Kinetic Analysis of Chalcone Epoxidation in a Biphasic System

Wai Wing Leung and Ruben M. Savizky*

Department of Chemistry, The Cooper Union for the Advancement of Science and Art, 41 Cooper Square, New York, New York 10003, United States

The kinetics of chalcone epoxidation in a biphasic water/heptane medium system consisting of chalcone as the substrate, hydrogen peroxide as the oxidant, sodium hydroxide as the base, and dodecyltrimethylammonium bromide (DTAB) as the surfactant was investigated. The empirical rate law was established to be described as follows: rate = k[chalcone]$^{0.74}$[DTAB]$^{0.50}$[NaOH]$^{0.87}$[H$_2$O$_2$]$^{1.53}$. As a preliminary study, the apparent activation energy of the reaction was determined to be 25.9 kJ/mol.

Introduction

Epoxides possess important synthetic utility for industrial, mechanistic, and biochemical purposes.[1-6] Because of this, as well as their ease of preparation, they have been important and versatile intermediates in the field of organic synthesis for the past several decades.[1] Furthermore, epoxides can serve as reactants to provide important industrial products, such as surfactants or detergents (tensides), antistatic- or corrosion-protection agents, and additives to laundry detergents, lubricating oils, textiles, and cosmetics.[2] Epoxidation of carbon–carbon double bonds (C=C) in α,β-unsaturated ketones has been widely studied,[3-9] because they are an important class of carbonyl compounds.

The oxidation of α,β-unsaturated ketones with hydrogen peroxide, under alkaline conditions, to form epoxy ketones is known as the Weitz–Scheffer reaction[3,4] (see Scheme 1). With electron-deficient olefins, such as α,β-unsaturated ketones, basic conditions are favored. A hydroperoxide enolate is formed with the addition of a hydroperoxide anion to the enone. Sequentially, the hydroxide ion detaches, resulting in the formation of the epoxide. In the presence of an oxidant, the reaction typically proceeds under strong alkaline conditions. Hydrogen peroxide is commonly selected as the oxidant, because of its relatively inexpensive nature, and the resulting formation of innocuous water as a byproduct. Typically utilized bases include sodium hydroxide (NaOH), sodium carbonate (Na$_2$CO$_3$), and potassium hydroxide (KOH).[3]

Phase-transfer catalysis is a special form of heterogeneous catalysis, because it facilitates the transfer of one of the reactants into a phase that contains another reactant, where the reaction occurs. There are two types of liquid–liquid phase-transfer catalysis processes, depending on whether the reaction occurs in an organic phase or an aqueous phase. The most common is normal phase-transfer catalysis (NPTC), where the reaction occurs in the organic phase, as the anionic reactant from the aqueous phase is transferred via a lipophilic ion pair. The other type is inverse phase-transfer catalysis (IPTC), where the lipophilic substrate is transferred into the aqueous phase and reacts with the hydrophilic reactant.[10] (See Figure 1.) One method to transfer the lipophilic substrate into the aqueous phase (IPTC) is by utilizing water-soluble surfactants, such as micelles. Many quaternary ammonium

salts that contain one or two large alkyl groups, as well as two or three small groups, such as dodecyltrimethylammonium bromide (DTAB, CH$_3$(CH$_2$)$_{11}$N(CH$_3$)$_3$Br), form micelles when added to a two-phase aqueous–organic system beyond the critical micelle concentration (cmc) of surfactants. Micelles are able to solubilize the lipophilic substrate in equilibrium with the organic phase. The reaction then occurs at the surface of the micelles in the aqueous phase. Lastly, the reaction product, which is typically lipophilic, is transferred back into the organic phase.[10]

Boyer and co-workers[10,11] examined the IPTC process in the epoxidation of chalcone in a water/heptane biphasic medium. It was established that, under slow stirring conditions (100 rpm), the results fit accordingly with the IPTC process, where the solubilizing ability and the efficiency of the catalysis are dependent on the surfactant concentration. Under a fast stirring rate (1200 rpm), the influence of the DTAB concentration is not as significant. In this case, a large interfacial area results from the formation of an emulsion under vigorous stirring. This allows for a higher probability of the lipophilic substrate to react with the hydrophobic reactant at the interface. The surfactant is able to decrease the interfacial tension, expand the interfacial area, and stabilize the negative transition state developed, at the interface, near the ammonium groups of the surfactant.[10] Therefore, Boyer et al.[10] proposed this to be an interfacial catalysis (IC) process, wherein a small quantity of surfactant is sufficient to facilitate the catalytic pathway. (See Figure 2.)

In a water/heptane biphasic medium, Boyer et al.[12] were able to obtain an 88% yield of chalcone epoxide within 10 min. With a relatively high yield and fast reaction time, the kinetics of chalcone epoxidation in a water/heptane medium system will be studied to establish an empirical rate law. The achiral phase-transfer catalyst DTAB will be utilized. The aqueous phase will consist of the oxidant hydrogen peroxide, base sodium hydroxide, and the surfactant (see Scheme 2).

Scheme 1. Diagram of the Weitz–Scheffer Reaction
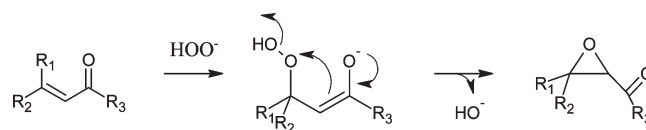
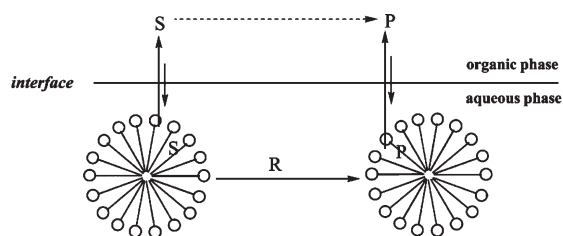* To whom correspondence should be addressed. Tel.: (212) 353-4372. E-mail: rsavizky@cooper.edu.

Figure 1. Inverse phase-transfer catalysis. (Legend: S, substrate; R, reactant; P, product.) [Reproduced with permission from ref 11, Copyright 2002, Royal Society of Chemistry.]
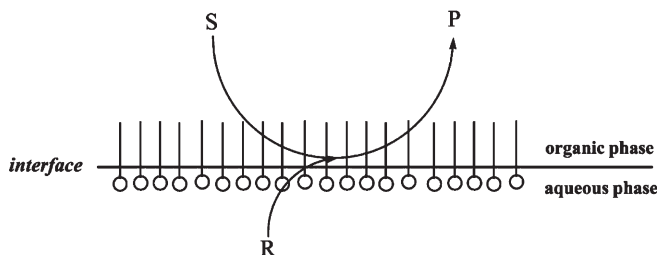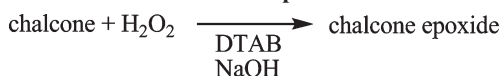

Figure 2. Interfacial catalysis. (Legend: S, substrate; R, reactant; P, product.) [Reproduced with permission from ref 11, Copyright 2002, Royal Society of Chemistry.]

Scheme 2. Reaction for Chalcone Epoxidation

$$\text{chalcone} + H_2O_2 \xrightarrow[\substack{DTAB \\ NaOH}]{} \text{chalcone epoxide}$$

At constant temperature, the rate of reaction is dependent on the concentration of the reactants as follows:

$$\text{rate} = kf([A],[B],[C],...) \quad (1)$$

where k is the rate constant and the argument "[A],[B],[C],..." represents the concentrations of reactants A, B, C, ..., respectively, at time t. The function $f([A],[B],[C],...)$ is a mathematical expression that is characteristic of the reaction. The function only involves the products of the concentrations, each raised to a certain power. Therefore, applying this to the overall reaction of chalcone epoxidation, the empirical rate expression is expressed as

$$\text{rate} = k[\text{chalcone}]^{\alpha}[\text{DTAB}]^{\beta}[\text{NaOH}]^{\gamma}[H_2O_2]^{\delta} \quad (2)$$

where α, β, γ, and δ are the orders with respect to chalcone, DTAB, NaOH, and H_2O_2, respectively. The exponents have no physical meaning other than indicating the overall effect of the various concentrations on the rate, and they are not related to the stoichiometric coefficients of the reaction, unless the reaction is elementary.[13] With five unknowns, this is a complex expression. Therefore, this requires studying the effect of each reactant on the rate independently.

To study the effect of one of the reactants, the other three reactants must be kept effectively constant.[14] This is attained by having the initial concentration of three of the reactants in large excess, relative to the remaining one; thus, they are effectively constant and can be combined with k to establish a pseudo rate constant. Therefore, the rate dependence on each reactant can be studied by expressing the rate laws as follows:

$$\text{rate} = k^{\text{I}}[\text{chalcone}]^{\alpha} \quad (\text{where } k^{\text{I}} = k[\text{DTAB}]^{\beta} \times [\text{NaOH}]^{\gamma}[H_2O_2]^{\delta}) \quad (3)$$

$$\text{rate} = k^{\text{II}}[\text{DTAB}]^{\beta} \quad (\text{where } k^{\text{II}} = k[\text{chalcone}]^{\alpha} \times [\text{NaOH}]^{\gamma}[H_2O_2]^{\delta}) \quad (4)$$

$$\text{rate} = k^{\text{III}}[\text{NaOH}]^{\gamma} \quad (\text{where } k^{\text{III}} = k[\text{chalcone}]^{\alpha} \times [\text{DTAB}]^{\beta}[H_2O_2]^{\delta}) \quad (5)$$

$$\text{rate} = k^{\text{IV}}[H_2O_2]^{\delta} \quad (\text{where } k^{\text{IV}} = k[\text{chalcone}]^{\alpha} \times [\text{DTAB}]^{\beta}[\text{NaOH}]^{\gamma}) \quad (6)$$

Utilizing a ln/ln graphical procedure, the gradient of the linear relationship between the natural logarithm of the rate and the natural logarithm of the reactant concentration would yield its respective order.

Taking a similar mathematical approach, the activation energy (E), or the minimum energy needed for the reaction to occur and the pre-exponential factor (A), could be determined through the following rearranged form of the Arrhenius equation:[13]

$$\ln k = -\frac{E_1}{RT} + \ln A \quad (7)$$

Experimental Section

Chemicals. The following chemicals were obtained from Sigma−Aldrich: dodecyltrimethylammonium bromide (DTAB), ~99% purity (Catalog No. D8638); hexanes, mixture of isomers (CHROMASOLV) for HPLC, ≥98.5% purity (Catalog No. 293253); hydrogen peroxide (H_2O_2), 30 wt % solution in water, ACS reagent-grade (Catalog No. 216763); 2-propanol (CHROMASOLV), for HPLC, ≥99.8% purity (Catalog No. 34863); and sodium hydroxide (NaOH) (Catalog No. S5881); *trans*-chalcone, 97% purity (Catalog No. 136123). Chalcone-α,β-epoxide (98% purity, Catalog No. L03874) was obtained from Lancaster Synthesis, Inc.

Reaction Procedure for Order Determination. The reaction occurred in a 20-mL Pyrex beaker thermostated in a water bath at a temperature of 20.0 ± 0.1 °C. The reaction was stirred with a Spinbar polytetrafluoroethylene (PTFE)-coated polygon magnetic bar, with dimensions of $^1/_2$ in. × $^1/_8$ in., on an Isotemp magnetic stirrer. Four milliliters (4 mL) of aqueous and organic phases were prepared, consisting of their specified reactant concentrations (DTAB, NaOH, and H_2O_2 for the aqueous phase and chalcone for the organic phase). The separate phases were initially equilibrated at a bath temperature of 20.0 °C, and then they were mixed rapidly at 1200 rpm. At a specified time, 2 μL of the emulsion were withdrawn and placed in a tube that contained 4 mL of heptane. The tube was shaken to allow for separation of the two phases. The ultraviolet (UV) absorbance was measured after each sampling. Absorbance of the aliquots was measured in a 0.1-cm cuvette in a Shimadzu Model UV-1601PC UV/visible spectrophotometer. The presence of chalcone was monitored at 300 nm, as a function of time. The products of the reaction were confirmed by a Varian ProStar high-performance liquid chromatography system that was supplemented with a UV detector.

Reaction Procedure for Activation Energy Determination. The reaction occurred in a 20-mL Pyrex beaker thermostated in a water bath (Lauda Ecoline Staredition E100). The reaction was stirred with a Spinbar PTFE-coated polygon magnetic bar, with dimensions of $^1/_2$ in. × $^1/_8$ in., on a Troemner submersible magnetic stirrer (Model 700). Four milliliters (4 mL) of the organic phase, consisting of 0.1 M chalcone in heptane, were prepared. Four milliliters (4 mL) of the aqueous phase consisting of 0.25 M DTAB, 0.5 M H_2O_2, and 0.05 M NaOH were
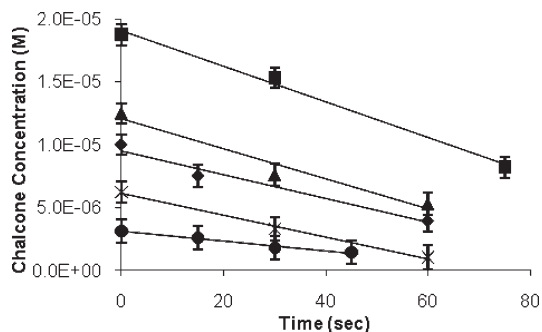
Figure 3. Determination of the initial rate, based on variation of the chalcone concentration (($\blacksquare$) 0.075 M, ($\blacktriangle$) 0.05 M, ($\blacklozenge$) 0.04 M, ($\times$) 0.025 M, and ($\bullet$) 0.0125 M).

Figure 4. Determination of order, based on variation of the chalcone concentration.

prepared. The separate phases were initially equilibrated at a bath temperature of 20.0 °C. The phases were mixed rapidly at 1200 rpm in the bath. At a specified time, 2 μL of the emulsion were withdrawn and placed in a tube containing 4 mL of heptane. The tube was shaken, to allow separation of the two phases. The UV absorbance was measured after each sampling. The reaction was repeated for bath temperatures of 25.0 and 30.0 °C.

Results and Discussion

To determine the order of each reactant in the rate law, the effect of its concentration on the reaction rate must be studied. Because of the complexity of a system with four reactants, each reactant was analyzed independently by varying its initial concentration, keeping the concentrations of the other reactants effectively constant by having relatively large excesses of each (generally at least an order of magnitude larger, but this was not always possible, because of solubility limitations). Sequentially, the reactant orders of chalcone, DTAB, NaOH, and H_2O_2 were examined. The reaction was monitored by measuring the disappearance of chalcone through its absorbance at the optimum wavelength, with respect to time. Rate data were collected in varying time intervals. Utilizing an initially established calibration curve, the corresponding chalcone concentration was plotted against time based on the criteria of ~10% of the initial chalcone concentration having been reacted, or a minimum of three initial data points. Each series of points, corresponding to a different initial reactant concentration, was fit to a straight line using a least-squares linear regression. Their gradients represent the initial reaction rates. The method will be demonstrated below for chalcone, with the remaining three compounds being subjected to the same analysis (see the Supporting Information).

Variation in Chalcone Concentration. The reaction was analyzed for chalcone concentrations of 0.0125, 0.025, 0.04, 0.05, and 0.075 M, with effectively constant DTAB, NaOH, and H_2O_2 concentrations of 0.1 M, 0.8 M, and 0.8 M, respectively. With concentrations of 0.8 M, NaOH and H_2O_2 are relatively present in excess, compared to the highest chosen chalcone concentration of 0.075 M. A DTAB concentration of 0.1 M was selected, since, as a suspected phase-transfer catalyst, it is expected to affect the reaction, even when present in small quantities, and is not expected to be consumed by the reaction. The initial rate data are shown in Figure 3. Expressing the natural logarithm of the initial chalcone concentration and its corresponding initial reaction rate (eq 8), the order and apparent rate constant, with respect to the chalcone concentration, were determined, based on the respective gradient and y-intercept of
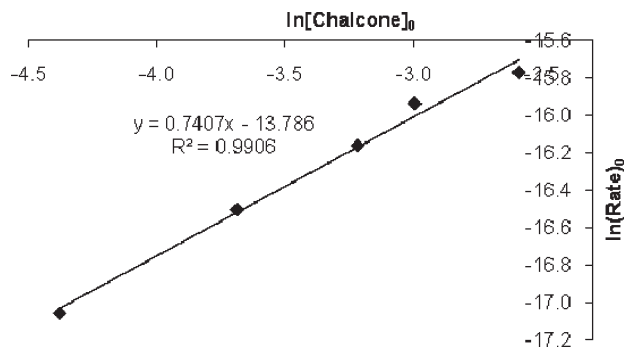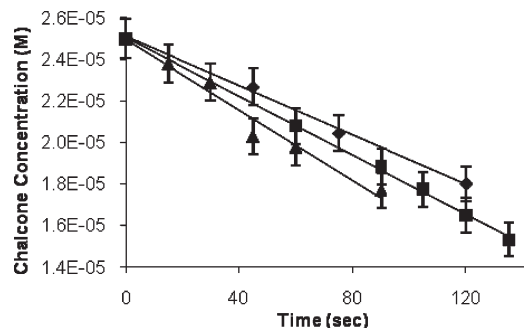

Figure 5. Determination of the activation energy (E), using the initial rate data at various temperatures (($\blacklozenge$) 20 °C, ($\blacksquare$) 25 °C, and ($\blacktriangle$) 30 °C).

their linear relationship (see Figure 4). The order, with respect to chalcone, is 0.74, with an apparent rate constant of 1.03×10^{-6} $M^{-0.26}$/s.

$$\ln \text{rate} = \alpha \ln[\text{chalcone}] + \ln k^{\text{I}} \qquad (8)$$

Through each analysis, the orders, with respect to the concentration of chalcone, DTAB, NaOH, and H_2O_2, were determined to be 0.74, 0.50, 0.87, and 1.53, respectively. As an activator, DTAB is able to increase the rate of reaction, even when present in small quantities, and reasonably has the lowest order (0.50), compared to the other reactants. Furthermore, in an interfacial catalytic system, the influence of catalytic concentration is not as significant and is supported by the determined DTAB order. The H_2O_2 oxidant has the highest order (1.53) and contributes ~40% of the overall order; this signifies its expected effect as an oxidant in the epoxidation of chalcone. Compared to the order of chalcone, the order of H_2O_2 is approximately doubled. Although the rate law is not elementary, it may be postulated that, stoichiometrically, 2 mol of H_2O_2 are required to react with 1 mol of chalcone. This would imply that the mechanism for the reaction, at least under these conditions, is more complex than that proposed in Scheme 1.

Activation Energy. Monitoring the disappearance of chalcone, with respect to time, at temperatures of 20 ± 0.05 °C, 25 ± 0.05 °C, and 30 ± 0.05 °C, the initial reaction rates were determined based on the gradient of their linear relationships (see Figure 5). Utilizing the Arrhenius equation (eq 7), the activation energy and pre-exponential factor were established to be $E = 25.9$ kJ/mol and $A = 1.783$ $M^{-2.6}$ s^{-1}, respectively (see Figure 6). Since the mechanism is complex and seemingly involves multiple steps, as well as being dependent on transport
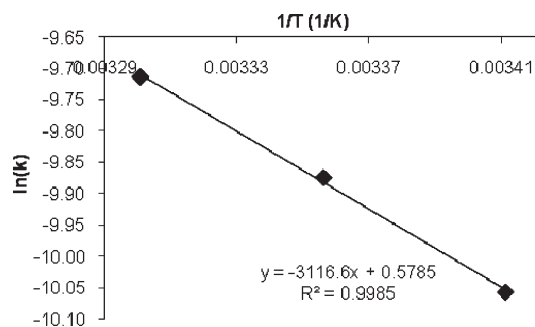
Figure 6. Arrhenius plot used to determine the activation energy (E).

phenomena, one should note that this value is only an apparent activation energy.

Conclusion

The independent effect of each reactant on the initial reaction rate was monitored via determination of the rate law. Through establishing linear relationships of the natural logarithm of initial reaction rate and its initial concentration, the order and apparent rate constant of each reactant were determined based on their respective gradients and y-intercepts. The orders, with respect to the concentrations of chalcone, DTAB, NaOH, and H_2O_2, were concluded to be 0.74, 0.50, 0.87, and 1.53, respectively. Therefore, the empirical rate law is

$$\text{rate} = k[\text{chalcone}]^{0.74}[\text{DTAB}]^{0.50}[\text{NaOH}]^{0.87}[H_2O_2]^{1.53}$$

The noninteger values for the reaction orders implies a complex mechanism, one that is due, at least in part, to the biphasic nature of the reaction. Note that diffusion, mixing effects, and other transport phenomena cannot be ignored, so these values may vary based on the size of the reaction vessel and/or different operating conditions.

As a preliminary study, the apparent activation energy of the reaction was examined based on the change in reaction rate at system temperatures of 20, 25, and 30 °C. Similarly, based on the slope and y-intercept of the linear relationship of the natural logarithm of the rate constant and the inverse of the system temperature, the apparent activation energy and pre-exponential factor were calculated to be 25.9 kJ/mol and 1.783 $M^{-2.6}$ s^{-1}, respectively. To the best of our knowledge, the activation energy of chalcone epoxidation has not been reported previously.

This research has presented a traditional method of analysis that can be applicable to many other reactions and reaction conditions. The numerical values for the reaction orders and apparent activation energy are dependent on reactor size and configuration, as well as mixing rates. However, in having established an empirical rate law, the optimal conditions of the reaction can be identified, which would be essential for laboratory settings or industrial-scale production.

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