Regiospecific Epoxidation of Carvone: A Discovery-Oriented Experiment for Understanding the Selectivity and Mechanism of Epoxidation Reactions

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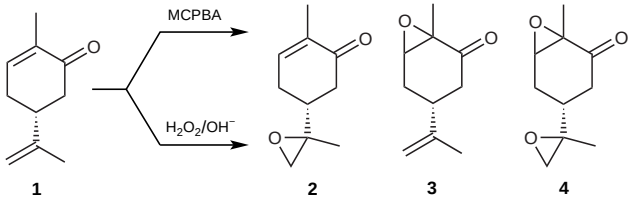
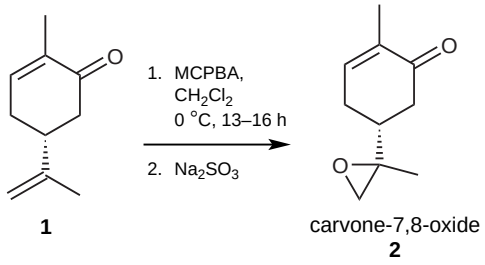
The conversion of alkenes to epoxides is a tremendously useful functional-group transformation in organic syntheses *(1–4)*. Epoxides are very useful synthetic intermediates owing to the high reactivity of the strained oxirane ring. The selectivity of epoxidation reactions can be readily controlled by choosing the appropriate reagents. Peroxy acids and alkaline H_2O_2 are two commonly used reagents for epoxidation reactions. Peroxy acids work well with electron-rich alkenes while alkaline H_2O_2 reacts preferentially with electron-deficient α,β-unsaturated ketones and aldehydes *(5)*.

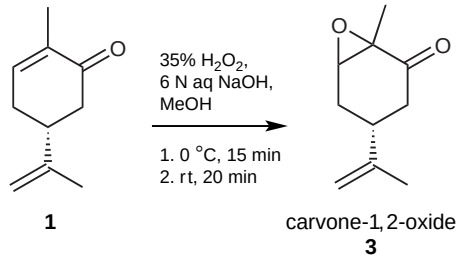
The importance of incorporating epoxidation reactions into the undergraduate organic chemistry laboratory curriculum can be illustrated by the number of related articles published recently in this *Journal (6–13)*. The epoxidation of alkenes by *m*-chloroperoxybenzoic acid (MCPBA) and alkaline H_2O_2 have been included in our third-year organic chemistry laboratory course for several years. Our experiment aims at strengthening students' understanding of the relationship between the selectivity and reaction mechanism of the two different epoxidation reactions, besides providing valuable practical exposure on the reaction manipulations.



Scheme I. Possible epoxidation products from (*R*)-(–)-carvone.



Scheme II. Epoxidation of (*R*)-(–)-carvone by MCPBA.



Scheme III. Epoxidation of (*R*)-(–)carvone by alkaline H_2O_2.

The respective selectivity of peroxy acids and alkaline H_2O_2 on the epoxidations of electron-rich alkenes and α,β-unsaturated carbonyl compounds can be well demonstrated by choosing an organic substrate that contains both functionalities. (*R*)-(–)-Carvone (**1**), an inexpensive naturally occurring compound isolated from spearmint, is an ideal substrate for the experiment. It consists of a cyclohexenone attached to an isopropenyl side chain, which contains an isolated C=C double bond. The reactions of (*R*)-(–)-carvone with MCPBA and alkaline H_2O_2 were found to be regiospecific with good reaction yields (Scheme I). The positions of the newly formed oxirane rings can be readily identified by ^{1}H NMR spectroscopy.

Several regioselective epoxidations of alkenes have been previously published in this *Journal*. A remarkable example is the selective epoxidation of an allylic alcohol. 2,3-Epoxygeraniol was selectively obtained when geraniol was treated with L-(+)-diethyltartrate, Ti(O*i*Pr)$_4$, and *t*-butylhydroperoxide at –23 °C *(6)*, while methyl trioxorhenium catalyzed the H_2O_2-epoxidation of geraniol yielding 6,7-epoxygeraniol as the major product *(13)*. The origins of the selectivity, however, were only barely discussed. The experiment described here was designed under a discovery-oriented approach and is suitable for intermediate- or advanced-level organic chemistry laboratory courses. The major objective of the experiment is to strengthen students' knowledge of the important features of epoxidation reactions and enhance their appreciation of the relationship between reaction mechanism and selectivity in organic syntheses. It has been well accepted that discovery-oriented experiments are far more effective for teaching and learning of reaction mechanisms *(8, 10, 14–18)*. Last but not least, the experiment described here does not require expensive reagents or difficult reaction conditions. Therefore, it can be readily adopted by most teaching laboratories.

Results and Discussion

The procedures for the reactions were adopted from the literature with minor modifications *(19–22)*. Details can be found in the Supplemental Material.[W] The MCPBA epoxidation was carried out by reacting a mixture of (*R*)-(–)-carvone and MCPBA in CH_2Cl_2 at 0 °C for 13–16 hours followed by an extractive workup (Scheme II). The alkaline H_2O_2 epoxidation, on the other hand, was carried out by reacting a mixture of (*R*)-(–)-carvone, 35% H_2O_2 and 6 M aqueous NaOH solution in methanol at 0 °C for 15 minutes and then at room temperature for 20 minutes (Scheme III). The product was isolated by extraction with CH_2Cl_2.

The selectivity of the reactions was determined by thin-layer chromatography (qualitative) and ^{1}H NMR spectroscopy (quantitative). Both of the MCBPA and alkaline H_2O_2 epoxidations of (*R*)-(–)-carvone were shown to be regiospecific with good reaction yields. The average yields of the MCPBA and alkaline H_2O_2 epoxidations obtained by our students were 78% and 80%, respectively.[1] The MCPBA epoxidation occurred exclusively at the isopropenyl moiety of (*R*)-(–)-carvone, yielding carvone-7,8-oxide (**2**). On the other hand, the enone C=C double bond was selectively converted by alkaline H_2O_2 into the epoxide carvone-1,2-oxide (**3**). Both products were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy as well as mass spectrometry, and the spectroscopic data were compared with the literature values *(19–22)*.

Thin-layer chromatography (TLC) provides a quick and inexpensive qualitative method for analyzing the reaction selectivity since compounds **2** and **3** have different R_f values.[2] In our trials, both reactions gave their respective desired products as a single spot on TLC, indicating that the reactions were specific. Instructors are advised to provide students with authentic samples for comparisons.

^{1}H NMR spectroscopy provides a highly reliable method for analyzing the compositions of the reaction products. The epoxides can be easily identified by comparing their ^{1}H NMR spectra with that of (*R*)-(–)-carvone. The raw products of both reactions were sufficiently pure that column chromatographic separation was not necessary to obtain reasonably clean NMR spectra.

(*R*)-(–)-Carvone has three vinyl protons. The two ^{1}H NMR signals at δ = 4.76 and 4.81 ppm were assigned to the two geminal vinyl protons of the isopropenyl group and the downfield multiplet at 6.76 ppm was assigned to the β-proton of the enone moiety (Figure 1). The resonance signals at δ = 4.81 and 4.76 were absent for the MCPBA epoxidation product, suggesting that the epoxidation occurred preferentially at the isopropenyl C=C bond (Figure 2). On the other hand, the multiplet at 6.76 ppm was missing from the NMR spectrum of the alkaline H_2O_2 epoxidation product, indicating that the enone C=C bond was selectively converted into an epoxide (Figure 3).

The specificities of the reactions were further confirmed by ^{1}H NMR spectroscopy. The α,β-epoxyketone **3** obtained from alkaline H_2O_2 epoxidation shows a multiplet at δ = 3.46 ppm assigned to the methine proton of the newly formed oxirane ring. This signal is absent from the NMR spectrum obtained for the MCPBA epoxidation product mixture. This suggested that MCPBA did not react with the enone of **1** to give an epoxide. The epoxide protons of carvone-7,8-oxide (**2**) obtained from MCPBA epoxidation, on the other hand, shows signals at 2.58–2.72 ppm. The signals partially overlapped with those of the protons of the cyclohexenone ring. Therefore, they are not very useful in ruling out the presence of **2** or diepoxycarvone **4** from the product mixture obtained from alkaline H_2O_2 epoxidation. Fortunately, the ^{1}H NMR signal of the methyl group of the epoxypropyl moiety of **2** (δ = 1.32, 1.33 ppm)[3] can be easily distinguished from the resonances of the methyl groups that attached to the epoxy ring (δ = 1.40 ppm) and of the isopropenyl moiety (δ = 1.72 ppm) in **3** (Figure 4). The resonance at δ = 1.32–1.33 ppm was not observed in the NMR spectrum obtained from the alkaline H_2O_2 epoxidation mixture, suggesting that the isopropenyl group is unreactive toward alkaline H_2O_2.

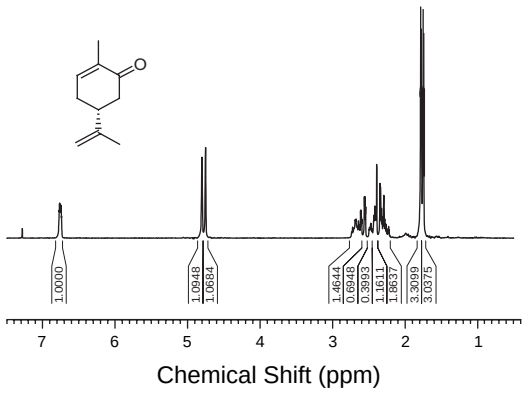


Figure 1. ^{1}H NMR spectrum of *(R)*-(–)-carvone (**1**).

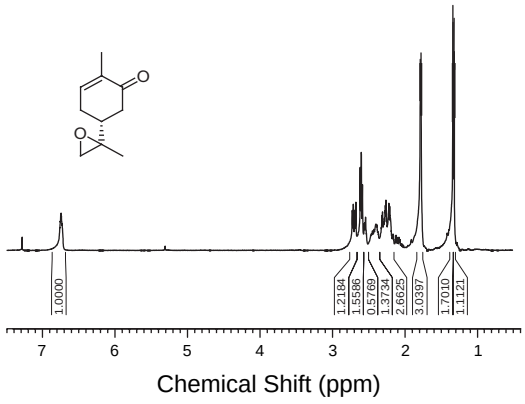


Figure 2. ^{1}H NMR spectrum of carvone-*7*,8-oxide (**2**).

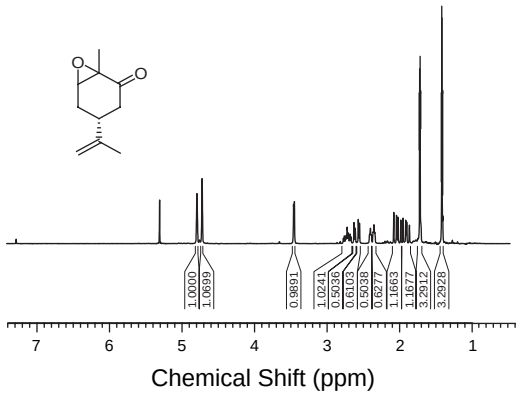


Figure 3. ^{1}H NMR spectrum of carvone-1,2-oxide (**3**).

The reaction products can also be characterized by IR spectroscopy if a high-field NMR spectrometer is not available. The IR spectra of the C=O and C=C bond regions for compounds **1**–**3** are shown in Figure 5. The absorption bands at 1675 and 1645 cm^{-1} in Figure 5A were assigned to the enone C=O and the isopropenyl C=C bond of carvone,

respectively. The C=O band was red-shifted from the typical C=O stretching of 1710 cm^{-1} to 1675 cm^{-1} because of an enone conjugation. The enone C=C absorption band was not observed because the intensity of alkene absorption in a s-trans enone is usually very low *(23)*. In Figure 5B, the C=O absorption band remained at 1675 cm^{-1} but the isopropenyl C=C absorption band at 1645 cm^{-1} was absent. This suggested that the enone moiety remained intact but the isopropenyl C=C bond was reacted. It further supported carvone-7,8-oxide as the product. In Figure 5C, the C=O absorption was blue-shifted to 1709 cm^{-1} but the isopropenyl C=C absorption remained at 1646 cm^{-1}. It suggested that the conjugation of enone was lost and the isopropenyl C=C bond was retained, implying that the epoxidation occurred selectively at the α,β-unsaturated ketone.

Students should be impressed by the excellent selectivity of these two reactions and are asked to provide mechanistic explanations in their laboratory report. The selectivity can be explained in terms of the roles played by the alkenes. Alkene acts as a nucleophile in the peroxy acid epoxidation but as an electrophile in the alkaline H_2O_2 reaction *(1, 5, 24)*. Epoxidation of alkenes by peroxy acids is a concerted process involving the nucleophilic attack on the peroxy O−O bond by the π-electrons of the C=C bond (Scheme IV). Therefore this reaction is generally favorable with electron-rich alkenes and electron-deficient peroxy acids. Hence, electron-deficient alkenes such as α,β-unsaturated ketones are unreactive with peroxy acids. α,β-Unsaturated ketones and aldehydes, on the other hand, react with H_2O_2 under alkaline conditions to give epoxides via a Michael-type 1,4-nucleophilic addition (Scheme

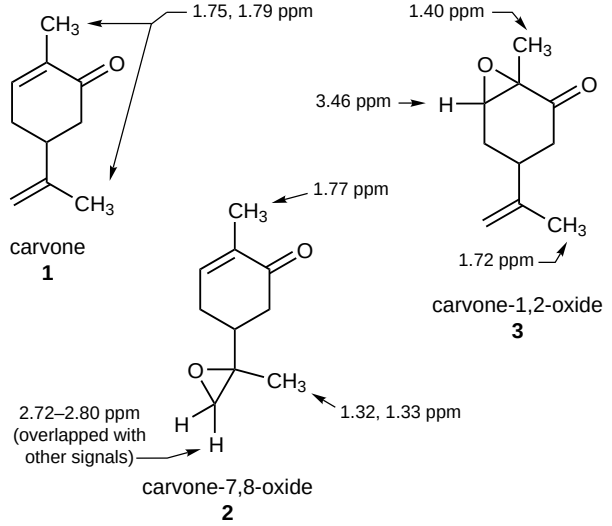
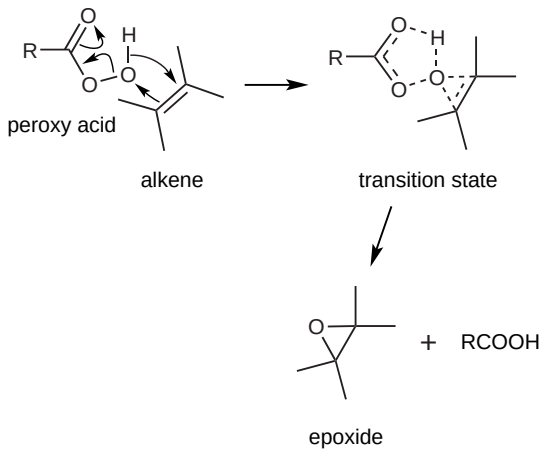


Figure 4. Characteristic ^1H NMR signals of carvone (**1**) and the epoxide products **2** and **3**.



Scheme IV. Proposed mechanism for the epoxidation reaction of an alkene by a peroxy acid.

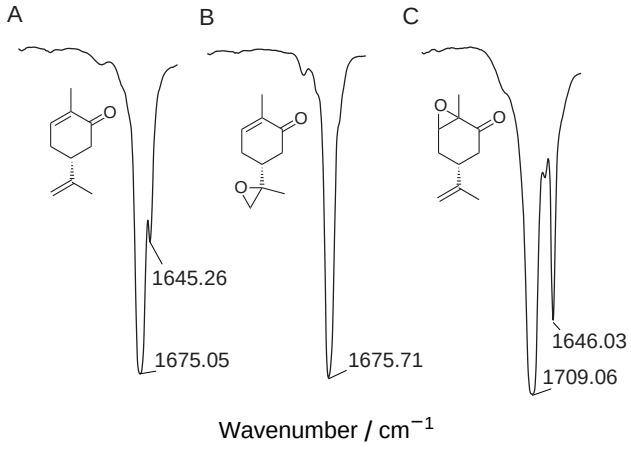
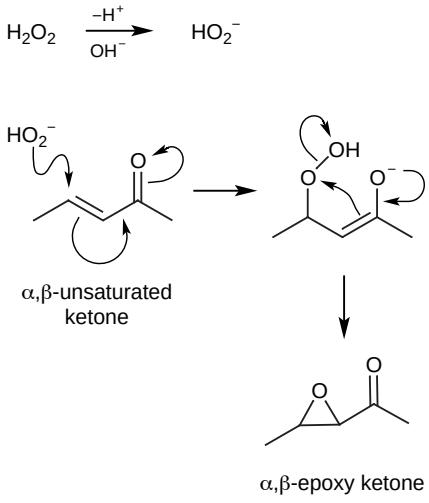


Figure 5. Partial IR spectra of the C=O and C=C bond regions for compounds **1–3.**



Scheme V. Proposed mechanism for the epoxidation reaction of an enone by alkaline H_2O_2.

V). The carbon–carbon double bond of an alkene ordinarily does not undergo nucleophilic addition. When the substrate is a α,β-unsaturated ketone, however, the anionic intermediate is an enolate ion and is stabilized. Therefore, the reaction becomes much more feasible.

This discovery-oriented experiment can be formally completed in one 3–4 hour laboratory session[4] and is suitable for organic chemistry laboratory courses of intermediate or advanced level. This experiment can arouse students' appreciation of the importance of having a good knowledge of reaction mechanisms if one wants to be a good synthetic organic chemist. In addition, students gain exposure to the applications of thin-layer chromatography and spectroscopic techniques for the identification of organic compounds.

Hazards

(*R*)-(–)-carvone, methanol, and deuterochloroform are harmful volatile organic substances. Deuterochloroform is a mutagen and suspected to be carcinogenic. They should be handled in a well-ventilated fumehood with great care. 35% H_2O_2, *m*-chloroperoxybenzoic acid, and 6 M NaOH solution are corrosive. 35% H_2O_2 and *m*-chloroperoxybenzoic acid are oxidizing. H_2O_2 can cause blistering to skin. Latex or nitrile gloves must be worn when handling these chemicals. *m*-Chloroperoxybenzoic acid is shock sensitive and is usually stabilized by ca. 25% of water. This compound should be handled with great care and should never be dried or ground. Dichloromethane, hexane, and ethyl acetate are volatile organic solvents and should be handled in a well-ventilated area. Hexane and ethyl acetate are flammable liquids and should be kept away from ignition sources. The ethanolic solution of phosphomolybdic acid for visualizing TLC plates is toxic and should be handled with care.

Acknowledgments

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[W]Supplemental Material

Students' handout, instructors' notes, detailed experimental procedures, NMR, IR and mass spectra, and detailed interpretation of spectra are available at this issue of *JCE Online.*

Notes

1. The experiment was run in a class of 44 third-year undergraduate students. The reaction yields obtained ranging from 57% to 91% for the MCPBA epoxidation and 58% to 95% for the alkaline H_2O_2 epoxidation.

2. The R_f values of **2** and **3** were determined to be 0.46 and 0.26, respectively. The analysis was performed on Merck TLC plates (silica gel 60) using a solvent mixture of hexane/ethyl acetate (10:1) as the eluent.

3. The epoxide was formed as a pair of diastereoisomers. Detailed discussion can be found in the Supplemental Material.[W]

4. Since the MCPBA epoxidation needs 13–16 hours of reaction time, instructor may ask students to come to the laboratory on the day before and set up the reaction, which may require about half an hour. To maintain the reaction mixture at 0 °C, keep the reaction mixture in a refrigerator set to 0–2 °C overnight. The students then come back on the next day to work up the MCPBA epoxidation reaction mixture and perform the alkaline H_2O_2 epoxidation.

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