## **Epoxidation of Alkenes with Bicarbonate-Activated** Hydrogen Peroxide

Huirong Yao and David E. Richardson\*

Center for Catalysis, Department of Chemistry University of Florida, Gainesville, Florida 32611-7200

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We describe here the discovery of the bicarbonate-catalyzed epoxidation of alkenes with aqueous hydrogen peroxide at nearneutral pH. For some substrates, the procedure is comparable in apparent synthetic utility to the best methods now available for H<sub>2</sub>O<sub>2</sub>-based alkene expoxidations that avoid extensive hydrolytic formation of diol (e.g., ligand-accelerated methyltrioxorhenium/ H<sub>2</sub>O<sub>2</sub><sup>1</sup>). The new process features a stable main group catalyst/ activator of unexpected simplicity (bicarbonate ion) and can be applied readily in water or mixed aqueous solutions under homogeneous conditions.

Hydrogen peroxide is a high oxygen content, environmentally friendly oxidant for which water is the sole byproduct in heterolytic oxidations,<sup>2</sup> but it is a slow oxidant in the absence of activation<sup>3</sup> due to the poor leaving tendency of the hydroxide ion.4 Transition metal salts or complexes have been used as catalysts for alkene epoxidations with aqueous H<sub>2</sub>O<sub>2</sub>. <sup>5,6</sup> Other methods for activation of H2O2 include forming reactive peroxyacids from carboxylic acids,7 forming peroxycarboximidic acid from acetonitrile (Payne oxidation),8 generation of peroxyisourea,9 or using sodium perborate or sodium percarbonate (Na<sub>2</sub>-CO<sub>3</sub>·1.5H<sub>2</sub>O<sub>2</sub>) in strongly basic solution. <sup>10</sup> Such systems can have one or more disadvantages, such as toxic or rapidly decomposed metal catalysts, oxidative decomposition of organic ligands, organic byproducts, or strongly acidic or basic reaction conditions that decompose the desired epoxide product.

A method for activating hydrogen peroxide with bicarbonate ion was described by Drago and co-workers11 and Richardson et al. 12 in their studies of sulfide oxidations in alcohol/water solvents. In the bicarbonate-activated peroxide (BAP) system, <sup>13</sup> the active

Table 1. Oxidation of Water-Soluble Alkenes by Hydrogen Peroxide in Sodium Bicarbonate (1 M) Solutions in D<sub>2</sub>O (25 °C)<sup>a</sup>

Substrate	Alkene: H <sub>2</sub> O <sub>2</sub> : HCO <sub>3</sub>	Time	Conv. (%)	Product(s) (%)
NaO <sub>3</sub> S	1:1.5:10	15 h	>99	epoxide (90) diol (5)
NaO	1:3:10	4 h	95	epoxide (>99)
	1:1.5:10	3 h	70	epoxide (>99)
но	1:6:20	24 h	78	epoxide (97)
	1:6:20	24 h	40	epoxide(70) diol (20)
но	1:6:20	24 h	80	epoxide (45) diol (45)

<sup>a</sup> Product analysis by <sup>1</sup>H NMR. All reactions without bicarbonate gave no detectable epoxide products after 24 h. Dibasic ammonium phosphate was employed to maintain similar ionic strength and pH of reaction media in the control reactions.

oxidant peroxymonocarbonate ion,  $HCO_4^-$ , is formed with  $t_{1/2} \approx$ 5 min (eq 1), presumably via the perhydration of CO<sub>2</sub>

$$H_2O_2 + HCO_3^- \rightleftharpoons H_2O + HCO_4^-$$
 (1)

Peroxymonocarbonate is an anionic peracid with structure HOOCO<sub>2</sub><sup>-.14</sup> Kinetic and thermodynamic investigations of eq 1 give a value of  $E^0$  (HCO<sub>4</sub><sup>-</sup>/HCO<sub>3</sub><sup>-</sup>). 1.8 V (vs NHE), and HCO<sub>4</sub><sup>-</sup> is therefore a potent oxidant in aqueous solution. The maximum catalytic efficiency for oxidation of organic sulfides is observed in the pH range from 7 to 9, and the oxidation reactions are accelerated by increasing solvent water content.<sup>15</sup> The reactivity of HCO<sub>4</sub><sup>-</sup> toward sulfides suggested to us that it may also be useful in the preparation of epoxides in water and mixed solvents, and this was confirmed in the work described below.

The oxidation of water-soluble alkenes was carried out in D<sub>2</sub>O in an NMR tube with a stoichiometric excess of H<sub>2</sub>O<sub>2</sub> (1.5-6.0 equiv). For example, 1 mL of 0.1 M 4-vinylbenzenesulfonate with 1 M NaHCO<sub>3</sub> was prepared in D<sub>2</sub>O, and 30% H<sub>2</sub>O<sub>2</sub> was added (final  $[H_2O_2] = 0.15$  M, pH 8). <sup>1</sup>H NMR studies gave a  $t_{1/2}$  value of 1.5 h for the initial disappearance of alkene, and after 15 h, the starting material was converted to epoxide (90%), diol (5%), and other byproducts (5%). The same procedure was applied to several other water-soluble alkenes (Table 1). In all cases, reactions without added bicarbonate salt are negligible after 24 h under similar conditions (as a control, replacement of NaHCO<sub>3</sub> by (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub> provided comparable ionic strength and pH). The water-soluble alkenes in Table 1 are mostly terminal alkenes with nearby electron-withdrawing groups. The low electron density of these alkenes usually reduces their nucleophilicity toward electrophilic oxygen of peroxyacids. 16 The last two entries in Table 1 show that under the aqueous conditions of these reactions, readily hydrolyzed epoxides are partially converted to diols. This hydrolysis can be suppressed by using solvents with lower water content.17

We found that the BAP system can be applied to a variety of homogeneous alkene oxidations (including epoxidation of terminal

<sup>\*</sup> To whom correspondence should be addressed. Telephone: (352) 392-6736. Fax: (352) 392-3255. E-mail:der@chem.ufl.edu.

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<sup>(15)</sup> Although used in large concentrations, bicarbonate is a catalyst so the oxidations described here are low E factor reactions, in contrast to stoichiometric activators where a leaving group becomes a byproduct. See Sheldon, R. A. *J. Chem. Technol. Biotechnol.* **1997**, 68, 381. (16) (a) Prat, D.; Lett, R. *Tetrahedron Lett.* **1986**, 27, 707. (b) Prat, D.;

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<sup>(17)</sup> Conversion rates are lower in mixed organic/aqueous solvents, in part because bicarbonate solubility decreases and less catalyst can be used; however, bicarbonate salts with alkylated ammonium cations can be used to increase catalyst solubility (Yao, H.; Richardson, D. E., work in progress).

**Table 2.** Epoxidation<sup>a</sup> of Alkenes by Hydrogen Peroxide with Ammonium Bicarbonate in  $CD_3CN/D_2O$  (3:2, v:v)<sup>b</sup>

Substrate	Time	Conv. (%)	Product(s) (%)	
	24 h	40	epoxide(>99)	
	24 h	50	epoxide(90) diol(10)	
4	24 h	90	exo epoxide (>95)	
ОН	24 h 48 h	35 50	epoxide (>99) <sup>c</sup> epoxide (>99) <sup>c</sup>	
ОН	24 h 48 h	20 35	epoxide (>99)° epoxide (>99)°	
ОН	10 h 24 h	35 70	epoxide (80) <sup>c,d</sup> epoxide (60) <sup>c,d</sup>	
)=/OH	24 h 48 h	40 50	epoxides (>99) <sup>c,e</sup> epoxides (>99) <sup>c,e</sup>	

<sup>a</sup> Stoichiometry: alkene ~0.05 M, hydrogen peroxide ~0.3 M and ammonium bicarbonate ~0.2 M; 25 °C. <sup>b</sup> All reactions without bicarbonate gave negligible epoxide products after 24 h, except for 3-methyl-2-buten-1-ol (10% conversion to epoxide in 24 h). Dibasic ammonium phosphate was employed in controls to maintain similar ionic strength and pH of reaction media. <sup>c</sup> All allylic epoxides rearranged to form terminal epoxides as the major product. <sup>d</sup> The epoxide was not stable; decomposition products not identified. <sup>e</sup> Mixture of statistically distributed epoxide products.

alkenes, internal alkenes, and allylic alcohols) if a mixed solvent system is used. By using acetonitrile/water (3:2 v:v), epoxidations of hydrophobic alkenes were accomplished with  $\rm H_2O_2$  and  $\rm NH_4$ -HCO<sub>3</sub> (~0.2 M) at room temperature (Table 2).

Oxidation of styrene was followed in CD<sub>3</sub>CN/D<sub>2</sub>O (3:2, v:v) by using NMR. Addition of styrene (0.05 M) to a solution of H<sub>2</sub>O<sub>2</sub> (0.3 M) and NH<sub>4</sub>HCO<sub>3</sub> (0.2 M) yielded styrene oxide (40%) as the only product after 24 h. Because of peroxide disproportionation, excess hydrogen peroxide is needed to give a high yield of epoxide, and the epoxidation reaction was attempted preparatively in CH<sub>3</sub>CN/H<sub>2</sub>O (3:2, v:v). With 0.19 M NH<sub>4</sub>HCO<sub>3</sub>, 10 equiv of 30% aqueous H<sub>2</sub>O<sub>2</sub> gave styrene oxide in 75% distilled yield. <sup>18</sup> Other unfunctionalized alkenes in Table 2 ( $\alpha$ -methylstyrene and norbornene) form epoxide as the major product. The rate of alkene oxidation decreases significantly by replacement of acetonitrile with alcohol, e.g., ethanol or *tert*-butyl alcohol. For example, only trace oxidation products were detected for styrene after heating to 45 °C for 2 days in  $d_6$ -EtOH/D<sub>2</sub>O (3:2, v:v) with H<sub>2</sub>O<sub>2</sub> (0.3 M) and NH<sub>4</sub>HCO<sub>3</sub> (0.2 M). <sup>19</sup>

BAP oxidations of various allylic alcohols were also investigated. Allyl alcohol (0.1 M) and 2-cyclohexen-1-ol (0.1 M) have the least reactive double bonds, and only trace oxidation products are observed for dilute  $\rm H_2O_2$  (0.3 M) with  $\rm NH_4HCO_3$  (0.2 M) in  $\rm CD_3CN/D_2O$  after 24 h. Allylic alcohols with more substituted double bonds are epoxidized by the BAP system under similar conditions (Table 2). For all of the allylic alcohols epoxidation is strongly preferred over alcohol oxidation. In the case of geraniol, both allylic and remote alkene are oxidized with comparable rates. A striking feature in the BAP oxidation of these

allylic alcohols is that the major products are usually the rearranged epoxides, i.e., terminal epoxides.

It is necessary to distinguish the mechanism of alkene oxidations with the BAP system in CH<sub>3</sub>CN/H<sub>2</sub>O from that of Payne's procedure<sup>8</sup> in alcoholic solvent. Payne oxidations employ a slight excess of stoichiometric acetonitrile in alkaline hydrogen peroxide solution to produce a peroxycarboximidic acid, which oxidizes alkenes. The byproduct acetamide is obtained stoichiometrically from the reaction of peroxycarboximidic acid with alkene or hydrogen peroxide. In our study, oxidation of 4-vinylbenzenesulfonate with the BAP system in the presence of a stoichiometric amount of acetonitrile in D<sub>2</sub>O was investigated by using <sup>1</sup>H NMR. Over 90% of the alkene was converted to its epoxide product in 24 h, but no acetamide was detected in the <sup>1</sup>H NMR spectrum. In contrast, replacement of NaHCO<sub>3</sub> (pH. 8.4) or NH<sub>4</sub>HCO<sub>3</sub> (pH. 8.0) by Na<sub>2</sub>CO<sub>3</sub> (pH. 10.5) gave no oxidation products of the alkene after 24 h, but acetamide was formed. We conclude that the role of acetonitrile in the BAP system is to provide for substrate solubility and maintain high solvent polarity, favoring epoxidation by HCO<sub>4</sub>-.20

The mechanism for HCO<sub>4</sub><sup>-</sup> epoxidation may be closely related to that for typical peracids, i.e., the generally accepted butterfly transition state, <sup>21</sup> except that the proton transfer is to a carbonateleaving group (A) rather than to a carboxylates. Since the BAP reactions here are in aqueous or mixed aqueous solution, the intramolecular proton transfer that reduces charge separation in the transition state could also occur by solvent participation (e.g., B). Further studies on the detailed mechanism are in progress.

Our  $^{13}\text{C}$  NMR studies on  $H^{13}\text{CO}_4^-$  formation from  $H^{13}\text{CO}_3^-$  with 2 M  $\text{H}_2\text{O}_2$  in  $\text{CH}_3\text{CN/H}_2\text{O}$  (3:2, v:v) indicate  $K_{eq}$  (eq 1)  $\equiv$  [HCO $_4^-$ ][H2O]/[HCO $_3^-$ ][H2O $_2$ ]  $\approx$  35 (25 °C) with a  $t_{1/2}$  <5 min (pH = 7.4). After 20 h,  $\sim$ 50% of H2O $_2$  is consumed by decomposition based on the integration ratio of  $H^{13}\text{CO}_3^-$  and  $H^{13}\text{CO}_4^-$  in the spectrum. Therefore, decomposition of hydrogen peroxide in acetonitrile is relatively slow compared to the formation of HCO $_4^-$ . Oxidation reactions of alkenes with moderate reactivity can be achieved by forming HCO $_4^-$  with a small excess of  $H_2\text{O}_2$  despite the accompanying decomposition of  $H_2\text{O}_2$  in the presence of CH $_3\text{CN}$  as a cosolvent.  $^{22}$  Catalyst lifetime is not a major concern given the low cost and high stability of bicarbonate ion.

We believe BAP oxidations can be useful when a mild, low environmental impact oxidation method is desirable.<sup>23,24</sup> Some limits to the utility of the method remain to be overcome (e.g., low conversions for less nucleophilic substrates, hydrolysis of sensitive epoxides). Kinetic studies and development of optimal catalysts and synthetic methods for alkenes and other substrates are in progress.

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<sup>(18)</sup> Procedure: 6.30 g of NH<sub>4</sub>HCO<sub>3</sub> (79 mmol) and 38 mL of H<sub>2</sub>O<sub>2</sub> (30%, 360 mmol) were dissolved in 130 mL water, mixed with 240 mL of acetonitrile, and 4 mL of styrene (35 mmol) was added. The rt reaction was allowed to proceed in the dark without stirring for 24 h. The reaction mixture was diluted with 200 mL of water and extracted with chloroform (5  $\times$  200 mL). The filtrate was washed with water (2  $\times$  40 mL), dried, and concentrated by removal of solvent. Fractional distillation of the crude product gave 3.1 g of styrene oxide (75%).

<sup>(19)</sup> The observations of solvent dependence in the BAP epoxidations contrast with those for the  $H_2O_2$ /dicyclohexylcarbodiimide (DCC) system reported by by Majetich and co-workers. The best solvents for the DCC-activated epoxidation are hydroxylic ones such as methanol, ethanol or 2-propanol (except pure water).

<sup>(20)</sup> In addition, the same reaction was carried out in mixed  $CD_3CN/D_2O$  (1:7, v:v) solvent that was buffered with  $(NH_4)_2HPO_4$  to maintain similar pH and ionic strength compared to a bicarbonate solution, and only 5% of alkene conversion was observed after 24 h. In contrast to the simplicity of the homogeneous BAP procedure, the Payne procedure requires stirring and continuous addition of peroxide and base,

<sup>(21)</sup> See Bach, R. D.; Glukhovtsev, M. N.; Gonzalez, C. *J. Am. Chem. Soc.* **1998**, *120*, 9902–9910 and references therein.

<sup>(22)</sup> As was found in Payne's study, decomposition of H<sub>2</sub>O<sub>2</sub> is significantly accelerated in the higher pH media of CH<sub>3</sub>CN/H<sub>2</sub>O with added Na<sub>2</sub>CO<sub>3</sub>, and acetamide byproduct is observed.

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