The Oxidation of Cinnamaldehyde with Alkaline Hydrogen Peroxide

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Abstract

The oxidation of cinnamaldehyde (3-phenyl-2-propenal) by alkaline peroxide results in epoxidation of the double bond to form cinnamaldehyde epoxide (3-phenyl-2,3-epoxy-propanal) which undergoes further reaction by ring opening and side chain cleavage to yield benzaldehyde and acidic fragments. The reactions are first-order in the organic substrates and perhydroxyl anion and second-order overall. In the presence of alkali alone, two further reactions take place in which cinnamaldehyde and cinnamaldehyde epoxide side chains are cleaved by reaction with hydroxide ion to form benzaldehyde and side chain fragments. These reactions are first-order in the organic substrates and hydroxide ion and second-order overall. Increasing solvent polarity accelerates the rates of reaction and reaction mechanisms have been proposed to describe the observed kinetic behavior. The stereoselectivity of the epoxidation reaction has been examined in terms of an existing model for epoxidation of α,β-unsaturated ketones by alkaline peroxide.

Introduction

Epoxides may be conveniently synthesized from alkenes by reaction with peroxy reagents such as *m*-chloroperbenzoic acid [1,2], peracetic acid [3], and alkaline hydrogen peroxide [4–7]. It is has been shown that epoxidation mechanisms differ with the reagent [2,3,6,7] and solvent system [2] employed. Comprehensive mechanistic and kinetic studies of the reaction of α,β-unsaturated ketones with alkaline peroxide have been reported [6–9], however similar investigations with α,β-unsaturated aldehydes have not been undertaken. The current literature presents insufficient information about reactions involving α,β-unsaturated aldehydes and alkaline peroxide to allow general conclusions to be drawn, particularly with regard to kinetic schemes and reaction products [10–13]. Most authors [4,10,11,13,14] agree that the carbon–carbon double bond of α,β-unsaturated aldehydes undergoes epoxidation by nucleophilic attack of the perhydroxyl anion at the β-position in a Michael addition similar to that reported for α,β-unsaturated ketones [6–9], however further reaction of the formed epoxide has only occasionally been considered [13,14].

In this article we present rate and mechanistic information for the epoxidation and epoxide ring cleavage of a model α,β-unsaturated aldehyde, cinnamaldehyde, along with rates and mechanisms of secondary reactions involving nucleophilic attack by the hydroxide ion. The effects

International Journal of Chemical Kinetics, Vol. 25, 901–911 (1993)
 CCC 0538-8066/93/110901-11

of solvent on the rate of epoxidation are examined as are factors affecting the stereoselectivity of the epoxidation reaction.

Results

Kinetic Schemes

Results obtained with cinnamaldehyde (3-phenyl-2-propenal) in the absence of dissolved oxygen indicated that the α,β-unsaturated aldehyde behaved in a similar manner to previously studied α,β-unsaturated keytones [7] when exposed to solutions of alkaline hydrogen peroxide. Cinnamaldehyde reacted quickly with alkaline peroxide to form cinnamaldehyde epoxide (3-phenyl-2,3-epoxy-propanal) which was cleaved more slowly to yield benzaldehyde. Gas chromatograms always exhibited peaks due to the presence of *cis* and *trans* epoxide isomers in ratios of ca. 1:8 by peak area (Fig. 1). Although other oxidation products such as benzoic and cinnamic acids would have been easily detected by GC, no evidence for their formation was observed. Kinetic profiles showing typical

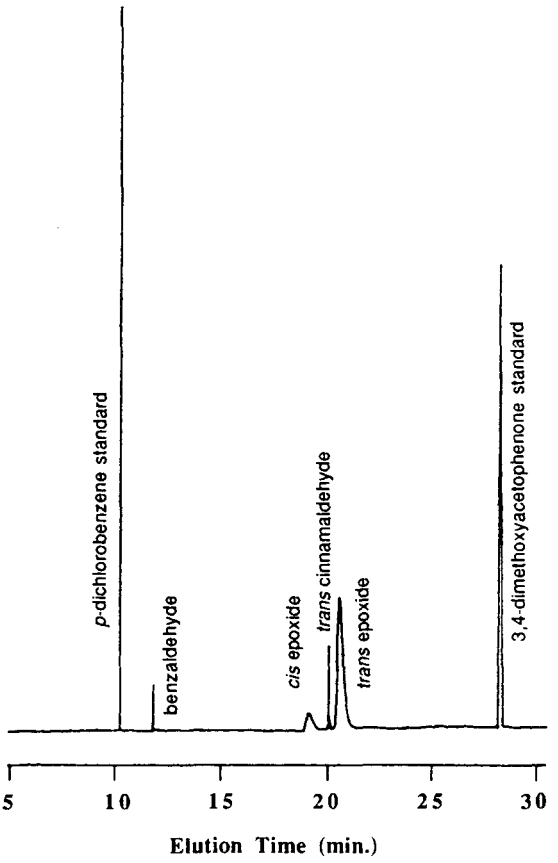


Figure 1. Gas chromatograph of extracted sample from the reaction of *trans* cinnamaldehyde with alkaline hydrogen peroxide. Reaction time = 10 min., pH 10.1, 0.179 *M* peroxide, and 25°C.

concentration-time dependencies of the starting material and reaction products are presented in Figure 2.

Kinetic and stoichiometric information (to be discussed later) indicated that reactions (1) and (2) were the major reactions occurring in the presence of alkaline hydrogen peroxide.

(1) $\underset{\text{cinnamaldehyde}}{\text{ArCH=CHCHO}} + \text{HOO}^- \xrightarrow{k_1} \underset{\text{epoxide}}{\text{ArCH(O)CHCHO}} + \text{OH}^-$

(2) $\underset{\text{epoxide}}{\text{ArCH(O)CHCHO}} + \text{HOO}^- \xrightarrow{k_2} \underset{\text{benzaldehyde}}{\text{ArCHO}} + \text{P}$

where *P* represents side chain cleavage products containing 2 carbon atoms.

Reactions carried out with cinnamaldehyde and cinnamaldehyde epoxide in the presence of alkali alone suggested the participation of a further two reaction pathways in which cinnamaldehyde and the epoxide were degraded to benzaldehyde. Both reactions were observed to follow first-order kinetics with respect to the alkali and substrate, and second-order kinetics overall. Kinetic information and reaction stoichiometries monitored by alkali consumption (Table I) indicated that reactions (3) and (4) took place in the presence of alkali, but at much slower rates than (1) and (2) when alkaline peroxide was present.

(3) $\underset{\text{cinnamaldehyde}}{\text{ArCH=CHCHO}} + \text{OH}^- \xrightarrow{k_3} \underset{\text{benzaldehyde}}{\text{ArCHO}} + \text{P}$

(4) $\text{ArCH(O)CHCHO} + \text{OH}^- \xrightarrow{k_4} \text{ArCHO} + \text{P}$

The average stoichiometric ratio of 2.3 in Table I for the reaction of alkali with cinnamaldehyde (3) suggests that, after initial cleavage of the cinnamaldehyde side chain, further quantities of alkali were consumed in reactions with the side chain fragment, *P*. In contrast, only one equivalent of alkali was used in the reaction with epoxide (4) indicating that the side chain fragment from this reaction was stable towards further reaction with base.

Peroxide stoichiometries in reactions (1) and (2) were evaluated during the first 20 min of reaction. After such time, base catalyzed decomposition of peroxide (5) and consumption by side chain fragments became the dominant modes of peroxide depletion and failed to reflect the peroxide stoichiometries in reactions (1) and (2). Stoichiometries calculated during the initial

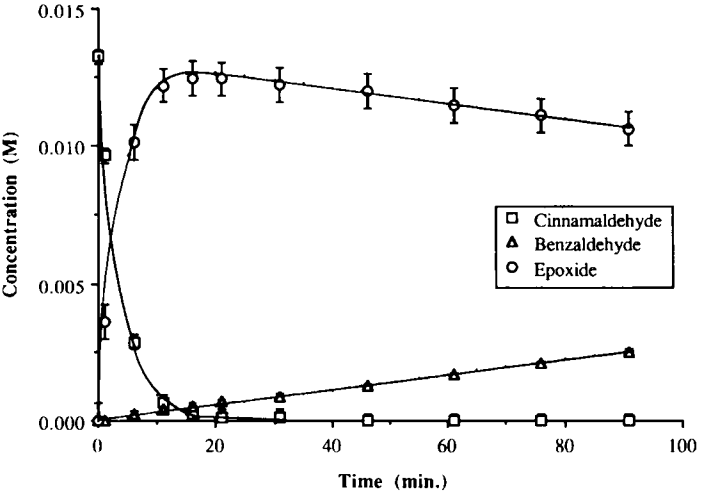


Figure 2. Typical concentration-time profiles showing reaction of cinnamaldehyde with alkaline peroxide to form benzaldehyde and cinnamaldehyde epoxide. 0.187 M peroxide, pH 10.1, and 25°C. Illustrated curves are mathematical fits of experimental data.

stages of kinetic runs were consistent with the consumption of about 1 mol of peroxide per mol of cinnamaldehyde and epoxide reacted (Table II). The fate of the side chain fragment, P, was not studied further, but previous work carried out with other α,β-unsaturated aldehydes [13] suggests that P was further oxidized by perhydroxyl anion to yield 2 equivalents of formic acid (6).

$$H_2O_2 + HOO^- \longrightarrow H_2O + O_2 + OH^- \quad (5)$$

$$P + HOO^- \longrightarrow 2HCOO^- \quad (6)$$

Calculation of Rate Constants

Estimates of pseudo-rate constants, k_1' and k_2', for reactions (1) and (2) were obtained from pseudo-first-order plots of cinnamaldehyde and epoxide disappearance. Pseudo-first-order plots for reaction of the epoxide were constructed using data obtained after the complete reaction of cinnamaldehyde (eg. after 20 min. in Fig. 2). Maintenance of constant alkali and peroxide concentrations meant that peroxide loss due to base catalyzed decomposition (reaction 5) could be ignored in the reaction system.

Pseudo-first-order rate constants for the major reactions (1) and (2) were calculated using a reaction simulation program in which the reaction schemes and estimates of the corresponding rate constants (k_1', k_2') were entered as input. Reaction rates for eqs. (3) and (4) were too small in comparison with (1) and (2) to allow accurate calculation of the pseudo-first-order rate constants (k_3', k_4') by the simulation program. In kinetic runs carried out in alkali alone, second-order rate constants for reactions (3) and (4) (k_3, k_4) were independently found to have values of 0.000047 ± 0.000007 L mol^{-1} s^{-1} and 0.0027 ± 0.0002 L mol^{-1} s^{-1} respectively at 25°C.

TABLE I. Stoichiometries for the reaction of base with cinnamaldehyde (3) and cinnamaldehyde epoxide (4) at 25°C.

Time (min.)	Δ Cinnamaldehyde ($\times 10^3$ M)	Δ NaOH ($\times 10^3$ M)	Δ NaOH / Δ Cinnamaldehyde	Δ Epoxide ($\times 10^3$ M)	Δ NaOH ($\times 10^3$ M)	Δ NaOH / Δ Epoxide
30	0.14	0.32	2.3	0.72	0.53	0.74
60	0.16	0.48	2.8	1.57	1.75	1.11
90	0.18	0.43	2.3	2.29	2.32	1.01
120	0.20	0.36	1.8	2.56	2.67	1.04
150	0.26	0.63	2.4	3.17	3.01	0.95
180	–	–	–	3.44	3.54	1.03
210	–	–	–	3.93	3.98	1.01
			Average = 2.3		Average = 0.98	

Refined pseudo rate constants (k_1' and k_2') were calculated from initial estimates by an iterative simplex algorithm contained in the simulation program. Combinations of k_1' and k_2' were substituted into differential equations describing reactions (1) and (2) until theoretical responses of the reacting species were judged to best match experimental kinetic data by minimization of a least squares fit. Calculated pseudo-first-order rate constants for reactions (1) and (2) are presented in Table III.

Perhydroxyl anion concentrations shown in Table III were calculated from the peroxide acid-base equilibrium constant which was obtained using the method of Teder and Tormund [15].

$$(7) \qquad H_2O_2 + OH^- \rightleftharpoons HO_2^- + H_2O$$

The equilibrium constant for reaction (7) in the 1:1 methanol/water solvent employed was determined to be $K_7 = 178 \pm 8\ M^{-1}$. The temperature dependence of K_7 was negligible across the range studied (15–35°C).

Rate constants for reactions 1 and 2 (k_1 and k_2) were determined from plots of k_1' and k_2' against perhydroxyl anion (HOO^-) concentration since

$$k_1' = k_1[HOO^-] \quad \text{and}$$

$$k_2' = k_2[HOO^-].$$

These plots, shown in Figure 3, illustrate the adherence of reactions (1) and (2) to second-order kinetics. The complete set of second-order rate constants for reactions (1)–(4) at 25°C are presented in Table IV. Arrhenius plots of the rate constants, k_1 and k_2, obtained at pH 9.5 resulted in

TABLE II. Initial peroxide stoichiometries in reactions (1) and (2); 0.179 M H_2O_2, pH 10.1, and 25°C.

Time (min.)	Δ Cinnamaldehyde ($\times 10^3$ mols)	Δ Benzaldehyde ($\times 10^3$ mols)	Δ H_2O_2 ($\times 10^3$ mols)	Δ H_2O_2 / Δ (Cinnamaldehyde + Benzaldehyde
5	6.80	0.25	7.6	1.08
10	8.99	0.39	11.3	1.20
15	9.41	0.55	12.0	1.20
20	9.53	0.68	15.3	1.50
			Average	1.24

TABLE III. Pseudo-first-order rate constants for reactions (1) and (2).

Temperature (°C)	pH	$[H_2O_2]$ (M)	$[HOO^-]$ ($\times 10^4$ M)	k_1' ($\times 10^4$ s^{-1})	k_2' ($\times 10^6$ s^{-1})
25.0	9.2	0.121	3.4	3.9	9.3
25.0	9.5	0.104	5.8	6.6	13.8
25.0	10.1	0.097	21	23.5	17.3
25.0	10.1	0.179	40	44.7	41.2
25.0	10.0	0.291	52	53.7	41.5
25.0	10.8	0.108	120	124	95.7
35.0	9.5	0.097	5.5	15.6	26.3
17.6	9.5	0.107	6.0	4.1	9.9

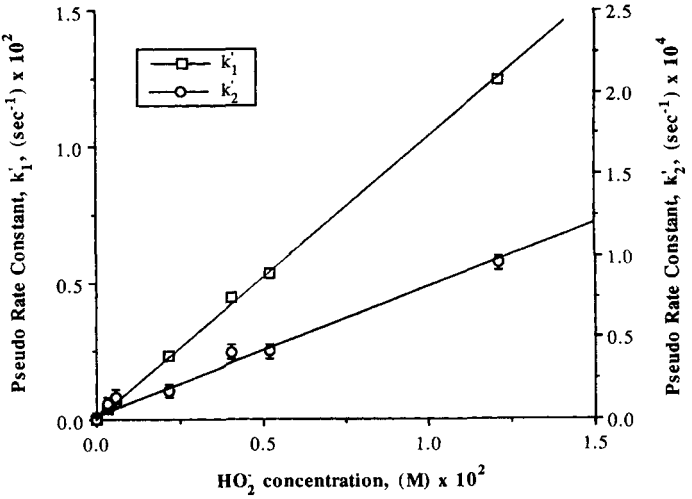


Figure 3. Perhydroxyl anion dependence of pseudo-first-order rate constants, k_1' and k_2'. Regression coefficients: $r^2 = 1.00$ (k_1'), $r^2 = 0.99$ (k_2').

TABLE IV. Observed second-order rate constants for reactions (1)–(4) with cinnamaldehyde at 25°C. Previously reported [7] second-order rate constants for equivalent reactions with the analogous ketone, benzalacetone, are provided for comparison.

Second-Order Rate Constants (L mol^{-1} s^{-1})	Cinnamaldehyde (1:1 MeOH/H_2O solvent)	Benzalacetone (Aqueous solvent)
k_1	1.03 ± 0.01	0.22
k_2	0.0076 ± 0.0004	0.05
k_3	0.000047 ± 0.000007	0.00016
k_4	0.0027 ± 0.0002	0.0032

activation energies of 62 ± 6 kJ/mol and 46 ± 5 kJ/mol for reactions (1) and (2) respectively and suggested that temperature does not exert a strong influence on the epoxidation and ring cleavage reactions over the temperature range studied (15–35°C).

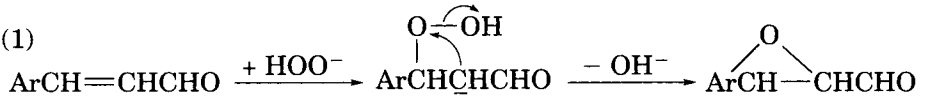
Discussion

Reaction Mechanisms

The reaction stoichiometries, kinetic behavior and relative magnitudes of rate constants (Table IV) are in good agreement with analogous results reported for α,β-unsaturated ketones [7]. The similarity of these sets of results strongly suggests that α,β-unsaturated aldehydes and α,β-unsaturated ketones undergo common mechanisms of reaction. The rate constant representing nucleophilic addition of the perhydroxyl anion to cinnamaldehyde (k_1) is significantly higher than that reported for the analogous ketone, benzalacetone, which is in accordance with the general observation that aldehydes are more reactive than ketones toward nucleophilic addition [16].

Experimental evidence from this work is consistent with the generally accepted idea that the rate-determining step in epoxidation of unsaturated carbon to carbon bonds involves nucleophilic attack by the perhydroxyl anion at the β-position of the α,β-unsaturated aldehyde in a Michael type reaction [1,6–10,14].

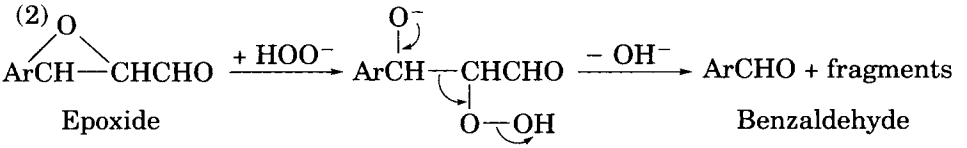
(1)



Cinnamaldehyde Epoxide

Results with cinnamaldehyde also support the supposition that the rate-determining step in the cleavage of the epoxide in reaction (2) is the slow initial attack of perhydroxyl anion at the sterically less hindered α-position as reported for α,β-epoxy ketones [7,8], esters [14], and 1,2-epoxy-1-methylethylbenzene [17].

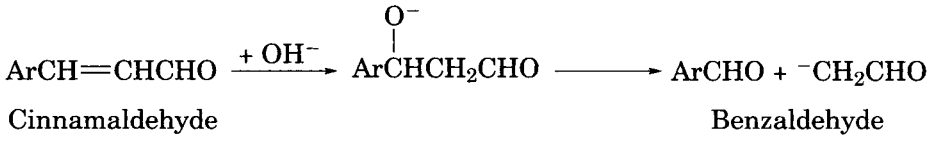
(2)



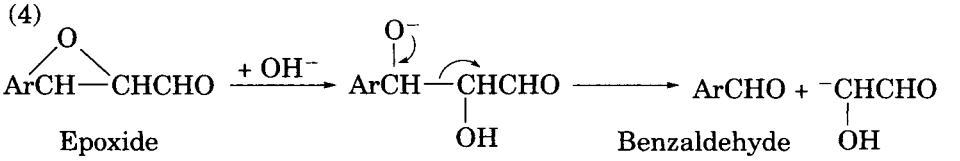
Epoxide Benzaldehyde

The observed second-order kinetics and stoichiometric evidence suggests that the alkaline cleavages of cinnamaldehyde and cinnamaldehyde epoxide side chains are initiated by nucleophilic attack of the hydroxide ion at the β- and α-carbons respectively in a similar manner to mechanisms (1) and (2).

(3)



(4)



Solvent Effects

The effects of solvent on the rate of epoxidation (1) can be examined by comparison of the rate constant for reaction of cinnamaldehyde, k_1, with equivalent rate constants for other α,β-unsaturated aldehydes in different solvents. The epoxidation of cinnamaldehyde at 30°C in a methanol solvent has been reported [14] to follow second-order kinetics with a rate constant of 0.0774 L mol^{-1} s^{-1}. This rate constant is more than an order of magnitude lower than the corresponding value in the current work (Table IV) which was carried out in 1:1 methanol/water solvent. These results strongly suggest that the epoxidation reaction (1) is favored by increasing solvent polarity, probably as a result of increased stabilization of the proposed anionic reaction intermediate.

Confirmation of the positive effect of polar solvents on the rate of epoxidation is found in the reaction of 3,4-dimethoxycinnamaldehyde at 25°C in aqueous solution [13]. The reported second-order rate constant of 1.34 L mol^{-1} s^{-1} for this reaction is slightly larger than the equivalent value in this study. Electron releasing aromatic substituents have previously been shown to exert a negative influence on the rate of nucleophilic additions similar to (1) so that, given the overall electron releasing properties of the *ortho* and *para* methoxy substituents, 3,4-dimethoxycinnamaldehyde would be expected to exhibit a lower rate constant in a 1:1 aqueous methanol solvent. The reversal of this trend is almost certainly a result of the positive effect on rate of the more polar aqueous solvent used in the study with 3,4-dimethoxycinnamaldehyde.

Epoxidation Stereochemistry

The alkaline epoxidation of several unsaturated ketones has been observed to be a highly stereoselective process [9]. It has been proposed that maximum overlap of electronic orbitals in the transition state molecule by coplanar alignment is more important than steric considerations in accounting for such high stereoselectivity. For α,β-unsaturated ketones, maximum orbital overlap is seriously compromised by repulsions involving the acetyl group. For this reason, epoxidation of the ketone analogue of

cinnamaldehyde, benzalacetone, has been shown to yield the corresponding *trans* epoxide isomer exclusively [18]. In the case of cinnamaldehyde, the acyl substituent has been replaced by a smaller hydrogen atom which would be expected to reduce stereoselectivity by lessening the repulsions which diminish orbital overlap in the transition state anion. By this reasoning, the detection of appreciable amounts of *cis* cinnamaldehyde epoxide in the current work (ca. 1:8 cis : trans ratio) can be satisfactorily rationalized.

In the absence of unfavorable electronic interactions, steric factors in the transition state anion leading to cinnamaldehyde epoxide would also support the detection of a mainly *trans* product (Fig. 4). Nucleophilic attack by the perhydroxyl anion at the β-position results in sp^3 hybridization of the $\alpha-\beta$ carbon–carbon bond, thereby allowing rotation of the side chain about the bond axis. In this situation, rotation to favor the *cis* epoxide is severely limited due to steric hindrance from the aromatic ring.

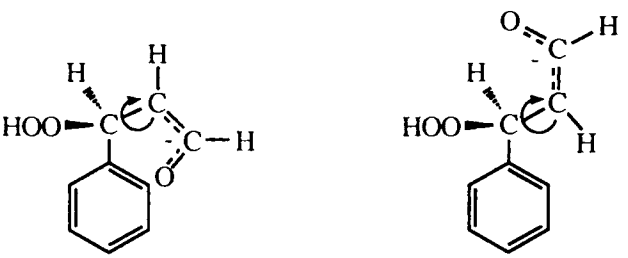
Experimental

Equipment

Sample analyses were carried out using a Hewlett-Packard 5890 Series II gas chromatograph fitted with a BP 20 fused silica polar phase capillary column (25 m × 0.22 mm i.d.). Eluting compounds were detected with a flame ionization detector. Proton nmr spectra were recorded on a Bruker AM 300 MHz spectrometer at 25°C.

Materials

Model compounds and other reagents were obtained from commercial sources. Commercial supplies of cinnamaldehyde (Fluka) were purified by vacuum distillation (b.p. 77–78°C, 1 mmHg) as were samples of benzaldehyde (Aldrich, b.p. 60–61°C, 10 mmHg). Analysis of the purified cinnamaldehyde by gas chromatography indicated > 99.5% abundance of the *trans* isomer. Aqueous hydrogen peroxide (Ajax, 30% w/v, 10.5 M by iodometric titration) was used without further purification and transition metal decomposition of peroxide was minimized by using semiconductor



(a) (b)

Figure 4. Conformations of transition state molecule leading to formation of *cis* (a) and *trans* (b) cinnamaldehyde epoxide.

grade (99.99%) sodium hydroxide (Aldrich). Solvent methanol was distilled and dried over molecular sieves and deionised 18 MΩ water was employed.

Cinnamaldehyde epoxide (3-phenyl-2,3-epoxy-propanal) was synthesized by oxidation of cinnamaldehyde with alkaline tert-butyl hydroperoxide (Aldrich, 70%) using the method of Payne [19]. The cinnamaldehyde epoxide was purified by vacuum distillation, b.p. 83–84°C, 1 mm Hg, (lit. b.p. 66–68°C, and 0.2 mm Hg [19]) and was recovered as a clear, viscous liquid. The IR spectrum of the product was identical to that previously reported [19]. Analysis of the product by GC-MS and ^{1}H-nmr indicated formation of 2 epoxide diastereomers in a ca. 1:8 ratio based on GC peak areas. Comparison of the GC elution order of the epoxide isomers with the elution order of other structurally related *cis* and *trans* isomers (*cis* and *trans* cinnamaldehyde and methyl cinnamate) indicated that the *trans* epoxide isomer was the major product. MS [M^+ 148(12), 147(20), 131(5), 119(25), 105(12), 92(13), 91(100), and 90(28)]. ^{1}H-nmr ($CDCl_3$); *cis* isomer; δ 3.50, dd, J 4.6 Hz, 6.1 Hz; 4.34, d, J 4.6 Hz; 9.05, d, 5.9 Hz. *trans* isomer, δ 3.40, dd, J 1.8 Hz, 6.0 Hz; 4.12, d, J 1.8 Hz; and 9.14, d, J 6.0 Hz.

Method for Kinetic Runs

Kinetic experiments were carried out in a stoppered polyethylene reaction vessel immersed in a constant temperature water bath. A 1:1 water/methanol solution (200.0 mL) containing cinnamaldehyde (2.8 mmol) and an unreactive standard (3,4-dimethoxyacetophenone, 1.3 mmol) was thermally equilibrated for several minutes and dissolved oxygen was purged with a slow stream of nitrogen. Kinetic runs were initiated by adding the required amounts of sodium hydroxide and hydrogen peroxide to reach the desired conditions. Samples for analysis (10 mL) were periodically withdrawn and iodometric titrations were carried out to determine total peroxide levels. Approximately constant sodium hydroxide and hydrogen peroxide concentrations were maintained by adding the calculated amounts of each based on pH measurements and iodometric titration respectively. In blank runs carried out in the absence of peroxide, alkali consumption was followed by titration with standardized hydrochloric acid (0.01 M).

Analysis of Samples

Samples withdrawn during kinetic runs were quenched by acidification with phosphate buffer (5 mL, 2 M, pH 6.5). The quenched sample was saturated with sodium chloride and extracted with dichloromethane (3 × 5 mL portions). A second standard (*p*-dichlorobenzene, 0.014 M, and 5.00 mL) was added to each extracted portion and the total volume was made up to 25.00 mL.

Extracted samples were analyzed by gas chromatography. Baseline resolution of extracted components was achieved using a simple temperature gradient program (60°C isothermal 5 min., 140°C at 10°C/min, and 200°C at 5°C/min). Cinnamaldehyde, benzaldehyde, and cinnamaldehyde epoxide peak areas were referenced to the peak areas of the standards employed.

Concentrations were determined from standard curves relating peak area ratios to concentration over the experimental working range.

Acknowledgment

The authors gratefully acknowledge financial support provided by the Australian Research Council, Interox Pty. Ltd. and Australian Newsprint Mills Pty. Ltd.

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Received February 5, 1993
Accepted April 22, 1993