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Facile Dephosphonylation of β-Ketophosphonic Acids: Mechanistic Studies

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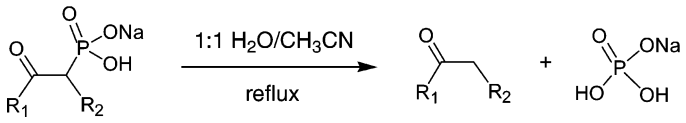
ABSTRACT



We have found that β-ketophosphonic acids can undergo facile dephosphonylation under fairly mild conditions. The rate of dephosphonylation is dependent on the electronic nature of the substituent on the carbon atom α to phosphorus, with electron-withdrawing groups accelerating the process. ^{31}P NMR studies were used to probe the mechanism for the process.

The phosphonate functionality has played an important role in organic chemistry, especially through the Horner−Wadsworth−Emmons olefination reaction, which has been used extensively to construct the carbon framework of diverse synthetic targets.[1−2] Phosphonates and phosphonic acids have also been important in the bioorganic arena. In fact, there are several therapeutic agents that contain the phosphonate moiety as a critical pharmacophore.[3] With certain antiviral nucleosides, replacement of a phosphate by a phosphonate has provided analogues that are resistant to dephosphorylation, thereby paving the way for drugs against human immunodeficiency virus (HIV), hepatitis B virus, and cytomegalovirus.[4]

We have been interested in interfering with the serine proteases cathepsin G and chymase, which are involved in inflammatory processes. Our research effort led us to a novel class of inhibitors that contain a key β-ketophosphonic acid group.[5] In particular, we identified and biologically characterized potent, dual cathepsin G/chymase inhibitor **1**.[5b] During our studies, we noticed that **1** has a tendency to dephosphonylate to **2** under fairly mild conditions. In contrast to the decarboxylation of β-ketocarboxylic acids, the spontaneous dephosphonylation of β-ketophosphonic acids is quite rare. A literature search revealed just a single report of dephosphonylation of a β-ketophosphonic acid.[6] Specifically, Kluger found that the monosodium salt of acetonylphosphonic acid thermally decomposes on melting around 150 °C to produce acetone and sodium metaphosphate.[6] A related base-catalyzed dephosphonylation of diethyl β-ketophosphonate derivatives containing electrophilic keto groups has also been reported.[7] To shed light on this area, we have examined the dephosphonylation of structural analogues of **1** with respect to stereoelectronic influences. In addition, we conducted ^{31}P

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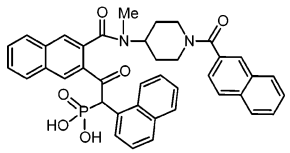
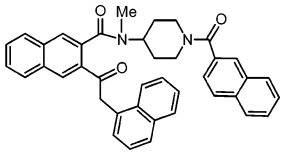
NMR studies to probe the mechanism of this dephosphonylation process. The results from this study are reported herein.



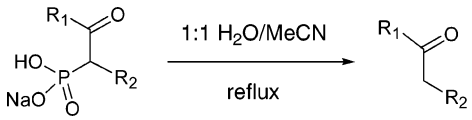
1



2

Aqueous solutions of the bistromethamine salt of **1** proved to be unstable on standing at room temperature over a wide pH range. We isolated and identified the major decomposition product as dephosphonylated material **2**. This result prompted us to investigate this facile dephosphonylation process in a more systematic manner to gain a better understanding of the factors that are responsible. Thus, we exposed the monosodium salts of several β-ketophosphonic acids to a refluxing solution of water−acetonitrile (1:1) and calculated reaction half-lives for the dephosphonylation (Table 1). Substrates **1** and **3**−**6**, each of which has benzene-based aromatic groups for R_2, exhibit similar half-lives. However, for **7**, which possesses an aliphatic methyl group for R_2, we observed a comparatively slow dephosphonylation rate. Compound **8**, which has an electron-withdrawing nitro aromatic group for R_2, dephosphonylated more readily. These results, albeit limited in scope, illustrate the role of the R_2 substituent and reflect on the importance of an electron-withdrawing group in facilitating the dephosphonylation. In contrast, the R_1 group appears to exert little influence (cf. **5** vs **6**).

Table 1. Dephosphonylation of β-Ketophosphonic Acids[a]



	R_1	R_2	$t_{1/2}$ (min)[b]
1[c]	- -	- -	50
3	2-naphthyl	1-naphthyl	22
4	Ph	1-naphthyl	25
5	2-naphthyl	Ph	27
6	Me	Ph	19
7	Ph	Me	169
8	2-naphthyl	4-$NO_2C_6H_4$	1.5

[a] Reactions were conducted at 78 °C with a concentration of 0.01 mM at pH 6.8−7.5. [b] Half-lives were determined by monitoring the appearance of dephosphonylated product over time by HPLC. [c] See text for structure.

In contemplating the mechanistic pathway for this reaction, three possible alternatives come to mind. There could be (1) a Horner−Emmons-like process involving the hydrated form of the ketone carbonyl, (2) direct attack of water on the phosphorus atom with elimination of phosphate, or (3) spontaneous dephosphonylation by elimination of phosphite (Figure 1, eqs 1−3, respectively). From our results in Table 1, it is not possible to discriminate between these mechanisms.

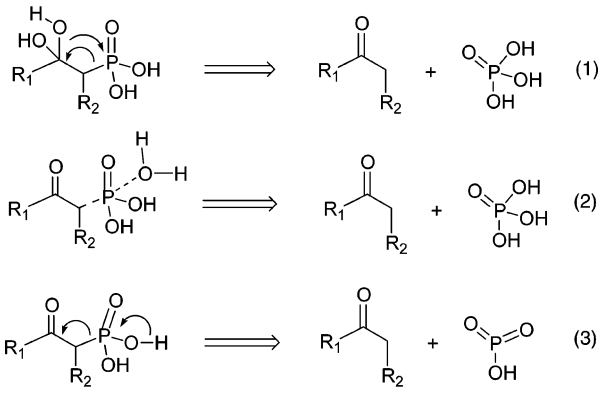
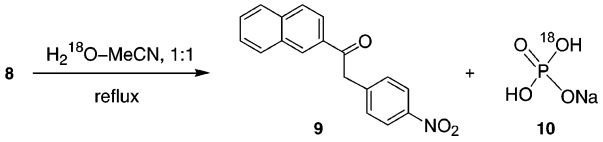


Figure 1. Possible mechanisms for dephosphonylation of β-ketophosphonic acids: (1) Horner−Emmons-like decomposition; (2) addition of water to phosphorus; (3) spontaneous decomposition.

To investigate the mechanism further, and in a more direct manner, we performed the dephosphonylation on **8** by using ^{18}O-enriched water (water−acetonitrile, 1:1; reflux) and then characterized the products by ^{31}P NMR (Scheme 1). Dephosphonylation of **8** with natural-abundance water served as a control. After 15 min, the reactions were separated into organic and aqueous phases. As expected, the major product isolated from the organic phase was **9**. From the reaction using ^{18}O-enriched water, no ^{18}O isotope shift of the ketone carbonyl of **9** was observed by ^{13}C NMR, thus ruling out dephosphonylation via the hydrated ketone carbonyl (Figure 1, eq 1). The major component of the aqueous phase was ^{18}O-labeled sodium phosphate (**10**), as detected by the ^{18}O isotope-induced shift of the ^{31}P signal of phosphate by using ^{31}P NMR (Figure 2); no other products from ^{18}O incorporation were detected. Formation of ^{18}O-labeled sodium phosphate indicates that a Horner−Emmons-type elimination process (Figure 1, eq 2) is unlikely.[8] However, a Horner−Emmons-type elimination process cannot be ruled out for the reported phosphonate ester examples,[7] especially when one takes into account the high degree of ketone carbonyl

Scheme 1. Dephosphonylation of **8** in ^{18}O-Enriched Water



(8) On exposure of the corresponding diethyl phosphonate of **3** to the conditions of Table 1 for up to 2 h, no dephosphonylation was observed.

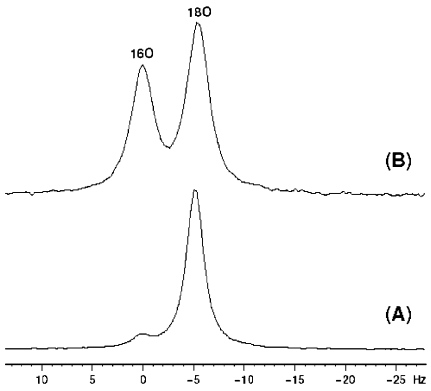


Figure 2. ^{31}P NMR spectra showing the isotope shift from ^{18}O (5.3 Hz). (A) Sample taken from the aqueous fraction of the reaction involving ^{18}O water. (B) Sample from A that was spiked with the aqueous fraction of the reaction involving ^{16}O water. Spectra are referenced to ^{16}O phosphate (0.0 ppm, $T = 5$ °C).

hydration expected for these substrates.[7b] Sodium metaphosphate is the phosphate-containing species expected to form by spontaneous decomposition (Figure 1, eq 3). Because monomeric metaphosphate (eq 3) would be a highly reactive species,[9] it is conceivable that it could hydrate under the reaction conditions to form sodium phosphate, thus making the pathways of eqs 2 and 3 indistinguishable.[10] Therefore, the ^{31}P NMR studies do not provide definitive evidence for a single pathway.

Dephosphonylation of **3** was examined at pH 3 (refluxing 1:1 water−acetonitrile) and pH 10 (refluxing 1:1 buffer−acetonitrile), and the product mixtures were analyzed by HPLC after a 10-min reaction course.[11] At pH 3, 7% of the corresponding ketone was formed; at pH 10, 19% was formed. This result indicates that there is a slower rate of dephosphonylation at lower pH. The facility of this reaction can be further appreciated by the fact that **8** dephosphonylated to the extent of 28% in 5.5 h at 23 °C. A dependency of reaction rate on pH is consistent with our suggested mechanisms (eqs 2 and 3).

In summary, we have found that α-substituted β-ketophosphonic acids dephosphonylate under relatively mild conditions. The rate of dephosphonylation appears to be dependent on the nature of the substituent at the α carbon, with electron-withdrawing groups facilitating the process. Our ^{31}P NMR results support two possible mechanisms, one involving addition of water to the phosphorus atom, followed by cleavage of the phosphorus−carbon bond to form ketone and phosphate products (Figure 1, eq 2), and the other involving spontaneous decomposition (Figure 1, eq 3) followed by hydration of monomeric metaphosphate.

Acknowledgment. We thank Prof. Daniel Comins for valuable suggestions. We appreciate receiving some cogent remarks from the referees.

Supporting Information Available: Procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) On heating sodium metaphosphate (City Chemical LLC) in ^{18}O-enriched water at 78 °C, no formation of ^{18}O-labeled sodium phosphate was observed by ^{31}P NMR over 2.5 h.

(11) The free phosphonic acid was used at each pH. Rates were compared at 10 min because the product mixture became complex at pH 10 after 10 min.