Inorg. Chem. **2008**, *47*, 1173–1178

Inorganic Chemistry Article

The Mechanism of Carbon Dioxide Catalysis in the Hydrogen Peroxide N-Oxidation of Amines

Bharathi Balagam and David E. Richardson*

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

Received July 13, 2007

The reactivity of the peroxymonocarbonate ion, HCO_4^- (an active oxidant derived from the equilibrium reaction of hydrogen peroxide and bicarbonate), has been investigated in the oxidation of aliphatic amines. Tertiary aliphatic amines are oxidized to the corresponding N-oxides in high yields, while secondary amines give corresponding nitrones. A closely related mechanism for the H_2O_2 oxidation of tertiary amines catalyzed by CO_2 (under 1 atm) and H_2O_2 at 25 °C is proposed. The rate laws for the oxidation of N-methylmorpholine (**1**) to *N*-methylmorpholine *N*-oxide and *N*,*N*-dimethylbenzylamine (**2**) to *N*,*N*-dimethylbenzylamine *N*-oxide have been obtained. The second-order rate constants for the oxidation by HCO_4^- are $k_1 = 0.016\ M^{-1}\ s^{-1}$ for **1** in water and $k_1 = 0.042\ M^{-1}\ s^{-1}$ for **2** in water/acetone (5:1). The second-order rate constants for tertiary amine oxidations by HCO_4^- are over 400-fold greater than those for H_2O_2 alone. Activation parameters for oxidation of **1** by HCO_4^- in water are reported ($\Delta H^\ddagger = 36 \pm 2$ kJ mol^{-1} and $\Delta S^\ddagger = -154 \pm 7$ J mol^{-1} K^{-1}). The BAP (NH_4HCO_3-activated peroxide) or CO_2/H_2O_2 oxidation reagents are simple and economical methods for the preparation of tertiary amine N-oxides. The reactions proceed to completion, do not require extraction, and afford the pure N-oxides in excellent yields in aqueous media.

Introduction

Amine oxides are useful in a number of applications[1] and are essential components in many consumer product formulations.[2] Heterocyclic amine oxides are compounds of interest as hypoxia-selective cytotoxins in the clinical treatment of solid tumors.[3] N-Oxides are also used as stoichiometric oxidants in various other useful synthetic reactions such as the osmium-catalyzed dihydroxylation of olefins,[4,5] the ruthenium-catalyzed oxidation of alcohols,[6] and the Mn−salen catalyzed epoxidation of olefins.[7]

Amine oxides can be prepared via the noncatalytic oxidation of tertiary amines by H_2O_2 in a slow reaction.[8,9] Preparation of tertiary amine N-oxides by the use of hydrogen peroxide frequently leads to low yields of products containing varying amounts of hydrogen peroxide and requiring further purification;[10] however, hydrogen peroxide has the distinct advantage of producing water as the only oxidant byproduct. Various more reactive electrophilic oxidants can be employed for the oxidation of tertiary amines including peracids,[11,12] magnesium monophalate,[13] 2-sulfonyloxaziridines,[14] α-azohydroperoxides[15] and dioxiranes.[16] In contrast to hydrogen

---

* To whom correspondence should be addressed. E-mail: der@chem.ufl.edu.

(1) Swern, D. *Bailey's Industrial Oil and Fat Products*; John Wiley and Sons: New York, 1979; Vol. 1, p 655.

(2) Pattison, S. E. *Fatty Acids and Their Industrial Applications*; Marcell Dekker: New York, 1968; p 133.

(3) Priyadarsini, K. I.; Dennis, M. F.; Naylor, M. A.; Stanford, M. R. L.; Wardman, P. *J. Am. Chem. Soc.* **1996**, *118*, 5648.

(4) Vanrheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth.* **1988**, *Coll. Vol. VI*, 342.

(5) Kolb, H. C.; Vanknieuwenhze, M. S.; Sharpless, K. B *Chem. Rev.* **1994**, *94*, 2483−2547.

(6) Ley, S. V.; Norman, J.; Griffith, W. P; Marsden, S. P. *Synthesis* **1994**, 639.

(7) Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. *Tetrahedron Lett.* **1999**, *40*, 1989.

(8) Meisenheimer, J. *Ber.* **1919**, *52B*, 1667.

(9) Meisenheimer, J.; Bratring, K. *Justus Liebigs Ann. Chem.* **1913**, *397*, 286.

(10) Cope, A. C.; Towele, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3423.

(11) Swern, D. *Chem. Rev.* **1949**, *45*, 1.

(12) Mosher, H. S.; Turner, L.; Carusmith, A. *Orgainic Synth.* **1963**, *Coll. Vol. IV*, 828.

(13) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thomson, N. *Synthesis* **1987**, 1015.

(14) Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem* **1988**, *53*, 5856.

(15) Baumstart, L. A.; Dotrong, M.; Vasquez, P. C. *Tetrahedron Lett.* **1987**, *28*, 1963.

(16) Ferrer, M.; Sanchez-Baeza, F.; Messguer, A. *Tetrahedron* **1997**, *53*, 15877.

10.1021/ic701402h CCC: $40.75

peroxide, salts of carboxylic acids are formed when organic peracids such as peracetic and perbenzoic acids are used. In some cases Cope eliminations have been reported to occur during oxidation of amines with highly branched carbon chains.[17] *m*-Chloroperbenzoic acid (MCPBA) is a widely used peracid for laboratory scale reactions, but safety and cost considerations discourage its use for large-scale syntheses.

Various patents report the use of CO_2 as an effective catalyst for industrial amine oxidations by hydrogen peroxide,[18−20] but the mechanism of catalysis has not been proposed to our knowledge.

We report here an efficient and economical method of preparation of amine N-oxides based on H_2O_2/bicarbonate chemistry. In addition, we have investigated the closely related mechanism of CO_2 catalysis in peroxide oxidations of amines. The chemistry of both methods is associated with the labile hydration/dehydration equilibrium of carbon dioxide in water. On the basis of our previous work, we hypothesized that peroxymonocarbonate will be formed via a labile pre-equilibrium reaction between bicarbonate ion and hydrogen peroxide (eq 1) and subsequently oxidize the amine to amine oxide (eq 2).[21,22]

$$H_2O_2 + HCO_3^- \rightleftharpoons HCO_4^- \quad K_{eq} = 0.33 = k_f/k_r \qquad (1)$$

$$HCO_4^- + R_3N \rightarrow R_3NO + HCO_3^- \quad k_1 \qquad (2)$$

Peroxymonocarbonate is a moderately reactive heterolytic oxidant with the structure $HOOC(O)O^-$ and can be classified as an anionic peracid in neutral to moderately basic solutions. The deprotonated, dianionic form predominates in strongly basic solutions ($pK_a(HCO_4^-) = 10.6$). The rate constants k_f and k_r are for the forward and reverse reactions in eq 1, respectively. The mechanism of eq 1 presumably involves the equilibrium protonation and dehydration of bicarbonate ion followed by the addition of hydrogen peroxide (as H_2O_2 or OOH^-) to CO_2. In experiments that support the intermediacy of CO_2 in the formation of HCO_4^-, we have demonstrated that the equilibration of eq 1 is accelerated in the presence of catalysts for the dehydration of bicarbonate, and the kinetics of eq 1 are consistent with the model.[23]

Relatively few kinetic studies have been done for oxidations of amines to amine oxides, but the mechanism is generally accepted to involve nucleophilic attack by the amine in the case of electrophilic oxidants. In 1963, a mechanism for tertiary amine oxidation was offered by Oswald and Guertin.[24] Kinetic studies of the reaction were carried out by Katritzky and Lagowski[25] in 1971 for amine oxide formation from pyridine and perbenzoic acid, showing the reactions are second order. Few other kinetic reports are available for hydrogen peroxide oxidation of tertiary amines.[26]

Our recent kinetic investigations of bicarbonate-catalyzed organic sulfide oxidations[22] and methionine oxidation by H_2O_2 in water[23] strongly support the role of peroxymonocarbonate (HCO_4^-) as an electrophilic oxidant. In this continuation of our detailed study of peroxocarbonate reactivity, we have investigated the rate laws for the oxidation of tertiary amines by bicarbonate-activated peroxide (BAP) and the mechanism of CO_2 catalysis. Our present investigation has demonstrated that peroxymonocarbonate (or its kinetic equivalent) is the active species involved in the CO_2-catalyzed amine oxidation by hydrogen peroxide.

Results and Discussion

Kinetics. The oxidations of various aliphatic tertiary amines in D_2O were monitored spectrometrically by NMR. The amine was added to pre-equilibrated solutions of hydrogen peroxide and $NaHCO_3$/NH_4HCO_3 catalyst at the start of the reaction. $(Na)_2HPO_4$/$(NH_4)_2HPO_4$ and $NaClO_4$ were used to maintain a constant ionic strength and to set a comparable pH in kinetic studies of the uncatalyzed background reaction. We investigated possible buffer effects by comparing the rates of *N*-methylmorpholine (NMM) oxidation in H_2O_2 solutions with no added salts and with added $(NH_4)_2HPO_4$ and $NaClO_4$. No significant differences were detected in the oxidation rates, but we controlled ionic strength in some studies described below using $(NH_4)_2HPO_4$ and $NaClO_4$. The polydentate ligand diethylenetriaminepentaacetic acid (DTPA) was used in several experiments (up to 5 mM) and was found to have no effect on the observed rate constants, indicating that trace metals do not have a catalytic role.

The use of NH_4HCO_3 as the source of HCO_3^- allows higher catalyst concentration than the use of alkali metal salts before solubility saturation effects become apparent. In addition, NH_4HCO_3 conveniently decomposes to NH_3, CO_2, and H_2O, allowing the catalyst to be removed by evaporation and eliminating the need for extraction of the product. BAP reactions were followed for the two most reactive tertiary amines (NMM and *N*,*N*-dimethylbenzylamine) to at least 75% conversion, and no evidence for deviation of second-order behavior was observed. The contribution of the noncatalytic background oxidation was subtracted to obtain the phenomenological rate law for the catalytic path. For the background reactions with no bicarbonate added, only a small percentage of the reaction could be recorded (6−10%).

Note that the reaction kinetics were studied in D_2O with small amounts of H_2O introduced with other reagents. However, reactions are shown below with exchangeable hydrogens as H instead of D for convenience.

---

(17) Cope, A. C.; Acton, F. M.; Pikes, R. A. *Org. React.* **1960**, *11*, 379.
(18) Thomas, D. H.; Krzystowczyk, D. H. U.S. Patent 6,037,497, 2000.
(19) Smith, R. F.; Chen, Y.-D. M.; Wilson, Jr. R. W.; Shah, M. P.; Smith, K. R.; McGee, S. B. U.S. Patent 5,693,861, 1997.
(20) Elnagar, H. Y. U.S. Patent 6,121,490, 2000.
(21) Richardson, D. E.; Yao, H.; Xu, C.; Drago, R. S.; Frank, K. M.; Wagner, G. W.; Yang, Y.-C. In *Proceedings of the 1998 ERDEC Scientific Conference on Chemical and Biological Defence Research*; Aberdeen Proving Ground, 1999.
(22) Richardson, D. E.; Yao, H. R.; Frank, K. M.; Bennett, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1729−1739.
(23) Richardson, D. E.; Regino, C. A. S.; Yao, H. R.; Johnson, J. V. *Free Radical Biol. Med.* **2003**, *35*, 1538−1550.
(24) Oswald.A. A.; Guertin, D. L. *J. Org Chem* **1973**, *28*, 658.
(25) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocycles N-Oxides*; Academic Press: London, New York, 1971; Vol. 19, p 69.
(26) Gee, J. C.; and Williamson, R. C. *J. Am. Oil Chem. Soc.* **1997**, *74*, 65.

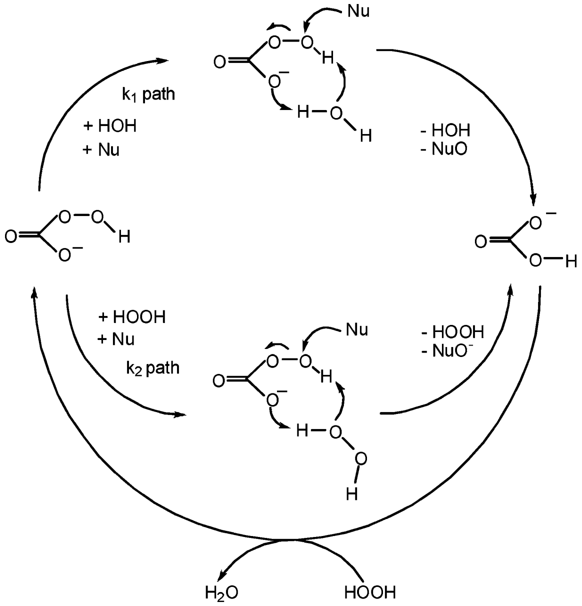


Figure 1. Mechanism for the BAP-catalyzed oxidation of nucleophiles. The upper pathway is promoted by water, while the lower pathway is promoted by H_2O_2 and is observed only at high concentrations of peroxide. Regeneration of HCO_4^- proceeds via the dehydration of bicarbonate and addition of peroxide to CO_2 (as either H_2O_2 or OOH^-).

Mechanism. The proposed mechanism for the oxidation of nucleophiles by bicarbonate-activated hydrogen peroxide is based on a general mechanism for electrophilic peroxide oxidations[22,27] and is shown in Figure 1. The mechanism involves nucleophilic attack of substrate at the electrophilic oxygen of HCO_4^-. In the case of protic solvents such as water, proton transfers can lead to displacement of HCO_3^- and immediate formation of NuO.

Equations 1 and 2 (upper pathway of Figure 1) summarize the simple mechanism for bicarbonate catalysis, while the background (eq 3) and peroxide-catalysis (eq 4, lower pathway of Figure 1) pathways must often be considered.[22] The kinetics in this study will be modeled with the assumption that eq 4 is negligible under the conditions used in this work (i.e., assuming $k_1 >> k_2[H_2O_2]$), as there was no kinetic evidence for its importance.

$$R_3N + H_2O_2 \rightarrow R_3NO + H_2O \quad k_0 \qquad (3)$$

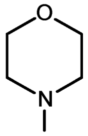
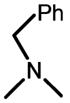
$$HCO_4^- + R_3N + H_2O_2 \rightarrow R_3NO + HCO_3^- + H_2O_2 \quad k_2 \qquad (4)$$

Due to the multiple equilibria and reactions, the initial hydrogen peroxide concentration $[H_2O_2]_0$ is related to reactant and product concentrations at time t by eq 5 when HCO_3^- or CO_2 is present.

$$[H_2O_2]_0 = [H_2O_2]_t + [OOH^-]_t + [HCO_4^-]_t + [CO_4^{2-}]_t + [R_3NO]_t \qquad (5)$$

In addition, the acid–base equilibrium of the amine must be considered. Since the reaction conditions are second order with $[H_2O_2]_0/[\text{amine}] < 10$, we used numerical methods to generate the concentration–time profiles for the mechanism of eqs 1–3 and fit the experimental observations to obtain values for rate constants k_0 and k_1. The resulting rate constant values for two tertiary amines are given in Table 1.

Table 1. Kinetic Parameters for Amine Oxidations by Bicarbonate-Activated Hydrogen Peroxide[a]

Substrate	$10^3\ k_0/M^{-1}s^{-1\ b}$	$k_1/M^{-1}s^{-1}$	k_1/k_0
	0.035±0.001	0.016 ± 0.001	460
	0.10 ± 0.01	0.042 ± 0.002	420

[a] Conditions: 25 °C, [A] = 0.05 M, $[H_2O_2] = 0.25-0.5$ M, $[HCO_3^-] = 0-0.5$ M, solvent for NMM, D_2O; for *N*,*N*-dimethylbenzylamine, acetone-d_6/D_2O, 1:5. The k_1 values were estimated by numerical fitting as described in the text. [b] k_0 is the second-order rate constant for the background reaction $NRR'R'' + H_2O_2 \rightarrow N(O)RR'R'' + H_2O$. p$K_a$(NMM) = 7.4, p$K_a$(DMBA) = 8.8. Errors shown are quoted as standard errors.

An approximation to the observed kinetics can be obtained analytically by using eq 6, which assumes that $[H_2O_2] >> [\text{amine}]$ and the pH is not so high that H_2O_2 and HCO_4^- are significantly deprotonated (pH < 9).

$$\frac{d[R_3NO]}{dt} = k_1[HCO_4^-][NR_3] = \frac{k_1K_{eq}[HCO_3^-][H_2O_2]A_f[A]}{1 + K_{eq}[H_2O_2]} + k_0A_f[H_2O_2][A] \qquad (6)$$

where [A] = $[\text{amine}]_{\text{total}}$ and

$$A_f = \text{fraction of unprotonated anime} = \frac{K_a(R_3NH^+)}{K_a(R_3NH^+) + [H^+]}$$

Alternatively, the rate law can be expressed by eq 7, where k_{obs} is given by eq 8, based on the assumptions above. At lower $[H_2O_2]_0/[A]$ values, the denominator in eq 8 varies significantly with reaction time as peroxide is consumed.

$$\frac{d[R_3NO]}{dt} = k_{obs}[H_2O_2][A] \qquad (7)$$

$$k_{obs} = \frac{k_1K_{eq}[HCO_3^-]A_f}{1 + K_{eq}[H_2O_2]} + k_0A_f \qquad (8)$$

Rate constants for oxidation by peroxymonocarbonate were found to be over 400-fold greater than those for the direct reaction with H_2O_2 (Table 1). This result is consistent with previous observations for ethyl phenyl sulfides and predictions from a Brønsted analysis,[22] providing strong

---

[27] Bennett, D. A.; Yao, H.; Richardson, D. E. *Inorg. Chem.* **2001**, *40*, 2996–3001.

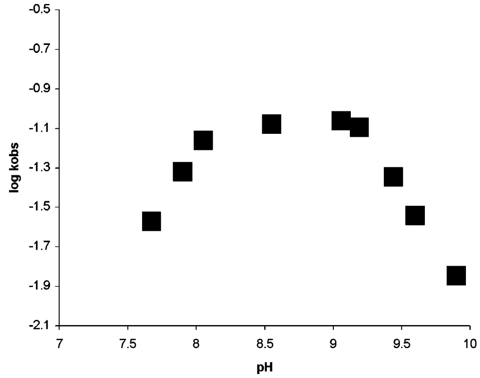


Figure 2. Observed rate constants for bicarbonate catalyzed oxidation of NMM. $[HCO_3^-] = 0.25$ M, $[H_2O_2] = 0.5$ M.

evidence that the acceleration of oxidation in the presence of bicarbonate arises from the formation of the more electrophilic oxidant HCO_4^-.

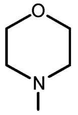
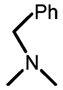
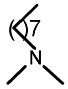
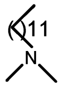
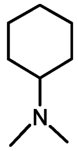
pH Studies. We examined the pH dependence of the oxidation of NMM (Figure 2). Studies on the pH dependence of observed rate constants by using phosphate buffers showed that changes in the kinetic constants are negligible within the experimental error in the pH range of 8−9. Above pH 9 and below pH 8, the catalytic rate does decline significantly. It was noted in a previous publication that increasing the pH to >9 leads to a decrease in the oxidation rates for bicarbonate-activated peroxide,[22] presumably the result of the deprotonation of HCO_4^- to form CO_4^{2-}, which is a less electrophilic oxidant than HCO_4^-. The decreased rate at pH < 8 is due to the protonation of amine.

Although the maximum rates are correctly predicted by the mechanism to be in the pH 8−9 range, the observed reaction rate declines more steeply than predicted by the model outside of this range, especially at high pH values. At higher pH values, decomposition of peroxide is accelerated and may reduce the observed rates.

Activation Parameters for NMM Oxidation. The temperature dependence of the catalytic NMM oxidation from 25 to 45 °C was studied in D_2O with 0.5 M H_2O_2 and up to 0.25 M bicarbonate. The second-order rate constant (after correction for background oxidation) was used to construct an Eyring plot of $\ln(k_1/T)$ vs $1/T$, and activation parameters were derived from a regression analysis: $\Delta H^\ddagger = 36 \pm 2$ kJ mol^{-1} and $\Delta S^\ddagger = -154 \pm 7$ J mol^{-1} K^{-1} (errors are standard errors, $N = 8$). An Eyring analysis of the background data for direct H_2O_2 oxidation led to $\Delta H^\ddagger = 68 \pm 5$ kJ mol^{-1} and $\Delta S^\ddagger = -101 \pm 17$ J mol^{-1} K^{-1}. The latter values can be compared with those in the literature for H_2O_2 oxidation of 2-morpholinoethyl-N-phenyl carbonate ($\Delta H^\ddagger = 71$ kJ mol^{-1} and $\Delta S^\ddagger = -95$ J mol^{-1} K^{-1}).[28] The enthalpy of activation is considerably lower for the bicarbonate-catalyzed oxidation and is responsible for the increased reaction rate. The strong negative entropy of activation is consistent with a bimolecular mechanism as shown in Figure 1.

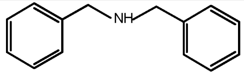
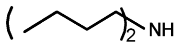
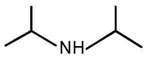
Oxidation of Other Amines. The activity of BAP for oxidation of various other tertiary and secondary amines was also examined (Tables 2 and 3) under synthetic conditions (in water or water/acetone). We observed a steady increase in the required time of reaction with an increase in the pK_a of substrate. The lower reaction rate can be attributed to increased protonation of amine at the reaction pH value for more basic amines.

Table 2. Synthetic Applications of BAP for N-Oxidation of Tertiary Amines[a]

Substrate	Time/h	N-oxide % Yield[b]	pH[c]	pKa[d]
	1h	93	8.7±0.2	7.4
	2h	92	9.0±0.2	8.8
	5h	91	9.7±0.2	9.86
	5h	88	9.1±0.2	9.78
	6h	92	9.0±0.2	10.72

[a] Conditions: $[A] = 0.1$ M, $[H_2O_2] = 0.5$ M, $[HCO_3^-] = 0.25$ M, $T = 25$ °C, solvent is H_2O for NMM, acetone/H_2O = 1:5 for all other substrates. [b] Isolated yield. [c] pH of reaction mixture. [d] pka of substrate.

Table 3. Activity of BAP for Oxidation of Secondary Amines[a]

Substrate	Time/h	Nitrone %Yield[b]	pH[c] (pKa)[d]
	4	94	10.34 (8.8±0.2)
	6	92	10.2 (11.0±0.2)
	24	64	10.21 (10.8±0.2)

[a] Conditions: $[A] = 0.1$ M, $[H_2O_2] = 0.5$ M, $[HCO_3^-] = 0.25$ M, $T = 25$ °C. [b] Isolated yield. [c] pH of reaction mixture. [d] pKa of substrate.

CO_2-Catalyzed Oxidation of Tertiary Amines. We studied the amine oxidation reaction using CO_2 gas (1 atm pressure) and aqueous H_2O_2 at room temperature (Table 4). One patent report on amine oxidation by CO_2/H_2O_2 has described the active agent for this reaction as an "unidentified complex".[18] Our investigation of CO_2/H_2O_2-catalyzed amine

---

(28) Gerhard, L. *J. Chem. Soc. Perkin Trans.* **2001**, *2*, 864.

Table 4. NMM Oxidation Using CO_2 and H_2O_2[a]

[amine]/[H_2O_2]	*t*/h	% yield (NMR)	pH[b]
1:5	1.0	99	6.87
1:2	1.0	37	7.27
	2.0	53	
1:1.5	0.5	24	7.07
	1.0	40	
	2.0	53	
	3.0	64	

[a] Conditions: $[A] = 0.1$ M, $[H_2O_2] = 0.15-0.5$ M, $T = 25$ °C. [b] pH of reaction mixture.

oxidations demonstrates that peroxymonocarbonate is the active species involved in the peroxidation of tertiary amines.

When CO_2 gas at 1 atm pressure is bubbled into a solution of a tertiary amine in water for 5−10 min, a rapid drop of pH from ~10 to ~7 is observed as a result of the formation of the quaternary ammonium salt, $R_3NH^+HCO_3^-$. This was followed by the addition of hydrogen peroxide (35%) with continued CO_2 bubbling for another 1 h, whereupon essentially complete conversion to amine oxide is observed when $[H_2O_2]/[\text{amine}] = 5$. Evaporation of water results in high purity amine oxide in excellent yields. The activity of CO_2 for oxidation NMM with various concentrations of H_2O_2 is given in Table 4.

Reported methods using CO_2 as catalyst generally involve high-temperature and high-pressure reaction conditions.[18−20] We have found that the reaction proceeds efficiently at room temperature with CO_2 gas at 1 atm pressure. This synthetic method thus proves to be very simple, economical, and green with no need for extraction procedures since the catalyst is a gas.

The observed reaction rates are completely consistent with the predictions from the mechanism and the associated rate constants and equilibrium constants described above. The combination of eq 1 with the aqueous acid−base equilibration of CO_2/HCO_3^- (eq 9) and amine (eq 10) leads to the equilibrium formation of HCO_4^- in solutions of aqueous CO_2, H_2O_2, and amine as described by eq 11. Previously reported kinetic results[22] are consistent with the equilibration reaction of eq 1 proceeding via the perhydration of CO_2 formed in equilibrium with HCO_3^-. The perhydration of CO_2 results in the formation of HCO_4^-, which in turn oxidizes tertiary amine to amine oxide (eq 2).

$$CO_2(g) \rightleftharpoons HCO_3^- + H^+ \quad K' \qquad (9)$$

$$H^+ + NR_3 \rightleftharpoons R_3NH^+ \quad 1/K_a \qquad (10)$$

$$CO_2(g) + H_2O_2 + R_3N \rightleftharpoons R_3NH^+ + HCO_4^- \qquad K'' = \frac{K'K_{eq}}{K_a} \qquad (11)$$

Once amine is completely consumed, the equilibrium of eq 11 shifts back to form CO_2 and excess peroxide, and the overall reaction is given by eq 12.

$$H_2O_2 + R_3N \xrightarrow{CO_2} R_3NO \qquad (12)$$

The value of K'' can be calculated readily from known values of K' and K_a(NMM), and $K'' = 0.13$ atm^{-1} at 25 °C. With $[H_2O_2] = 0.2$ M, $[\text{NMM}] = 0.1$ M, and 1 atm of CO_2, the estimated $[HCO_4^-] = 0.036$ M. The initial rate for oxidation of the amine (eq 6) would be ~2 mM min^{-1}, which is consistent with reaction times in Table 4 when adjustments are made for the observed pH values.

As indicated in the patent literature, further acceleration can be achieved by increasing the CO_2 pressure above 1 atm, and this observation is understandable given the increased production of HCO_4^- as described quantitatively by eq 11.

Conclusions

The BAP reagent provides a convenient, high-oxygen efficiency method for the conversion of tertiary amines to amine oxides. The most convenient BAP method for amines is to introduce CO_2 as the catalyst, which when combined with hydrogen peroxide provides an economical and relatively nontoxic alternative to other peroxidants. Organic products can be readily separated by simple evaporation of solvent without solvent extraction. The kinetic and spectroscopic results strongly support the formation of peroxymonocarbonate as the oxidant in the catalytic reactions. The second-order rate constants for sulfide oxidations by peroxymonocarbonate are over 400- fold greater than those for hydrogen peroxide.

Amine oxides are useful mild oxidants for synthetic oxidations, and in other work we have shown that they can be produced in situ from amines and used in transformations in which hydrogen peroxide itself is not directly applicable, such as in the osmium-catalyzed asymmetric dihydroxylation of alkenes.[29]

Experimental Section

Materials. Amines and hydrogen peroxide (35%) were purchased from Sigma-Aldrich. Reagent grade solvents and acetone (AAPER) were purchased and used without further purification. Sodium bicarbonate (Mallinckrodt) and sodium/ammonium dibasic phosphate (Sigma) were purchased as analytical grade reagents and used without further purification. High-purity ammonium bicarbonate (99.99+%, Aldrich) was used, and water was purified by using a Sybron/Barnstead water purification system. Deuterium oxide (99.9%, Cambridge Isotope Laboratories, Inc.) was used in ^{1}H NMR studies. The 35% H_2O_2 stock solution was regularly standardized iodometrically.

Kinetics. Amine oxidations were carried out in D_2O and D_2O/co-solvent media. Solutions containing hydrogen peroxide and ammonium bicarbonate were allowed to pre-equilibrate for ~20 min prior to the addition of the amine. ^{1}H NMR spectral measurements were carried out on a Gemini 300 MHz or a VXR 300 MHz NMR instrument with temperature control of ±0.1 °C. The hydrogen peroxide concentration was up to 0.5 M, and the ammonium bicarbonate concentration was in the range of 0.25−0.5 M. Ionic strength was maintained at 1.0 using ammonium phosphates or sodium phosphates. Rate constants for the uncatalyzed oxidation reactions, in 0.5 M hydrogen peroxide solution and within the corresponding pH range, were measured in sodium phosphate monobasic/dibasic media at a total ionic strength of 1.0 The

---

(29) Balagam, B.; Mitra, R.; Richardson, D. E. *Tetrahedron Lett.*, in press.

substrate concentration used was 0.05 M. Overall plots of ln([H_2O_2]$_t$/[A]$_t$) vs t were consistently linear with $R^2 > 0.99$ in most cases (the reaction stoichiometry is 1:1 H_2O_2/A), indicating second-order kinetics. In the case of the uncatalyzed reaction at low concentration of hydrogen peroxide, the reactions were extremely slow; in such cases data for only a small percentage of the reaction were obtained.

A pH-dependence study for the oxidation of NMM was performed in D_2O solutions with 0.5 M hydrogen peroxide with 0.25 M of catalyst as sodium or ammonium bicarbonate. The ionic strength was maintained at 1.0 by addition of sodium/ammonium phosphates and $NaClO_4$. The pH of the corresponding aqueous media for the above solutions ranged from 7.6 to 9.9. Depending on the pH of the solution the mixture was allowed to stand for 15−30 min before kinetic measurements were taken. Reactions were usually followed for at least 75% conversion.

In the case of CO_2/H_2O_2-catalyzed reactions, the concentration of substrate was maintained at 0.1 M and H_2O_2 concentration was in the range of 0.1−0.5 M. CO_2 bubbling was at 1 atm pressure.

Oxidation of NMM Using NH_4HCO_3 and H_2O_2 (Typical Procedure). A 50 mL round bottomed flask was charged with 1.975 g (25 mmol) of NH_4HCO_3 and 4.85 mL (50 mmol) of 35% H_2O_2 in 25 mL of water. The solution was stirred for 15 min. To this BAP solution, 1.09 mL (10 mmol) of NMM was added in one portion. The reaction mixture was stirred for 1 h. After the completion of reaction, the solvent was evaporated by rotary evaporation to obtain the crude amine oxide product. The crude product was purified by column chromatography (silica gel, 100−200 mesh; MeOH/CH_2Cl_2 = 10:90) to yield 1.08 g (93%) of *N*-methylmorpholine *N*-oxide as a white solid.

Oxidation of NMM Using CO_2 and H_2O_2 (Typical Procedure). A 25 mL round bottomed flask was charged with 1.09 mL (10 mmol) of NMM in 10 mL of water. CO_2 gas was bubbled through the solution under 1 atm pressure for 10 min. To this solution, 4.85 mL (50 mmol) of 35% H_2O_2 was added in one portion. The reaction mixture was stirred and CO_2 gas was bubbled for another 30 min. After the completion of reaction, the water was removed by rotary evaporation to obtain the amine oxide crude product. The crude product was purified by column chromatography (silica gel, 100−200 mesh; MeOH/CH_2Cl_2 = 10:90) to yield 1.11/g (95%) of *N*-methylmorpholine *N*-oxide as a white solid.

Acknowledgment. This work was supported by a grant from the Army Research Office.

IC701402H