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Triphenylphosphine Reduction of Saturated Endoperoxides

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Abstract

Triphenylphosphine reduction of saturated endoperoxides derived from 6,6-dimethylfulvene and spiro[2.4]hepta-4,6-diene in the presence of nucleophiles results in the formation of products that mainly stem from deoxygenation followed by carbocation formation. Nucleophilic attack by solvent proceeds by an $\text{S}_{\text{N}}1$ like mechanism; allyl shifts and cyclopropylcarbinyl-cyclobutyl rearrangements also occur. With the systems lacking carbocation-stabilizing groups, the deoxygenation step is preceded by attack of H_2O at the phosphorus.

The reduction of cyclic peroxides¹ and ozonides² with triphenylphosphine has been known for a long time. In the case of unsaturated endoperoxides, the reaction results in deoxygenation, leading to ene epoxides,³ although a few exceptions have been observed.⁴ In the case of 1,2-dioxetanes, the reaction with PPh_3 leads to a cyclic phosphorane that undergoes O-P cleavage followed by an intramolecular $\text{S}_{\text{N}}2$ reaction to give epoxides in a stereospecific manner.⁵ With bicyclic 1,2-dioxetanes, on the other hand, where backside attack is impeded, eliminations to allylic alcohols are observed.⁶ Samuelsson and co-workers reported that prostaglandin endoperoxides PGG_2 (**1a**) or PGH_2 (**1b**) upon reduction with PPh_3 give the corresponding *cis*-1,3-diol (**2**), $\text{PGF}_{2\alpha}$.⁷ Clennan and Heah found that saturated bicyclic endoperoxides give with PPh_3 in the presence of H_2O *trans*-1,3-diols;⁸ moreover, they were able to detect the cyclic phosphorane intermediates by NMR and postulated for their formation a biphilic insertion of PPh_3 into the O-O linkage. They also offered a mechanism for phosphorane decomposition involving heterolytic cleavage of the phosphorane to give a zwitterion that reacts with water *via* backside displacement ($\text{S}_{\text{N}}2$) to give the *trans*-diol **5** (Scheme 1). On the other hand, the studies by Westheimer and co-workers,⁹ as well as McClelland and co-workers¹⁰ have shown, with careful mechanistic work, that the hydrolysis of pentaaryloxyphosphoranes occurs by an “inner sphere” mechanism (attack at phosphorus).

The base hydrolysis appears to be an associative process proceeding through a hexacoordinated phosphoroxanide ion, whereas the acid-catalyzed reaction is a dissociative pathway resembling the acetal or orthoester hydrolysis. Also contrary to the “outer sphere” mechanism, Taylor and Greatrex reported that a *cis*-1,4-diphenyl substituted 4,5-epoxy-1,2-dioxine resulted in the hydrolysis of the phosphorane intermediate at phosphorus rather than at the carbon center to give a *meso*-1,4-diol, in addition to deoxygenation products.¹¹

Herein we disclose our results from PPh_3 reductions of saturated endoperoxides derived from 6,6-dimethylfulvene and spiro[2.4]hepta-4,6-diene that have unraveled new pathways involving carbocation intermediates and rearrangements. We also report that the origin of the above-mentioned discrepancy regarding the stereochemistry of the diols **2** and **5**, and hence the mechanism of phosphorane decomposition during PPh_3 reductions of saturated endoperoxides in the [2.2.1] and [2.2.2] series in the presence of H_2O is likely just due to a misassignment of the 1,n-diol stereochemistry.

In the course of our studies on peroxides derived from fulvenes and fulvene analogs,¹² we investigated the triphenylphosphine reductions of 6,6-dimethylfulvene and [2.4]spirohepta-4,6-diene since our systems promised some unusual behavior due to the presence of the vinyl and cyclopropyl groups adjacent to the peroxy carbons, respectively.

After singlet oxygenation of 6,6-dimethylfulvene at $-78\text{ }^\circ\text{C}$ in CH_2Cl_2 , and subsequent diazene reduction at low temperature, as described previously,¹³ the saturated endoperoxide **6** was treated with 1.2 equivalents PPh_3 at $0\text{ }^\circ\text{C}$, and the mixture was stirred at room temperature for 10 h. The product mixture was chromatographed on silica gel to give one major product, **7**, and a minor product, **8**, a known aldehyde.¹⁴ For characterization purposes the latter was converted to its oxime **8a** (*syn* and *anti* isomers in ca. 1:1 ratio) (Scheme 2).

We then decided to carry out the PPh_3 reduction in the presence of a nucleophile, and for reasons of easier purification/ isolation of products we chose acetic acid instead of water. The reaction was conducted in CH_2Cl_2 at $0\text{ }^\circ\text{C}$ in the presence of a slight excess of acetic acid. Under these conditions, a mixture of six products was formed, four carrying the acetoxy group. They were separated by silica gel chromatography (after treating the mixture with cold ether/petroleum ether and removing most of the $\text{Ph}_3\text{P}=\text{O}$ by filtration) and identified as the products shown in Scheme 3.

The results presented above deserve some comment: Oxetane **13** is most likely formed from **12** by an $\text{S}_{\text{N}}2'$ reaction. Under the conditions, **13** undergoes oxetane cleavage to give the allenic aldehyde **8** (Scheme 4). Compound **7** is formed from **14** by proton loss. Azine **9** in Scheme 3 is formed from **8** with hydrazine, a disproportionation product of diazene,¹⁵ in a serendipitous manner: the latter was present in the mixture in large excess since after reduction and filtration of KOAc, the solution was treated with PPh_3 without aqueous workup.

The hydroxyacetates **10a** and **b** (*cis* and *trans*) were isolated as mixtures, whereas **11a** was obtained in pure form. Through repeated chromatography the major isomer **10a** could be isolated free of **10b**. An attractive mechanism for the formation of **7**, **8** as well as **10** and **11** would feature oxetane **13** as the key intermediate (Scheme 4). The assignment of the *cis* and *trans* isomers of **10** is based on independent synthesis of an authentic sample of **10a** from **6** by NaBH_4 reduction in MeOH at $0\text{ }^\circ\text{C}$ followed by monoacetylation of the resulting *cis*-1,3-diol with acetyl chloride in CH_2Cl_2 in the presence of NEt_3 .

The intermediacy of oxetane **13** and its role as a precursor of **8** as well as **11a/b** has precedent. The diphenyl analog of **13** has been prepared by Abe and Adam et al.¹⁶ and also by Abe et al.¹⁷ (Scheme 5). The latter group observed that **16** undergoes rearrangement to form **17**, the corresponding allene aldehyde of type **8**. On the other hand, with $\text{CH}_3\text{CO}_2\text{H}$ the same oxetane was reported to give mostly the *cis*-acetoxy alcohol **18** with traces of the hydroxyacetates **19** and **20**. In our case, products **10a**, **b** and **11a**, **b** do not have to stem from **13** and can directly be formed from **12** by loss of $\text{Ph}_3\text{P}=\text{O}$, followed by capture of the allyl cation **14** by the acetate ion. We believe that **11b** is a secondary product stemming from **11a** by an intramolecular acyl transfer.¹⁸

Next, we studied the triphenylphosphine reduction of the saturated endoperoxide **21** derived from [2.4]-spiro-4,6-heptadiene **21**.¹⁹ Considering the significant stabilizing effect of a cyclopropyl group on adjacent carbocations when the three-membered ring and the carbocation are fixed in a bisected conformation,²⁰ we expected a similar mechanism as with **6** with possible carbocation rearrangement involving the cyclopropyl group. These expectations were borne out by the following experiments. The saturated endoperoxide **21** derived from spiro[2.4]hepta-4,6-diene, prepared as previously described,¹⁹ reacted with PPh₃ in the presence of acetic acid at room temperature to give a mixture of three products all of which contained an acetoxy group and which were separated from one another by silica gel chromatography. They were identified as **22**, **23a** and **23b** (in order of their *R_f* values with 1:1 pet.ether/EtOAc, respectively) by means of their spectral and accurate HRMS data. The formation of the hydroxy acetates **23a** and **23b** is analogous to that of **10a** and **10b** from **6**, and is indicative of a carbocation intermediate derived from the initial bicyclic phosphorane by way of Ph₃ P=O extrusion. In particular the formation of the 1-acetoxycyclo[3.2.0^{1,5}]heptan-2-ol (**22**, a single stereoisomer) constitutes clear-cut evidence for the intervention of a carbocation intermediate of the type **26**, undergoing a cyclopropyl-carbinyl-cyclobutyl rearrangement,²¹ followed by capture of the cyclobutyl cation by the acetate ion.

Both **23a** and **23b** were stable toward AcOH under the reaction conditions applied to **21** and did not undergo rearrangement to **22**. The mechanism outlined in Scheme 7 satisfactorily accounts for all three products.

The question remained whether the parent 2,3-dioxabicyclo[2.2.1]heptyl system **3** and its [2.2.2]octyl homologue **27** lacking carbocation stabilizing groups indeed undergo PPh₃ reduction by an S_N2-like attack of the nucleophile (e.g., H₂O) at the bridgehead carbon. Our results, as presented above, do not support the S_N2 mechanism, though it is clear that carbocation-stabilizing groups at the α-position would dramatically influence the mechanistic pathway in the deoxygenation step. We therefore subjected the saturated endoperoxide derived from cyclopentadiene as well as 1,3-cyclohexadiene to PPh₃ reduction in the presence of water.

In our hands, the sole products formed from both reactions were exclusively the *cis*-diols **28a** and **28b** (in 92 and 79% yields, respectively, from the corresponding dienes) with no traces of the *trans* isomers. These results confirm Samuelsson's earlier report on the isolation of the *cis*-diol **2** from prostaglandin endoperoxide **1** with PPh₃ and render the S_N2 pathway less likely. We propose the mechanism shown in Scheme 9 for PPh₃ reduction of endoperoxides of the type **3** and **27** lacking carbocation-stabilizing groups adjacent to the peroxo carbons in the presence of H₂O.

Authentic samples of **28a** and **28b** were independently synthesized by thiourea reduction of the respective unsaturated endoperoxides **3** and **27**, followed by diazene reduction of the resulting unsaturated *cis*-diols in methanol (diazene generated in situ from potassium azodicarboxylate with AcOH in MeOH at 0 °C).

In conclusion, we have shown that PPh₃ reductions of saturated endoperoxides such as **6** and **21** containing vinyl or cyclopropyl groups α to the peroxo carbon facilitate direct deoxygenation and carbocation formation. The initial biphilic insertion of PPh₃ into the peroxo bridge had elegantly been demonstrated by Clennan and Heah.⁸ However, it is quite likely that the deoxygenation step in the case of **28a** or **28b** proceeds by heterolytic O-P cleavage of the cyclic phosphorane intermediate of the type **4** followed by attack of water at the phosphonium ion before **31** collapses to Ph₃ P=O and the *cis*-diol (Scheme 9). With a vinyl or cyclopropyl group present at the carbon adjacent to the bridgehead position (as in **12** and **24**), facile Ph₃ P=O loss from intermediate **30** occurs leading to an allyl or cyclopropylcarbinyl cation that

undergoes S_N1 substitution either directly or after allyl shift (both *cis* and *trans* hydroxyacetates are formed in each case), or cyclopropylcarbinyl-cyclobutyl rearrangement, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.PPh₃ Reductions of 2,3-Dioxabicyclo[2.2.1]heptanes^a^a Previous work by Samuelsson (1→2) and Clennan and Heah (3→5).

Scheme 2.

PPh_3 Reduction of the Saturated Fulvene Endoperoxide **6** without H_2O

Scheme 3.
Reaction **6** with PPh_3 in the Presence of AcOH

Scheme 4.
Mechanisms for the Formation of Compounds **7**, **8**, **10** and **11**

Scheme 5. Abe et al.'s Pathway to a 6-Oxabicyclo[3.2.0]hept-1-ene (**16**) and its Decomposition Products

Scheme 6.
 PPh_3 Reduction of **21** in the Presence of AcOH

Scheme 7.
Mechanism for the PPh_3 Reduction of **21**

Scheme 8.

Ph_3P Reduction of 2,3-Dioxabicyclo[2.2.1]heptane-and [2.2.2]octane and Independent Syntheses of the *cis*-Diols

Scheme 9.
 Ph_3P Reduction of **3** in the Presence of H_2O