Kinetics and Mechanism of the Oxidation of Secondary Hydroxylamines to Nitrones with Hydrogen Peroxide, Catalyzed by Methylrhenium Trioxide

Timothy H. Zauche and James H. Espenson*

Ames Laboratory and Department of Chemistry, Iowa State University, Ames, Iowa 50011

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Secondary hydroxylamines, $(RCH_2)_2NOH$ and $(R_2CH)_2NOH$, were converted to nitrones, $RCH_2N(O)=CHR$ and $R_2CHN(O)=CR_2$, in >94% yield with hydrogen peroxide as an oxygen donor and methylrhenium trioxide (MTO) as a catalyst. High concentrations of hydrogen peroxide were used so that the methylrhenium diperoxide, $CH_3Re(O)(\eta_2\text{-}O_2)_2(H_2O)$, was the dominant and reactive form of the catalyst. Representative rate constants are as follows: k/L mol^{-1} s^{-1} = 150 (R = Me), 52 (Et), 13.8 (Pr^i), and 3.33 ($PhCH_2$) in methanol at 25.0 °C. There is no H/D kinetic isotope effect on the rate constant for this step. The data are interpreted to infer the intervention of an oxygenated intermediate, $(RCH_2)_2N(O)OH$, which then rapidly dehydrates to yield the nitrone. Two products are formed from unsymmetrical hydroxylamines, the ratio of which establishes the reactivities of the intermediate toward the competing elimination reactions: $(RCH_2)(R'CH_2)NOH \rightarrow \{(RCH_2)(R'CH_2)N(O)OH\} \rightarrow \chi RCH_2N(O)=CHR' + (1-\chi)R'CH_2N(O)=CHR$.

Introduction

Methylrhenium trioxide (CH_3ReO_3, abbreviated as MTO) has proved to be an efficient oxidation catalyst with hydrogen peroxide as the oxygen source. This catalyst, first prepared as a minor side product,[1] can now be obtained easily.[2] The scope of the catalytic oxidations is quite wide, and a considerable diversity of substrates will react.[3−13] Particularly germane to the present studies are the reports that MTO catalyzed the oxidation of primary and secondary amines to hydroxylamines, nitrosoalkyls, nitroalkyls, and nitrones.[14−17] The net reactions of the hydroxylamine, either as the starting material or prepared in situ from a secondary amine, are given in eq 1, along with the formula of the presumed intermediate that represents the result of the transfer of an oxygen atom so typical of MTO−hydrogen peroxide reactions. Hereinafter, we use one of the two generalized formulas for the hydroxylamines, as the other follows easily from it.

We were attracted to a study of the oxidation of secondary hydroxylamines to nitrones by their value as synthetic intermediates, which is important in medicinal and natural product chemistry.[18−24] Highly functionalized nitrogen heterocycles can

$$(RCH_2)_2NOH + H_2O_2 \xrightarrow{\text{cat. MTO}} \{(RCH_2)_2N(O)OH\} \xrightarrow{-H_2O} RCH_2N(O)=CHR \quad (1)$$

be synthesized from nitrones and olefins in 1,3-dipolar cycloaddition reactions.[25,26] Nitrones are also widely used as radical traps.[27−35]

Catalysts other than MTO have been used for the oxidation of amines or hydroxylamines to nitrones; SeO_2 catalyzes the reaction of hydrogen peroxide and amines to form nitrones, but the yields are not always high.[36] Tungstate is effective as a catalyst only for certain amines.[37,38] Imine oxidation also provides nitrones in stoichiometric reactions with permanganate, peroxy acids, and dimethyldioxirane.[39−41]

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Since much of the earlier work with MTO has focused on the preparative aspects,[14−17] we have chosen to explore the mechanism of the MTO system. There are two principal themes of reaction mechanism we have developed in this study, one pertaining to the oxidation step, the other to the dehydration of the first-formed intermediate, previously postulated, but without experimental proof.[36]

Experimental Section

Materials. Certain reagents were purchased: *N*,*N*-diethylhydroxylamine, *N*,*N*-dimethylhydroxylamine (as a 2 M solution in methanol), *N*,*N*-dibenzylhydroxylamine, several secondary amines, 30% hydrogen peroxide, and methylrhenium trioxide (Aldrich); HPLC grade organic solvents (Fisher); $CD_3(CH_3)NH$ (Cambridge Isotopes). *N*-Hydroxypiperidine, diisopropylamine, *N*-ethyl-*N*-isopropylhydroxylamine, and *N*-*tert*-butyl-*N*-benzylhydroxylamine were prepared according to the literature.[42]

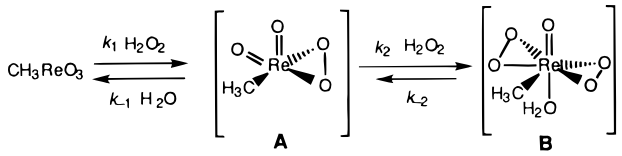
N-Benzyl-*N*-alkylhydroxylamines, with alkyl = Me, Et, and Pr^i, were synthesized by the following procedure based on MTO catalysis. The given amine was oxidized with hydrogen peroxide (1 equiv) and 4−8% MTO in 50 mL of methanol by adding the catalyst slowly until a yellow color persisted, signaling an MTO−amine complex and thus indicating that the hydrogen peroxide had entirely reacted. At that point 5 mL of saturated aqueous sodium carbonate was added. The resulting nitrogen compounds were a mixture owing to competing rates of oxidation of the amine and hydroxylamine; they were extracted with 3 × 20 mL of ether and concentrated by rotary evaporation to 3 mL. The hydroxylamine was then separated by column chromatography on silica gel, eluting usually with an ethyl acetate−hexane mixture. The pure hydroxylamine was collected in 20−30% yield; the yield undoubtedly could have been improved, but this procedure sufficed to prepare high-purity hydroxylamines for the kinetic studies.

Stock solutions of the hydroxylamine and MTO were made in methanol and used within 2 days. The 30% hydrogen peroxide was standardized iodometrically; it was stable for long periods; dilute solutions made from it by dilution in methanol were standardized every 3−4 h.

Kinetics. These experiments were carried out in methanol by spectrophotometry with Shimadzu 2501 and 3101 instruments, monitoring the product buildup of alkyl nitrones at 235 nm and aryl nitrones at 295 nm. The reactions were carried out in a quartz cuvette in air, since this reaction, like other MTO-catalyzed oxidations, showed no effect on changing from an atmosphere of argon to one of air or oxygen. Because the molar absorptivities of the nitrones are so large, ∼4 × 10^3 L mol^{-1} cm^{-1} (235 nm) and ∼1.2 × 10^4 L mol^{-1} cm^{-1} (290 nm), a cell of 0.02 cm was usually used to keep the absorbance change within a permissible range. Except for two special cases discussed later, the reactions reached a final stable absorbance. A typical procedure is the following: MTO and hydrogen peroxide were mixed in the reaction cell and allowed to stand for 4−5 min until the catalytically active peroxorhenium compounds had formed. The hydroxylamine was then added, the solution thoroughly mixed (∼20 s), and the data acquisition started. In addition to these experiments, some measurements were made at 360 nm, where **B** [$CH_3Re(O)(\eta^2\text{-}O_2)_2(OH_2)$] has a unique absorption band ($\epsilon \sim 1.2 \times 10^3$ L mol^{-1} cm^{-1}). These measurements allowed us to follow the concentration of one of the active forms of the catalyst with time.

We anticipated that a problem might arise from the pH of the medium. If the medium were too acidic, protonation of the hydroxylamine would reduce its concentration by some amount and lower the rate as a consequence. If it were too basic, catalyst decomposition would set in by several pathways, prominent among them under these conditions being the reaction between MTO and HO_2^-.[43] Experiments with *N*,*N*-diethylhydroxylamine gave the same rate constant in methanol as when buffered by an acetic acid−sodium acetate (1.8:1) solution added at ca. 20 times the concentration of the hydroxylamine, showing that the buffer was not needed.

Scheme 1



Kinetic Data. The absorbance−time curves were analyzed by either or both of two methods. Certain sets of kinetic data followed first-order kinetics, and the rate constant was determined by a nonlinear least-squares fit to eq 2 More frequently, the initial rate method was

$$\mathrm{Abs}_t = \mathrm{Abs}_\infty + (\mathrm{Abs}_0 - \mathrm{Abs}_\infty)\mathrm{e}^{-kt} \qquad (2)$$

used, since the distribution of the catalyst among the forms MTO, **A** [$=CH_3Re(O)_2(\eta^2\text{-}O_2)$], and **B** did not remain completely constant during the course of the experiment; further discussion of this point will be given later. The concentration of the product was calculated from the absorbance at each time, with hundreds or thousands of values collected in each data file (eq 3). The concentration−time data were then fitted

$$[\mathrm{nitrone}]_t = C_t = [(\mathrm{RCH_2})_2\mathrm{NOH}]_0\frac{\mathrm{Abs}_0 - \mathrm{Abs}_t}{\mathrm{Abs}_0 - \mathrm{Abs}_\infty} \qquad (3)$$

to a power series, $C_t = m_0 + m_1 t + ... + m_n t^n$, with the program KaleidaGraph. The initial rate, $(\mathrm{d}C/\mathrm{d}t)_{t=0}$ or v_i, is the value of m_1.[44,45] This procedure is particularly useful when the catalyst species change in proportion to one another during the course of the run, but it is somewhat less accurate than the method based on the integrated rate equation.

Reaction Products. The nitrones were identified by their ^{1}H-NMR spectra in CD_3OD. Many of these products have been reported previously,[16,17,36−41] and for some, NMR data were reported in $CDCl_3$. The chemical shifts are collected in Table S-1 of the Supporting Information.

Hydroxylamines with inequivalent R groups produce two nitrones. Their ratio was determined by integrating the NMR signals (cf. tabulated specta in the Supporting Information); triplicate determinations on independent samples were made.

Results

MTO Speciation during the Catalytic Cycles. We refer first to the two reactions with hydrogen peroxide, shown in Scheme 1. On their own, MTO, **A**, and **B** will attain *equilibrium* concentrations governed by the values of K_1 and K_2, the equilibrium constants for reactions in that scheme, and the peroxide concentration. The same is not true during a catalytic reaction cycle during which steady-state conditions apply. To illustrate this phenomenon, the absorbance was recorded at 360 nm over the time in which dibenzylhydroxylamine was being converted to the nitrone. At this wavelength, **B** is the only absorbing species; the starting material, product, MTO, and **A** do not contribute to the light absorption. As shown in Figure 1, [**B**] fell to some 80% of its starting value (i.e., from the equilibrium value, MTO and hydrogen peroxide having been allowed to equilibrate before the hydroxylamine was added) and then rose. Then, after nitrone formation was complete, [**B**] rose to the same concentration it had at the start. The reason is simple enough: the steady-state concentration of **B** and of the other rhenium species are governed not only by the rate

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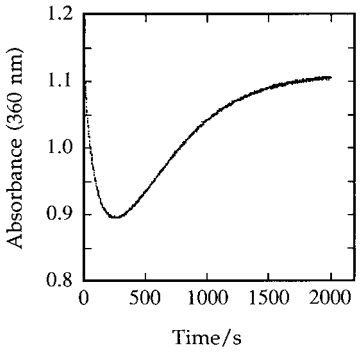


Figure 1. A recording of the concentration of **B**, the catalytically-active methylrhenium diperoxide, during the course of the oxidation of dibenzylhydroxylamine. The concentration of **B**, the only species in the solution that absorbs at 360 nm, drops to ca. 80% of its initial value during the reaction and is fully restored at the end. Concentrations: 0.98 mM $(PhCH_2)_2NOH$, 200 mM H_2O_2, 0.87 mM MTO.

constants in Scheme 1 but also by the rate constant for the reaction of each peroxorhenium compound with the hydroxylamine. Analysis of the full time course of the kinetics by following the buildup of the nitrone would thus be quite complex, since the proportions of **A** and **B** did not remain constant. This problem was circumvented by the use of initial rates in experiments in which such conditions prevailed.

Reaction Kinetics. It was necessary to show that the two methods for the analysis of kinetic data were equivalent. Experiments carried out on Et_2NOH were analyzed by both methods. Assume that the reaction under the conditions chosen (high $[H_2O_2] = 0.2-0.3$ M) is dominated by a reaction between **B** and Et_2NOH, eq 4, expressed by the rate law, eq 5, written in terms of initial rates in which $[\mathbf{B}] \cong [Re]_T = [MTO] + [\mathbf{A}] + [\mathbf{B}]$ and k_4 represents the bimolecular rate constant for the indicated reaction. Experiments were then carried out over a

$$\mathbf{B} + (RCH_2)_2NOH \xrightarrow{k_4} \mathbf{A} + (RCH_2)_2N(O)OH \qquad (4)$$

$$v_i = k_4[\mathbf{B}][R_2NOH]_0 \cong k_4[Re]_T[R_2NOH]_0 \qquad (5)$$

range of MTO concentrations, 0.07−0.52 mM. In each case v_i was evaluated by polynomial fitting. The values of v_i were then correlated with the concentrations of **B** and hydroxylamine. We show the result as a plot of v_i against the product of these concentrations (in this set of experiments, one of the concentrations is constant, however). According to eq 5 the values of v_i should define a straight line that passes through the origin. The data are shown in Figure 2. The least-squares slope of the line gives $k_4 = 52 \pm 1$ L mol^{-1} s^{-1} (25 °C in methanol).

The method of pseudo-first-order kinetics was then applied to the same data. The rate constant so evaluated, designated k_ψ, should be directly proportional to $[Re]_T$ given this rate law. To allow a presentation of the results of this method alongside those of the other, the product $k_\psi[Et_2NOH]_0$ is displayed on the *y*-axis, and the same concentration product on the *x*-axis. As shown in Figure 2, the plots are coincident within the experimental error. The first-order kinetic treatment gives $k_4 = 51 \pm 2$ L mol^{-1} s^{-1}. These findings taken together validate both methods of data treatment and the rate law given in eq 5.

Why are the values of k_4 so close, when it was shown (Figure 1 and accompanying discussion) for a related reaction that [**B**] changed over the course of the reaction? Two reasons can be cited: first, the decrease in $[\mathbf{B}]_{ss}$ is governed here by $k_4 = 52$ L mol^{-1} s^{-1}, different from that for the dibenzylhydroxylamine, Figure 1, with $k_4 = 3.33$ L mol^{-1} s^{-1}. More importantly, the convergence of the two methods reflects the averaging of the

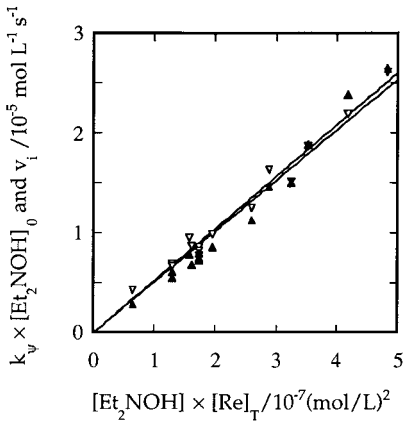


Figure 2. A comparison of two methods (initial rates, filled symbols, and pseudo-first-order kinetics, open symbols) for the evaluation of the kinetic data for the reaction of Et_2NOH (0.928 mM) and H_2O_2 (0.20−0.30 M) catalyzed by MTO (0.07−0.52 mM). The solutions also contained HOAc (12.1 mM) and NaOAc (8.3 mM).

Table 1. Rate Constants for the Catalytic Oxygenation of Hydroxylamines in Methanol at 25.0 °C

entry	hydroxylamine	k_4/L mol^{-1} s^{-1}	% yield of nitrone[a]
1	*N*,*N*-dimethyl	150 ± 6	85
2	1-hydroxypiperidine	64 ± 1	99
3	d_{10}-1-hydroxypiperidine	63 ± 2	99
4	*N*,*N*-diethyl	52 ± 1	97
5	*N*-ethyl-*N*-isopropyl	35.4 ± 0.6[b]	98
6	*N*-benzyl-*N*-methyl	26 ± 4	55[c]
7	*N*-benzyl-*N*-ethyl	15.8 ± 0.3	95
8	*N*,*N*-diisopropyl	13.8 ± 0.6	94
9	*N*-benzyl-*N*-isopropyl	7.0 ± 0.2	98
10	*N*,*N*-dibenzyl	3.33 ± 0.05	99
11	*N*-benzyl-*N*-*tert*-butyl	0.94 ± 0.05	99

[a] Based on NMR peak integrations. [b] Determined from fit to first-order kinetics. [c] The low yield is a consequence of subsequent nitrone decomposition (see text).

contributions from both peroxorhenium complexes. This reaction is given in eq 6. In general, as has been found for many

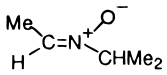
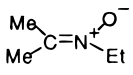
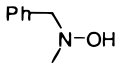
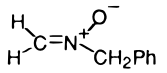
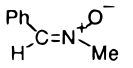
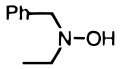
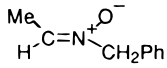
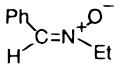
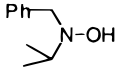
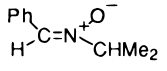
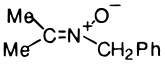
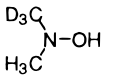
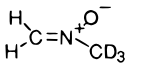
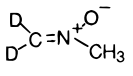
$$\mathbf{A} + (RCH_2)_2NOH \xrightarrow{k_3} MTO + (RCH_2)_2N(O)OH \qquad (6)$$

types of substrates, k_3 is about the same as k_4, or a factor of 2−3 larger at most. As such, a change in the proportions of **A** and **B** during the course of the reaction, which is exemplified in Figure 1, will not have a large effect on the kinetic analysis.

Nonetheless, we made it our practice to use preferentially the method of initial rates. The rate constants calculated on that basis for the 11 dialkylhydroxylamines are given in Table 1. An example of a product buildup curve is given in Figure 3, which depicts the rise in nitrone concentration from the reaction of *N*-ethyl-*N*-isopropylhydroxylamine.

In those instances where two nitrones were formed, entries 6−7, 9, and 11, the kinetic data were acquired at a wavelength at which only one of the nitrones absorbs. This is critical for the initial rate method. In fact, this work illustrates an important but subtle distinction between a rate and a rate constant. The value of k_ψ represents the rate constant for forming all the products, in this case the single rate constant leading to the intermediate, irrespective of its partitioning to products and of the relative contributions to the absorbance. On the other hand, the initial rate from the buildup of one nitrone represents just the rate constant leading to that product. The actual value of k_4 requires division of v_i by $[RR'NOH]_0[Re]_T$ *and by F*, the fraction formed of the particular nitrone being monitored. For these cases, the k_4 values summarized in Table 2 were calculated

Table 2. Ratio of Nitrone Products from Asymmetric Hydroxylamines

Entry	Hydroxylamine	Major Nitrone	Minor Nitrone	Ratio = k_{5a}/k_{5b}	Normalized ratio[a]
5				6.0	3.0
6				~1.1	~0.7[b]
7				1.6	1.6
9				4.4	2.2
12				2.9	2.9

[a] Normalized on the basis of the number of available protons. [b] This number is imprecise since *N*-benzylmethyleneamine *N*-oxide decomposes under these conditions.

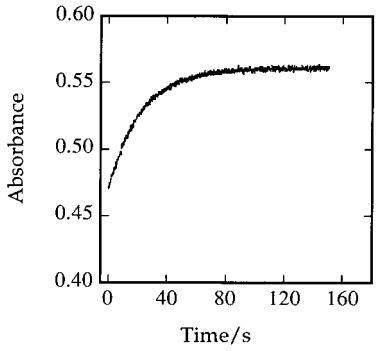


Figure 3. The increase in absorbance at 230 nm accompanying the buildup of the nitrone from the reaction of *N*-ethyl-*N*-isopropylhydroxylamine and hydrogen peroxide in methanol at 25 °C. Concentrations were 0.20 M H_2O_2, 2.03 mM R_2NOH, and 1.32 mM MTO. The reaction kinetics as shown occur in a single stage; the later partitioning to two nitrones takes place quite rapidly (see text).

by this procedure. Entry 5 in that table constitutes the single exception: the absorption bands of the two nitrones were not distinct, and thus the pseudo-first-order kinetic treatment was needed.

Products. The nitrones from all of the reactions were identified by their NMR spectra. These spectra agree with the structure and with literature values, where known. This information is given in Table S-2, in the Supporting Information. The chemical shifts are consistent with the structures given. The data presented in Table 2 shows that, in all reactions save two, the yield of nitrone (or nitrone pair, considering the asymmetric hydroxylamines) is quantitative. The nitrone from the oxidation of dimethylhydroxylamine was formed in an 85% yield, based on an in-situ NMR determination. By a similar method, *N*-benzyl-*N*-methylhydroxylamine gave but 55% nitrone. This nitrone, *N*-methylene-*N*-benzylamine *N*-oxide, is subject to the hydrolysis reaction shown in eq 7. The resulting *N*-benzylhydroxylamine is subject to further MTO-catalyzed oxidation to the oxime.[14]

Partitioning to the Products. Unsymmetric hydroxylamines give rise to a pair of nitrones, since the subsequent elimination reaction can involve the hydrogen on either of the α-carbon atoms. Scheme 2 presents this situation more fully. The ratio of the two nitrones determined by ^{1}H-NMR affords the ratio of the rate constants k_{5a}/k_{5b}, which are clearly (because of the concentration dependences that enter the kinetic expression) fast steps following the rate-controlling step.

$$\mathrm{PhCH_2N(O){=}CH_2} \xrightarrow{\mathrm{H_2O}} \mathrm{HCHO + PhCH_2NHOH} \xrightarrow{\mathrm{MTO}} \mathrm{PhCH{=}NOH} \quad (7)$$

For the kinetics analysis, the initial rate of formation of product **a** is given by eq 8, which provides the basis for the evaluation of k_4 in these cases, as described in the preceding section.

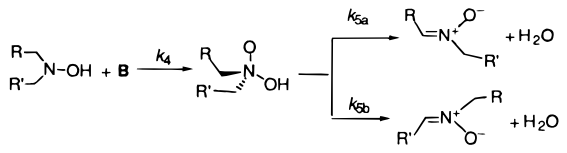
$$(v_i)_{\mathbf{a}} = \frac{k_4[\mathrm{RR'NOH}][\mathrm{Re}]_T}{1 + \dfrac{k_{5b}}{k_{5a}}} \quad (8)$$

Kinetic Isotope Effects. The rate constants for *N*-hydroxypiperidine and its d_{10} derivative are the same; compare entries 2 and 3 in Table 2. This is as to be expected, given the mechanistic implications of eqs 1 and 4: the first step is an oxygenation process, and the C−H bonds on the α-carbons are not involved. On the other hand, there is every reason to anticipate that the second step of the reaction, nitrone formation, will exhibit a significant kinetic isotope effect, given the representation in Scheme 2. The kinetic isotope effect will not show up in the kinetics. Thus we prepared $(CH_3)(CD_3)NOH$ in situ by the MTO-catalzyed oxidation of the commercially-available amine. The ratio of the resulting nitrones could be determined quantitatively from the ^{1}H-NMR spectra, allowing a resolution of the kinetic isotope effect. The value k_H/k_D (the ratio of k_5 values for elimination from a C−H bond relative to a C−D bond) was found to be 2.9 (Table 2, Entry 12).

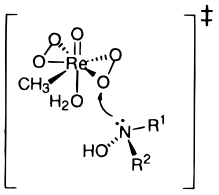
Discussion

Oxidation Mechanism. Given the many parallels in the kinetic data between the present set of data and the oxidation of other substrates in MTO-catalyzed reactions of hydrogen

Scheme 2



peroxide, the data suggest that the k_4 step (reaction 4) is rate-controlling. The mechanism of this reaction is then nucleophilic attack of the nitrogen lone pair on one of the four peroxo oxygens of **B**. The peroxide groups have been electrophilically activated by coordination to the electropositive +7 rhenium center. We also note that the rate constants for 1-hydroxypiperidine and its d_{10} derivative are the same, indicating that there is no involvement of a proton on the α-carbon in the transition state. This is a telling point, in that nitrone formation ultimately requires its elimination. The transition state for a nucleophilic process can be depicted like this:



The kinetic trends within the simplest of the series R_2NOH must be considered. The rate constants for $R^1 = R^2 =$ Me, Et, Pr^i, and c-C_5H_{10} are 150, 52, 14, and 62 L mol^{-1} s^{-1}, respectively. One wonders at the virtual absence of a parallel effect in the case of a seemingly analogous series of R_2S compounds, the rate constants for which are 2.0×10^4 (R = Et), 1.6×10^4 (R = Pr^i), and 2.0×10^4 (R = C_5H_{10}) L mol^{-1} s^{-1}.[12] It appears that the trend for the hydroxylamines represents a steric effect. It is not a large trend, the values of $\Delta G^{\ddagger}$ at the extremes differing by only 14 kJ mol^{-1} along the series. Steric effects would, of course, be expected more for trivalent nitrogen than for divalent sulfur. We further note that steric effects have been observed for the oxidation of phosphines; to cite but one example, note the difference between (p-$MeC_6H_4)_3P$ and (o-$MeC_6H_4)_3P$, with rate constants of 9×10^5 and 1.9×10^5 L mol^{-1} s^{-1}.[8] Under the conditions adopted for the kinetic experiments the peroxorhenium compound **B** is dominant, with **A** playing a minor role. Nonetheless, we would anticipate a parallel transition state for it which would be more important at lower peroxide concentrations.

The Hydroxylamine *N*-Oxide. The immediate product of the oxygen transfer reaction is an intermediate dialkylhydroxylamine *N*-oxide that has not been directly observed. This species is postulated here on grounds of the operative O-transfer mechanism, and thus the material that can reasonably be obtained from the reaction which **B**. This intermediate, moreover, can yield the nitrone product by a precedented elimination step. Since the product-forming step is much more rapid than the initial reaction, it does not contribute directly to the rate equation. The nitrone-forming step is shown in Scheme 2. The hydroxylamine *N*-oxide intermediate was previously postulated in the oxidation of secondary amines with hydrogen peroxide catalyzed by selenium dioxide[36] and tungstates.[38] In neither case, however, was it identified or detected during the reaction.

The Elimination Reaction. In light of data from the literature[17] that give a different yield of these products, we examined further the values for entry 6. As noted, the ^{1}H-NMR data gave one nitrone, $CH_3N(O)$═CHPh, in a yield of 48 ± 7%. By difference, the second nitrone, $PhCH_2N(O)$═CH_2, was formed in 52% yield. This is the ratio reported in Table 2. Further checking was required, however, in that the literature reported an isolated yield of 70% $CH_3N(O)$═CHPh from the MTO-catalyzed reaction of the parent amine with urea−hydrogen peroxide (UHP) at 0 °C. We obtained an NMR yield of ∼40%, the balance being the other nitrone. A repeat determination by UV−vis using hydrogen peroxide gave the yield as 50 ± 10%.

Because nitrone formation makes no direct kinetic contribution, this step must be explored by indirect means. Kinetic isotope effects have afforded a way of examining this mechanism. The reactions of the 1-hydroxypiperidine derivatives (h_{10} and d_{10}) do not speak to this point; each reacts independently (and, as it turns out, at the same rate). A suitable compound was found in $(CH_3)(CD_3)NH$. Two nitrones were easily detected and determined by their ^{1}H-NMR spectra. The rate constant ratio is $k_H/k_D = 2.9$, for cleavage of a C−H bond relative to a C−D bond.

Different compounds provided other means of exploring the elimination reaction. The data in Table 2 show the relative rates of formation of the pairs of nitrones that result from the sequence of oxidation and elimination processes. Since oxidation is not the determinant of the product ratio, the relative rates of elimination can be determined. Moreover, it may be useful to compare the relative rates after normalization per α-hydrogen, to correct for statistical effects. This, too, is given in Table 2.

For an E2 elimination mechanism,[46] the more conjugated and substituted product is favored. These factors are manifest in the values recorded, in Table 2, although for entry 9 the two factors are in opposition. The effects do appear to be systematic in that a relation such as eq 9 holds among *different* compounds.

$$\frac{k_{Et}}{k_{Bn}}\frac{k_{Bn}}{k_{Pr}} \approx \frac{k_{Et}}{k_{Pr}} \qquad (9)$$

For example, k_{Bn} in this interpretation can be transferred from one compound to the next. The relative rate for elimination from a given R group appears to be transferable from one compound to another, supporting a common mechanism.

The gist of the elimination mechanism is that a conjugate base attacks the CH proton at almost the same time the conjugate acid attacks the OH group. The kinetic isotope effect establishes that C−H bond breaking is well advanced in the transition state. The conjugate base and acid are most likely H_2O and H_3O^+, although this point remains uncertain.

Acknowledgment. This research was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Chemical Sciences, under Contract W-7405-Eng-82.

Supporting Information Available: ^{1}H-NMR data for the starting materials and products (3 pages). Ordering information is given on any current masthead page.

IC970649D

(46) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 1167.