel reaction paths involving rate-determining β-carbon protonation of both enol and enolate ion. Analysis of the data in terms of this scheme shows enolate to be 10^8 times more reactive than enol. Arguments are advanced to the effect that all of the present data are consistent with stepwise reaction mechanisms and do not require a concerted reaction path.

The equilibrium between simple monofunctional aldehydes and ketones and their enol isomers, eq 1, is generally quite mobile, and its position usually favors the carbonyl isomer quite strongly. This has made direct observation of simple enols difficult and has hampered the development of their chemistry.



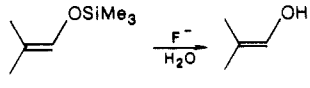
(1)

Simple enols can, however, be produced in greater than equilibrium proportions by, for example, the rapid reaction of alkali metal enolates with water, eq 2. The isomerization of enols to their keto tautomers may, moreover, be slowed markedly by an appropriate selection of double-bond substituents.[1] We have



(2)

shown, for example, that the enol of isobutyraldehyde can be generated in aqueous solution from lithium isobutyraldehyde enolate and that its conversion to isobutyraldehyde in that medium is sufficiently slow to allow rate measurements by conventional or stopped-flow methods.[2] In this paper we describe that work, which was published before only in preliminary form, in full. We also show that this enol can be produced in aqueous solution from its potassium salt as well as by reaction of its trimethylsilyl ether with fluoride ion, eq 3. We also report measurements of the rate



(3)

of enolization of isobutyraldehyde, determined by iodine scavenging, which, when combined with our rates of ketonization, provide the keto–enol equilibrium constant for this system in aqueous solution. Our rate measurements in basic solution give a value of the acidity constant of isobutyraldehyde enol ionizing as an oxygen acid, and that, in combination with the keto–enol equilibrium constant, provides the acidity constant of isobutyraldehyde ionizing as a carbon acid.

Experimental Section

Materials. Isobutenyl trimethylsilyl ether was prepared from isobutyraldehyde and trimethylsilyl chloride, and it was converted to lithium isobutyraldehyde enolate by treatment with methyllithium in tetrahydrofuran solution.[3] When this method of forming lithium enolates is used, triphenylmethane or 2,2′-bipyridine are sometimes employed as indicators to determine whether sufficient methyllithium has been supplied. We found, however, that triphenylmethane, even at the very low concentrations required for this purpose, was not soluble in the essentially aqueous solutions formed when small quantities of this lithium enolate stock solutions were added to water for kinetic determinations and that the suspensions thus formed, through barely discernible as such by the naked eye, interfered badly with kinetic measurements. Bipyridyl indicator, on the other hand, presented no difficulty; nevertheless, we used no indicator most of the time and simply supplied a 10% excess of methyllithium to ensure complete formation of the lithium enolate.

Potassium isobutyraldehyde enolate was made from isobutyraldehyde and potassium hydride.[4] Metal enolate stock solutions were stored under argon in Pierce Reacti vials fitted with Pierce Mininert valves; samples for kinetic measurement were withdrawn by hypodermic syringe. Isobutyraldehyde for kinetic determinations was fractionally distilled under argon; all other materials were the best available commercial grades. Solutions were prepared by using deionized water, purified further by distillation, or D_2O (Merck Sharp & Dohme, 99.8 atom % deuterium) as received.

(1) (a) Hart, H. *Chem. Rev.* **1979**, *79*, 515–528. (b) Toullec, J. *Adv. Phys. Org. Chem.* **1982**, *18*, 1–77. (c) Nugiel, D. A.; Rappaport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 3669–3676.

(2) Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1982**, *104*, 6122–6123.

(3) House, H. O.; Gzuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336. House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.*, **1971**, *36*, 2361–2371.

(4) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913–3918.

0002-7863/86/1508-6314$01.50/0