1-Oxo-2-oxa-1-phosphabicyclo[2.2.2]octane: A New Mechanistic Probe for the Basic Hydrolysis of Phosphate Esters

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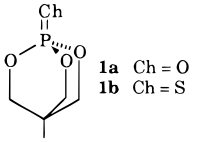
Abstract: Synthesis of the title compound **2** was accomplished in a multistep sequence starting from hypophosphorous acid. In strong base, the bicyclic phosphinate **2** hydrolyzes 2 orders of magnitude faster than the bicyclic phosphate $OP(OCH_2)_3CCH_3$ (**1a**) and the acceleration is entirely enthalpic. This rate enhancement is attributed to the greater ease with which **2** achieves the five-coordinate transition state. The molecular structure of **2**, determined by X-ray means, compared with that of **1a** reveals no evidence of strain within either bicyclic framework. The observed acceleration does not support the contribution of a stereoelectronic effect in the hydrolysis of six-membered ring phosphates.

Introduction

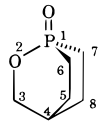
The mechanism of phosphate ester hydrolysis has recently attracted much attention because of the crucial biological importance of this reaction.[1−4] On the basis of *ab initio* molecular orbital calculations[2] and laboratory experiments,[3] Gorenstein and co-workers advocated the importance of the role of kinetic stereoelectronic effects in the reactions of organophosphorus compounds. Rate enhancements observed for cyclic or bicyclic phosphates compared with their acyclic analogs were suggested to be due, at least in part, to stereoelectronic effects that facilitate cleavage of the apical P−O or P−N bonds in trigonal bipyramidal intermediates. These stereoelectronic effects presumably arise from antiperiplanar (app) interactions of the breaking apical bond with electron lone pairs on equatorially positioned oxygen or nitrogen atoms.

These studies were frustrated to some extent, however, by the conformational flexibility of the monocyclic and decalin-type bicyclic phosphate esters employed. Thus, a conformationally biased system which also possesses stereoelectronically favorable electron pairs at the oxygens was introduced by incorporating the phosphate ester residue into the bicyclo[2.2.2]-octane framework of compound **1a**.[4] It was observed at pH 14



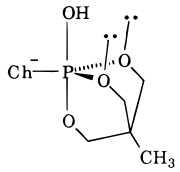
1a Ch = O
1b Ch = S

1

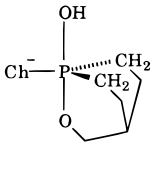


2

that compound **1a** hydrolyzes 5.0×10^3 times faster than triethyl phosphate (**3**), while the thiono analogue of **1**, namely **1b**, hydrolyzes 0.81×10^3 times faster than triethyl thionophosphate under the same conditions. The rate enhancements observed for the bicyclic phosphates with respect to their acyclic analogs were attributed at least in part to stereoelectronic effects, since in the bicyclic phosphate systems there are two lone electron pairs forced to be app to the breaking P−O bond in transition state **A**, while this constraint is not operative in the acyclic analogs.[4]



A



B

Subsequently we became interested in attempting to devise further tests of the role of antiperiplanar electron pairs in rate enhancements of the hydrolysis of bicyclic six-membered ring phosphates. To this end 1-oxo-2-oxa-1-phosphabicyclo[2.2.2]-octane (**2**) was synthesized. This compound has only one hydrolyzable P−O bond, and in contrast to **1**, two ring O atoms are replaced by two methylene groups, thus providing CH_2 groups in the trigonal bipyramidal transition state **B** instead of the two O atoms that are crucial to the manifestation of the stereoelectronic effect in **A**. A comparison of the rates of the base-catalyzed hydrolysis of **2** and **1a** could be expected to allow a direct assessment of the rate enhancement in bicyclic **1a** by a stereoelectronic effect. According to the antiperiplanar lone pair hypothesis (ALPH), **1a** is expected to hydrolyze faster than **2**. However, we found that the bicyclic phosphinate **2** hydrolyzed more than 2 orders of magnitude faster than **1a**. Furthermore, by comparing rates of the base-catalyzed hydrolysis of **2** and its acyclic analog, $EtOP(O)Et_2$ (**4**), we could expect to estimate the rate enhancement in a bicyclo[2.2.2]octane system in the absence of a stereoelectronic effect. If the rate enhancement of **2** over **4** was found to be smaller than that for **1a** over **3**, the stereoelectronic effect in **1a** would be substantiated. Somewhat surprisingly, we find that this factor for **2** relative to **4** is more than an order of magnitude greater than for **1a** compared with that of **3**. In an effort to identify the source of this acceleration, the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were estimated from Eyring theory. However, these

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experiments required the replacement of 1,4-dioxane[4] by 1,2-dimethoxyethane as an organic solvent. For this and additional reasons discussed later, we are unable to make direct comparisons of our rate constants for **1a** and **3** with those reported earlier.[4]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Nicolet NT-300 NMR spectrometer in chloroform-*d* as solvent, and chemical shifts are reported in parts per million downfield from tetramethylsilane using chloroform (^{1}H, 7.26 ppm) and chloroform-*d* (^{13}C, 77.10 ppm) resonances as secondary standards. ^{31}P NMR spectra were recorded on a Bruker WM-300 spectrometer for the chloroform-*d* solutions, and chemical shifts are externally referenced to 85% H_3PO_4 with positive values downfield from the standard. Solvents were reagent grade, predried over molecular sieves, and, when necessary, distilled from sodium−benzophenone ketyl prior to use.

^{31}P NMR spectra for the kinetic experiments were obtained with a Bruker WM-200 spectrometer at 81.0 MHz, employing the following parameters: sweep width, 8064 Hz; memory size, 16K; pulse width, 15 μs; relaxation delay, 0.5 s. The number of transients was selected according to $t_{1/2}$ values for the reactions and was between 50 and 200 for **1a**, depending on temperature, and was 500 for **3** and **4** at all temperatures. Integrations of these spectra were performed using the NMR1 program. The processing of the FID included exponential multiplication with a line-broadening of 1.0 Hz and zero-filling to 64K. Each signal was fitted to a Lorentzian curve three times using a curve-fitting routine. Mean integrations were then calculated.

Relaxation times (T_1) were measured with a Bruker WM-200 spectrometer by the inversion−recovery method for at least seven different τ values. Further calculations were performed using NMR1 software. ^{31}P NMR spectra for the $^{18}OH^-$-catalyzed hydrolysis of **2** were obtained with a Varian VXR 300 spectrometer at 121.4 MHz (3824.1 Hz sweep width, 27 008 data points).

Ethyl diethylphosphinate (**4**) was prepared from tetraethyldiphosphine disulfide according to literature procedures,[5,6] purified by chromatography on silica gel (chloroform), and distilled twice *in vacuo*. Bp: 86−88 °C, 11 Torr (lit.[6] bp 87−9 °C, 12 Torr. ^{1}H NMR: δ 1.07 (dt, CH_3CP, ^3J(HP) = 17.6 Hz, ^3J(HH) = 7.6 Hz), 1.24 (dt, CH_3COP, ^3J(HH) = 7.1 Hz, ^4J(HP) = 0.5 Hz), 1.64 (dq, CH_2P, ^2J(HP) = 13.9 Hz, ^3J(HH) = 7.6 Hz), 3.98 (dq, CH_2OP, ^3J(HP) = 7.1 Hz, ^3J(HH) = 7.1 Hz). ^{31}P NMR: δ 59.97.

The bicyclic phosphate **1a** was prepared as described previously,[7] and triethyl phosphate (**3**) purchased from Aldrich was used without further purification.

Although the sequential transformation of H_3PO_2 to $CH_3OP(O)H_2$ (**5**) to $CH_3OPH(O)CH_2CH_2CO_2Me$ (**6**) to $MeOP(O)(CH_2CH_2CO_2Me)_2$ (**7**) to $MeO(O)P\overline{CH_2CH_2C(OH)=C(CO_2Me)CH_2}$ (**8**) to $MeO(O)P(CH_2CH_2)_2C=O$ (**9**) was reported earlier,[8] the following procedure to obtain **9** was found to be superior.

1-Methoxy-1-oxophosphorinan-4-one (9). A 50% solution of hypophosphorous acid (Aldrich) was dried *in vacuo* overnight, leaving a solid[9] (9.89 g, 0.150 mol). This crude acid was treated with trimethyl orthoformate (18.0 mL, 0.165 mol) at room temperature, and the solution was stirred for 2 h. The solution was added dropwise to a mixture of methyl acrylate (13.5 mL, 0.165 mol) and ethyldiisopropylamine (2.6 mL, 0.015 mol) at 5 °C. After the reaction mixture had been allowed to stand at room temperature for 3 d, chloroform (50 mL) was added and the solution was washed with saturated cold aqueous $NaHCO_3$. The water phase was extracted with chloroform (5 × 20 mL). The extract and washings were combined and dried over $MgSO_4$. Removal of the solvent and volatile impurities *in vacuo* (10 h, 0.02 Torr) gave **6** (21.8 g, 87.5%) as a colorless oil. ^{1}H NMR: δ 2.04 (dtd, CH_2P, ^2J(PH) = 15.2 Hz, ^3J(HH) = 7.6 Hz, ^3J(HPCH) = 1.8 Hz), 2.5−2.7 (m, CH_2CO), 3.67 (s, CH_3O_2C), 3.75 (CH_3OP, ^3J(HCOP) = 11.8 Hz), 7.14 (dt, HP, ^1J(HP) = 547.8 Hz, ^3J(HPCH) = 1.8 Hz). ^{13}C NMR: δ 23.25 (d, CP, ^1J(CP) = 95.2 Hz), 25.7 (s, CH_2-CO), 51.54 (s, CH_3O_2C), 52.32 (d, CH_3OP, ^2J(COP) = 5.4 Hz), 171.72 (d, COO, ^3J(PCCC) = 12.2 Hz). ^{31}P NMR: δ 39.76.

A mixture of crude **6** (21.8 g, 0.131 mol) and methyl acrylate (13.0 mL, 0.144 mol) was added dropwise to a solution of sodium methoxide (made from 0.65 g, 0.028 mol, of sodium in methanol, 8.2 mL) at 3−5 °C. When the addition was complete, the mixture was allowed to warm to room temperature and was then diluted with chloroform (100 mL). The solution was neutralized with acetic acid (1.8 mL, 0.031 mol) and then washed with ice-cold water and aqueous $NaHCO_3$. The aqueous washings were extracted with chloroform (3 × 20 mL). The organic extracts were dried over $MgSO_4$, and the solvent was evaporated *in vacuo* (24 h, 0.04 Torr), leaving crude **7** as a yellow oil (31.47 g, 95%). ^{1}H NMR: δ 2.05 (dt, CH_2P, ^2J(HP) = 13.4 Hz, ^3J(HH) = 7.9 Hz), 2.54−2.65 (m, CH_2CO), 3.68 (s, CH_3O_2C), 3.68 (d, CH_3OP, ^3J(HCOP) = 10.6 Hz). ^{13}C NMR: δ 22.78 (d, CP, ^1J(CP) = 93.1 Hz), 26.36 (s, CH_2CO), 51.05 (d, CH_3OP, ^2J(CP) = 5.2 Hz), 51.87 (s, CH_3O_2C), 172.28 (d, CO_2, ^3J(CCCP) = 14.8 Hz). ^{31}P NMR: δ 56.11. The preparation was contaminated with *ca.* 6% of **8** (δ(^{31}P) 48.65) and *ca.* 4% of an unidentified impurity (δ(^{31}P) 45.84).

A solution of sodium *tert*-amyl oxide (made from sodium hydride, 3.6 g, 0.150 mol, and *tert*-amyl alcohol, 16.5 mL, 0.150 mol, in benzene, 100 mL) was added to a solution of **7** (31.5 g, 0.125 mol) in benzene (180 mL) at room temperature. The reaction mixture was warmed, and a distillate of bp 54−65 °C followed by another up to 80 °C was slowly collected at atmospheric pressure. The cooled residue was filtered and washed with benzene, and the solid was added portionwise to a vigorously stirred aqueous solution of concentrated HCl (16.6 mL) in 22 mL of water at 5−8 °C. The organic phase was extracted with chloroform (5 × 50 mL), dried over $MgSO_4$, and concentrated overnight *in vacuo*, affording crude **8** (24.0 g, 87%) as a brown oil. A sample of this material was purified on a silica gel column with chloroform−methanol (40:1, v/v) to give a colorless oil which solidified after a few weeks at room temperature. ^{1}H NMR: δ 1.98 (dt, CH_2P, ^2J(PH) = 15.6 Hz, ^3J(HH) = 7.1 Hz), 2.57−2.79 (m, CH_2P, CCH_2C), 3.72 (d, CH_3OP, ^3J(HCOP) = 10.9 Hz), 3.76 (s, CH_3O_2C), 12.6 (br s, HO). ^{13}C NMR: 21.40 (d, *C*PC, ^1J(CP) = 88.9 Hz), 21.65 (d, CP*C*, ^1J(CP) = 90.4 Hz), 28.09 (d, CH_2CP, ^2J(CCP) = 5.9 Hz), 50.63 (d, CH_3OP, ^2J(COP) = 4.2 Hz), 51.82 (s, CH_3O_2C), 92.59 (s, C-3 based on the usual lack of two-bond coupling to ^{31}P), 171.15 (d, C-4 or CO, ^3J(CCCP) = 14.4 Hz), 172.04 (d, C-4 or CO, ^3J(CCCP) = 12.4 Hz). ^{31}P NMR: δ 48.91. Compound **8** was found to be 100% enolized as judged from the ^{13}C and ^{1}H NMR spectra.

A mixture of crude **8** (24.0 g, 0.109 mol) and 0.01 M HCl (25 mL) was kept at 98 °C for 3 d. After cooling, the solution was saturated with sodium chloride and extracted with chloroform (10 × 20 mL). The organic extract was dried over $MgSO_4$, concentrated, and distilled to give **9** (7.19 g, 40.7%) as a colorless oil which immediately crystallized. Bp: 130−135 °C, 0.3 Torr; (lit.[8] bp, 135 °C, 1 Torr). Mp: 56−57.5 °C (lit.[8] mp 38−40 °C, 51−52 °C hemihydrate). ^{1}H NMR: δ 2.19 (dt, CH_2P, ^2J(HCP) = 16.4 Hz, ^3J(HH) = 6.7 Hz), 2.67−2.77 (m, CH_2CO), 3.82 (d, CH_3OP, ^3J(HP) = 10.8 Hz). ^{13}C NMR: δ 23.68 (d, CH_2P, ^1J(CP) = 89.2 Hz), 36.75 (d, CH_2CP, ^2J(CP) = 4.5 Hz), 50.97 (d, CH_3OP, ^2J(CP) = 7.6 Hz), 206.81 (d, C=O, ^3J(CP) = 9.3 Hz). ^{31}P NMR: δ 48.29.

1-Methoxy-4-methylene-1-oxo-phosphorinane (10). To a suspension of freshly sublimed potassium *tert*-butoxide[10] (2.64 g, 23.3 mmol) in dry ether (40 mL) at room temperature was added portionwise methyltriphenylphosphonium iodide[11] (9.41 g, 23.3 mmol). The yellow slurry was refluxed for 15 min, and then most of the ether was distilled off.[12] The ketone **9** (3.3 g, 21 mmol) was then added in portions followed by benzene (5 mL). The reaction mixture was stirred at 40 °C for 1 h, cooled to room temperature, and partitioned between chloroform and water. The water phase was extracted with chloroform

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(4 × 20 mL), and the organic extracts were dried over $MgSO_4$. Most of the triphenylphosphine oxide formed was removed on a silica gel column with chloroform−methanol (100:1, v/v), and the residue was distilled to give **10** (2.22 g, 66.6%) as a yellow mobile oil. Bp: 70−73 °C, 0.1 Torr. ^{1}H NMR: δ 1.7−2.0 (m, CH_2P), 2.3−2.6 (m, CH_2-CH_2P), 3.70 (d, CH_3OP, ^3J(HP) = 10.7 Hz), 4.71 (s, H_2C=C). ^{13}C NMR: δ 27.02 (d, CH_2P, ^1J(CP) = 85.9 Hz), 39.22 (d, CH_2CH_2P, ^2J(CCP) = 5.9 Hz), 50.26 (d, CH_3OP, ^2J(COP) = 6.0 Hz), 112.52 (s, CH_2=C), 144.80 (d, C=CH_2, ^3J(CCCP) = 10.4 Hz). ^{31}P NMR: δ 50.44.

1-Methoxy- and 1-(Hydroxymethyl)-1-oxo-phosphorinane (11 and 12, Respectively). To a solution of **10** (2.20 g, 13.9 mmol) in THF (13 mL) was added a solution of 1 M borane−THF complex in THF (16.6 mL, 16.6 mmol, Aldrich) at 6−10 °C followed by stirring at room temperature for 2 h. Water (2 mL) was then added at 2 °C followed by a solution of 180 mg of solid NaOH in 4 mL of water. Finally, hydrogen peroxide (1.67 mL, 30% solution) was added dropwise, and the mixture was stirred at 10 °C for 2 h. The solvent was evaporated at room temperature, and the residue was partitioned between chloroform and water. The organic phase was dried over $MgSO_4$, concentrated in vacuo, and chromatographed on a silica gel column with chloroform−methanol (100:1, v/v) to give a 1:1 mixture of isomers of **11** (0.581 g, 23.5%). ^{1}H NMR: δ 1.2−2.1 (m, CH_2-CH_2), 3.1 and 3.25 (2 br s, OH), 3.36 (d, CH_2O, ^3J(HH) = 5.9 Hz), 3.42 (d, CH_2O, ^3J(HH) = 6.1 Hz), 3.61 and 3.62 (2 d, CH_3OP, ^3J(HCOP) = 10.7 Hz). ^{13}C NMR: δ 24.85 (d, CH_2P, ^1J(CP) = 86.3 Hz), 24.43 (d, CH_2P, ^1J(CP) = 86.7 Hz), 25.23 (d, CH_2CP, ^2J(CCP) = 3.7 Hz), 26.33 (d, CH_2CP, ^2J(CCP) = 4.7 Hz), 39.19 (d, CH, ^3J(CCCP) = 7.1 Hz), 39.93 (d, CH, ^3J(CCCP) = 5.8 Hz), 50.00 (d, CH_3OP, ^2J(COP) = 6.8 Hz), 50.45 (d, CH_3OP, ^2J(COP) = 6.3 Hz), 65.02 and 66.02 (2 s, CH_2O). ^{31}P NMR: δ 52.21 and 53.69. The water phase was acidified with 4 mL of HCl (1:1 concentrated HCl/H_2O v/v) and refluxed for 12 h. Water was evaporated, and then the residue was co-evaporated with water twice (2 × 30 mL) followed by drying *in vacuo* over NaOH pellets. The oily residue was extracted with methanol at room temperature, and the extracts were filtered, evaporated, and left *in vacuo* for 2 d to give the crude acid **12** (1.3 g, 57%) as a yellow oil. ^{13}C NMR (CD_3OD): δ 26.90 (d, CH_2P, ^1J(CP) = 100.0 Hz), 27.19 (d, CH_2CP, ^2J(CCP) = 3.9 Hz), 40.89 (d, HC, ^3J(CCCP) = 5.9 Hz), 68.06 (s, CH_2OH). ^{31}P NMR (CD_3OD−CH_3-OH): δ 52.23.

1-Oxo-2-oxa-1-phosphabicyclo[2.2.2]octane (2). A mixture of the crude acid **12** (1.24 g, 7.56 mmol), dicyclohexylcarbodiimide (DCC, 1.87 g, 9.06 mmol), 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 0.184 mg, 1.51 mmol), triethylamine (10 mL), and THF (50 mL) was refluxed for 9 h. Volatiles were then evaporated under vacuum, and the residue was suspended in benzene and filtered. The oil obtained upon evaporation of the solvent under vacuum was chromatographed on silica gel with chloroform to give crude **2** (0.71 g, 64%). Crystallization from benzene−hexane afforded 336 mg of pure **2**. Mp: 220−223 °C. ^{1}H NMR: δ 1.73−1.77, 1.9−2.3 (2 m, CH_2CH_2CH), 4.51 (dd, CH_2O, ^3J(HP) = 5.4 Hz, ^3J(HH) = 1.4 Hz). ^{13}C NMR: δ 21.83 (CH_2P, ^1J(CP) = 81.4 Hz), 25.94 (d, CH_2CP, ^2J(PC) = 5.7 Hz), 26.43 (d, CCCP, ^3J(CCCP) = 47.6 Hz), 76.90 (d, CH_2OP, ^2J(COP) = 4.4 Hz). ^{31}P NMR: δ 46.05. IR (benzene): ν(P=O) 1271 and 1229 cm^{-1}. IR (tetrachloroethylene): ν(P=O) 1262 and 1229 cm^{-1}. MS: *m*/*e* 146.04956, calcd for $C_6H_{11}O_2P$, 146.04968. MS: *m*/*e* 146.0 (100), 131.0 (14), 116.0 (37), 88.0 (23), 68.1 (29.9), 54.0 (92.1). Anal. Calcd for $C_6H_{11}O_2P$ (found): C, 49.31 (49.34); H, 7.59 (7.46); P, 21.20 (21.24).

Basic Hydrolysis of 3 and 4. In a 10 mm NMR tube, 1,2-dimethoxyethane (DME) (1.50 mL) and 0.62 M NaOH in D_2O (1.20 mL) were mixed. The temperature of the solution was sustained for 30 min in the probe of the spectrometer. Then, compound **3** (11.5 μL, 67.7 μmol) or **4** (10.0 μL, 66.6 μmol) was injected, and the reaction was monitored at different temperatures (Table 1).

Basic Hydrolysis of 1a. In a 10 mm NMR tube, a solution of **1a** (66.95 μmol) in DME (1.50 mL) was mixed with D_2O (1.10 mL). The temperature of the solution was sustained for about 1 h in the probe of the spectrometer. Then, 7.32 M NaOH in D_2O (100 μL) was injected, the sample was shaken well, and the reaction was monitored at five temperatures (Table 1).

Table 1. Observed and Calculated[a] Pseudo-First-Order Rate Constants[b] (s^{-1}) for the Hydrolysis of **1a**, **2**, **3**, and **4**[c]

temp, K	10^3k (**1a**)	10^3k (**2**)	10^6k (**3**)	10^6k (**4**)
254		7.16 ± 0.18		
		7.31 ± 0.09		
259		13.44 ± 0.26		
		13.04 ± 0.42		
264		22.17 ± 0.48		
		23.20 ± 0.32		
269		32.39 ± 0.55		
		32.92 ± 0.28		
274	0.1044 ± 0.0011	53.27 ± 0.98		
	0.0993 ± 0.0007	52.8 ± 1.1		
279	0.2082 ± 0.0016			
	0.2112 ± 0.0017			
284	0.3271 ± 0.0018			
	0.3637 ± 0.0030			
289	0.6105 ± 0.0089			
	0.6450 ± 0.0059			
294	1.0570 ± 0.0096			
	1.063 ± 0.018			
	1.100 ± 0.012			
298				11.272 ± 0.074
303				18.418 ± 0.088
308				27.26 ± 0.28
313				42.47 ± 0.20
				60.12 ± 0.63
318			7.21 ± 0.13	
323			10.26 ± 0.16	
328			17.01 ± 0.21	
333			24.68 ± 0.56	
338			30.36 ± 0.35	
343			42.67 ± 0.35	
304[a]	3.08 ± 0.13	628 ± 55	2.39 ± 0.26	19.55 ± 0.29

[a] Based on a ln k *vs* $1/T$ relationship. [b] The error ranges are the standard deviations. [c] 0.6 M NaOH in 44% aqueous 1,2-dimethoxyethane.

Basic Hydrolysis of 2. A 25 mL flask containing a magnetically stirred mixture of DME (1.50 mL) and 0.62 M NaOH in D_2O (1.20 mL) was cooled to the required temperature in a well-insulated ethanol bath using an RK20 thermostat (Brinkmann) equipped with an RKS control unit. A solution of **2** in D_2O (47 μL, 68 μmol) was then injected followed by quenching at various time intervals by injection of glacial acetic acid (47 μL, 1.1 equiv). At selected temperatures this procedure was repeated seven to eight times to monitor the progress of hydrolysis for at least 2 half-lives. After quenching, the slightly acidified solutions were transferred to 10 mm NMR tubes, and ^{31}P NMR spectra were recorded employing the following parameters: sweep width, 8064 MHz; memory size, 16K; pulse width, 90° (23.5 μs); relaxation delay, 45 s; number of transients, 40.

Integration Correction Factors. It appeared that full relaxation of ^{31}P nuclei would be achieved in about 1 min, thus precluding direct quantitative measurements especially for the reactions having half-lives of only several minutes. Thus, we decided to acquire ^{31}P NMR data under nonequilibrium conditions and later correct for the observed integrals by multiplication of the ester-to-Na salt ratios by the appropriate correction factor (Table 2). The validity of this approach was confirmed by comparing molar ratios measured gravimetrically (for **1a**) with those obtained from ^{31}P NMR integrals. Surprisingly, the estimated error for three different concentrations was less than 1%. By contrast, ^{31}P NMR integrals of **2** and the sodium salt of **12** could be obtained directly from spectra of the quenched mixtures by using sufficiently long delays.

The correction factors were obtained according to the following procedure. The solution of the sodium salt (*ca.* 68 μmol) in DME (1.50 μL) and D_2O (1.20 mL) obtained after complete hydrolysis of **1a**, **3**, or **4** with excess base at room temperature was slightly acidified by adding 1.1 equiv of glacial acetic acid to react with the excess base. Glacial acetic acid was not added to the sample of hydrolyzed **3**, because its hydrolysis rate at 24 °C is negligibly slow. Then, *ca.* 34 μmol of the ester was added in each case, and ^{31}P NMR spectra were collected

Table 2. Relaxation Times T_1 (s), ^{31}P NMR Chemical Shifts (ppm), and Correction Factors for the Mixtures of Esters and Their Respective Na Salts

ester	T_1 (δ(^{31}P))	Na salt	T_1 (δ(^{31}P))	correction factor[a]
1a	9.4 ± 0.5 (−5.21)	$HOCH_2CMe(CH_2O)_2PO_2^-Na^+$	5.4 ± 0.1 (−2.86)	1.585 ± 0.025
2	9.0 ± 0.4 (54.52)	**12** (Na)	1.9 ± 0.2 (38.51)	not used
3	13.3 ± 0.1 (−0.10)	$(EtO)_2PO_2^-Na^+$	11.8 ± 0.3 (+0.97)	1.120 ± 0.013
4	10.3 ± 0.06 (66.13)	$Et_2PO_2^-Na^+$	4.3 ± 0.3 (47.80)	1.635 ± 0.033

[a] The error is the standard deviation calculated as $[[\sum\chi^2 - (\sum\chi)^2/n]|(n-1)]^{1/2}$.

Table 3. Calculated Enthalpies,[a] Entropies,[a] and Free Energies[b] of Activation for the Hydrolysis of **1a**, **2**, **3**, and **4** in Strong Base

	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, kcal/mol ($\times 10^{-3}$)	$\Delta G^{\ddagger}_{300}$, kcal/mol
1a	17.99 ± 0.34	−10.9 ± 1.2	21.3
2	12.93 ± 0.34	−16.9 ± 1.3	18.0
3	14.92 ± 0.79	−35.2 ± 2.4	25.5
	14.8[c]	−34.4[c]	25.1
	14.1[d]	−34[d]	24
4	15.14 ± 0.35	−30.3 ± 1.1	24.2
	14.3 ± 0.5[e]	−35.2[e]	24.9
	15.8[f]	−26.8[f]	23.8

[a] The error ranges are the standard deviations. [b] At 300 K. [c] Reference 26 (in H_2O). [d] Reference 29b (recalculated values from the data in ref 26). [e] Reference 26 (in 50% EtOH/H_2O). [f] Reference 27 (in 83.3% DMSO).

Table 4. Acceleration Factors[a] and Differences[a] in Enthalpies of Activation ($\Delta\Delta H^{\ddagger}$) and Entropies of Activation ($\Delta\Delta S^{\ddagger}$) for Pairs of Esters

pairs of esters				
"faster"	"slower"	acceleration	$\Delta\Delta H^{\ddagger}$, kcal/mol	$\Delta\Delta S^{\ddagger}$, kcal/mol ($\times 10^{-3}$)
2	**1a**	204 ± 20	−5.06 ± 0.68	−6.0 ± 2.5
4	**3**	8.18 ± 0.90	+0.22 ± 1.1	+4.9 ± 3.5
2	**4**	(32.1 ± 2.9) × 10^3	−2.21 ± 0.69	+13.4 ± 2.4
1a	**3**	(1.29 ± 0.15) × 10^3	+3.1 ± 1.1	+24.3 ± 3.6

[a] The error ranges are the standard deviations.

first with the spectral parameters used in the kinetic studies (pulse width, 15 μs; relaxation delay, 0.5 s) for at least three different numbers of transients (between 50 and 200 for **1a**, between 100 and 600 for **3** and **4**). Then, ^{31}P NMR spectra were observed for the same sample using a 90° pulse and relaxation delays (70 s for **1a** and **3** and 52 s for **4**) for at least three different numbers of transients (between 10 and 40 for **1a**, between 30 and 300 for **3** and **4**). The sequence was completed by once again recording spectra with parameters used in the kinetic measurements (as in the first step). This sequence allowed us to calculate at least six different values of a given correction factor by dividing the ester-to-Na salt molar ratios obtained from spectra under full relaxation by those ratios found from spectra in which short delays had to be applied. This three-step sequence was repeated for *ca.* 1:1 and 2:1 molar ratios of ester to Na salt, thus bringing the number of correction factor values to at least 18. Mean values and standard deviations were then calculated (Table 2).

Data Analysis. Pseudo-first-order rate constants at the same base concentration and the Arrhenius parameters were calculated by least-squares analysis.[13] Enthalpies and entropies of activation were calculated at 304 K in the normal manner using standard Eyring theory. Pertinent data with their standard deviations are collected in Tables 3 and 4.

Hydrolysis of 2 with $Na^{18}OH$ in D_2O. To a solution of 7.32 M NaOH in D_2O (47.2 mg) containing $H_2{}^{18}O$ (95%, Aldrich, 51.8 mg) in a 5 mm NMR tube was added **2** (28.5 mg, 0.195 mmol). After 2 h at room temperature, the clear solution was diluted with D_2O (0.6 mL) and its ^{31}P NMR spectrum was recorded. Two signals at 40.620 (^{16}-OP^{16}O) and 40.582 (^{16}OP^{18}O) ppm in a 49:51 ratio were observed.

Product Analysis of Hydrolysis of 2. A solution of **2** (24.0 mg, 0.164 mmol) in D_2O (0.5 mL) showed a single ^{31}P NMR resonance at

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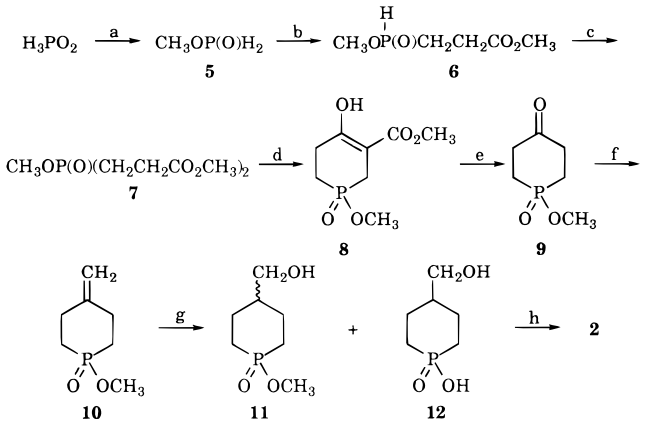
Scheme 1[a]



[a] Conditions: (a) $HC(OMe)_3$; (b) $H_2C{=}CHCO_2Me$, *i*-Pr_2NEt; (c) $H_2C{=}CHCO_2Me$, MeONa; (d) *t*-AmONa, benzene; (e) 0.01 M HCl; (f) $Ph_3P{=}CH_2$; (g) $BH_3{\cdot}THF$, then NaOH/H_2O_2; (h) DCC/DMAP, THF.

59.2 ppm, and the following ^{13}C NMR signals: δ 20.34 (d, CH_2P, ^1J(CP) = 81.7 Hz), 24.87 (d, *C*H_2CP, ^2J(CP) = 5.9 Hz), 25.87 (d, *C*CCP, ^3J(CCCP) = 49.0 Hz), 78.26 (d, CH_2OP, ^2J(CP) = 6.0 Hz). After injection of a solution of 0.6025 M NaOH in D_2O (0.30 mL, 1.1 equiv), the following spectral data for the Na salt of **12** were observed. ^{31}P NMR: δ 40.62. ^{13}C NMR: δ 25.97 (d, *C*H_2CP, ^2J(CP) = 4.8 Hz), 27.07 (d, *C*H_2P, ^1J(CP) = 86.5 Hz), 39.20 (d, *C*CCP, ^3J(CCCP) = 5.4 Hz), 65.65 (s, *C*H_2OH). No other signals were detected in these spectra.

Crystal Structure Analysis of 2. Crystals of **2** were grown from a dichloromethane solution layered with hexane. Some difficulty was encountered in finding a single crystal which yielded accurate cell constants, apparently because of a large mosaic spread. All nine non-hydrogen atoms were located by direct methods.[14] All of the expected hydrogen atoms were located in subsequent difference Fourier maps and were refined with isotropic thermal parameters. One of the hydrogen atoms would not refine with a reasonable thermal parameter in full-matrix least squares cycles. A check of F(obs) versus F(calc) revealed two reflections (indices 750 and 910) for which F(obs) − F(calc) was greater than 10σ(F). Upon exclusion of these reflections from the final least squares cycles, all of the hydrogen atoms refined satisfactorily. Refinement was carried out using the SHELX-76 programs. All calculations were performed on a Digital Equipment Corp. MicroVAX II computer using the CAD4-SDP package.[15]

Results and Discussion

Synthesis of 2. The synthesis of **2** was accomplished in an eight-step sequence (Scheme 1) starting from H_3PO_2.[9] Sequential Michael-type additions of the P−H subunits in **5** and **6** to methyl acrylate followed by a Dieckmann cyclization of **7** gave enol **8**,[8] which after decarboxylation in dilute acid[16] afforded

(14) (a) SHELXS-86, G. M. Sheldrick, Institut für Anorganische Chemie der Universität, Gottingen, FRG. (b) Sheldrick, G. M. In *Computing in Crystallography*; Schenk, H., Olthof-Hazekamp, R., Van Koningsveld, H., Bassi, G. C., Eds.; Delft University: Delft, 1978.

(15) Enraf-Nonius: Delft, Holland. Neutral atom scattering factors and anomalous scattering corrections were taken from the *International Tables for X-ray Crystallography*; The Kynoch Press: Birmingham, England, 1974; Vol. IV.

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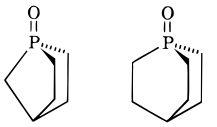
2-methoxy-2-oxo-4-phosphorinanone (**9**) in 29% overall yield. We found this procedure superior to the one which involved the purification of **6**, **7**, and **8** after each step.[8] The ^{31}P and ^{13}C NMR spectra of crude **6** revealed the presence of **7**, and crude **7** contained up to 10% **8**. Although basic catalysts selected by Gallagher[8] for the stepwise addition to methyl acrylate worked quite well in the presence of ethyldiisopropylamine, some **7** was formed in the first step as shown by ^{31}P NMR spectroscopy, and sodium methoxide was a strong enough base to promote the cyclization of **7** to **8** even at room temperature, as was also shown by ^{31}P NMR spectroscopy.

The Wittig reaction of methylenetriphenylphosphorane[12] with ketone **9** gave 1-methoxy-4-methylene-1-oxophosphorinane (**10**) in 66% yield. Hydroboration of **10** followed by oxidation[17] led to two products which were identified as a 1:1 mixture of *cis*/*trans*-4-(hydroxymethyl)-1-methoxy-1-oxophosphorinane (**11**), and 4-(hydroxymethyl)-1-hydroxy-1-oxophosphorinane (**12**).

Several attempts to cyclize **11** in the presence of acidic or basic catalysts failed. However, when crude **12** was treated with DCC/DMAP[18] for 9 h under reflux, the cyclization occurred and **2** was isolated in 64% yield. We also observed fairly efficient cyclization to **2** when **12** was warmed *in vacuo*.

The structure of **2** was substantiated by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies. Whereas the ^{1}H NMR spectrum was straightforward, the ^{13}C NMR spectrum displayed some intriguing features. The signal for C-3 was found *ca.* 11.5 ppm downfield of chemical shifts of the analogous carbons (CH_2OH) in the monocyclic isomeric esters **11**. Furthermore, the methine carbon in **2** resonated 13 ppm upfield compared with that in **11**, and revealed a very large three-bond coupling (47.6 Hz) to phosphorus. The latter phenomenon has its precedent in bicyclic phosphine oxides such as 1-oxo-1-phosphabicyclo[2.2.1]heptane **13** and 1-oxo-1-phosphabicyclo[2.2.2]octane (**14**), for which



13 **14**

^{3}J(CCCP) values of 63 and 47 Hz, respectively, were observed.[19] Finally, comparison of the ^{31}P NMR spectra of **11** and **2** showed an upfield shift by *ca.* 7 ppm for the bicyclic compound. Similar shielding of the phosphorus atom was observed earlier for **1a** ($\delta(^{31}P)$ −7.97)[20] compared with triethyl phosphate ($\delta(^{31}P)$ −1.0).[21] Significant upfield shifts of C-4 in the ^{13}C and P in the ^{31}P NMR spectra of **2** compared with **11** may be caused by the relatively close proximity of these nuclei in **2**. It may be that the value of ^{3}J(C-4, P) in **2** is solely a result of multipath coupling,[19] but through-space spin interactions cannot be ruled out.

Mechanism of Hydrolysis in Strong Alkali and Product Identification. Nucleophilic attack of hydroxide ion at the phosphorus atom during hydrolysis of **1a** and **3** was confirmed by Gorenstein *et al.*[4] by comparing rates of hydrolysis of these esters and their thiono counterparts. Using ^{18}O-enriched water, Haake and co-workers[22] showed that basic hydrolysis of **4** involves exclusive attack at phosphorus. Although it is unexpected that basic hydrolysis of **2** would occur *via* nucleophilic attack at the C−O−P carbon atom,[23] this possibility was tested by carrying out the hydrolysis of **2** with a $Na^{18}OH/D_2O$ solution and recording the ^{31}P NMR spectrum of the reaction mixture. As expected on the basis of the $^{16}O/^{18}O$ isotope effect,[24] two ^{31}P signals separated by 0.038 ppm were observed, thus clearly indicating exclusive nucleophilic attack at phosphorus for this compound. Furthermore, comparisons of the ^{13}C NMR spectra of **2** taken in D_2O and chloroform-*d* solutions with the ^{13}C NMR spectra of **12** formed in the alkaline hydrolysis of **2** in D_2O indicated that **2** is indeed the starting material and that the Na salt of **12** is the product in our kinetic studies.

Kinetics. Kinetic studies by NMR spectroscopy can be properly conducted only when ratios of reacting species can be extracted quantitatively from the peak areas. This is particularly important because of the relatively long T_1 relaxation times of the ^{31}P nucleus in our case. In order to measure ratios of esters **1a**, **2**, **3**, and **4** to their respective monosodium salts by ^{31}P NMR spectroscopy in a quantitative manner, measurements of ^{31}P T_1 relaxation times were required (Table 2).

Because an acceleration factor for the basic hydrolysis of the pair of esters **1** and **3** was established previously,[4] we attempted to follow the basic hydrolysis of **2** and **4** under the same conditions (1,4-dioxane/H_2O, 60:40, v/v, at 304 K) and to use ^{31}P NMR spectroscopy as we did earlier. This attempt failed in the case of **2** because only a single resonance at 38.51 ppm for the sodium salt of **12** was found after *ca.* 2 min, and no other signals emerged within the next few hours. When 1/2 equiv of base was used at room temperature, signals at 54.98 and 38.51 ppm, assigned to bicyclic **2** and the sodium salt of **12**, respectively, were observed. With this amount of base, we were able to follow the kinetics of hydrolysis of **2** at 1 °C for 1 h, at which point the base was exhausted. Unfortunately, the data obtained did not follow the second-order kinetics equation expected for this compound, which was based on the kinetic results obtained for its acyclic counterpart **4**.[25−27] It became obvious that, under pseudo-first-order conditions, the basic hydrolysis of **2** is a fast process which at room temperature takes less than 1 min for completion.

Because kinetic studies of **2** required rate data at temperatures below 0 °C, dioxane had to be replaced by another organic solvent; 1,2-dimethoxyethane (DME) was chosen. However, the same ratio of D_2O to DME, as well as the base and ester concentrations, was maintained as reported earlier.[4] In all our measurements the reactions followed good first-order kinetics over 2 half-lives. Thus, $\ln x = f(t)$ is a straight line with a regression coefficient $r = 0.999$. For compounds **1a** and **2**, the kinetic runs were repeated twice, and the calculated rate constants agreed within less than ±5% for **1a** and within less than ±2% for **2**. In a separate ^{31}P NMR experiment, it was demonstrated that **2** is not hydrolyzed by a small excess of glacial acetic acid. Thus, the ^{31}P signal of **2** at 54.76 ppm remained when a solution containing acid-quenched aqueous base, dioxane, and **2** was subjected to ^{31}P NMR observation under the same conditions as in the kinetics experiments. For compound **4** a single series of experiments at five temperatures over a 20 °C range was obtained. The correlation coefficient for the $\ln k$ *vs* $1/T$ relationship was found to be 0.9994, and the

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calculated activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table 3) based on these data are in good agreement with literature values.[26,27] Because of this good agreement, only a single series of kinetic runs was conducted for **3**.

Comparison of the rate constants extrapolated to 304 K (Table 1) for **2** and **4** shows that hydrolysis of the bicyclic phosphinate **2** is 32×10^3 times faster than that of its acyclic counterpart **4**, while the rate enhancement for the bicyclic triester **1a** relative to acyclic **3** is only 1.3×10^3. Although significant errors can be introduced through extrapolation, there is no doubt that the basic hydrolysis acceleration for the phosphinate pair **2**/**4** is more than an order of magnitude greater than that for the phosphate pair **1a**/**3**. Assuming that this type of acceleration is associated mainly with stereoelectronic effects,[4] the present data suggest that such influences are absent in the base hydrolysis of **1a**. A more definitive test for the nonexistence of stereoelectronic effects in the hydrolysis of the phosphates investigated here requires a discussion of activation parameters.

Mechanistic and Structural Considerations. The experimental enthalpies and entropies of activation for the compounds studied here are collected in Table 3, and the differences in these parameters for pairs of esters are given in Table 4 along with their hydrolysis accelerations. Before addressing the relative rates of the bicyclic esters **1a** and **2** and of the acyclic esters **3** and **4**, we address first the acceleration of the hydrolysis of bicyclic **1a** over its acyclic analogue **3** and of bicyclic **2** over its acyclic counterpart **4**.

Recent calculations at the HF/3-21+G(d,d) and MP2/6-31+G* levels[28] for $(MeO)_2P(O)OH$ and its cyclic analogue $(CH_2O)_2P(O)OH$ revealed that although the strain in the ground state of the latter molecule postulated earlier[29] was confirmed to exist, it did not contribute to the rate acceleration of the cyclic over the acyclic ester. Moreover, these calculations showed that $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ for formation of both trigonal bipyramidal (TBP) transition states (TS) were only negligibly different. It was also found that the destabilization of the cyclic TS that must then be compensating for the ground-state destabilization caused by strain stems from the impossibility of the cyclic TS to achieve the most favored conformation adopted by the acyclic TS. It was concluded from further calculations that $\Delta G^{\ddagger}$ for the cyclic phosphate ester was more greatly lowered by solvation effects than $\Delta G^{\ddagger}$ for the acyclic analogue, thus accounting for the rate acceleration of the former over the latter molecule.

Because of the presence of six-membered rings in **1a** and **2**, ground-state strain in these bicyclic molecules is likely to be considerably less than in the five-membered ring $(CH_2O)_2P(O)OH$ discussed above. Indeed, compared with acyclic[30−32] and monocyclic[33,34] analogues, no significant distortions of the O−P−C and C−P−C bond angles are observed for **2** (Figure 1). Morevoer, there are no unexpected differences between the structural metrics for **2** and **1a**.[35] In the phosphorinane ring of **2**, lengthening of the P−C(6) and P−C(7) bonds (1.78 Å) compared to the P−O bonds in **1a** (1.58 Å) is apparently compensated by a decrease of the P−C(6)−C(5) and P−C(7)−C(8) bond angles in **2** to *ca.* 109° from *ca.* 115° for the P−O−C angles in **1a**, and an increase of the C(7)−C(8)−C(9) and C(6)−C(5)−C(4) angles to *ca.* 113° in **2** *vs* 108.7° for the O−C−C angles in **1a**. At the site of cleavage in **2**, the P−O(2) bond length and the P−O(2)−C(3) angle have almost the same values as their respective counterparts in **1a**. Although the O(2)−C(3) bond in **2** is shorter (1.47 Å) compared with the O−C bonds in **1a** (1.53−1.56 Å), the former value was previously observed in 1,3,2-dioxaphosphorinanes.[36] Thus, we do not expect a significant influence of strain arising from bond angle distortions in **1a** or **2**.

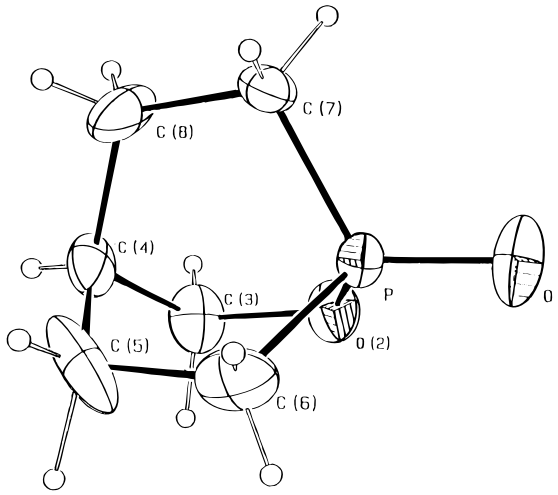

Figure 1. Molecular structure of **2** ($PO_2C_6H_{11}$, fw 146.13, $P2_12_12_1$, colorless, $a = 10.147(3)$ Å, $b = 10.400(2)$ Å, $c = 6.425(2)$ Å, $Z = 4$, $R_w = 0.0465$, GOF = 1.68). Ellipsoids are drawn at the 50% probability level.

Upon attack of **1a** or **2** by an OH^- to form a five-coordinate TS, the XPX angle that becomes the $X_{eq}-P-X_{eq}$ angle increases from *ca.* 103° to about 120° and the OPX angle that becomes the $O_{ax}-P-X_{eq}$ angle decreases from 103° to about 90°. Examination of molecular models reveals that a dominant effect of these changes is to increase the $P-O_{ax}-C$ angle beyond 115°, while other interactions already present in the bicyclic framework remain about the same. Although the degree to which a 1-phosphabicyclo[2.2.2]octane skeleton can accommodate bond angle changes while adopting a TBP structure is yet to be established, we suggest that the transition state in the hydrolysis of **1a** and **2** is a strained trigonal bipyramid whose conformation is even more unfavorable than that adopted by $(CH_2O)_2P(O)OH$.[28] This may be particularly true for the TS of **2** in which there are four pairs of synperiplanar H−H interactions arising from adjacent CH_2-CH_2 units, plus four syn-1,3 H−H interactions. By contrast there are no synperiplanar hydrogens in **1a**, and only three syn-1,3 H−H interactions are present. Compensating for the H−H interactions in **2**, however, are the lower energies observed for trigonal bipyramids having two equatorial C atoms than for comparable trigonal bipyramids containing two equatorial O atoms.[1a] A schematic enthalpy diagram for the hydrolyses of **1a** and **2** is given in Figure 2. In this figure the assumption that the initial energy states for **1a** and **2** are very close is based on a lack of evidence of strain within either bicyclic framework. The close proximity of the energy states for the hydrolysis products is based on the assumption that the six-membered rings are strain free. It seems likely then that

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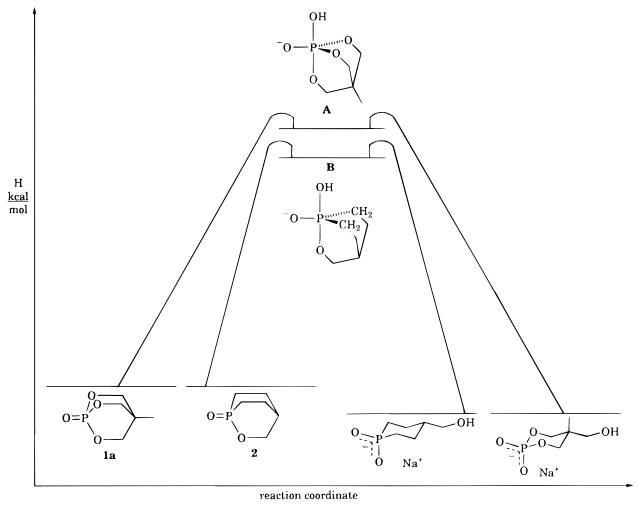

Figure 2. Schematic enthalpy diagram for the hydrolysis of bicyclic phosphate **1a** and phosphinate **2**.

solvation effects are largely responsible for the acceleration by 10^3 (Table 4) of the bicyclic esters over their acyclic analogues.

From the values of $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ in Table 3 it is seen that $\Delta G^{\ddagger}$ for the hydrolysis of **1a** is more negative than for **2**, and that these reactions are dominated by the enthalpy of activation term. While it may be that $\Delta G^{\ddagger}_{solv}$ lowers the overall $\Delta G^{\ddagger}$ for **2** more than for **1a**, it is not clear why this should be so, particularly because **2** contains fewer polar linkages for solvent interaction. Moreover, the rates of their acyclic counterparts **3** and **4** are quite comparable. Perhaps the lower enthalpy required to achieve the five-coordinate TS for **1a** over **2** is dominated by the observation that two equatorial carbons in the TS of **2** give rise to a lower energy than two oxygen atoms occupying these positions.[1a]

Conclusions. The approximately 200-fold observed rate enhancement in the basic hydrolysis of bicyclic phosphinate **2** over bicyclic phosphate **1a** is entirely enthalpic. This result is interpreted in terms of a lack of a stereoelectronic effect in the hydrolysis of six-membered ring phosphates. The 10^3-fold accelerations in the hydrolyses of bicyclic esters over their acyclic counterparts appear to be largely due to solvation effects.

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Supporting Information Available: Tables of crystallographic data and a computer drawing for **2** (8 pages). See any current masthead page for ordering and Internet access instructions.

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