Fast Oxidation of Organic Sulfides by Hydrogen Peroxide by In Situ Generated Peroxynitrous Acid**

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Dedicated to Professor Bernt Krebs
on the occasion of his 60th birthday

The oxidation of organic sulfides RSR′ by hydrogen peroxide to form sulfoxides and, in a consecutive slower step, sulfones is a well established procedure.[1] The rate of such oxidations can be enhanced by the use of organic peroxides or peroxy acids instead of H_2O_2 and, catalytically, by the activation of H_2O_2 through coordination to metal centers.[1] The reaction of H_2O_2 with nitrous acid at low pH leads to peroxynitrous acid ONOOH,[2] an isomer of nitric acid which is a much more powerful oxidant than H_2O_2.[3] The use of ONOOH for the oxidation of organic substrates is limited by the fact, however, that this peroxy acid is an unstable species that isomerizes at ambient temperature with a half-life of about 1 s to form nitric acid. Since ONOOH is also generated by the reaction of superoxide with NO, its role in biological systems is currently of great interest.[4]

The peroxynitrite anion $ONOO^-$ is considerably more stable than the acid ONOOH. As a result, most of the studies with the oxidant peroxynitrous acid have been carried out in such a way that, after the fast generation of ONOOH from H_2O_2 and HNO_2 at low pH,[2] the decay of ONOOH was blocked by the addition of alkali. The cooled, stable alkaline peroxynitrite solutions thus prepared were taken as stock material.[5] The approach presented here is basically different in that the short-lived oxidant ONOOH is generated in situ as a very reactive intermediate according to Equation (1). This

$$HNO_2 + HOOH \xrightarrow{k_f} ONOOH + H_2O \qquad (1)$$

$$ONOOH \xrightarrow{k_d} HNO_3 \qquad (2)$$

$$A + ONOOH \xrightarrow{k_A} A{=}O + HNO_2 \qquad (3)$$

reaction is a fast process. After its generation, ONOOH is used for the fast second-order oxidation of suitable organic substrates A [Eq. (3)]. The oxidation competes with the decay of ONOOH [Eq. (2)]. As a consequence, this approach is applicable only when the rate of reaction (3) is higher than that of (2), that is when $k_A[A]$ is much greater than k_d. One should note that reactions (1) and (3) form a catalytic cycle, in which the catalyst HNO_2 converts H_2O_2 into the more powerful oxidant ONOOH. The number of cycles is controlled by the competition between reactions (2) (decay of ONOOH) and (3) (oxidation of the substrate by ONOOH).

For solubility reasons, organic substrates require organic media. To our knowledge, the generation of ONOOH according to Equation (1) in organic media has not yet been investigated. The time dependence of the absorbance at 260 nm for the reaction of H_2O_2 with HNO_2 in acetonitrile [6] at 293 K is shown in Figure 1.[7] The fast formation of ONOOH with an experimental pseudo-first-order rate constant $k_f = 1.2 \pm 0.2\ s^{-1}$ is followed by its first-order decay to HNO_3 with $k_d = 0.61 \pm 0.05\ s^{-1}$. Under comparable conditions, the rate constant k_d for the reaction in water is $1.07 \pm 0.05\ s^{-1}$.[9] This means that acetonitrile (with an admixture of 5 M H_2O) is suitable for the generation of ONOOH according to Equation (1), and that the rate of decay of ONOOH in acetonitrile is close to that in water.

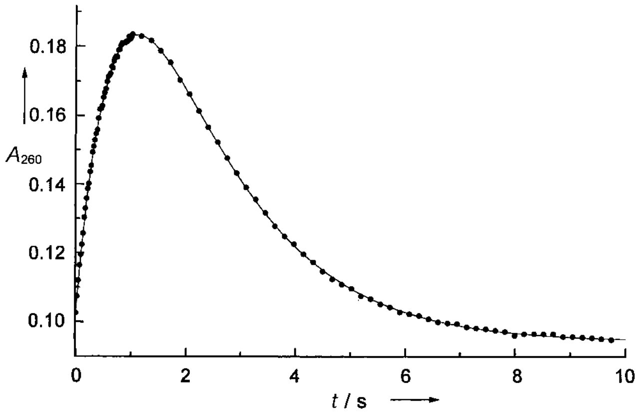

Figure 1. Time dependence of the absorbance at 260 nm for the reaction of H_2O_2 with nitrous acid in acetonitrile at 293 K ($[H_2O_2] = 5$ mM, $[NaNO_2] = 0.5$ mM, $[HClO_4] = 0.1$ M, I = 0.6 M ($NaClO_4$), $[H_2O] = 5$ M). The rate constants $k_f = 1.2\ s^{-1}$ and $k_d = 0.61\ s^{-1}$ for the formation and decay of peroxynitrous acid were obtained from the sum of two exponentials[7] (solid line).

We have tested the practical applicability of in situ generated peroxynitrous acid as an oxygen-transfer agent in acetonitrile for several classes of organic substrates under standardized conditions.[10] These conditions were such that there was a 2.5-fold excess of organic substrate relative to H_2O_2, and the reaction was monitored cerimetrically by the loss of H_2O_2. Houk et al.[11] reported recently the results of calculations suggesting that oxygen transfer from ONOOH to ethylene is energetically feasible. This led us to study the epoxidation of several olefins according to reaction sequence (1)–(3) at $[HNO_2]:[H_2O_2] = 1:4.4$. The result was negative in the sense that the consumption of H_2O_2 for substrate oxidation was zero for cyclohexene and allyl alcohol, and very minor for 2-methoxypropene, ethylvinyl ether, and 2,3-dimethyl-2-butene. Under the given conditions, the reaction of these olefins with ONOOH is apparently too slow to compete with the isomerization of ONOOH to HNO_3 [Eq. (2)]. It was not surprising to find that N-oxidation of amines such as pyridine and substituted pyridines was not to be observed. In the given acidic medium, protonation reduces the concentration of free amine to a minimum.

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Organic sulfides RSR′ turned out to be very suitable substrates for the fast sulfoxidation with in situ generated ONOOH [Eq. (4)]. As shown in Figure 2 for the system

$$\mathrm{RSR'} + \mathrm{ONOOH} \rightarrow \mathrm{RSOR'} + \mathrm{HNO_2} \qquad (4)$$

$PhSMe/H_2O_2/NaNO_2$, the sulfoxidation of PhSMe in the absence of nitrite is a rather slow process.[12] The addition of 15 mM of nitrite triggers an instantaneous, partial oxidation of PhSMe, as monitored by a sharp drop in the H_2O_2 concentration. The size of this instantaneous drop increases with the concentration of nitrite. For $[NaNO_2] = 30$ mM (which corresponds to $[H_2O_2]$: $[NaNO_2] = 6.7{:}1$), all of the H_2O_2 oxidant is consumed within one minute. This means that, in terms of catalysis, one molecule of HNO_2 passes almost seven cycles according to reactions (1) and (3), thus "activating" seven molecules of H_2O_2 by the formation of ONOOH. Owing to the greater reactivity of ONOOH relative to that of H_2O_2, the sulfoxidation of PhSMe is drastically accelerated.

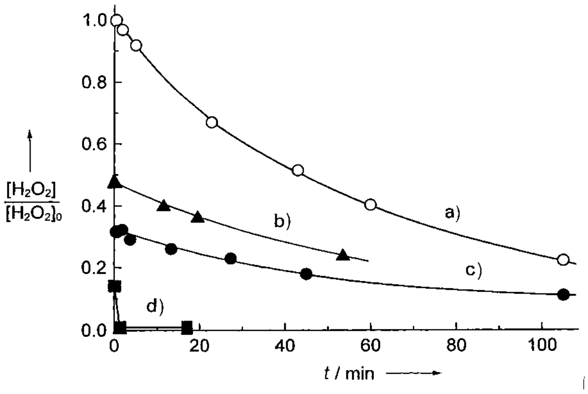

Figure 2. Time dependence of the concentration of H_2O_2 for the reaction of PhSMe with H_2O_2 in acidified acetonitrile at variable concentrations of HNO_2 under standard conditions[10] ($[H_2O_2] = \text{constant} = 0.2$ M; $[NaNO_2] = 0$ M (a), 0.015 M (b), 0.020 M (c), 0.030 M (d)).

The sulfoxidation of dimethyl sulfide according to Equations (1)–(3) is accelerated by nitrite in an analogous manner. The noncatalyzed oxidation in the absence of nitrite is faster by a factor of 19 than that of PhSMe. Correspondingly, a nitrite concentration of only 10 mM ($[H_2O_2]{:}[NaNO_2] = 20{:}1$) is sufficient to make the oxidation of Me_2S complete within one minute. These data mean that the catalyst HNO_2 cycles twenty times. As outlined above, the condition for a maximum number of cycles in the system Me_2S/H_2O_2 is given by $k_{Me_2S}[Me_2S] \gg k_d$.[14] The validity of this condition was tested by a series of experiments with variable concentrations of Me_2S and constant concentrations of H_2O_2 and $NaNO_2$. As shown in Figure 3, in the absence of Me_2S there is an initial loss of 10% of H_2O_2. This loss corresponds to the conversion of HNO_2 into ONOOH, which decays to HNO_3 with the rate constant k_d.[16] At $[Me_2S] = 5$ mM the oxidation of Me_2S by ONOOH begins to compete with the decay of ONOOH, an indication that the size of $k_{Me_2S}[Me_2S]$ is getting closer to that of k_d. This effect is more pronounced at $[Me_2S] = 10$ mM. Finally, at $[Me_2S] = 50$ mM the peroxynitrous acid formed reacts preferentially with Me_2S; the condition $k_{Me_2S}[Me_2S] \gg k_d$ is fulfilled and all of the H_2O_2 is consumed by substrate oxidation within one minute. These results allow the estimate[17] that k_{Me_2S} is greater than $10^2\,M^{-1}s^{-1}$. This means that, compared to the second-order rate constant k for the noncatalyzed Me_2S oxidation by H_2O_2 (Table 1), the reactivity of ONOOH is more than three orders of magnitude greater than that of H_2O_2.

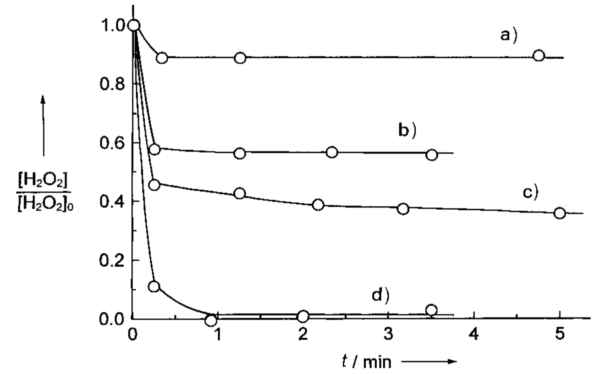

Figure 3. Time dependence of the concentration of H_2O_2 for the reaction of Me_2S with H_2O_2 in acidified acetonitrile at various concentrations of Me_2S at 20 °C ($[H_2O_2] = 0.005$ M, $[NaNO_2] = 0.0005$ M, $[H_2SO_4] = 0.08$ M, $[H_2O] = 5$ M; $[Me_2S] = 0$ M (a), 0.005 M (b), 0.010 M (c), 0.050 M (d)).

Table 1. Kinetic data for the sulfoxidation of organic sulfides by H_2O_2 in acidified acetonitrile in the absence and presence of nitrous acid.

Sulfide	$10^4 k$[a] [$M^{-1}s^{-1}$]	$([HNO_2]{:}[H_2O_2])_{lim}$[b] [mM]:[mM]	Catalytic cycles
PhSMe	31 ± 3	30:200	6.7
$(PhCH_2)_2S$	70 ± 6	20:200	10
Me_2S	580 ± 50	10:200	20

[a] Second-order rate constant k for the sulfoxidation at 293 K in the absence of the catalyst under standard conditions.[10] [b] Limiting concentration ratio at which (and above which) catalyzed sulfoxidation is complete within one minute under standard conditions.[10]

Product formation in the systems $PhSMe/H_2O_2/NaNO_2$ and $Me_2S/H_2O_2/NaNO_2$ was additionally controlled by GC analysis.[18] Under standard conditions ($[\text{substrate}] > [H_2O_2]$),[10] the sulfoxides $PhSOCH_3$ and CH_3SOCH_3 were the only products. Further oxidation to the corresponding sulfones is slower by several orders of magnitude than the sulfoxidation [Eq. (4)],[3] and is only observed when the substrate concentration is less than that of H_2O_2 and with long reaction times.

The sulfoxidation of dibenzyl sulfide was also studied in detail. It follows from the data summarized in Table 1 that, at $[H_2O_2]{:}[NaNO_2] = 10{:}1$, formation of dibenzyl sulfoxide is complete within one minute. $(PhCH_2)_2S$ was chosen as a model compound to test the synthetic potential of the method for the fast preparation of sulfoxides at the gram level. An aqueous solution of $NaNO_2$ was quickly added to an acidified, well-stirred acetonitrile solution of $(PhCH_2)_2S$ containing an excess of H_2O_2.[19] After a reaction time of only five minutes at ambient temperature, pure dibenzyl sulfoxide was isolated in a yield of 91%.

In conclusion, the present approach provides an experimentally simple and time-saving method for the fast and convenient preparation of sulfoxides. The method is based on nonexpensive, commercial chemicals (H_2O_2, $NaNO_2$, H_2SO_4, and CH_3CN) and can be classified as a sulfoxidation reaction with "activated" H_2O_2. The activation consists of the fast reaction of H_2O_2 with HNO_2 in acidified CH_3CN to form the unstable, yet highly reactive, oxidant peroxynitrous acid ONOOH as an intermediate species in situ. The experimental conditions can be easily set in such a way that the reaction of the electrophile ONOOH with the nucleophile RSR′ is fast enough to compete successfully with the decay of ONOOH to nitric acid. Under these optimized conditions, HNO_2 acts as a catalyst, quickly carrying oxygen atoms from H_2O_2 to the sulfide in the form of ONOOH.

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[1] S. Uemura in *Comprehensive Organic Synthesis*, *Vol. 7 (*Eds: B. M. Trost, I. Fleming, S. V. Ley), Pergamon, Oxford, **1991**, pp. 762–769.

[2] W. G. Keith, R. E. Powell, *J. Chem. Soc.* A **1969**, 90.

[3] P. Amels, H. Elias, K.-J. Wannowius, *J. Chem. Soc. Faraday Trans.* **1997**, *93*, 2537–2544.

[4] In vivo, the reaction of $O_2^{\cdot-}$ with NO leads to the anion $ONOO^-$, which is in equilibrium with the acid ONOOH. The reaction of superoxide with NO is faster than that with superoxide dismutase (SOD). For the biological relevance of ONOOH see, for example, W. A. Pryor, G. L. Squadrito, *Am. J. Physiol.* **1995**, *268*, L699–L722.

[5] See, for example, a) R. Radi, J. S. Beckman, K. S. Bush, B. A. Freeman, *J. Biol. Chem.* **1991**, *266*, 4244–4250; b) W. A. Pryor, X. Jin, G. L. Squadrito, *Proc. Natl. Acad. Sci. USA* **1994,** *91*, 11173–11177; c) A. Al-Ajlouni, E. S. Gould, *Inorg. Chem.* **1996**, *35*, 7892–7896; d) S. Goldstein, G. Czapski, *Inorg. Chem.* **1995**, *34*, 4041–4048.

[6] The use of commercial H_2O_2 as a reagent necessarily introduces some water into the system. The solvent acetonitrile with a constant admixture of water (5 M) was therefore taken as the standard reaction medium.

[7] The absorbance/time data shown in Figure 1 were obtained with a multi-wavelength stopped-flow spectrophotometer described earlier.[8] The absorptivity of ONOOH in the range 250–350 nm is greater than that of nitrous and nitric acid. The initial increase in absorbance *A* at 260 nm corresponds therefore to the formation of ONOOH, the consecutive decrease to its decay. The rate constants k_f and k_d were obtained from Equation (5) using the *A/t* data (a_1, a_2 = amplitudes).

$$A = a_1\exp(-k_f t) + a_2\exp(-k_d t) + A_\infty \qquad (5)$$

[8] C. Drexler, H. Elias, B. Fecher, K. J. Wannowius, *Fresenius J. Anal. Chem.* **1991**, *340*, 605–615.

[9] D. J. Benton, P. J. Moore, *J. Chem. Soc. A* **1970**, 3179–3182.

[10] Standard procedure and conditions: A solution of H_2O_2, H_2SO_4, and H_2O in CH_3CN (1 mL) was quickly mixed with a solution of the organic substrate A and $NaNO_2$ in CH_3CN (1 mL) to obtain the reaction mixture with $[H_2O_2] = 0.2\,M$, $[HNO_2] = 0–45\,mM$, $[A] = 0.5\,M$, $[H_2SO_4] = 0.08\,M$, and $[H_2O] = 5\,M$ (the pK_a of HNO_2 is 3.3; to liberate HNO_2 from $NaNO_2$, the condition $-lg[H^+] < 3$ has to be fulfilled). The mixture was stirred at ambient temperature. At adequate time intervals, samples (0.2 mL) were taken and diluted with water for the cerimetric determination of H_2O_2.

[11] K. N. Houk, K. R. Condroski, W. A. Pryor, *J. Am. Chem. Soc.* **1996**, *118*, 13002–13006.

[12] The value of $k = (31 \pm 3) \times 10^{-4}\,M^{-1}s^{-1}$ (see Table 1) was obtained by fitting of the $[H_2O_2]/t$ data shown in Figure 2 a to Equation 6. This

$$[H_2O_2] = [H_2O_2]_o\exp(-k[PhSMe]t) \qquad (6)$$

value is very close to $k = 37.3 \times 10^{-4}\,M^{-1}s^{-1}$ as reported for the sulfoxidation of PhSMe with H_2O_2 in EtOH (6% H_2O).[13]

[13] G. Modena, L. Maiola, *Gazz. Chim. Ital.* **1957**, *87*, 1306–1316.

[14] The reaction between Me_2S and ONOOH in water was recently shown to be second-order, first-order in both reactants.[3] The oxidation of organic sulfides by hydroperoxides is generally found to be a second-order process.[15]

[15] J. O. Edwards in *Peroxide Reaction Mechanisms* (Ed.: J. O. Edwards), Wiley-Interscience, New York, **1962**, pp. 67–106.

[16] It was confirmed by experiment that ONOOH, when generated according to Equation (1), does not decompose H_2O_2 according to the reaction $ONOOH + H_2O_2 \rightarrow HNO_2 + H_2O$.

[17] At the lowest Me_2S concentration, $[Me_2S] = 5\,mM$, almost half of the H_2O_2 is consumed for the fast Me_2S oxidation by ONOOH (see Figure 3). This means that the Me_2S concentration at which $k_{Me_2S}[Me_2S] = k_d$ is smaller than 5 mM and, hence, $k_{Me_2S} > 0.61/0.005 = 122\,M^{-1}s^{-1}$.

[18] GC analysis was carried out with an Auto System Gas Chromatograph with FI detector (Perkin-Elmer) and a 15-m capillary column (Alltech; Heliflex AT-1000) at 150 °C (Me_2S) and 170 °C (PhSMe). The samples were neutralized with NaOH before injection.

[19] Concentrated H_2SO_4 (1 mL, 98%) and technical grade, stabilized 35% H_2O_2 (4 mL, 47 mmol) were added to a well-stirred solution of $(PhCH_2)_2S$ (5.3 g, 25 mmol) in CH_3CN (250 mL) at ambient temperature. To start the fast catalyzed reaction, a solution of $NaNO_2$ (320 mg, 4.7 mmol) in water (2 mL) was added in one portion (**caution**: the reaction is exothermic! In the case of larger batches the reaction mixture should be efficiently thermostated). After a reaction time of five minutes the solution was set to pH 7 with a solution of NaOH (1 M) diluted with water (70 mL) and extracted with chloroform (3 × 130 mL). The chloroform phase was dried with $MgSO_4$ and taken to dryness in vacuo. The residue was recrystallized from EtOH. Yield: 5.1 g (91%). M.p. 133 °C (134–135 °C[20]). ^1H NMR and IR spectroscopy as well as C,H,N analysis proved the identity of the product as dibenzyl sulfoxide.

[20] *Handbook of Chemistry and Physics*, 51st ed., The Chemical Rubber Co. **1970–1971**.

Synthesis, Structure, and Reactivity of a Palladium Hydrazonato Complex: A New Type of Reductive Elimination Reaction To Form C–N Bonds and Catalytic Arylation of Benzophenone Hydrazone**

John F. Hartwig*

Reductive elimination reactions which form C–N bonds in amines[1–4] are important primary reactions in practical catalytic cycles for the synthesis of arylamines from aryl halides.[1, 5–8] Reductive elimination reactions that result in *N*-arylhydrazones would be an important new method for C–N bond formation by means of reductive elimination. The hydrazone products could be used in Fischer indole syntheses or, after conversion into the *N*-arylhydrazine, in condensation reactions to produce *N*-arylpyrazoles and *N*-arylpyrazolones.

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