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Epoxidation of Olefins with Formamide - Hydrogen Peroxide

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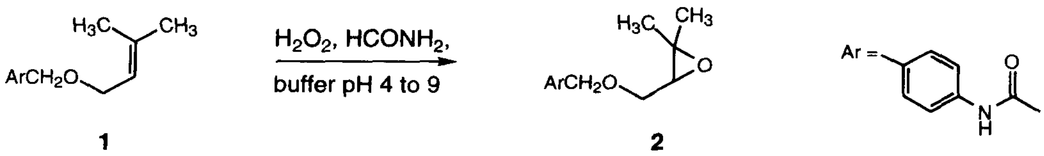
Abstract: *Olefins are converted to epoxides in aqueous medium using formamide-hydrogen peroxide as oxidant.*

A number of reagents have been described to mediate the epoxidation of olefins by hydrogen peroxide. These include many different iron and manganese porphyrins,[1a] selenic acids,[1b] hexafluoroacetone,[1c] activated derivatives of carboxylic and phosphonic acids, isocyanates, diimides, and nitriles.[2] We now report that simple amides activate hydrogen peroxide for olefin epoxidation in aqueous medium in a pH-independent manner. In particular, formamide-hydrogen peroxide is found to be a mild and efficient epoxidation reagent.

We recently showed that acetonitrile-hydrogen peroxide, a reagent initially described by Payne,[3] can be used in conjunction with antibodies to effect catalytic, enantioselective epoxidation of unfunctionalized olefins.[4] In the course of these investigations, we found that under slightly more acidic conditions (pH 6.5) than those recommended by Payne ($NaHCO_3$ buffer, pH 8), the epoxidation reaction was promoted by the reaction product acetamide almost as efficiently as by acetonitrile itself. A survey of simple amides as epoxidation promoters was conducted using the oxidation of olefin **1** (250 μM) to epoxide **2** as model reaction. Initial rates were measured by following product formation over time by reversed-phase HPLC. At pH 6.5 (50 mM phosphate buffer) in the presence of 725 mM (2.5 % v/v) H_2O_2 and 250 mM reagent at 20 °C, epoxidation of **1** to **2** takes place at the rate of approximately 2 to 20 % per day, giving the following reactivity order for simple amides compared to acetonitrile: $HCONH_2$ (7.7), $HCONHCH_3$ (5.4) >> $HCON(CH_3)_2$ (1.0), CH_3CN (1.0), CH_3CONH_2 (0.70)>> $CH_3CON(CH_3)_2$ (0.24), $CH_3CONHCH_3$ (0.15). The pH-rate profile (figure 1) shows that the epoxidation with formamide, the most efficient promoter at pH 6.5, is completely pH-independent within the stability range of the formed epoxide (pH 4 to 9), and is insensitive to the nature of the buffer system used. By contrast, the acetonitrile reaction seems to follow a more complex path with pH and buffer dependency.



The results of the epoxidation with formamide-hydrogen peroxide for a series of representative alkenes are reported in Table 1. We obtained good yields of epoxides with tri- and *Z*- di-substituted olefins, which are the more reactive. No reaction was observed with a selection of *E*- disubstituted and terminal olefins (*E*-β-methyl styrene, *E*-2-hexen-1-ol, 5-hexen-1-ol, 1-octen-3-ol, styrene). Epoxidation of bifunctional alkenes with this reagent takes place at the more reactive double bond (**7** and **8**), with a selectivity for the double bond without allylic hydroxy group which complements the Sharpless epoxidation.[5]

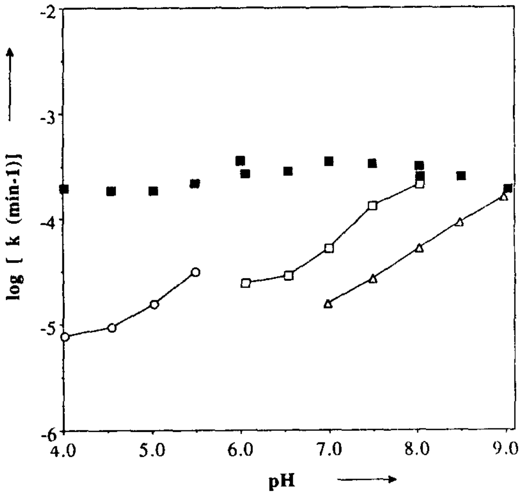
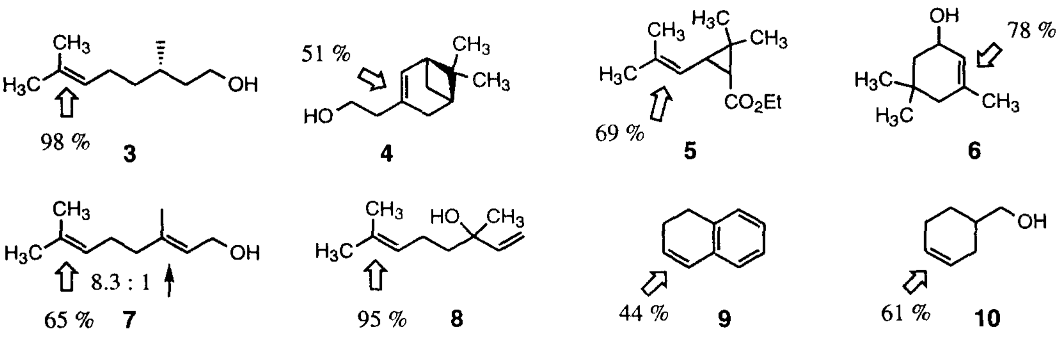


Figure 1. pH-rate profile as $\log(k_{app}[min^{-1}])$ for the epoxidation of **1** to **2** with formamide-H_2O_2 (■, all buffers) and acetonitrile-H_2O_2 in citrate (○), phosphate (□) or borate (△) buffers. Initial rates (< 5% conv.) measured in water at 20 °C with 250 μM **1**, 100 mM $HCONH_2$ or CH_3CN, 725 mM H_2O_2, 50 mM Na_2SO_4, 50 mM buffer (citrate pH 4 to 5.5, phosphate pH 6 to 8, borate pH 7 to 9).

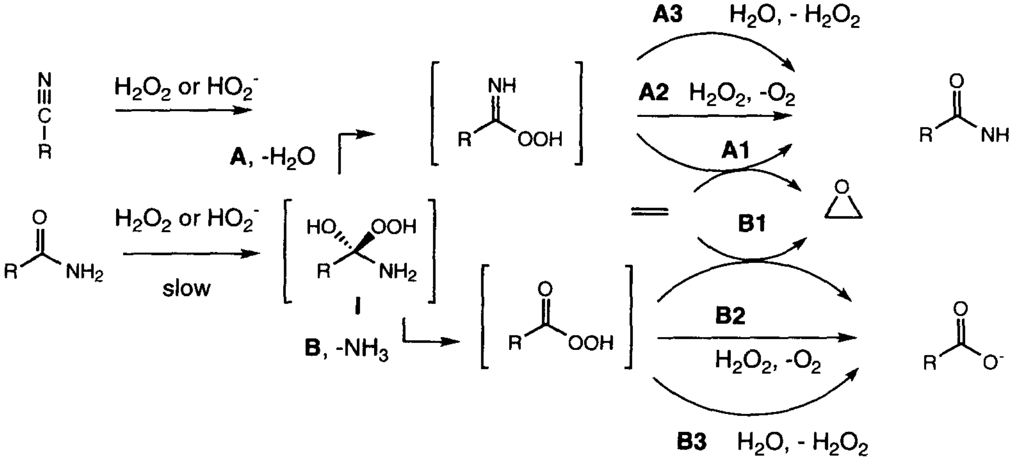
Table 1. Epoxidations with Formamide-hydrogen peroxide.[a]



[a] Isolated yields after purification by chromatography on silicagel. Site of epoxidation indicated by arrow. No significant stereoselectivity was observed with chiral substrates. Conditions: 1 mmol olefin, aq. NaH_2PO_4 pH 6.0 with MeOH cosolvent (dioxane for **9**), 10 eq.$HCONH_2$, 15 eq. H_2O_2, 50 °C, 3 hours.[b] 37 °C, 3h, 20 % diepoxide and 12 % starting material were also isolated.

In the Payne reaction, H_2O_2 or its anion first adds to acetonitrile to form a peroxy carboximidic acid, which then either delivers oxygen to the alkene, or reacts again with H_2O_2 to form acetamide and singlet oxygen. Since H_2O_2 promotes amide bond hydrolysis,[6] the epoxidation with the amide promoters should start by addition of H_2O_2 at the acyl carbon. The resulting tetrahedral intermediate **I** could collapse either to a peroxy carboximidic acid (path A) or to a peracid (path B) as the active oxidant.[7,8] Alkene epoxidation (A1 or B1), oxidation of H_2O_2 to oxygen (A2 or B2), or hydrolysis (A3 or B3) could then take place.

In the absence of olefin, formamide reacts rapidly with H_2O_2 to give ammonium formate and oxygen. Approximately 2 equivalents H_2O_2 are needed to hydrolyze all of the formamide, and only 45 % of the formamide is hydrolyzed with 1.0 equivalent H_2O_2.[9] This suggests that the reaction proceeds via pathway B2 (stoichiometric hydrolysis of formamide by two equivalents of H_2O_2), and not A2 (formamide-catalyzed consumption of H_2O_2) or B3 (H_2O_2 catalyzed hydrolysis of formamide). The preferred epoxidation pathway is thus probably B1, which involves performic acid as oxidant,[10] and consumes one equivalent of each formamide and H_2O_2 per oxidized olefin.[11]



If the epoxidation of olefins with formamide-H_2O_2 involves performic acid, which is a rather strong peracid, as active oxidant, the selectivity of the reagent is quite surprising. We propose that the exceptional mildness of performic acid under these conditions results from the fact that olefin epoxidation takes place in competition with the reaction of the peracid with H_2O_2 (path B2). There H_2O_2 acts as a reducing agent, and can consume all of the peracid if the olefin is not sufficiently reactive to compete. Therefore no epoxidation takes place with unreactive olefins.[12]

In summary, we have disclosed a new aspect of the chemical reactivity of simple amides. Similarly to the nitriles, formamide is otherwise relatively inert. Epoxidation with formamide - hydrogen peroxide is pH-independent and thus leaves complete freedom to manipulate the pH parameter.[13] These features make this reagent attractive for epoxidation in buffered aqueous or aqueous/organic media. Its utilization for antibody mediated, enantioselective epoxidation will be reported in due course.

Experimental Procedure. The olefin (1 mmol), formamide (0.4 mL, 10 mmol), hydrogen peroxide (1.6 mL of 30 % aq. soln., 15 mmol) and buffer (6 mL of 0.5 M NaH_2PO_4, pH 6.0) were heated at 50 °C and then diluted with methanol or dioxane to obtain a clear solution (4 to 8 mL). The reaction mixture was stirred at 50 °C for 3 to 10 hours, which generally resulted in complete disappearance of the olefin. Aqueous saturated NaCl (10 mL) was added and the solution was extracted with ethyl acetate (4 x 10 mL). After drying ($MgSO_4$) and evaporation, the crude product was purified by flash chromatography on silicagel (hexane/ethyl acetate) to give the pure epoxide (clear colorless oil, 44 - 98 % yield).[14]

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[5] Sharpless, K.B.; Verhoeven, T.R.; *Aldrichimica Acta* **1979**, *12*, 63. See also ref. 1b. Under carefully controlled conditions, epoxidation with *m*-CPBA gives similar selectivities.

[6] Losse, G.; Zönnchen, W.; *Justus Liebigs Ann. Chem.* **1960**, *636*, 140. The deprotection of N-formylated amino-acids and peptides reported by these authors (using 15 % v/v H_2O_2 at 60 °C for 2 hours) was mistakenly attributed to an oxidation of the formyl group to CO_2. Our ^{1}H-NMR experiments unambiguously show the quantitative formation of formate from formamide. It should also be noted that formamides are orders of magnitude more reactive towards hydrolysis than a peptide bond, and that hydrolytic degradation of proteins by hydrogen peroxide is usually not observed.

[7] For amide bond hydrolysis, cleavage of the C-N bond follows preequilibrium addition of H_2O to the carboxyl to form the tetrahedral intermediate. The ratio of oxygen exchange vs. hydrolysis in the reaction of ^{18}O-labeled benzamide with NaOH was reported to be 4 to 1. It was 1 to 1 for N-methyl benzamide and zero for N,N-dimethyl benzamide. see: Bunton, C.A.; Nayak, B.; O'Connor, C.; *J. Org. Chem.* **1968**, *33*, 572 and ref. cited therein. Oxygen exchange with formamide and H_2O_2 would lead to the peroxy carboximidic acid.

[8] These peracids would be in the protonated form at pH 6.0: pK_a (HCO_3H) = 7.1, pK_a (CH_3CO_3H) = 8.2. See Richardson, W.H. in *"The Chemistry of Functional Groups, Peroxides"*, Ed. S. Patai, **1983**, chapter 5, pp. 129-155.

[9] The reactions were carried out with 10% v/v $HCONH_2$ and 15 % v/v H_2O_2 or 7.5 % v/v H_2O_2 resp., in 50 mM phosphate buffer, pH 6.0, at 50 °C for 3 hours, and then diluted with D_2O and analyzed by ^{1}H-NMR.

[10] Performic acid forms spontaneously in mixtures of formic acid and hydrogen peroxide. Epoxidation under these strongly acidic conditions is very efficient but leads directly to the diol by hydrolysis. We did not observe any epoxidation using sodium formate at pH 6.0. See Swern, D., *Org. React.* **1953**, *7*, 378-433, p. 384, and ref. cited therein.

[11] Another possible mechanism compatible with the stoichiometry of hydrolysis involves direct oxygen transfer from hydroperoxide **I** to the olefin or to H_2O_2 concerted with C-N bond cleavage. Although certain stable hydroperoxides epoxidize olefins (ref. 1c), we consider this mechanism unlikely here because tetrahedral intermediate **I** is expected to be very unstable and collapse rapidly to the peracid.

[12] Since hydroperoxides also oxidize terminal double bonds (ref. 1c), having intermediate **I** instead of performic acid as oxidant requires a similar argument to explain the chemoselectivity of formamide-H_2O_2.

[13] In the absence of litterature data for pH-rate profiles of aqueous epoxidations with either peracids or peroxides, the exact origin of this effect is unclear at that point. *m*-CPBA oxidizes olefins in biphasic systems in the presence of basic buffers (pH > 8): Anderson, W.K.; Veysoglu, T.; *J. Org. Chem.* **1973**, *38*, 2267.

[14] All products gave satisfactory ^{1}H-NMR and MS data and were compared with reference epoxides prepared by epoxidation with *m*-CPBA.

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