Epoxide Formation by Ring Closure of the Cinnamyloxy Radical
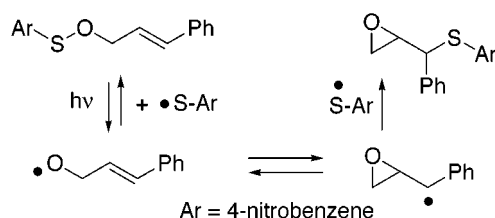
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ABSTRACT

Ar = 4-nitrobenzene

The cinnamyloxy and oxiranyl benzyl radicals were generated by photolysis of alkyl 4-nitrobenzenesulfenates. The yet unprecedented epoxide ring formation from a primary alkoxy radical was observed. Experimental evidence supports the fact that the mode of ring opening of the oxiranyl carbinyl radical system is thermodynamically driven. B3LYP/6-31G* calculations indicate that the closed form of the radical is ∼5 kcal/mol more stable than the open one.

The oxiranyl carbinyl radical **1**, shown in Scheme 1, usually rearranges by a fast carbon−oxygen bond cleavage to form the allyloxy radical **2**,[1] except for the rearrangement with R_3 or R_4 = phenyl or vinyl. In that case, a carbon−carbon bond cleavage to form **3** has been reported.[2] C−O bond fragmentation forms a highly reactive oxygen-centered radical from a carbon-centered radical due to the relief of ∼27.5 kcal/mol ring strain.

Scheme 1. Modes of Ring Opening of the Oxiranyl Carbinyl Radical
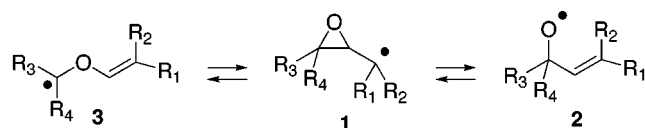
The formation of an allyloxy radical by this process has been used in synthesis for further radical reactions, such as 5-*exo* cyclization to a remote double bond.[3]

It was also incorporated in tandem sequences involving [1,5] hydrogen abstractions[4] or β-scissions[2b,5] followed by radical cyclizations. The mechanistic aspect of this rearrangement has attracted considerable interest, as the C−O bond cleavage in an epoxide caused by a radical is a very fast process, and the oxiranyl carbinyl radical **1** is difficult to detect or trap.[6] Recently, it has been trapped for the case where R_1,R_2 = cyclohexyl, and an approximate rate constant of $k = 3.2 \times 10^{10}$ s^{-1} for the ring opening to the

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allyloxy radical has been determined.[7] This observed rate is consistent with the results of high-level computational studies, which predict a low barrier, <4 kcal/mol, for the C−O bond cleavage of **1**.[8] Evidence for the reversibility of this reaction, i.e., the cyclization of allyloxy radical **2** to oxiranyl carbinyl radical **1** has also been reported for cases when alkoxy radical **2** is either secondary[9] or tertiary[4b,5c,10] ($R_3 = R_4 =$ alkyl). The rate of this cyclization was measured experimentally at 70 °C ($k = 2 \times 10^8$ s^{-1})[11] for $R_3 =$ Ph and $R_1 = R_2 = R_3 =$ H.

Here, we report a study of the rearrangement of **1** with R_1 = Ph and $R_2 = R_3 = R_4 =$ H. Radical **1** was trapped with an arylthiyl radical when either **1** or **2** was generated, which proved that cinnamyloxy radical **2** undergoes ring closure to give epoxide **1**. To the best of our knowledge, this is the first example of a primary alkoxy radical undergoing epoxide ring closure. This experimental evidence supports the hypothesis that the ring opening of oxiranyl carbinyl radical **1** is not kinetically but thermodynamically governed, as suggested by Ziegler.[10d,11] Generation of radicals **1** and **2** was achieved by photolysis of alkyl 4-nitrobenzenesulfenates **4** and **5**, as shown in Scheme 2. The *p*-nitrobenzene group

Scheme 2. Sulfenates Are Versatile Precursors for the Generation of Alkoxy and Alkyl Radicals
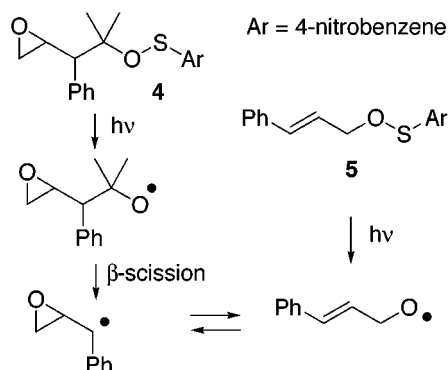
confers to the sulfenate both stability, owing to its electron-withdrawing properties, and UV absorbance at ~350 nm. Light of that wavelength cleaves the oxygen−sulfur bond homolytically, forming an alkoxy radical as well as a sulfenyl radical. When the alkoxy radical is tertiary, it will undergo a β-scission, losing a molecule of acetone, and give an alkyl radical. This versatile method for the generation of both alkoxy and alkyl radicals has been used to study the mode of ring opening of the oxyranyl methyl radicals.[12]

Cinnamyl 4-nitrobenzenesulfenate **5** was prepared by the reaction of cinnamyl alcohol with 4-nitrobenzenesulfenyl chloride in the presence of triethylamine.[13] Sulfenate **4** was prepared via the synthesis shown in Scheme 3. Cinnamyl chloride was reacted with acetone in the presence of zinc in an aqueous solution of ammonium chloride to yield 2-methyl-3-phenylpent-4-en-2-ol **6** in 91% yield. Epoxidation of the terminal alkene was achieved using *m*-chloroperbenzoic acid in methylene chloride. The corresponding epoxy alcohol **7** was obtained in 82% as a mixture of diastereoisomers with

Scheme 3. Synthesis of the Radical Precursor **4**
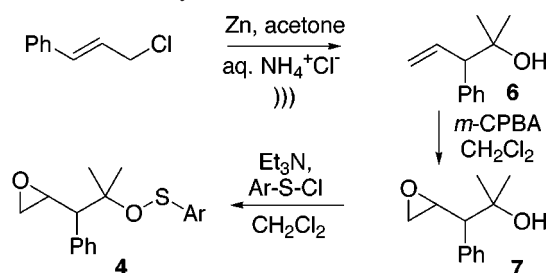
a ratio ~2.5:1, determined by integration in ^{1}H NMR analysis. The major diastereoisomer was isolated and reacted with triethylamine and 4-nitrobenzenesulfenyl chloride in methylene chloride. Sulfenate **4** was obtained as a single diastereoisomer in a 39% yield after purification.

Photolysis of sulfenates **4** was performed in a Rayonet UV reactor equipped with 350 nm wavelength light bulbs in deuteriobenzene as the solvent. The reaction was monitored by ^{1}H NMR analysis. The major products of the reaction were identified by comparing their ^{1}H NMR spectra with the one obtained from an independently prepared material, except for 1,2-epoxy-3-phenyl-3-propyl-4-nitrobenzene sulfide **8**, which was isolated by flash chromatography and fully characterized. Cinnamaldehyde, 4-nitrobenzene disulfide, and a 1:1 ratio of two diastereoisomers of sulfide **8** are the major products of the reaction. Our proposed mechanism to account for their formation is shown in Scheme 4. Photolysis of sulfenate **4** cleaves the O−S bond

Scheme 4. Mechanism of Photolysis of **4** and **5**
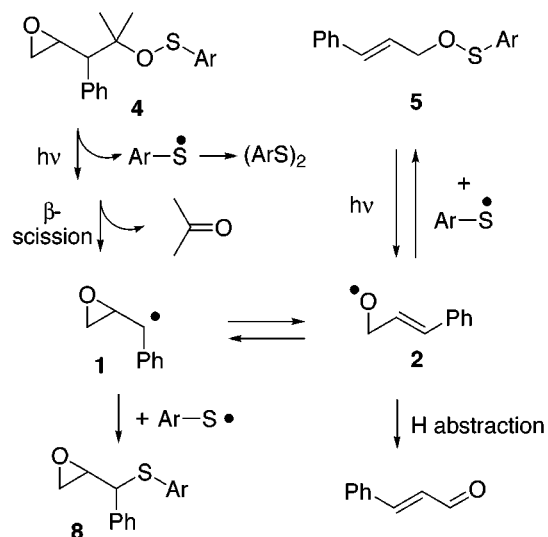
homolytically, forming the 4-nitrobenzenethiyl radical as well as the corresponding tertiary alkoxy radical. The later undergoes a β-scission, forming oxiranyl benzyl radical **1**. In this process, a molecule of acetone is liberated and its formation was detected by ^{1}H NMR analysis. Coupling of

the oxiranyl benzyl radical and the arylthiyl radical forms sulfide **8**. Epoxide ring opening also occurs via a C−O bond cleavage to form cinnamyloxy radical **2**. Coupling between this radical and the arylthiyl radical produces sulfenate **5**. During the course of the reaction, **5** appears as an intermediate that is slowly consumed, as can be observed by the disappearance of the doublet at $\delta = 4.14$ ppm in Figure 1.
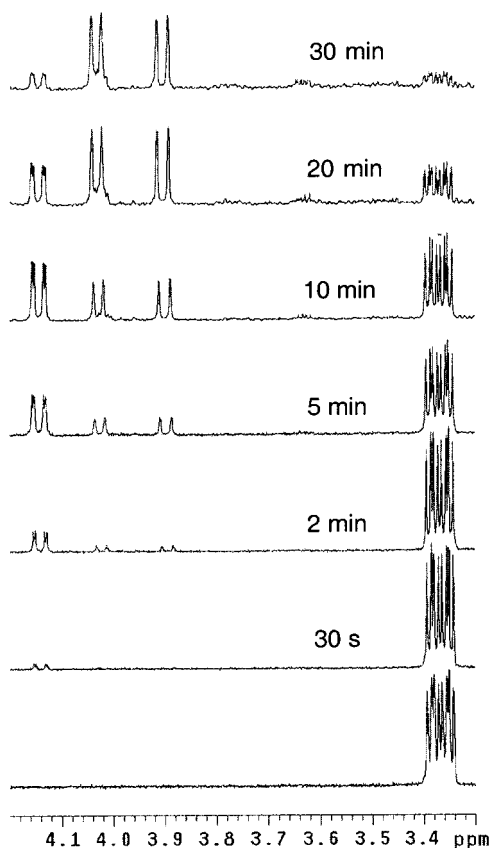

Figure 1. Partial ^{1}H NMR spectra, in C_6D_6, of the products of the photolysis of sulfenate **4** as a function of time. δ 3.37 (m, sulfenate **4**, methine H of epoxide), 3.9 (d, 1st diastereoisomer of sulfide **8**, H α to epoxide), 4.02 (d, 2nd diastereoisomer of sulfide **8**, H α to epoxide), 4.14 (d, sulfenate **5**, 2H on C α to O).

Under photolytic conditions, the O−S bond of sulfenate **5** is homolytically cleaved, forming back cinnamyloxy radical **2** as well as the arylthiyl radical. Formation of cinnamaldehyde can be explained by hydrogen abstraction on the cinnamyloxy radical by the arylthiyl radical or dispropor-

tionation. The disulfide is formed by self-coupling of the arylthiyl radical.

Photolysis of sulfenate **5** was performed under similar conditions and afforded very similar products. This implies that cinnamyloxy radical **2** undergoes ring closure to oxiranyl benzyl radical **1**, which is subsequently coupled with the arylthiyl radical to form sulfide **8**.

This observation is consistent with the previously observed reversibility of the oxiranyl carbinyl rearrangement. It supports the fact that the ring opening of the oxiranyl carbinyl radical is not kinetically but thermodynamically governed.[10d,11] Therefore, in the photolysis of **4**, sulfide **8** is the product of a coupling reaction rather than a "trapping" reaction, which suggests a kinetically controlled mechanism.

To further investigate the formation of **8**, the relative energies of the cinnamyloxy- and oxiranylbenzyl radicals were calculated, as well as their relative coupling products, i.e., cinnamyl benzylsulfenate and 1,2-epoxy-3-phenyl-3-propyl phenyl sulfide. All geometries were optimized at the B3LYP/6-31G*[14] level of calculation[15] using Gaussian 98[16] and are shown in Figure 2. Interestingly, these theoretical
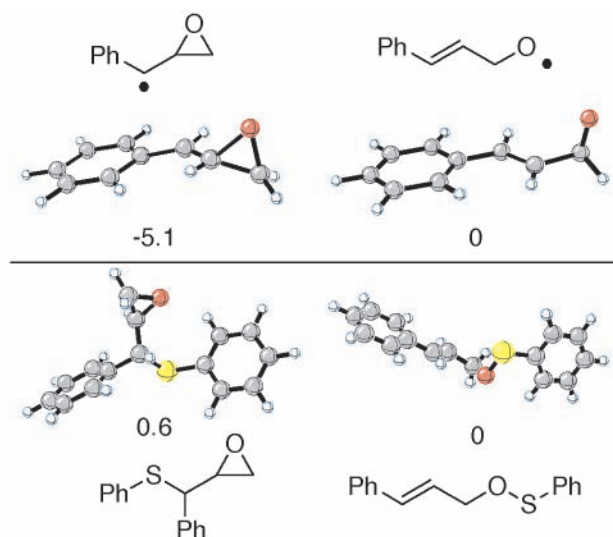

Figure 2. Relative energies in kcal/mol of the open and closed forms of the oxiranyl benzyl radical as well as their respecting coupling products. Geometries optimized at the B3LYP/6-31G* level.

considerations show that the closed form of the cinnamyloxy radical is more stable by ~5 kcal/mol than the open form.

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The epoxide ring-containing radical is the thermodynamically preferred product. This result is consistent with previous calculations on the oxiranyl methyl and allyloxy radicals, which predict the later to be more stable by ~1 kcal/mol.[8b] Introduction of a phenyl stabilizes preferentially the oxiranyl carbinyl radical by approximately 5−7 kcal, consistent with our calculated value.

Photolysis of sulfenate **4** yields first sulfenate **5** as an intermediate that is observed by ^{1}H NMR analysis while no sulfide **8** is detected, as shown in Figure 1. The different rates of coupling of **1** and **2** with the arylthiyl radical are probably at the origin of this observation. Even thought **1** is more stable than **2**, a rapid equilibrium exists between these two forms. The arylthiyl radical seems to couple fast enough to **2** rather than to **1**, forming preferentially sulfenate **5** over sulfide **8**. Under photolytic conditions, sulfenate **5** undergoes O−S bond homolysis, the exact reverse reaction of the coupling reaction of **2** and the arylthiyl radical. However, sulfide **8** does not react under photolytic conditions and once formed accumulates over the course of the experiment. Therefore, formation of sulfide **8** is suggested to be the result of a photodynamic equilibrium involving the radicals **1**, **2**, and arylthiyl as well as the light-reactive sulfenate **5** and the light-unreactive sulfide **8**.

In conclusion, experimental evidence suggests that the rearrangement of the oxiranyl carbinyl radical is thermodynamically driven. In light of these results, the assumption that the ring closure of the allyloxy radical is negligible in the estimation of the rate of ring opening of the oxiranyl methyl radical seems to be incorrect.[7] Thus, the proposed rate constant $k = 3.2 \times 10^{10}$ s^{-1} is likely to be a lower limit of the actual one.

Supporting Information Available: Experimental procedures for the preparation and photolysis of radical precursors **4** and **5**. Cartesian coordinates of the structures presented in Figure 2 with the corresponding energies and ZPEs. ^{1}H NMR, ^{13}C NMR, and IR spectra of compounds **4**, **5**, and **8**. ^{1}H NMR spectra of the products of photolysis of **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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