β-(Phosphatoxy)alkyl and β-(Acyloxy)alkyl Radical Rearrangements: Evidence for Nondissociative Mechanisms

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A knowledge of the fundamental chemistry of nucleotide C4′ radicals is, we believe, relevant to the understanding of the mechanism of oligonucleotide strand scission by a number of antitumor antibiotics that function primarily by the abstraction of hydrogen atoms from the sugar–phosphate backbone.[1] To this end we[2] and Giese[3] have been studying the previously undescribed β-(phosphatoxy)alkyl radical migration in a series of model experiments with a view to determining the reaction mechanism. A stereochemical probe demonstrated the migration to be intramolecular and to proceed preponderantly, but not exclusively, with retention of configuration at phosphorus.[2b] This suggested that the migration was occurring through two competing three- and five-membered cyclic transition states with a preference for the former or through one of two possible fragmentation/in-cage recombination processes.[2b] We have therefore designed a system in which a dissociative mechanism would give rise to a regiospecifically labeled 1,3-diene (or its radical cation): reassociation could then take place at either end. Inspection of the label distribution in the product would then enable a distinction to be made between the dissociative and nondissociative pathways. Below we set out the results of such an experiment as well as its application to the parallel, long-standing problem of the β-(acyloxy)alkyl migration.[4]

Reduction of 6-phenylseleno-2-cyclohexen-1-one[5] with $NaBD_4/CeCl_3$ gave the corresponding alcohol, which was converted to the phosphate ester **1** and the benzoate ester **2** by conventional means. Tributyltin hydride reduction of **1**, initiated with AIBN in benzene at reflux, gave a mixture of reduction and migration products characterized by the partial 300-MHz ^1H NMR spectrum shown in Figure 1.[6]

The most striking feature of this spectrum is the equal intensity, within the limits of experimental error, of the olefinic signals H_c and H_d of the homoallylic ester as compared to the unequal ratio of olefinic signals H_s and H_t of the allylic ester in which H_s is diminished.[7,8] These results can be explained only by the predominance of a nondissociative migration (Scheme 1). The initially formed radical **3** either is reduced directly by the stannane, giving **4**, or suffers a nondissociative migration to give the allylic radical **5** which may be quenched by the stannane at either terminus to give the homoallylic and allylic phosphates **6** and **7**, respectively. The observed equal ratio of H_c and H_d derives from **6**, while the unequal ratio of H_s and H_t derives from the summation of **4** and **7**.

The alternative fragmentation pathway (Scheme 2) proceeding via **3** to either **8** or **9** would lead, following readdition at both terminii of the cyclohexadiene or its radical cation, to the two allylic radicals **5** and **10**, quenching of which at either end would lead to the two homoallylic phosphates **6** and **11** as well as the two allylic phosphates **7** and **12**. Clearly this product combination, together with the reduction product **4**, would provide an unequal

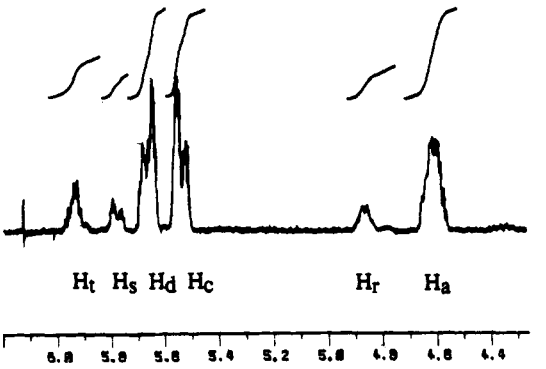
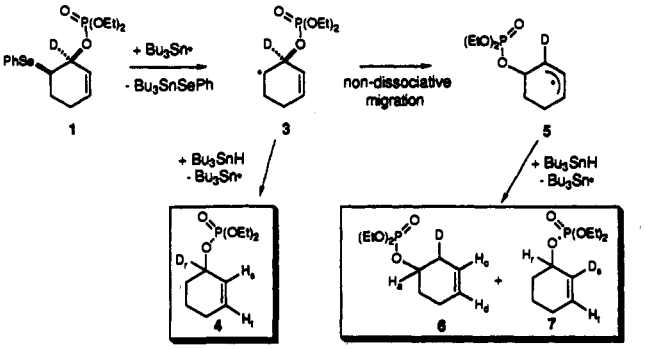
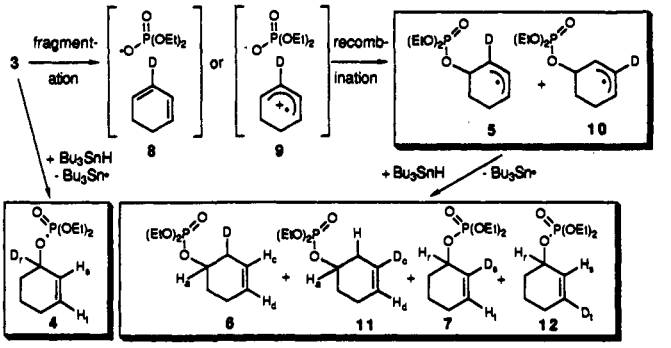


Figure 1. Partial 300-MHz ^1H-NMR spectrum resulting from the treatment of **1** with tributyltin hydride and AIBN in benzene at reflux.

Scheme 1



Scheme 2



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(5) Prepared by standard methods from cyclohexenone.

(6) Typical experimental details: to a solution of **1** or **2** (0.35–0.5 mmol) in C_6H_6 (40 mL) at reflux under N_2 were added tributyltin hydride (150 mol %) and AIBN (5 mol %) in C_6H_6 (20 mL) over 16 h with the aid of a motor driven syringe pump. After the addition, heating was continued until completion (4–24 h). After cooling of the solution, the solvent was stripped off and organotin residues were removed by filtration on silica gel (eluent, EtOAc/hexane 1/1). The products were examined by ^1H NMR at 300 MHz with the aid of spectra of pure authentic samples. Peak ratios were determined by integration of the spectrum with an estimated error of ~5%.

(7) Spectral assignments were made with the help of extensive decouplings on authentic unlabeled samples of all products.

(8) Control experiments eliminated any possibility of scrambling of the label through 3,3-sigmatropic rearrangement of the allylic phosphates under the reaction conditions.

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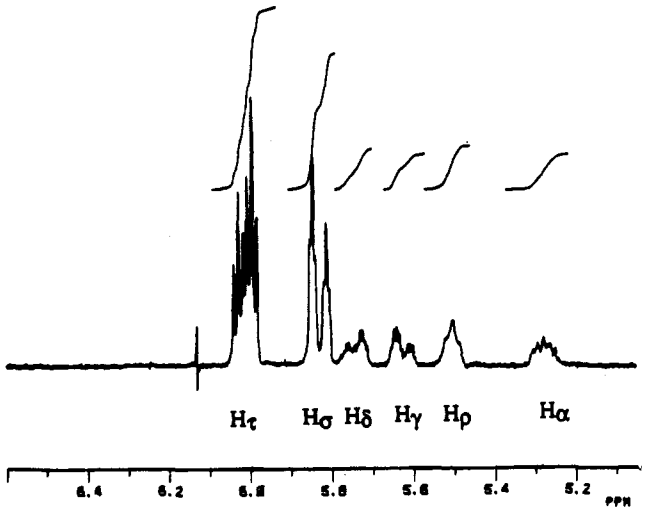
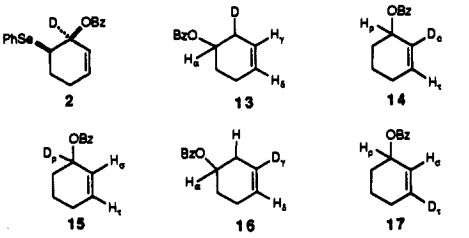


Figure 2. Partial 300-MHz ^{1}H-NMR spectrum resulting from the treatment of **2** with tributyltin hydride and AIBN in benzene at reflux.

ratio of H_c and H_d, diminished in H_c and, in the event of equal readdition at both ends of **8** and/or **9**, an equal ratio of H_s and H_t.[9]

Treatment of **2** with stannane under the same conditions provided the partial spectrum outlined in Figure 2, from which, pursuing the same logic, it is immediately obvious that this (acyloxy)alkyl migration occurs mainly through a nondissociative process to give **13** and **14**, as well as the reduction product **15**, rather than through a fragmentation/readdition sequence giving, in addition to **13**, **14** and **15**, the products **16** and **17**.

Inspection of Figures 1 and 2 also leads to the conclusion that, for experiments conducted under closely similar conditions, significantly more reduction is observed in the acyloxy series and hence that the phosphatoxy migration is substantially faster than the acyloxy migration.



In conclusion, both the β-(phosphatoxy)alkyl and β-(acyloxy)-alkyl radical migrations have been demonstrated to proceed, at least for the present substitution patterns and conditions, via nondissociative processes. The details of the three-center mechanism, predominant in the former, and the five-center mechanism, favored in the latter, are under active investigation in this laboratory.

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Supplementary Material Available: 300-MHz ^{1}H NMR spectra of authentic samples of unlabeled **1**, **2**, **4**, **6**, **13**, and **14** and **1-d_1** and **2-d_1** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Evidently, equal rates of readdition at either end of **9** and **10** need not necessarily hold within the solvent cage. The observed equal ratio of H_c and H_d is, however, sufficient alone to exclude the fragmentation readdition pathways.