



Secondary Isotope Effects in Dioxirane Epoxidations. Concerted or Step-Wise Mechanism?

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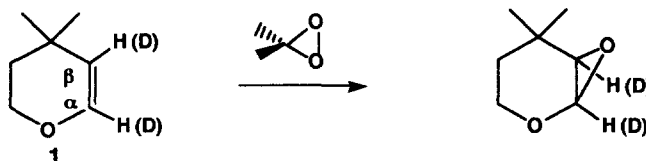
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Abstract: The inverse α - and β -secondary isotope effects found for the epoxidation reaction of dimethyl dioxirane (DMD) with alkenes support a non polar concerted mechanism.
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The discovery of the novel three-membered cyclic peroxides and their isolation^{1,2} in large quantities has attracted much attention and led to a remarkable array of oxidation reactions in the last ten years.³ Dioxiranes are easily prepared by the reaction of the corresponding ketones with caroate (KHSO₅) and isolated as their ketone solution by distillation (eq.1).



Among the various types of oxyfunctionalization reactions by dioxiranes, the most studied and synthetically useful is the epoxidation of alkenes. Several mechanistic studies of dimethyl dioxirane (DMD) epoxidation reactions have been reported that include stereochemistry,^{1,2,4} kinetics^{5,6} and solvent effects.⁷ It has been generally accepted that the epoxidation of alkenes by DMD involves a concerted spiro "butterfly" type transition state. Only one secondary deuterium isotope effect study on the mechanism of this reaction is currently available. For example, Murray and coworkers have reported⁸ the α -secondary isotope effects on the epoxidation of 4,4-dimethyl-2,3-dihydro- γ -pyran **1**, and its deuterium analogues. The authors concluded that the epoxidation mechanisms reported previously do not accommodate their results and suggested an unsymmetrical concerted transition state for this reaction.



In view of the fact that the double bond carbons, C_α and C_β , of substrate **1** are regiochemically different with substantial differences in electron density, the mechanistic information derived from this system may not be representative of simple alkenes.

In this work we present α - and, for the first time, β - secondary deuterium isotope effects that elucidate the nature of the transition state of the oxygen transfer in the epoxidation of alkenes by DMD.

In order to measure the β -secondary isotope effect, we prepared the alkenes 1-phenyl-3-methyl-2-butene, (**2-d₀**) and its deuterated analogue 1-phenyl-3-methyl-1', 1', 1'-d₃-2-butene-4, 4, 4-d₃ (**2-d₆**) in high purity.⁹ These substrates are well suited for an isotopic intermolecular competition, because they bear two geminal methyl groups, hydrogen **2-d₀** and deuterium **2-d₆**, next to the reactive double bond carbon. The β -secondary isotope effect k_H/k_D , was measured by integrations of the ¹H NMR and gas chromatography signals⁹ of the products **3-d₀** and **3-d₆** from the epoxidation reaction of DMD with a mixture of **2-d₀** and **2-d₆** in a ratio 1:1. These results are summarized in Table 1.

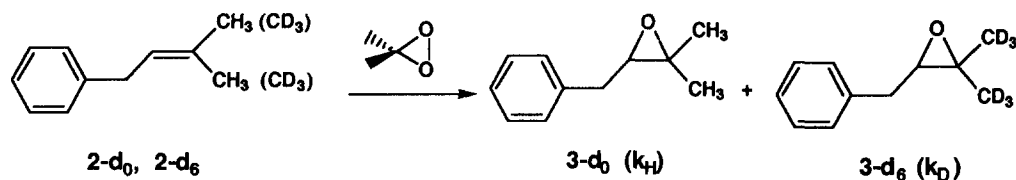


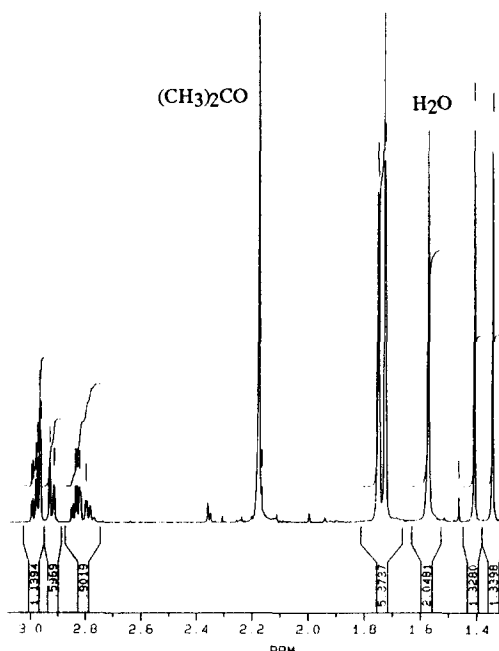
Table 1. β - Secondary Isotope Effects of DMD Epoxidation of **2-d₀** and **2-d₆**

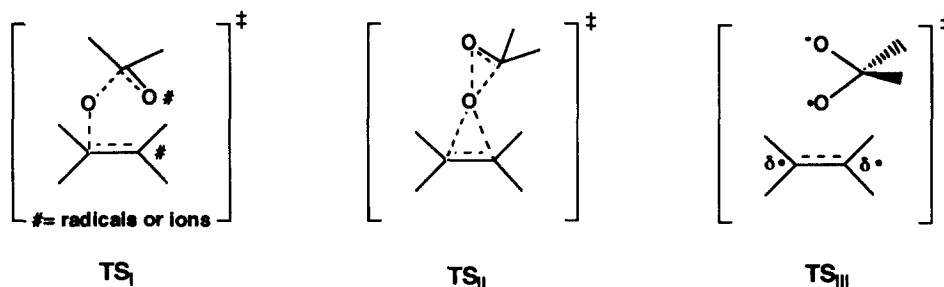
%Conversion	k_H/k_D by NMR ^a	k_H/k_D by GC. ^{b,9}
14	-	0.95
20	1.00	0.95
33	1.01	0.93
55	1.00	0.93

^aThe error was $\pm 5\%$ ^bEach value is the average of three consecutive measurements. The error was $\pm 2\%$.

The small inverse isotope effect found in the intermolecular competition between **2-d₀** and **2-d₆**, excludes the formation of a dipolar or diradical transition state TS_I, as shown below. In TS_I transition state the hyperconjugative effects¹⁰ involving six hydrogen atoms in **2-d₀** versus six deuterium atoms in **2-d₆**, are expected to be normal and large ($k_H/k_D \sim 1.1$ per deuterium atom). The results are consistent with a concerted mechanism as shown by TS_{II}. In a nonpolar TS_{II} transition state, the steric interactions

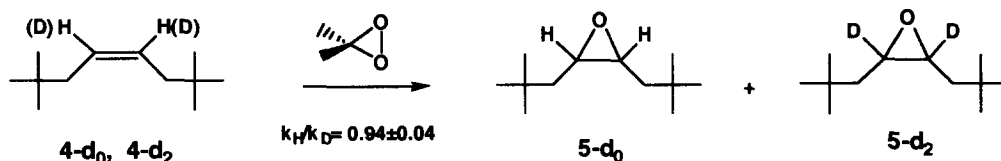
Figure 1. Determination of k_H/k_D by integration of the proper ¹H NMR signals of the products **3-d₀** and **3-d₆** (33% conversion).





in going from a less crowded ground state to a more crowded transition state would lead to a small inverse secondary isotope effect, as found.

To assess the extent of bond making and bond breaking in the transition state, we measured the intermolecular α -secondary isotope effect for the reaction of DMD with a 1:1 mixture of the symmetrical alkenes 2, 2, 7, 7-tetramethyl-4-cis-octene (**4-d₀**) and its (**4-d₂**) analogue.¹¹



The small inverse α -secondary isotope effect found in this reaction ($k_H/k_D = 0.94 \pm 0.04$), indicates a rather small change in the hybridization of the two carbons (sp^2 to sp^3) in going from the ground state to the transition state of this epoxidation.¹⁰ This result is consonant with the oxygen transfer in a concerted mechanism, shown by transition state TS_{II}.¹⁰ The smaller inverse isotope effect, - which implies little bond making in the transition state - of the **4-d₂** substrate ($k_H/k_D = 0.94$) when compared to the mono-deuterated substrates **1 α -d** ($k_H/k_D = 0.85$) and **1 β -d** ($k_H/k_D = 0.77$), is probably due to nonbonded interactions involving the two large neopentyl groups and the incoming dimethyl dioxirane molecule.

Minisci and coworkers have recently reported that DMD is in equilibrium with its bis oxo biradical and that epoxidation¹² and certain other oxidations¹³ proceed by the involvement of free radicals. However, this mechanism was recently challenged by results published by Ingold and coworkers.¹⁴

Adam, in a qualitative orbital analysis and energy profile of dioxy diradical, pointed out the possibility of its intermediacy in epoxidation and C-H bond oxygen insertion reactions.^{3c} In fact, dioxy diradical approach to the double bond in a concerted mechanism shown by transition state TS_{III}, is consistent with the observed stereospecificity of the epoxidation reaction and certainly not excluded by our results. Further theoretical calculations may shed some light on the factors that distinguish mechanisms TS_{II} and TS_{III}.

In conclusion, our results on the epoxidation of alkenes with DMD are consistent with the oxygen transfer in a nonpolar concerted transition state that confirms the previous spiro "butterfly" mechanism derived from stereoelectronic and kinetic studies.

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9. 1-Phenyl-3-methyl-1', 1', 1'-d₃-2-butene-4, 4, 4-d₃ (**2-d₆**) was prepared by Wittig coupling of triphenyl phosphoranylidene 1-phenyl-butane with acetone-d₆ in ether and was purified by preparative GC. ¹H NMR of the protio olefin **2-d₀**: (CDCl₃) δ 7.20 (m, 5H), 5.30 (m, 1H), 3.32 (d, J=7.3Hz, 2H), 1.71 (d, J=1.2Hz, 3H), 1.70 (d, J=0.8Hz, 3H). A 75-ft 50% phenyl- 50% methyl silicon capillary column was capable to separate the protio **3-d₀** from the deuterio **3-d₆** product.
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11. Olefin **4-d₂** was prepared by LiAlD₄ reduction of 3,3-dimethylbutyric acid. Subsequent mesylation of the corresponding alcohol-d₂, gave in good yield the mesylate-d₂. The above mesylate reacted with triphenyl phosphine and yielded the corresponding Wittig salt-d₂, which was treated with BuLi in THF in a continuous flow of molecular oxygen, and gave the cis alkene **4-d₂** in 90% geometrical purity. The same procedure was followed for the preparation of the protio analogue **4-d₀**. In this case, instead of LiAlD₄, LiAlH₄ was used. ¹H NMR of the protio olefin: (CDCl₃) δ 5.57 (m, 2H), 1.97 (d, J=5.7Hz, 4H), 1.8 (s, 18H).
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