Oxiranylidene-2,2-bis(phosphonate): Unambiguous Synthesis, Hydrolysis to 1,2-Dihydroxyethylidene-1,1-bis(phosphonate), and Identification as the Primary Product from Mild Na_2WO_4/H_2O_2 Oxidation of Ethenylidene-1,1-bis(phosphonate)

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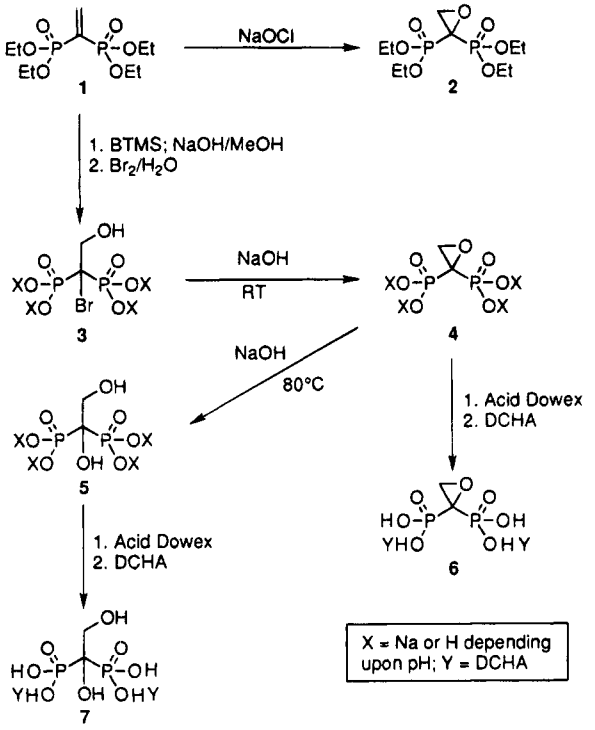
Particular steric and electronic congeners of pyrophosphate exhibit biological activities ranging from modulation of bone metabolism to inhibition of specific DNA polymerases and other enzymes.[1] Our continuing interest in pyrophosphate analogues containing a potentially reactive group led us to consider the synthesis of oxiranylidene-2,2-bis(phosphonic acid) (**4**), a pyrophosphate analogue salt containing an epoxide functional group. Synthesis of both **4** and its tetraethyl ester (**2**) by Na_2WO_4/H_2O_2 oxidation of, respectively, ethenylidene-1,1-bis(phosphonic acid) (EBP) or its tetraethyl ester (**1**) was reported in the patent literature over 20 years ago, but yields and analytical data confirming the product structures were not given.[2] Gatrone has reported that EBP is oxidized to phosphoric acid by this method.[3] He found that adjustment of the reaction pH to 6–7 gave a different product, identified on the basis of its ^{31}P and ^1H NMR spectra as not the expected epoxide **4**, but instead 1,2-dihydroxyethylidene-1,1-bis(phosphonic acid) (**5**). This compound was observed to undergo decomposition at pH 2 to phosphoric acid and acetylphosphonic acid. Acid-dependent decomposition was proposed to be a general reaction of β-hydroxy-substituted alkylidenebisphosphonic acids.[3]

In our initial synthetic approach to **4** (Scheme 1), we prepared the tetraethyl ester **2** of this epoxide (recently also made[4] by alkaline hydroperoxidation of **1**[5]) via oxidation of **1** with aqueous sodium hypochlorite.[6] However, attempted silyldealkylation of **2** using bromotrimethylsilane (BTMS)[7] gave more than one product, redirecting us to EBP as our synthetic starting point.

The tetrasodium salt of EBP[8] was treated with Br_2–H_2O, rapidly and cleanly converting it to the bromohydrin

Scheme 1



3, recrystallized from water (NaBr salt-out, room temperature) to an analytically pure product (32.7%).

Addition of **3** to a concentrated, chilled, deuterium oxide solution of NaOH resulted overnight in the desired product, which was precipitated by NaBr–MeOH. Washing with MeOH provided the sodium salt of the epoxide **4** (75–80% purity by ^{31}P NMR; contained some methanol by ^1H NMR). This was converted to the dicyclohexylammonium ($DCHA^+$) salt **6** by rapidly drawing an aqueous solution through an acid Dowex 50 column into ethanolic DCHA, thus minimizing any acid-catalyzed hydrolysis. The crude **6** (64%) was recrystallized from ether/acetone/1-propanol and acetone/1-propanol, mp 167–168 °C (9%); characterization data, Table 1.

Synthesis of the diol **5** began with preparation of the sodium salt of the epoxide as described above. A concentrated solution of **4** containing excess NaOH was heated to 80 °C. Phosphorus and proton NMR showed complete hydrolysis within 2 days. The product was precipitated with NaBr–MeOH and washed with MeOH to provide **5** as a sodium salt, 95% pure by ^{31}P NMR and containing some methanol by ^1H NMR. Stirring with acid Dowex 50 in H_2O for about 1 h, filtration and vacuum rotary evaporation at 40 °C gave a gummy residue which was dissolved in D_2O (no significant decomposition evident by ^{31}P NMR). Addition of DCHA followed by rotary evaporation, washing with ether, and recrystallization from ether/acetone/1-propanol and acetone/1-propanol provided **7** (14%), characterized as reported in Table 1.

The ^1H NMR chemical shifts of the epoxide ring protons in **2**, **4** and **6** are close to 3 ppm,[9] and the epoxide ring ^{13}C NMR resonances in **2** and **4** occur near 47–54 ppm. These values lie within the expected ranges for epoxides, but upfield of typical values for alcohols.[10] In

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(8) EBP was previously isolated as a free acid (NMR only) by silyldealkylation of **1** with BTMS in CCl_4, methanolysis, treatment with KOH, and reacidification using an acidic ion-exchange resin.[5] Using neat BTMS,[7] we were able to isolate the tetrakis(trimethylsilyl) ester intermediate by distillation, which afforded the analytically pure (C, H, P) Na_4^+ salt of EBP (65%), characterized by ^{31}P, ^1H, and ^{13}C NMR.

(9) ^1H–^{31}P NMR spin–spin coupling in the epoxide β-protons appears as a triplet in our 360 MHz ^1H spectra, whereas the pattern for the tetramethyl ester[5] β-protons has been reported as a 5-line signal.

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Table 1. Characterization Data for Compounds 2–7

compd	NMR (δ, J in Hz)[a] ^{1}H	^{31}P{^{1}H}	^{13}C{^{1}H}	MS[b]
2	3.14 (t, $^3J_{HP}$ = 5)[c]	15.5 (s)	47.3 (t, $^1J_{CP}$ = 183), 49.4 (s)	316.0840 (316.0841)
3[d]	4.12 (m)[e]	12.3 (s)	58.3 (t, $^1J_{CP}$ = 118), 64.7 (s)	
4	2.93 (t, $^3J_{HP}$ = 5)	13.1 (s)	50.7 (s), 53.6 (t, $^1J_{CP}$ = 150)	
5	3.90 (t, $^3J_{HP}$ = 11)[e]	16.8 (s)	65.1 (s), 75.6 (t, $^1J_{CP}$ = 131)	
6[f]	3.08 (t, $^3J_{HP}$ = 6)[c]	12.3 (s)		202.9499 (202.9511)
7[g]	3.98 (t, $^3J_{HP}$ = 10)[e]	16.1 (s)	63.7(s), 74.3 (t, $^1J_{CP}$ = 133)	220.9618 (220.9616)

[a] Bruker AM360. Solvents: $CDCl_3$ for **2**, D_2O for **3**–**7**. Solutions: **3** 1.4% w/w, pH = 4.5; **4** 1.3% w/w, pH = 11.1; **5** 3.0% w/w, pH = 11.1; **6** and **7** < 1% w/w. [b] HRMS (**2**) and FAB-HRMS (**6**, **7**) data recorded at the regional mass spectroscopy facility at UC Riverside; theoretical values are reported in parentheses. [c] See footnote 9. [d] Anal. for $C_2H_5BrNa_2O_7P_2\cdot(H_2O)_{1/2}$: C, H, Br. [e] Splitting patterns for the ^{1}H spectra of the β-hydroxy bisphosphonates are affected by the pH of the solution. [f] Anal. for $C_2H_6O_7P_2\cdot(DCHA)_2\cdot(H_2O)_{3/2}$: C, H, N. [g] Attempts to remove recrystallization solvents by pumping *in vacuo* at 74 °C decreased DCHA content, leaving a solid giving: Anal. for $C_2H_8O_8P_2\cdot(DCHA)_{1.7}\cdot(acetone)_{1/5}\cdot(1\text{-propanol})_{1/6}\cdot(H_2O)_{1/2}$: C, H, N. [DCHA, and solvate content except for H_2O, determined by ^{1}H NMR integration].

contrast, the protons on the hydroxy carbon in both the bromohydrin **3** and the diol **5** shift near 4 ppm.[11] In **3** C_β shifts at 65 ppm, and the diol carbons in **5** shift at 65 and 76 ppm, values more characteristic for alcohols.[10]

The similarity (allowing for differences in sample pH) between the ^{31}P and ^{1}H NMR data previously attributed to **5** (^{31}P{^{1}H} δ 13.6 (s); ^{1}H δ 3.11 (t), $^3J_{HP}$ = 6.0 Hz)[3] and those we record in Table 1 for the epoxide salts **4** and **6** is apparent, as is their divergence from our NMR data for **5**. To clarify this discrepancy, we have reinvestigated the Na_2WO_4/H_2O_2 oxidation of EBP. Reaction of tetrasodium EBP (0.8 mmol) in 2 mL of 30% H_2O_2 containing a catalytic amount of Na_2WO_4 for 3.5 h at 60 °C (N_2) produced ^{31}P NMR signals at δ 2.72 (66%), 13.23 (24%) and 16.7 (10%), consistent with overoxidation. When a solution of 1.1 mmol of tetrasodium EBP in 1.5 mL of 30% H_2O_2 containing 0.02 mmol of Na_2WO_4 was adjusted to pH 5.1 and heated to 50 °C for 5 h, the major product (in D_2O at pH 6.9) had ^{31}P NMR δ 13.7 (s), ^{1}H NMR δ 2.9 (t) $^3J_{HP}$ = 5.9 Hz, ^{13}C NMR δ 49.4 (s) and 51.3 (t), with small peaks at δ 2, 12 (EBP) and 17.5. The ^{31}P and ^{1}H NMR data for the main product resemble the values reported for the diol **5**,[3] but taken together with our ^{13}C NMR data are only consistent with the epoxide **4**. This assignment was confirmed by two additional experiments. Firstly, the area of the major peak in the ^{31}P spectrum of the reaction mixture was increased on spiking with authentic **4**. Secondly, addition of NaOH to the reaction mixture, followed by heating at 50 °C for 4 h, resulted in the conversion of approximately 1/3 (^{31}P NMR) of the main product into the diol **5**, identified by ^{31}P (authentic compound spiking), ^{1}H, and ^{13}C NMR.

Gatrone *et al.*[13] and Nash *et al.*[14] have proposed that the product from Na_2WO_4/H_2O_2 oxidation of EBP chelates transition metals, lanthanides, and actinides and subsequently can be decomposed under acidic conditions to release the metal. The half-life for decomposition of the product itself to phosphoric acid at pH 2 was reported as approximately 15 days at room temperature, and 9 days at 50 °C, in a process proposed to be general for β-hydroxy alkylidenebisphosphonates.[3]

We find, however, that both the diol **5** and the bromohydrin **3** (which is also a β-hydroxy alkylidenebisphosphonate) are stable at pH 2 and room temperature. An immediate ^{31}P NMR of **5** (from **3**) in D_2O after pH adjustment to 2 showed only a trace peak near δ 0 in addition to the signal at δ 17.3 due to **5**. After 40 days at room temperature, the peak at δ 0 amounted to less than 3% of the integrated area of the diol peak. Similarly, after 7 days at room temperature, a D_2O solution of **3** at pH 2 had virtually no change by ^{31}P NMR: **3** (δ 12.7) still contributed 99% of the observed peaks (trace peaks were seen at δ −0.05 and 17.4 ppm). These results suggest that β-hydroxy bisphosphonates may be more stable than previously postulated.[15]

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Supporting Information Available: Synthetic procedures, detailed NMR spectra, and other characterization data for the tetrakis(trimethylsilyl) ester of EBP, Na_4^+ salt of EBP, and **2**–**7**; details of ^{31}P NMR stability studies on compounds **3**–**5** at pH 2 and for reaction mixtures from Na_2WO_4/H_2O_2 oxidations of the sodium salt of EBP (59 pages).

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(11) Br/OH orientation in the bromohydrin is confirmed by the $^{13}C_\alpha$ δ (identified by its $^1J_{CP}$ coupling), 58.3 ppm *vs* a singlet at 64.7 ppm for $^{13}C_\beta$. Nucleophilic attack at C_β in α,β-unsaturated phosphonates is well precedented.[12]

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(15) At pH 2, **4** prepared from **3** underwent slow decomposition to yield a new product occurring 4.3 ppm downfield from **4** (δ 13.0) in the ^{31}P NMR spectrum. After 16 days at 50 °C, about 1/3 was converted to this product, identified as the diol **5** by spiking with authentic compound. Significant peaks ascribable to either phosphoric acid or acetylphosphonic acid were not detected. In the absence of details on the acid decomposition experiments described in ref 3, we have not attempted rigorous kinetic investigations in our comparison studies with **4**. Nevertheless, the rate and chemical product differences we observe point to a possible influence of contaminating tungstate catalyst on the decomposition behavior of **4** acetone-precipitated from the Na_2WO_4/H_2O_2 reaction mixture.