A Reinvestigation of the Structure of the Transition State in Peracid Epoxidations. α- and *β*-Secondary Isotope Effects

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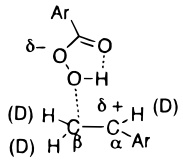
Received February 12, 1997

The epoxidation of alkenes by peracids is a synthetically useful transformation that has been used by chemists for many decades. Several mechanistic studies of this reaction have been reported that include stereochemistry,[1] as well as kinetics, solvent effects,[2] Hammet correlations,[3] and isotope effects.[4] The most popular mechanism was proposed[5] by Bartlett in 1950 and found support later from studies involving calculations[6] and experimental measurements.[7] It involves the symmetrical transfer of an oxygen atom to the alkene from the peracid monomer. However Bartlett's mechanism was challenged by Hanzlik and Shearer,[4] on the basis of α-secondary isotope effects of the peracid epoxidation of *p*-phenylstyrene and its deuterated analogues. They found a substantial inverse secondary isotope effect ($k_H/k_D = 0.82$) for deuterium substitution at the *β*-carbon (=CD_2) and no isotope effect ($k_H/k_D \approx 1$) for substitution at the α-carbon (=CDAr). The authors concluded that the epoxidation mechanism reported earlier by Bartlett does not accommodate their results and suggested a transition state which involves an open chain structure with a large degree of charge separation as shown in TS_I. Moreover a 1,3-dipolar addition mechanism involving a 1,2-dioxolane intermediate was also proposed,[8] but this mechanism was also challenged by results based on Hammet correlations and solvent effects.[9]



TS_I

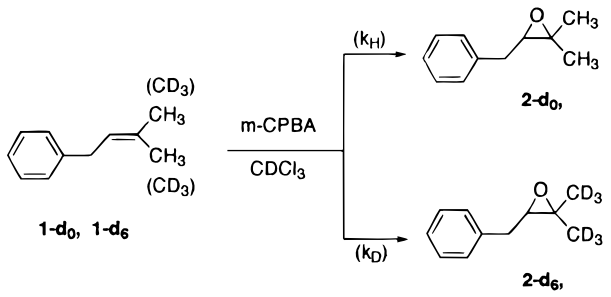
The controversy in the literature for the peracid epoxidation mechanism, as well as our own mechanistic studies on the epoxidation of alkenes with dimethyldioxirane,[10] prompted us to reinvestigate the nature of the transition state in the epoxidation reaction of alkenes by *m*-chloroperbenzoic acid. In this paper, we report the α- and—for the first time—the *β*-secondary isotope effects of the peracid epoxidations and discuss the formation of the possible transition state of this reaction, derived from the measured isotope effects.

Table 1. *β*-Secondary Isotope Effects of MCPBA Epoxidation of 1-d_0 and 1-d_6

% convrsn	k_H/k_D by NMR[a]	k_H/k_D by GC[b]
14	1.02	0.93
20	0.96	0.95
27	0.98	

[a] The error was ±5%. [b] Each value is the average of three consecutive measurements. The error was ±2%. A 75 ft 50% phenyl/50% methyl silicon a capillary column was able to separate the protio **2-d₀** from the deutero **2-d₆**.

In order to measure the *β*-secondary isotope effect, we prepared the alkenes 1-phenyl-3-methyl-2-butene, (**1-d₀**) and its deuterated analog 1-phenyl-3-(methyl-d_3)-2-butene-*4,4,4-d*$_3$ (**1-d₆**) in high purity. These substrates are well suited to test for a charge separation in the transition state by an isotopic intermolecular competition, because they bear two geminal methyl groups, in **1-d₀** and its deuterated **1-d₆** analog, next to the reactive double-bond carbon.[11]



Equimolar quantities of **1-d₀** and **1-d₆** were dissolved in chloroform-*d* and placed in an NMR tube. Small quantities of *m*-chloroperbenzoic acid were added, at room temperature, and after thoroughly shaking the NMR tube, the ^{1}H NMR spectrum of the reaction mixture was recorded. The formation of an epoxide was the only detectable product by ^{1}H NMR and gas chromatography analyses. The *β*-secondary isotope effect k_H/k_D, which is the result of an intermolecular isotopic competition between **1-d₀** and **1-d₆**, is propotional to the ratio of **2-d₀/2-d₆**. Reactions were run in less than 30% conversion to products. A typical ^{1}H NMR spectrum of the reaction mixture—20% conversion—of epoxides **2-d₀** and **2-d₆** (methyl signals at 1.42 and 1.36 ppm, benzylic hydrogens and hydrogens next to the oxygen between 2.8 and 3.3 ppm) and unreacted alkenes **1-d₀** and **1-d₆** (methyl signals at 1.75 and 1.73 ppm and the two benzylic hydrogens at 3.32 ppm) is shown in Figure 1. Integrations of the two methyl signals of **2-d₀** at 1.42 and 1.37 ppm as well as the hydrogens next to the oxygen and the benzylic hydrogens of both **2-d₀** and **2-d₆** determine the isotope effect k_H/k_D (**2-d₀/2-d₆** = k_H/k_D, Figure 1). The *β*-secondary isotope effect was also determined by the integration of gas chromatography signals of the products **2-d₀** and **2-d₆** (Figure 2). These results are summarized in Table 1.

The small inverse isotope effect found in the intermolecular competition between **1-d₀** and **1-d₆** excludes the formation of a dipolar transition state, TS_{II}, similar to that proposed earlier by Hanzlik and Shearer. In the

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S0022-3263(97)00268-5 CCC: $14.00

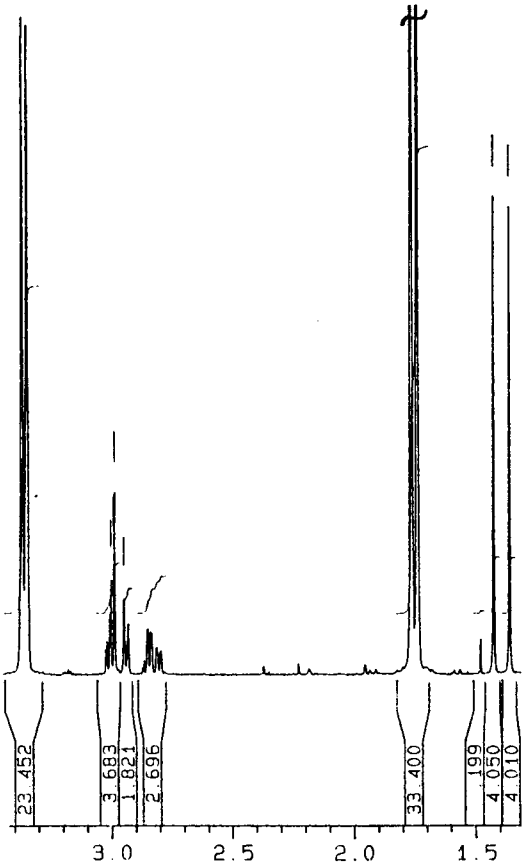


Figure 1. Determination of k_H/k_D by intergration of the proper ^{1}H NMR signals of the products **2-d$_0$** and **2-d$_6$** (20% conversion).

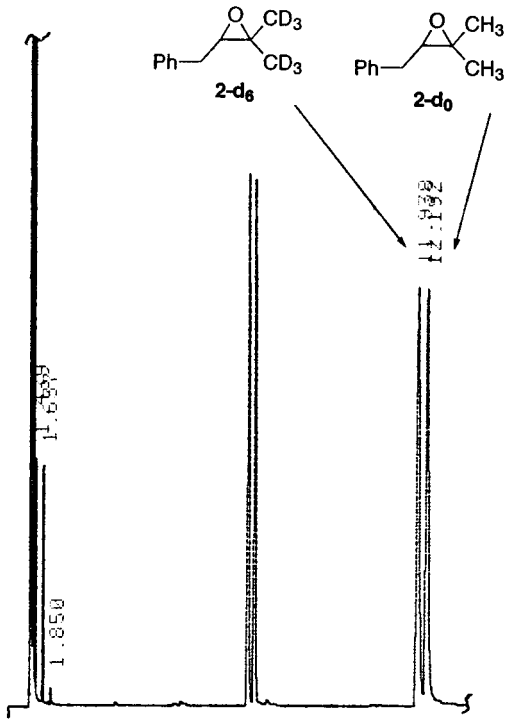
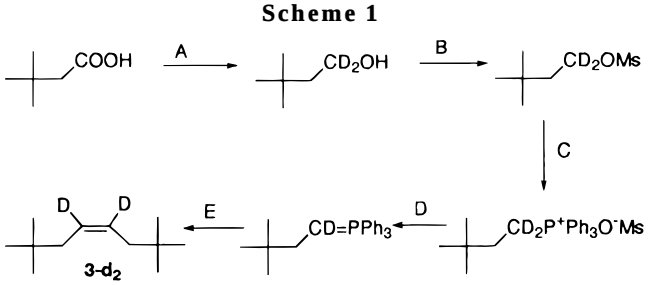


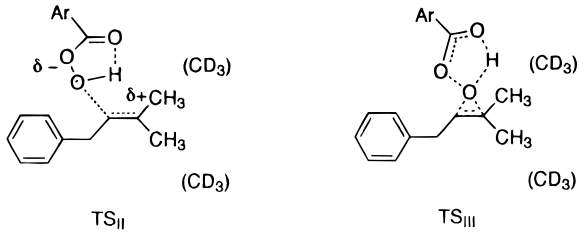
Figure 2. Determination of k_H/k_D by integration of the GC signals of the products **2-d$_6$** and **2-d$_0$**.

transition state TS_{II} the hyperconjugative effects[11] involving the six hydrogen atoms in **1-d$_0$** versus the six deuterium atoms in **1-d$_6$** are expected to give a normal and large isotope effect ($k_H/k_D \approx 1.05-1.1$ per deuterium atom), as found recently[12] in the dipolar cycloaddition of TCNE to 2,4-dimethylhexadiene. The results are consonant with a concerted mechanism as shown by TS_{III}. In the nonpolar TS_{III} transition state, the steric interactions 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.

Scheme 1



A = $LiAlD_4$, B = CH_3SO_2Cl/Et_3N, C = PPh_3, D = n-BuLi/THF, E = O_2 (bubbling)



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 MCPBA with a 1:1 mixture of the symmetrical alkenes 2,2,7,7-tetramethyl-4-*cis*-octene (**3-d$_0$**) and its deuterated analog (**3-d$_2$**). The preparation of **3-d$_2$** is summarized in Scheme 1.

Similarly the product ratio of **4-d$_0$/4-d$_2$** is proportional to the isotope effect k_H/k_D. Therefore the secondary isotope effect k_H/k_D was determined by the ^{1}H NMR integration of the hydrogens next to the oxygen in **4-d$_0$** at 3.01 ppm and the methylenic hydrogens signals of both **4-d$_0$** and **4-d$_2$** between 1.33 and 1.54 ppm. The substantial inverse α-secondary isotope effect found in this reaction ($k_H/k_D = 0.81 \pm 0.05$) indicates a rather large 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.[11] This result is also consonant with the oxygen transfer in a concerted mechanism, as shown by transition state TS_{III}.[11] Furthermore, these findings indicate a later transition state than that of the dimethyldioxirane oxidation, where a much smaller inverse isotope effect ($k_H/k_D = 0.95-1.00$) was found.[10] This fact is also consonant with the greater reactivity of dimethyldioxirane over MCPBA, in the epoxidation of even electron poor alkenes.

The previously reported[4] unsymmetrical, open chain transition state TS_I was deduced from the unequal inverse α-secondary isotope effects measured for the double-bond carbons C_α and C_β of arylstyrene. However, the double-bond carbons C_α and C_β are regiochemically different with substantial differences in electron density. Therefore, the mechanistic information derived from that system may not be applicable to simple alkenes.

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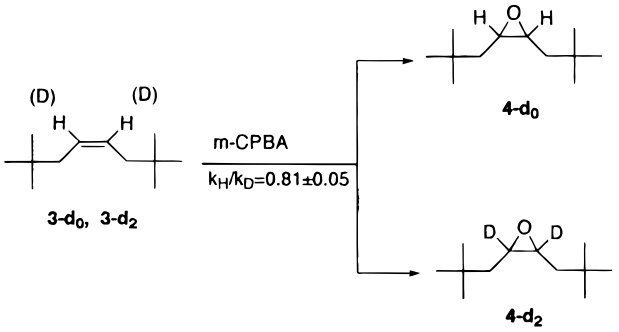

In conclusion, our results on the epoxidation of alkenes with *m*-chloroperbenzoic acid are consonant with the oxygen transfer in a nonpolar concerted transition state and confirm the previous spiro "butterfly" mechanism proposed earlier by Bartlett.

Experimental Section

All ^{1}H NMR (500 MHz and 360 MHz) spectra were taken in $CDCl_3$, except as noted. Chemical shifts are reported in δ (ppm) relative to internal tetramethylsilane. Analytical gas chromatography was performed by using a 75 ft 50% phenyl−50% methyl silicone capillary column and an FID detector. Reagents were obtained from Aldrich Chemical Co.

Preparation of 1-Phenyl-3-(methyl-*d*$_3$)-2-butene-*4,4,4-d*$_3$, (1-d$_6$). (a) In a high-pressure bottle, a mixture of 22.0 g (120 mmol) of 2-phenylethyl bromide and 31.5 g (120 mmol) of triphenylphosphine was stirred neat at 120 °C for a period of 16 h. After this, the phosphonium salt was obtained quantitatively in a glassy form, mp 90−95 °C. ^{1}H NMR: 8.15−7.10 (m, 20H), 4.40 (m, 2H), 3.05 (m, 2H)

(b) Nine grams (20 mmol) of the phosphonium salt prepared above were dissolved in 30 mL of dry tetrahydrofuran. To this solution, 10 mL (20 mmol) of 2 M *n*-BuLi in cyclohexane was added dropwise at 0 °C . After the solution was refluxed for 1 h, a deep red color appeared. To this ylide was added 1.3 g (20 mmol) of acetone-d_6 (99.5 atom % D) in 20 mL of tetrahydrofuran dropwise. After 10 h of reflux, the color still remained deep red. The addition of 50% excess of acetone-d_6 was required in order for all the ylide to react. After the standard workup procedure, the **1-d$_6$** was isolated in 65% yield. ^{1}H NMR analysis showed no methyl signals in **1-d$_6$** implying deuterium incorporation of more than 97%. Similarly, addition of acetone instead of deuterated acetone gave **1-d$_0$**. Both **1-d$_6$** and **1-d$_0$** were further purified by gas chromatography on a preparative Carbowax 20M, 6 ft × $^1/_4$ in. column. ^{1}H NMR of the protio olefin **1-d$_0$**: δ 7.31−7.15 (m, 5H), 5.36 (m, 1H), 3.32 (d, J = 7.3 Hz, 2H), 1.72 (d, J = 1.1 Hz, 3H), 1.70 (d, J = 0.6 Hz, 3H). ^{1}H NMR of the **1-d$_6$**: δ 7.30−7.17 (m, 5H), 5.34 (t, J = 7.3 Hz, 1H), 3.32 (d, J = 7.3 Hz, 2H).

Preparation of 3-d$_2$ and 3-d$_0$. (a) 3,3-Dimethyl-1-butanol-*1,1-d*$_2$. To 1.25 g (30 mmol) of $LiAlD_4$, 98% D, in 60 mL of dry ether, cooled to 0 °C was added dropwise 3.4 g (29 mmol) of 3,3-dimethylbutyric acid in 10 mL of dry ether. After 12 h of reflux, the reaction was worked up with base in the usual manner (1.3 mL of water, 1.3 mL of 15% NaOH, 3.9 mL of water). This solution was filtered, and the organic layer was washed twice with a saturated solution of NH_4Cl and once with brine and dried over sodium carbonate. Evaporation of solvent gave the title product in 80% yield. A similar procedure was followed to prepare 3,3-dimethyl-1-butanol. In this case the reduction of the acid was performed by $LiAlH_4$ to give 2.55 g, 84% yield of the above product. ^{1}H NMR of 3,3-dimethyl-1-butanol-*1,1-d*$_2$: 1.93 (s, 2H), 1.45 (br s, 1H, OH), 0.85 (s, 9H).

Preparation of the Methanesulfonyl Ester of the Above Alcohol. To a solution of 2.08 g (20 mmol) of the above alcohol-d_2 and 2.6 g (30 mmol) of triethylamine in 40 mL of dry dichloromethane cooled to −50 °C was added dropwise 2.28 (20 mmol) of methanesulfonyl chloride. After 30 min of additional stirring the reaction mixture was treated successively with ice cold 5% HCl aqueous solution, ice cold saturated sodium carbonate solution, and brine. After the organic layer was dried over magnesium sulfate, the solvent was evaporated to yield 4.1 g, 90% yield, of the above mesylate. The corresponding protio mesylate was prepared from the protio alcohol by the same procedure. ^{1}H NMR: 3.08 (s, 3H), 0.69 (s, 2H), 0.97 (s, 9H). ^{1}H NMR of the protio compound: 4.22 (t, J = 7.4, 2H), 2.98 (s, 3H), 1.67 (t, J = 7.4, 2H), 0.90 (s, 9H).

Preparation of the Phosphonium Salts of the Corresponting Mesylates. In a high-pressure bottle a mixture of 4.7 g (18 mmol) of triphenylphoshine and 3.2 g (18 mmol) of the above mesylate was stirred neat at 120 °C over night. After this, the phosphonium salt was obtained in gel form quantitatevely. ^{1}H NMR of deuterated phosphonium salt: 7.75 (m, 15H), 2.73 (s, 3H), 1.45 (d, J = 8.3 Hz, 2H), 0.97 (s, 9H). ^{1}H NMR of protio analog: 7.75 (m, 15 H), 3.25 (m, 2H), 2.73 (s, 3H), 1.45 (m, 2H), 0.93 (s, 9H).

***cis*-4,5-Dideuterated 2,2,7,7-tetramethyloctene.** In 30 mL of dry THF was dissolved 7.1 g (16 mmol) of the phosphonium salt prepared above. To this solution was added 8 mL of 2 M BuLi in cyclohexane dropwise until a red color appeared. The solution was cooled to −40 °C, and molecular oxygen was bubled until the dissapearance of the red color. After the standard workup procedure, **3-d$_2$** was isolated in crude form by distilation. Both **3-d$_2$** and **3-d$_0$** were purified by gas chromatography on a preparative Carbowax 10% 6 ft × $^1/_4$ in. column. The absence of olefinic signals of **3-d$_2$** in ^{1}H NMR indicates a deuterium incorporation of more than 97%. ^{1}H NMR: 1.97 (s, 4H), 0.93 (s 18H). ^{1}H NMR of protio analogue: 5.57 (t, J = 5.2 Hz, 2H), 1.97 (d, J = 5.2 Hz, 4H), 0.93 (s, 18H). GC MS: *m/e* 170, 155, 114, 99, 83, 71, 57 (100).

Acknowledgment. We thank professor G. J. Karabatsos for valuable comments. One preliminary experiment was performed at professor Foote's laboratory at UCLA, who is greatly acknowledged. The financial support of M. S. Hourdakis and Secretariat of Research and Technology (Grant PENED-94) are also acknowledged.

JO970268H