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Nissan Ashkenazi^a; Yoffi Segall^a; Yishai Karton^a; Sanjio S. Zade^b; Michael Bendikov^b

^a Department of Organic Chemistry, IIBR-Israel Institute for Biological Research, Ness-Ziona, Israel ^b

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel

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Ambident Electrophilicity of 5-Membered Ring Phosphate Triesters

Nissan Ashkenazi,¹ Yoffi Segall,¹ Yishai Karton,¹
Sanjio S. Zade,² and Michael Bendikov²

¹Department of Organic Chemistry, IIBR-Israel Institute for Biological Research, Ness-Ziona, Israel

²Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel

The reactions of 2-alkoxy-1,3,2-dioxaphospholane 2-oxide with various nucleophiles were studied both experimentally and theoretically. These studies show that 5-membered ring phosphate triesters act as ambident electrophiles: hard and bulky nucleophiles attack at the phosphorus while soft nucleophiles attack at the ring carbon.

Keywords 2-Alkoxy-1,3,2-dioxaphospholane 2-oxide; electrophilicity; steric bulk; hard and soft nucleophiles

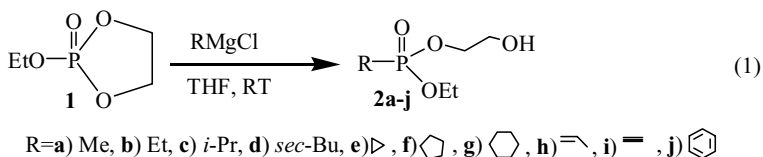
INTRODUCTION

Five-membered ring Phosphate esters play an important role in many key biochemical processes.¹ The parent phosphate triesters, 2-alkoxy-1,3,2-dioxaphospholane 2-oxides (commonly named alkyl ethylene phosphates), had been a subject of extensive research mainly in respect to hydrolysis and alcoholysis reactions, from both experimental² and theoretical³ aspects. In his pioneering work Westheimer established that these phospholanes hydrolyze about 10⁷ times faster than the corresponding acyclic system and exclusively via P-O cleavage, whereas C-O cleavage could not be observed.⁴ Surprisingly, phospholanes had seldom been used in nucleophilic organic transformations. Only a few examples of attacks by carabions, followed by a P-O bond cleavage were reported.⁵ In contrast, reactions with trialkylamines resulted in endocyclic C-O fission to form the corresponding phosphocholines.⁶ This

Address correspondence to Nissan Ashkenazi, Department of Organic Chemistry, IIBR-Israel Institute for Biological Research, P.O.Box 19, Ness-Ziona 74100, Israel. E-mail: nissan.ashkenazi@iibr.gov.il

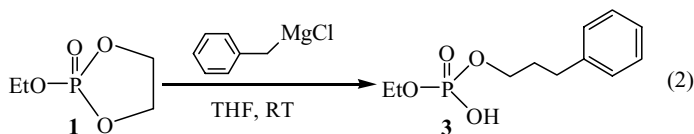
result is in somewhat contradiction with Bunton's suggestion that nucleophilic attacks on phosphate triesters follow Pearson's theory of hard and soft acid and bases.⁷

As we thought we could utilize the unique reactivity of this system,⁴ imposed by the 5-membered ring structure, we studied the reactions of 2-ethoxy-1,3,2-dioxaphospholane 2-oxide (**1**)^{2b} with various Grignard reagents [Equation (1)].⁸

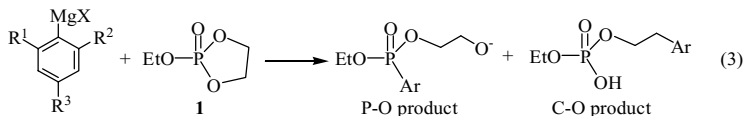


This reaction was found to be general for a large variety of carbanions (i.e., primary, secondary and cyclic alkyls, allyl, alkynyl and phenyl) as **1** was easily transformed to the corresponding phosphonates (**2a-j**) via a single P-O bond cleavage. This transformation is not trivial. Usually, phosphate triesters undergo multiple additions of Grignard reagents.⁹ To our knowledge, there was only one method known in the literature, by which a phosphate triester can be directly converted into the corresponding phosphonate.⁹

One exception to the generality of this reaction was found when benzylmagnesium halides were employed. This carbanion did not form the expected phosphonate, but rather the phosphate **3** as a single product [Equation (2)].¹⁰

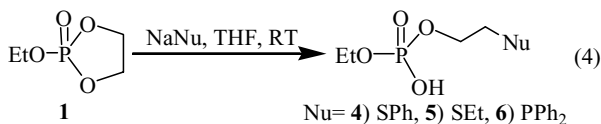


Although it might seem that **3** results from attack on the endocyclic carbon followed by C-O cleavage, there is no good explanation for such a unique reactivity of **1**. Comparing to the steric and electronic properties of the nucleophiles in equation 1, certainly the benzylic carbanion is neither bulkiest¹¹ nor the softest.¹² Nevertheless, the fact that this C-O cleavage was found to be as efficient as the P-O scission, demands a further insight into the reactivity of **1**. In order to evaluate the effect of steric bulk on the site of attack, we studied the reactions shown in Equation (3) and Table I.



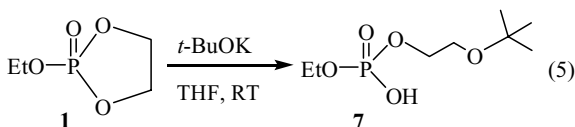
The results clearly indicate that increasing the size of the nucleophile prevents it from approaching the phosphorus, and forcing it to attack the ring carbon.

To study the applicability of Pearson's theory to **1**, we studied its reactions with various soft nucleophiles such as sulfur and phosphorus anions [Equation (4)].¹⁰



Only one product was obtained in each of these reactions (**4**, **5**, and **6**, respectively), which results from exclusive C-O cleavage. Indeed, the carbon atom is considered the softer electrophilic center of **1**.⁷

Testing the combination of both effects opposing each other (i.e., bulky but hard nucleophile) as shown in Equation (5) showed that in this case steric reasons would dictate the reaction course. Thus, reaction of **1** with potassium *t*-butoxide led exclusively to **7**.⁸

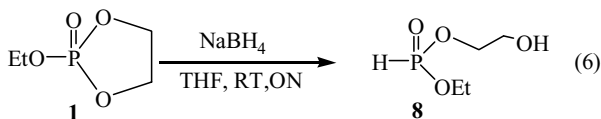


A highly interesting transformation is that of phosphates to the corresponding H-phosphonates. Previously, this was reported to be a two step transformation starting from an acyclic phosphate triester.¹³

TABLE I Reaction of **1** with Bulky Grignard Reagents

Substituents	Relative ratio of P-O product	Relative ratio of C-O product
R ¹ = R ² = R ³ = CH ₃ , X = Cl	1	7
R ¹ = CH ₃ , R ² = R ³ = H, X = Cl	1	0.3
R ¹ = OCH ₃ , R ² = R ³ = H, X = Br	1	0.2
R ¹ = R ² = R ³ = H, X = Cl	1	0

In contrast, **1** can be cleanly converted to the corresponding H-phosphonate (**8**) in a single step [Equation (6)].⁸



To shed more light on the selectivity of C-O vs. P-O cleavage, we have calculated the reaction pathways for the additions of methyl anion, hydroxide, methoxide, *t*-butoxide and thiomethyl anion to 2-methoxy-1,3,2-dioxaphospholane 2-oxide (**1b**) in the gas phase and in solution, using B3LYP/6-31+G* optimized geometries.¹⁰ C-O cleavage which leads to the formation of phosphate anions is always the thermodynamically preferred product. That is due to the fact that phosphate anion is thermodynamically relatively stable and a good leaving group. Calculating the corresponding transitions states (TS) we observed that in the gas phase C-O cleavage is also the kinetically preferred process for all nucleophiles. This is in good agreement with gas phase experiments conducted on nucleophilic attacks on acyclic phosphate triesters.¹⁴ In contrast, the calculated TS in solution showed that while in the case of hydroxide and methoxide attack at the phosphorus is kinetically preferred, the activation energy for attack by the sterically hindered *t*-butoxide and the soft thiomethyl anion is lower at the ring carbon.

In conclusion, 2-ethoxy-1,3,2-dioxaphospholane 2-oxide exhibits dual electrophilic character. The site of attack depends on the nature of the attacking nucleophile (softness vs. hardness, steric bulk, etc.). As no exocyclic bond fission could be observed we suggest that the 5-membered ring enhances not only the reactivity of the P atom, but also of the ring carbon. We have also shown that 2-alkoxy-1,3,2-dioxaphospholane 2-oxides can serve as good precursors for the synthesis of phosphonates.

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