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Kinetics of the Epoxidation of Geraniol and Model Systems by Dimethyldioxirane

A.L. Baumstark,* P.J. Franklin, P.C. Vasquez and B.S. Crow

Department of Chemistry, Center for Biotech and Drug Design, Georgia State University, Atlanta, Georgia 30303-3083, USA. Tel. +1 (404) 651-1716, Fax: +1 (404) 651-1416.

*Author to whom correspondence should be addressed; e-mail chealb@panther.gsu.edu.

Abstract: The mono-epoxidation of geraniol by dimethyldioxirane was carried out in various solvents. In all cases, the product ratios for the 2,3 and 6,7 mono-epoxides were in agreement with literature values. Kinetic studies were carried out at 23 ºC in the following dried solvent systems: acetone (k_2 = 1.49 $M^{-1}s^{-1}$), carbon tetrachloride/acetone (9/1, k_2=2.19 $M^{-1}s^{-1}$), and methanol/acetone (9/1, k_2 = 17 $M^{-1}s^{-1}$). Individual k_2 values were calculated for epoxidation of the 2,3 and 6,7 positions in geraniol. The non-conjugated diene system was modeled employing two simple independent alkenes: 2-methyl-2-pentene and 3-methyl-2-buten-1-ol by determining the respective k_2 values for epoxidation in various solvents. The kinetic results for each independent alkene showed that the relative reactivity of the two epoxidation sites in geraniol as a function of solvent was not simply a summation of the independent alkene systems.

Keywords: Mono-epoxidation, selectivity

Introduction

Dioxiranes are powerful oxidants that efficiently transfer an oxygen atom to a wide variety of organic substrates [1]. Numerous synthetically useful transformations have been carried out employing dioxiranes. Dioxirane chemistry provides a model for mechanistic insights into electrophilic oxygen-atom transfer in biological systems. Dimethyldioxirane (**1**), either generated *in situ* [2] or in isolated

solution [3], has been found to be a versatile epoxidizing reagent for a wide variety of alkenes. Epoxidation by **1** has been shown to be stereospecific and quantitative and to occur via a concerted electrophilic process with a "spiro" transition state [4]. The reaction of alkenes with **1** has been shown to be sensitive to steric factors. In general, *cis* alkenes have been found [4] to show greater reactivity than the corresponding *trans* compounds. Recently, product studies on the epoxidation of alkenes containing hydroxy groups have suggested [5,6] that (intermolecular) hydrogen bonding increases reactivity and affects product distributions. Computational studies have predicted [7] that hydrogen bonding of the hydroxy group of geraniol would lower the enthalpy of activation for epoxidation by a dioxirane. We report here a kinetics study on the mono-epoxidation of geraniol and selected model compounds by dimethyldioxirane in various solvents.

Results and Discussion

The reaction of dimethyldioxirane **1** with geraniol **2** in dried acetone, carbon tetrachloride/dried acetone (9/1) and methanol/acetone (9/1 wet and dried) was carried out at 23 ºC under conditions [5,6] in which only the mono-epoxides **3** and **4** were formed (Reaction 1). The combined yields of **3** and **4** were essentially quantitative with respect to **1**, the limiting reagent under these conditions. The products were isolated and characterized by NMR and GC/MS techniques. Results are summarized in Table 1.
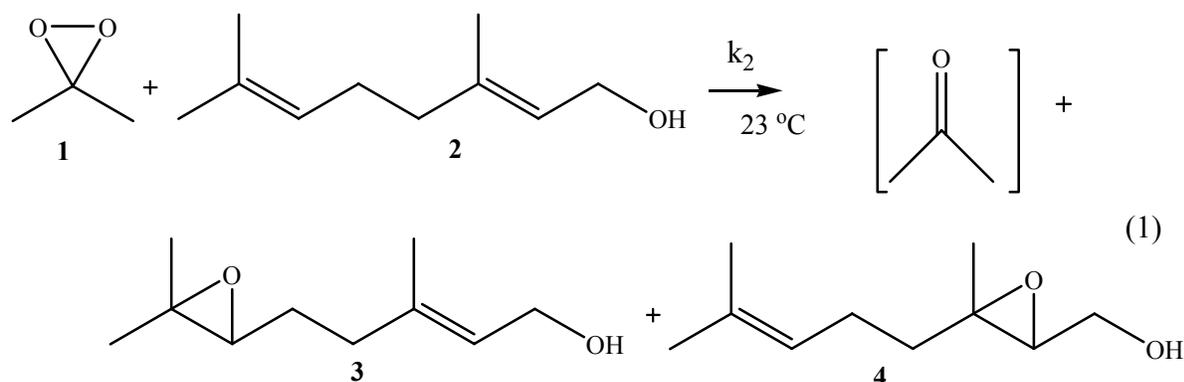

(1)

Table 1. Product distributions for the mono-epoxidation of geraniol by dimethyldioxirane at 23 ºC in various solvents.

Entry	Solvent	Product distribution, %			
		3		**4**	
1	Acetone[a]	68	(74)[c]	32	(26)[c]
2	CCl₄/Acetone (9:1)[a]	52	(51)[d]	48	(49)[d]
3	Methanol/Acetone (9:1)[a]	79	--	21	--
4	Methanol/Acetone (9:1)[b]	84	(88)[d]	16	(12)[d]

a) dried; b) wet; c) Ref. [5]; d) Ref. [6]

The product distributions (as determined by GC/MS and NMR spectroscopy ± 4%) were in good agreement with published studies [5,6]. The results in dried acetone/methanol (entry 3) have not been previously reported. The presence of fortuitous water seems to result in a slight increase in the yield of epoxide **3** at the expense of **4**. The reaction of two independent alkenes: 2-methyl-2-pentene (**5**) and 3-methyl-2-buten-1-ol (**6**), with **1** as a model for the geraniol system yielded the corresponding epoxides in quantitative yield, respectively (reactions 2 and 3), independent of solvent. The results for **5** in acetone were in agreement with published data [8].
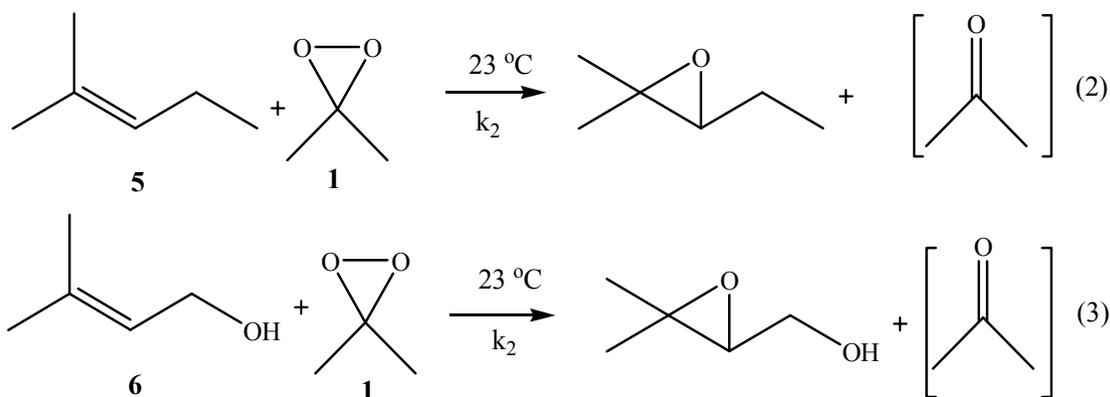
The reaction of **1** with the various alkenes was shown to be of the second order overall as expected (first order in both alkene and dioxirane). The second order rate constants (k_2s) were measured at 23 °C by monitoring the UV absorbance decay of **1** at 330 nm. The reactions were carried out in the following solvents: a) dried acetone, b) carbon tetrachloride/ dried acetone (9:1) and c) dried methanol/ dried acetone (9:1). The k_2 values for geraniol are reflective of those for the overall molecule (both sites). Pseudo first order conditions were employed for most of the k_2 determinations. Those in methanolic solvent for **5** and **6** were carried out under equal molar conditions.

Figure 1. Representative Data for the Mono-Epoxidation of Geraniol by **1** in Various Dried Solvents at 23 °C.
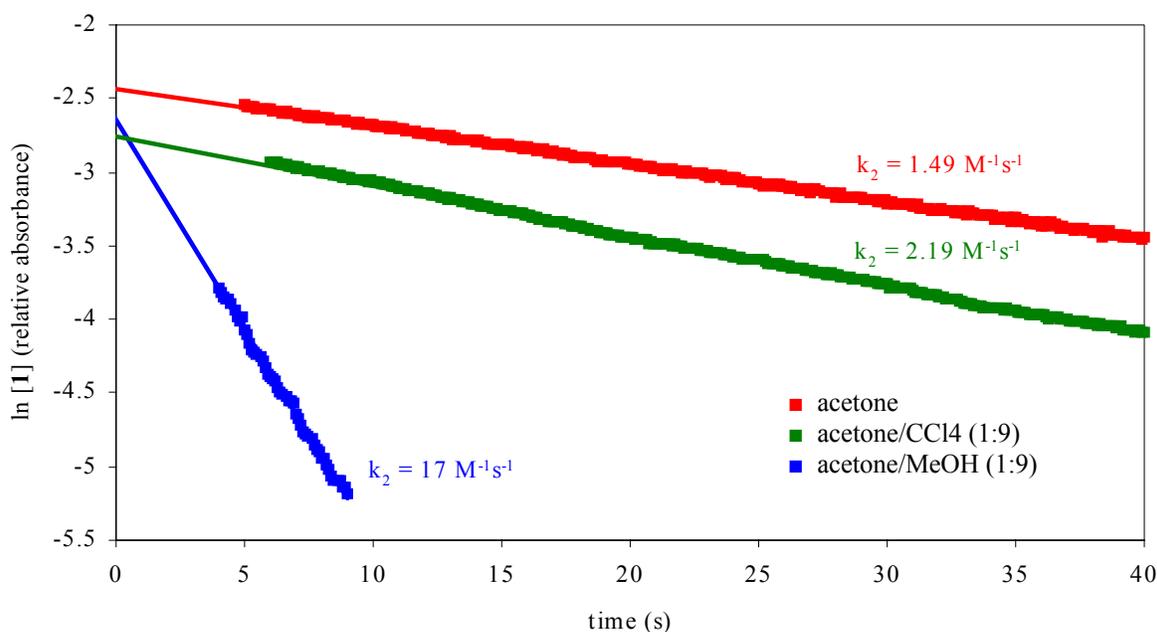
Figure 1 shows representative results for mono-epoxidation of geraniol by **1** in the three solvent systems. The k_2 values for epoxidation of alkenes **2**, **5** and **6** are listed in Table 2.

Table 2. Second order rate constants for the mono-epoxidation of alkenes **2**, **5** and **6** by **1** in various solvents at 23 ºC.

Alkene	Structure	Solvent[a]	k_2 $(M^{-1}s^{-1})$	k_{rel}
2		Acetone	1.49 ± 0.02[b]	$\equiv 1.0$
		CCl$_4$/Acetone (9:1)	2.19 ± 0.05[b]	1.5
		MeOH/Acetone (9:1)	17 ± 1[b]	11.4
5		Acetone	0.99 ± 0.02	$\equiv 1.0$
		CCl$_4$/Acetone (9:1)	1.10 ± 0.05	1.1
		MeOH/Acetone (9:1)	27 ± 2	27
6		Acetone	0.68 ± 0.02	$\equiv 1.0$
		CCl$_4$/Acetone (9:1)	2.03 ± 0.10	3.0
		MeOH/Acetone (9:1)	7.5 ± 0.5	11.5

a) dried; b) per molecule (both olefinic sites)

The separate second order rate constants for epoxidation of the 6,7 and 2,3 sites in geraniol were calculated from the overall k_2 values (Table 2) and the observed product distributions (Table 1). The results as well as the relative rate calculations in the three solvent systems are listed in Table 3. Interestingly, the relative behavior of the two independent sites in geraniol is different. The results for 2,3 and 6,7 epoxidation show some of the characteristics observed for the model systems (**5** and **6**) with interesting differences (*vide infra*).

Table 3. Calculated second order rate constants of epoxidation of 6,7 and 2,3 sites of geraniol at 23 ºC.

Entry	Solvent[a]	$k_{6,7}$ $(M^{-1}s^{-1})$	k_{rel}	$k_{2,3}$ $(M^{-1}s^{-1})$	k_{rel}
1	Acetone	2.03	$\equiv 1.0$	0.95	$\equiv 1.0$
2	CCl$_4$/Acetone (9:1)	2.28	1.1	2.10	2.2
3	MeOH/Acetone (9:1)	26	13	6.9	7.3

a) dried

Product studies for mono-epoxidation of geraniol by dimethyldioxirane are well documented [5,6]. Adam *et al*. [5,6] found that the reaction of dioxirane **1** with equimolar geraniol in acetone yielded 9% bis-epoxide and the mono-epoxides **3** and **4** in a 73:17 ratio. No bis-epoxide was noted when 0.3 equivalents of **1** were used. The present yield data, obtained under the latter conditions, are in good to excellent agreement with the published work, especially when one notes that adventitious moisture affects the **3** to **4** ratios. In addition, the variation in product ratio as a function of solvent is also in good agreement with published results.

The geraniol study was designed as an intramolecular competition experiment in which absolute rate studies were not necessary [6]. The results were explained as a combination of inductive effects and intermolecular/intramolecular hydrogen bonding dependent on solvent characteristics. In hydrogen-bonding solvents, the greater reactivity of the 6,7 site over that of the 2,3 position was ascribed to the greater nucleophilicity of the 6,7 position over the inductively deactivated 2,3 site. In the non-polar carbon tetrachloride solvent system, intramolecular hydrogen bonding at the 2,3 olefinic site was postulated to be responsible for the increased yield of **4**.

The absolute rate studies on geraniol show the situation to be complex. The studies on **5** and **6** provide insights and facilitate interpretation since they model each site in geraniol as if it were independent. Interestingly, other than the present work, there is only one other major kinetics study of dimethyldioxirane reactivity in various solvents. Gilbert *et al*. [13] reported the k_2 values for epoxidation of cis-stilbene by "acetone-free" **1**. At 2 °C, epoxidation in CCl_4 was found to be ~3-fold slower than in acetone.

The present study on **5** noted a very slight increase in relative reactivity upon addition of carbon tetrachloride relative to that in acetone, the opposite of that reported in the literature [13]. In addition, reactions carried out with added methanol showed a 27-fold increase, in agreement with our previous data on addition of water [3b]. The results for **6** provide interesting differences from those of **5**. In acetone, the k_2 value is somewhat lower than expected for a trisubstituted alkene. This lower reactivity is in agreement with our earlier observations [3b] on hydroxy-substituted alkenes. Deactivation of the alkene by an inductive effect is a possible explanation although gas phase calculations have suggested [7] that in the case of the 2,3 site of geraniol inductive effects are not involved. An explanation in which the hydroxy group interacts with acetone could also lead to reduced reactivity. The hydroxy-containing model compound **6** shows a larger increase in reactivity in carbon tetrachloride and a smaller one in methanol than those observed for **5**. This latter observation indicates that strong hydrogen bonding to the solvent may increase steric interactions and slow attack by **1** on **6**.

The k_{rel} values for geraniol (Table 2) indicate intermediate behavior as compared to that of **5** and **6**. Calculation of the individual k_2 values for sites 2,3 and 6,7 and subsequent comparison to the model systems provide important insights that can not be gained solely from the product studies. Both the calculated k_2 values and the k_{rel} values need to be analyzed. In methanol, the $k_{6,7}$ value is essentially identical to the k_2 value for **5**. However, the k_{rel} value for the formation of **3** is low. This indicates that the $k_{6,7}$ values in acetone and carbon tetrachloride are faster than expected. This suggests that the remote hydroxy group is exerting an effect on the 6,7-position that increases the reactivity in the less

polar/less hydrogen-bonding solvents. This effect could be an intramolecular hydrogen-bonding effect or a solvation effect. Analysis of product studies, alone, would not lead to this conclusion.

The analysis of the 2,3 site rate constant data reveals additional interesting insights. In methanolic solvent, the $k_{2,3}$ value is very similar to that for **6**. However, both those numbers are 3-fold less than the $k_{6,7}$ value and that for **5** in the same solvent. This clearly cannot be solely due to an inductive effect of a hydroxy group. It appears that hydrogen bonding between methanol and the hydroxy group results in decreased reactivity at the 2,3 position due to increased steric interactions (with essentially no effect at the 6,7 position). The $k_{2,3}$ and corresponding k_{rel} values in acetone and carbon tetrachloride are very similar to those for the model alkene **6**.

Conclusions

The kinetic data clearly show that the two epoxidation sites in geraniol are not simply a summation of the independent alkene system data. Instead there are subtle interactions between the two sites that mediate the final product distributions. Understanding of the mechanistic constraints on electrophilic oxygen-atom transfer chemistry provides important insights not only into synthetic applications but also into enzymatic-related systems.

Acknowledgments

Experimental

General

Glassware was treated by boiling in a solution containing 1% Na_2EDTA for approximately 1 h, washing with deionized water, rinsing with acetone and drying prior to use. All solvents (Aldrich) used were of either HPLC or anhydrous reagent grade. Kinetic experiments were carried out on a Shimadzu UV-1601 spectrometer connected to a HAAKE K constant temperature circulating water bath (T ± 0.3 ºC). GC-MS data were collected on a Shimadzu GC-17A gas chromatograph coupled to a Shimadzu QP-5000 mass spectrometer. ^{1}H-NMR spectra ($CDCl_3$) were recorded on a Varian 300 MHz Unity spectrometer. Geraniol (**1**), 2-methyl-2-pentene (**5**), 3-methyl-2-buten-1-ol (**6**) and Oxone® ($2HKSO_5•HKSO_4•K_2SO_4$) were obtained commercially (Aldrich) and were used without further purification. Isolated dried dioxirane **1** (0.1 M, in acetone) was prepared by a procedure [4] that was an adaptation of the experimental approach of Murray and Jeyaraman [3a]. Also see W. Adam *et al*. [3d].

Product Studies.

The reaction products for epoxidation of **2**, **5** and **6** by dimethyldioxirane were analyzed by GC/MS and ^{1}H-NMR spectroscopy. For mono-epoxides **3** and **4** the data were in agreement with literature values [9,10] in each case [5,6]. In all cases, the percentage conversion was quantitative with respect to **1**. The product study for geraniol was carried out under conditions [5] which only produced mono-epoxidation as follows: geraniol (50.0 mg, 0.325 mmol) was added to the appropriate dried solvent (11.25 mL) at ambient temperature. To this solution, 0.33 equivalents of **1** (1.25 mL, 0.078 M) in acetone were added followed by stirring for 1 h. The solvent was removed and the overall yield, as well as the product ratios for the mono-epoxides, were determined by integration of the olefinic and epoxide hydrogen peaks versus internal standard in the ^{1}H-NMR spectrum. GC/MS analysis was carried out to confirm the results. Product studies for the epoxides derived from **5** and **6** were carried out with a 3-fold excess of **1**. Quantitative conversion of the alkene to the epoxides was observed in both cases. Spectral data for the epoxide were consistent with the respective literature values [11,12].

Kinetic Studies

All solutions for kinetic experiments were prepared with dried solvents. The reactions were studied at 23 ± 0.3 ºC employing either a 10:1, 3:1, or 1:1 substrate to dimethyldioxirane ratio. The reactions were monitored by following the decrease in the absorbance at 330 nm (concentration of dioxirane). The following general approach was used in all kinetics experiments. A predetermined quantity of alkene of known concentration was placed in a standard UV quartz cuvette and allowed to equilibrate. The desired equivalents of dimethyldioxirane in dried acetone solution (≤ 0.1 M) were added via syringe and the solution was mixed rapidly. Under pseudo-first order conditions, the values of k_{obs} were calculated from linear plot of the natural log of the relative absorbance of the dioxirane against time. Data were collected for at least two half-lives for all the kinetic runs. The values for the second order rate constants were computed by dividing the k_{obs} value by the concentration of the reagent in excess. For the other conditions, the k_2 values were calculated using the standard approach for second order rate constants (for example, plots of the reciprocals of dioxirane concentration vs. time for equal molar conditions).

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