pH-Dependent Decomposition of β-Hydroxy-Substituted Organophosphorus Complexants

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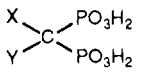
Summary: Substituted ethane-1,1-diphosphonic acids containing a β-hydroxyl group undergo facile pH-dependent decomposition to phosphoric acid and acetylphosphonate. The decomposition is observed in acidic medium, while the system is stable in basic solutions.

Sir: During the course of an on-going investigation of the aqueous complexation chemistry of transition metals, lanthanides, and actinides found in nuclear waste, we required several examples of disubstituted alkane-1,1-diphosphonic acids (**1**).[1] The literature contains a number



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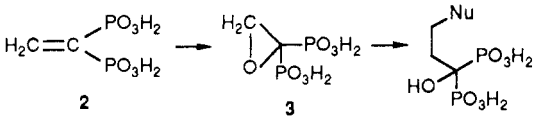
of synthetic methods for preparing substituted diphosphonic acids[2,3] and esters.[4] A variety of 2-substituted 1-hydroxyethane-1,1-diphosphonic acids (**4**–**6**) have been prepared via nucleophilic addition to the intermediate epoxide (**3**) obtainable from the oxidation of 1,1-vinylidenediphosphonic acid (**2**).[3] We were primarily interested in the preparation and complexation chemistry of 1,2-dihydroxyethane-1,1-diphosphonic acid (**4**). We would like to report the pH-dependent decomposition of **4**, which we observed during its synthesis. We believe that the decomposition reaction is general for 2-hydroxyalkane-1,1-diphosphonates.



2 **3**

4, Nu = OH
5, Nu = NR_2
6, Nu = SR

1,1-Vinylidenediphosphonic acid (**2**) gave phosphoric acid when reacted with hydrogen peroxide and a catalytic amount of sodium tungstate, rather than the expected epoxide **3**. We suspected that overoxidation was occurring due to the presence of excess peroxide. Sodium carbonate was slowly introduced until the pH of the reaction mixture was between 6 and 7 in order to avoid the overoxidation problem. Surprisingly, acetone precipitation provided the trisodium salt of 1,2-dihydroxyethane-1,1-diphosphonic acid (**4**), not the epoxide **3**. The ^1H NMR spectrum of DHEDPA (**4**) displayed a triplet at δ 3.11 ppm downfield from TMS (J_{HCCP} = 6.02 Hz). The decoupled ^{31}P chemical shift was observed at δ 13.6 ppm (downfield from external 85% H_3PO_4). The starting VDPA (**2**) had a ^1H resonance at δ 6.12 ppm (complex pattern) and a ^{31}P resonance at δ 12.1 ppm.

We attempted to convert the trisodium salt into the free acid of DHEDPA using an ion exchange procedure. The ^{31}P NMR spectrum of the isolated product, obtained by concentration of solvent in vacuo, had a peak at δ 3.10 ppm. This resonance is diagnostic for internal phosphoric acid (referenced to external 85% phosphoric acid).

We have determined that the transformation to phosphoric acid does not occur during the concentration of the solvent, but on the ion exchange column by examining the ^{31}P NMR spectrum of a D_2O solution of **4** after batchwise treatment with an acidic resin. This result suggests that we are observing an acid-catalyzed reaction.

Therefore, we examined the NMR spectrum of DHEDPA (**4**) as a function of pH. Aqueous solutions of DHEDPA (**4**) at pH's of 2, 6, and 10 were prepared by adding hydrochloric acid, sodium carbonate, and dilute sodium hydroxide, respectively, to a D_2O solution of **4**, such that the concentration of **4** is approximately 0.026 M.

At pH's equal to 6 or 10 no signals for phosphoric acid were observed in the ^{31}P NMR spectrum after standing at room temperature for up to 3 months. A similar result was observed after standing at 50 °C for 3 months. However, the acidic aqueous solution (pH 2) slowly decomposed to phosphoric acid at room temperature with no observed change in the pH of the solution. The half-life for the conversion to H_3PO_4 at pH 2 was crudely estimated to be 15 days by integrating the peaks in the phosphorus NMR spectrum. The decomposition to phosphoric acid in acidic media can be accelerated to a half-life of approximately 9 days, determined by integration of the ^{31}P peaks, by warming the solution to 50 °C using a thermostated water bath.

The ^{31}P NMR data for the pH 2 solution displayed a signal at δ −0.6 ppm downfield from external 85% phosphoric acid in addition to the peak at δ 3.10 ppm (phosphoric acid). In the initial NMR data, we observed that the additional resonance had approximately the same integral intensity as the peak for phosphoric acid. However, it does not intensify with time as does the phosphoric acid peak and actually begins to decrease in intensity after 1 half-life cycle. We have attributed the high-field resonance to acetylphosphonate (**8**). The tetramethyl ester of **8** was prepared according to the method of McConnell.[4f] Mild ester hydrolysis using trimethylsilyl iodide provided a sample of **8**. The ^{31}P NMR spectra for authentic **8** (δ −0.6 ppm) and the observed resonance in the reaction mixture are identical. It has been previously reported that acidic aqueous solutions of acetylphosphonate (**8**) hydrolyze with P–C bond cleavage,[2a] which further supports our observation of a decrease in the concentration of **8**.

From our analysis of the above data and observations

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(4) (a) Fitch, S. J.; Moedritzer, K. *J. Am. Chem. Soc.* **1962**, *84*, 1876. (b) Pudovik, A. N.; Konovalova, I. V. *Dokl. Akak. Nauk SSSR* **1962**, *143*, 875; *Chem. Abstr.* **1962**, *57*, 3480*a*. (c) Pudovik, A. N.; Konovalova, I. V.; Dedova, L. V. *Dokl. Akak. Nauk SSSR* **1963**, 616; *Chem. Abstr.* **1964**, 8060*a*. (d) Alfer'ev, I. S.; Bobkov, S. Y.; Kotlyarevskii, I. L. *Isv. Akad. Nauk. SSSR, Ser. Khim.* **1987**, 624; *Chem. Abstr.* **1988**, *108*, 94647*q*. (e) Nicholson, D. A.; Vaughn, H. *J. Org. Chem.* **1971**, *36*, 3843. (f) McConnell, R. L.; Coover, H. W. Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4450 and references therein.

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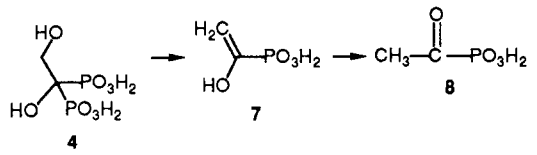
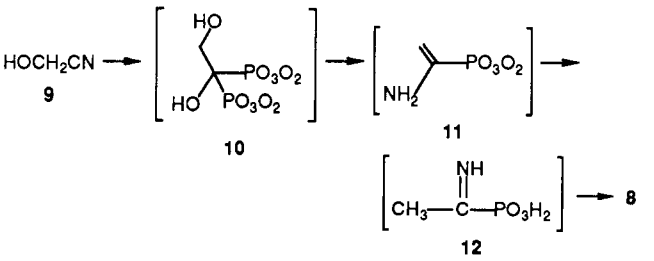
we may propose a potential pathway for the decomposition of DHEDPA (4). The formation of acetylphosphonate (8) can be accounted for by the loss of phosphoric acid generating enol-phosphonic acid 7, which is the tautomer of acetylphosphonate (8). The suggested pathway is cer-



tainly not unreasonable considering the Horner-Emmons reaction and the ease with which phosphorus forms P-O bonds. The observed pH dependency may be explained by the expected difficulty for an anionic center (PO_3H^- or PO_3^{2-}) to accept the additional electron density from the hydroxyl oxygen required to generate the P-O bond.

If the above mechanistic proposal has any validity, we should observe similar decomposition products for other β-hydroxyethane-1,1-diphosphonic acids. Fukuda[5] has reported that 2-hydroxy-1-aminoethane-1,1-diphosphonic acid (10) is stable in alkaline solution, which certainly carries the implication that it is not stable in acidic solutions. Although some of the ^1H NMR data reported by Fukuda for 10 was obtained in acidic media, no degradation products were mentioned. Therefore, we reexamined the properties of 10, especially the ^{31}P NMR data, by reacting hydroxyacetonitrile (9) and phosphorus acid. It should be noted that we did not attempt to isolate 10 or any salt of 10, but rather immediately acidified the solution to allow in situ decomposition to occur. The ^{31}P NMR data



indicated that the phosphorus-containing products are acetylphosphonic acid (8) and phosphoric acid.

We may presume that the reaction proceeds through the intermediacy of 2-hydroxy-1-aminoethane-1,1-diphosphonic acid (10), which, according to our proposed pathway, under the acidic conditions we utilized for workup would decompose through enamine 11 to the imine of acetylphosphonic acid (12) and phosphoric acid. The imine (12) would be expected to hydrolyze to the ketonic form and is not observed.

We are currently investigating the apparent pivotal role that a β-hydroxyl group performs in the facile decomposition of substituted alkyl diphosphonates by extending our study to longer alkyl groups. We will report the full details of our research in the near future.

Acknowledgment. This work was performed under the auspices of the Office of Basic Energy Sciences, Division of Chemical Sciences, U.S. Department of Energy under contract number W-31-109-ENG-38. I would like to thank Phil Horwitz for his advice and encouragement during this research. I would like to acknowledge the technical assistance of Paul Rickert and Carolyn Jacobs, an Argonne Department of Educational Programs Undergraduate Summer Research Participant.

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Stereoselective Cyclopropanation of the 10-Membered Enone. Total Synthesis of Bicyclohumulenone

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Summary: The stereoselective synthesis of bicyclohumulenone and a discussion of the diastereoselectivity of the cyclopropanation based on MM2 calculations are presented.

Sir: Macrocyclic compounds have conformational properties which are quite useful for stereochemical control in the syntheses of natural products.[1] We have recently demonstrated that the transannular [2,3]-Wittig rearrangements[2] of macrocyclic ethers yield germacrane lactones and the transannular Diels-Alder reactions[3] of macrocyclic trienes provide steroid A, B, C rings with higher degree of efficiency and stereoselectivity. In these "endocyclic" cyclizations, the interior side of π orbitals oriented horizontally to the plane of the ring is used for the carbon-carbon bond formation (Figure 1, 1). In this paper we report the first total synthesis of bicyclohumulenone (5)[4] via the "exocyclic" cyclization of the macrocyclic enolate 2.

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(4) Bicyclohumulenone was isolated from a species of liverworts, *Plagischila acanthophylla* subsp. *Japonica* (Matsuo, A.; Nozaki, H.; Nakayama, M.; Kushi, Y.; Hayashi, S.; Komori, T.; Kamijo, N. *J. Chem. Soc., Chem. Commun.* **1979**, *4*, 174), and it has an aroma reminiscent of a variety of odors based on the strong powdery, woody note, such as the odors of patchouli, vetiver, cedarwood, orris, moss, carnation, etc. Preparation of bicyclohumulenone by the transannular cyclization of humulene 9,10-epoxide was reported: Shirahama, H.; Hayano, Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980**, *21*, 4385.

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