1-Oxo-2,2,6,6-tetramethylpiperidinium bromide converts α-H \(N,N\)-dialkylhydroxylamines to nitrones via a two-electron oxidation mechanism

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Herein we provide experimental proof that 1-oxo-2,2,6,6-tetramethylpiperidinium bromide converts α-H \(N,N\)-dialkylhydroxylamines to nitrones via a two-electron oxidation mechanism. The reactions reported are rapid, proceed under mild conditions, and afford nitrones in excellent yields.

Nitroxides (aminoxyl radicals) have attracted considerable interest as catalysts in (bio)organic reactions1–5, electron paramagnetic resonance (EPR) probes6,7, and drugs that mitigate oxidative injury8–10. The stability of most nitroxides containing tertiary α- and α′- carbon atoms relative to their >N-O• group is sufficiently high to allow their isolation as pure compounds (Fig. 1, 2-2,2,6,6-tetramethylpiperidine 1-oxyl; TEMPO). In solutions, however, 2 readily undergoes redox interconversion to oxoammonium cation (1) and hydroxylamine (3).

Halides of 1 can be synthesized by oxidation of 2 with I2, Br2 and Cl2 (1 + \(\frac{1}{2}\)X2 \(\rightarrow\) 1.X) or by acid-catalyzed disproportionation of 2 (HCl + 2 \(\rightarrow\) Cl– + 3)11–14, while in biological systems reduction of oxygen-centered radicals by 2 affords 1,3,4. Oxoammonium salts are versatile oxidants that interconvert a number of functional groups. Their reactivity is illustrated by the conversion of primary and secondary alcohols to aldehydes and ketones, respectively, enolizable ketones to diketones, and \(N,N\)-dialkylamines to alkylamines 2,14–20. Most reactions of 1 proceed with formation of 2 and/or 3 as end-reaction products, thus allowing their performance under catalytic conditions where a terminal oxidant shifts the equilibria between 1, 2, and 3 in favor of 121.

While it has been shown that in neutral solutions 1 oxidizes hydroxylamine 3 to nitroxide 2 via electron transfer22,23, reactions of 1 with \(N,N\)-dialkylhydroxylamines containing an α-H atom have not been studied thus far. One-electron oxidation of α-H \(N,N\)-dialkylhydroxylamines yields nitroxides which exhibit half-lives ranging from seconds to hours. The low stability of these radicals has been associated with their disproportionation to the parent hydroxylamines and nitrones (Fig. 2)24–26, and, competitively, to N-C bond cleavage27–29. Herein, we report that 1 readily converts a series of α-H \(N,N\)-dialkylhydroxylamines to nitrones via a two-electron oxidation mechanism.

Results and Discussion

EPR and HPLC-UV analysis of the oxidation of \(N,N\)-dialkylhydroxylamines by 1.Br. The EPR spectra presented in Fig. 3A show the oxidation of hydroxylamine 3 (150 \(\mu\)M) by 1. In CH3CN containing either \(\text{I2} \text{ or 1.Br (50 \(\mu\)M), we did not observe well resolved EPR spectra (traces 1 and 2). Addition of 1.Br (Fig. 3A3; blue and black tracing, 25 \(\mu\)M and 50 \(\mu\)M, respectively) to a solution of 3 led to the formation of 2, as assessed by the appearance of the typical 3-line EPR spectrum of this nitroxide (\(a_0 = 1.715\text{ mT}\)). Following one-electron oxidation, in this reaction one molecule of 1 reacted with 3 to generate two molecules of nitroxide 2 (red tracing, 100 \(\mu\)M standard solution of 2). Under these experimental conditions, the oxidation of 3 was too fast to record its kinetic
profile by conventional EPR spectrometry. Similarly, the oxidation of the α-H hydroxylamines 4a–c (100 μM) by 1.Br (25 μM) proceeded with concomitant formation of nitroxide 2 (Fig. 3B, blue, red and black spectrum, respectively). As suggested by the constant magnitude of these spectra, each reaction was completed in less than 30 seconds, which is the approximate time required for sample preparation and data acquisition.

HPLC analysis of the reaction solutions revealed that the oxidation of 4a–c by 1 also led to formation of nitrones 6a–c (Fig. 3C; Supplementary Information; SI). The requirement for a slight stoichiometric excess of
the oxoammonium salt for complete oxidation of 4a–c most likely reflected the competition between 4a–c as reactants and the end-reaction product 3 for 1. In support of this assumption, the oxidation of hydroxylamine 4b (100 μM) by 1 (125 μM) to nitrone 6b (98 μM; Fig. 3C) was paralleled by formation of both nitroxide 2 (14 μM; Fig. 3D, blue tracing) and hydroxylamine 3 (79 μM; Fig. 3D, black tracing). Quantification of 3 was performed after its oxidation to 2 in alkaline milieu (N-O− + O2 → N-O● + O2●− 25; red tracing, 100 μM standard solution of 2). In the absence of oxoammonium salt, hydroxylamine 4b did not oxidize to nitrone 6b (Fig. 3C, open rectangles).

Similar distribution of the products was observed when reactions were carried out with 4a–c in CH3OH, C2H5OH, CH3CN, and CH2Cl2 with the notion that the oxoammonium cation 1 does not react with CH3CN and CH2Cl2 to any significant extent but does oxidize primary alcohols to aldehydes. Hence, in ethanol, the complete oxidation of hydroxylamine 4c to nitrone 6c required larger excess of 1 (Fig. 3C, filled rectangles). Ethanol, however, did not prevent the formation of 6c, which suggests that the formation of nitrones would be the preponderant process in polyfunctional compounds containing both OH and NOH groups. The stoichiometry of the reactions further suggests that nitrones were not formed via the intermediate formation and disproportionation of α-H nitroxides as completion of the latter process would require 2 molar equivalents of 1 for the oxidation of the hydroxylamines (Fig. 2). This conclusion was further supported by kinetic analyses of the decay of nitroxides 5b,c.

In Fig. 4A1 is shown the EPR spectrum of water containing ethanol (25%), ethylenediaminetetraacetic acid (EDTA; 100 μM), and hydroxylamine 4c (200 μM). Addition of NaOH (0.5 M) led to the appearance of the EPR spectrum of nitroxide 5c (in mT, aH = 1.0318; aN = 1.7607), which reflected the oxidation of the aminoxy anion of 4c by oxygen25 (Fig. 4A2; spectrum 3, computer simulation of the EPR spectrum of 5c). We then acidified the reaction solution to pH 6.0 with acetic acid and recorded both the decreases in the EPR spectrum of 5c (Figs 2B and 4A2, open circles; the spin concentration of 5c was determined by double integration of the EPR signals using authentic 2 as a standard) and the formation of nitrone 6c (as assessed by HPLC; Fig. 4B, filled circles). In agreement with Fig. 2, two molecules of 5c were consumed for each molecule of 6c formed in the reaction. Importantly, the half-life of 5c (t1/2 ~ 60 minutes) largely exceeded the time required for oxidation of 4c by 1, thus excluding

Figure 4. EPR analysis of the decay of nitroxide 5c and HPLC-monitored formation of nitrone 6c. A1- EPR spectrum of 4c (200 μM). A2- 4c plus NaOH (0.5 M). After incubation for 4 min, the reaction solution was titrated with acetic acid to pH 6.0 and consecutive EPR spectra were recorded with time intervals of 12 min. Arrows indicate the directions of the spectral changes. A3- computer simulation of the EPR spectrum of nitroxide 5c (simulation parameters: aH = 1.03 mT; aN = 1.76 mT; number of equivalent protons, 2). B- EPR (open circles)- and HPLC (filled circle)-monitored changes in the concentrations of nitroxide 5c and nitrone 6c. The data are presented as mean values of three independent experiments ± the standard error.
the generation and disproportionation of nitroxide 5c as a reaction mechanism responsible for the formation of nitrone 6c.

We further carried out experiments to verify whether nitroxide 5b is formed during the oxidation of hydroxylamine 4b by 1.Br. Reactions were carried out at room temperature in 25% methanol. Spectrum 1- 4b (200 μM) plus NaOH (0.5 M). Spectrum 2- Computer simulation of the EPR spectrum of nitroxide 5b (simulation parameters: \(a_H = 1.11 \text{ mT}; a_N = 1.76 \text{ mT}; \) number of equivalent protons, 4). Traces 3- Overlapped spectra of 5a (1 mM) plus 1.Br (1 mM; red tracing) and 5a (200 μM) plus NaOH (0.5 M; blue tracing).

Figure 5. EPR analysis of the oxidation of hydroxylamine 4b by 1.Br. Reactions were carried out at room temperature in 25% methanol. Spectrum 1- 4b (200 μM) plus NaOH (0.5 M). Spectrum 2- Computer simulation of the EPR spectrum of nitroxide 5b (simulation parameters: \(a_H = 1.11 \text{ mT}; a_N = 1.76 \text{ mT}; \) number of equivalent protons, 4). Traces 3- Overlapped spectra of 5a (1 mM) plus 1.Br (1 mM; red tracing) and 5a (200 μM) plus NaOH (0.5 M; blue tracing).

Figure 6. EPR (A)- and HPLC (B)-monitored oxidation of 4b by 2 to nitroxide 5b (A) and nitrone 6b (B). Reactions were carried out at room temperature in 25% methanol. A1- 4b (1 mM). A2, blue tracing- 2 (1 mM). A2, red tracing- 4b + 2; the first two lines in the EPR spectrum of 5b are denoted with red arrows. B- Formation of nitrone 6b in a solution of hydroxylamine 4b (1 mM) in the absence (open circles) and the presence (filled circles) of nitroxide 2 (1 mM). HPLC separations were performed as indicated in SI. The data are presented as mean values of three independent experiments ± the standard error.

We further carried out experiments to verify whether nitroxide 5b is formed during the oxidation of hydroxylamine 4b by 1, with the expectation that the large difference in the hyperfine splitting constants of 2 and 5b will allow their simultaneous EPR detection in the reaction milieu. In Fig. 5.1 is shown the EPR spectrum of 5b generated in an alkaline solution of 4b (in mT, \(a_H = 1.097; a_N = 1.761; \) spectrum 3, computer simulation of the EPR spectrum of 5b). In agreement with the data reported in ref.25, alkalinization of the solution of 4b led to the appearance of the EPR spectrum of 5b, which increased for ~1 min and then remained constant for ~30 min. Acidification of the reaction solution to pH 6.0 and following kinetic analysis of the decay 5b established that the half-life of this radical is ~4 min (data not shown), which provides ample time for its EPR analysis. In Fig. 5.3 is presented the EPR spectrum of a reaction solution consisting of hydroxylamine 4b (1 mM) and 1.Br (1 mM), which contains as a major component the three spectral lines of 2 (red tracing). By comparing the latter spectrum with that of 5b as a standard (4.9 μM; blue tracing), we observed that 5b was present in the reaction solution at a submicromolar concentration, or less than 0.1% of the expected (~0.8 mM) for one-electron oxidation of 4b; in Fig. 5.3, the first two spectral lines of 5b are denoted with arrows.
The data presented in Fig. 6A indicate that the trace amounts of nitroxide 5b were formed via a secondary reaction in which the end reaction product 2 oxidized the parent hydroxylamine 4b (Fig. 6A; 4b + 2 → 5b + 3); the EPR spectrum of 5b (~1 μM) could be observed upon addition of nitroxide 2 (1 mM) to a solution of hydroxylamine 4b (1 mM; Fig. 6A, red tracing). Incubation of this reaction solution led to a slow formation of nitrone 6b (Fig. 6B; yield of nitrone for 1 hour, 3%), presumably via disproportionation of 5b. While under these experimental conditions reaction 4b + 1 → 6b was completed in less than 1 minute (Fig. 1C), the data presented in Fig. 6B indicate that, when the oxoammonium salt 1 was used as an oxidant, the secondary oxidation of the hydroxylamine did not significantly contribute to the formation of nitrone 6b.

Altogether, the data obtained support a two-electron oxidation mechanism for the reaction between the α-H,N,N-dialkylhydroxylamines and 1, which is reminiscent of the oxidation of alcohols by oxoammonium salts 20 (Fig. 7). Accordingly, the stoichiometric oxidation of 4a-c by 1 is proposed to proceed via formation of reaction intermediates 7a-c with concomitant cyclic elimination of the end-reaction products 6a-c and 3.

Oxidation of α-H,N,N-dialkylhydroxylamines by 1.Br under preparative conditions. Nitrones are widely used as reagents in reactions of cycloaddition and alkylation with organometallics, and as EPR spin-trapping probes. Hence, considerable research effort has been directed toward the synthesis of this class of compounds. The oxidation of α-H,N,N-dialkylhydroxylamines has proven a principal method for the synthesis of nitrones, where HgO 30, Ag 2O 31, MnO 2 32, hypervalent iodine reagents 33, and copper complexes 34 have been successfully used as oxidants. An alternative that uses nontoxic reagents has been reported by Alderson et al. 35 and Cicchi et al. 36 in which NaBrO and NaClO oxidize α-H,N,N-dialkylhydroxylamines to nitrones with reaction times and yields ranging from 1 to 20 hours and 40% to 95%, respectively.

The high rates of oxidation of α-H,N,N-dialkylhydroxyl-amines by 1 and the excellent yields of nitrones under analytical conditions prompted us to scale-up the reactions to preparative amounts of hydroxylamines. At ambient temperature, 1–2 mmoles of 4a-c (dissolved in 90% methanol) were efficiently oxidized by 1.Br (Fig. 8). Hydroxylamines 4a,b,d are standard substrates of oxidation and provide a foundation for comparison of different synthetic protocols; depending on the oxidant used, reactions with 4a,b,d have been reported to proceed for hours and to afford nitrones.
with good to excellent yields. In agreement with the data presented in Fig. 3C, maximal yields of nitrones were obtained with the use of 1.2 molar equivalents of 1Br per mole of hydroxylamine. In the absence of NaHCO₃, the reactions proceeded with concomitant hydrolysis of the nitrones by HBr to aldehydes and N-alkylamines (data not shown). In the oxidation of 4d, formation of 6dd was not detected, whereas 4e afforded regioisomers 6e (yield, 78%) and 6ee (yield, 14%; SI). Notably, 1 selectively oxidized the NOH of 4e and not its OH group. Under these experimental conditions, oximes 8a,b did not react with 1 to any significant extent, indicating that the reaction is specific for hydroxylamines and that deprotonation of the NOH group did not promote its oxidation, presumably via preferential addition of the corresponding aminoxy anions to 1. As estimated with MarvinSketch (ChemAxon; Cambridge, MA), in aqueous solutions the pKa values of the NOH group of 4b, 8a and 8b are 15.57, 9.84 and 7.37, respectively.

Conclusions
The data presented herein expand the list of functional groups that can be interconverted by oxoammonium salts. We show that 1 converts the >N-OH group into a nitrene group via a two-electron oxidation mechanism in each of a series of α-H dialkylhydroxylamines. The reaction is rapid, proceeds under mild conditions, and affords nitrones in excellent yields.

The interconversion between nitrones and hydroxylamines is a viable strategy for carbon-carbon formation that, when coupled with acidic hydrolysis of nitrene derivatives, can be applied to structural diversification of aldehydes (R₁CH=N-OH → R₁CH=N(O)R₂ → R₁R₂NCH(OH)R₃ → R₁R₂C=N(O)R₄ → R₁R₂CO)⁴⁻⁵. To this end, the rapid oxidation of α-H N,N-dialkylhydroxylamines by oxoammonium salts may prove advantageous to the optimization of one-pot synthetic protocols. Since dealkylation of α-H N,N-dialkylhydroxylamines may also be of interest, the oxidation of this class of compounds by 1Br to nitrones can be followed by acid-catalyzed hydrolysis of the latter, which would afford aldehydes (or ketones) and N-alkylhydroxylamines.

Materials and Methods
Reagents. Hydroxylamines 4a,b were purchased from TCI America, Inc. (Montgomeryville, PA). All other chemicals, including nitrones 6b,c,d were purchased from Sigma (St. Louis, MO). Nitrone 6a was obtained via oxidation of 4a with Ag₂O as reported in ref.⁵. Nitrones 6a-d were used as external reference HPLC standards. Protocols for preparation of 1Br, 3 and 8a,e are included in SI, along with NMR, HRMS, and HPLC data.

General procedure for the oxidation of α-H N,N-dialkylhydroxylamines by 1Br. To a stirred suspension of α-H N,N-dialkylhydroxylamine (1 mmol) in methanol containing 10% water (v/v; 10 mL; 25° C) and NaHCO₃ (250 mg; 3 mmol) was added dropwise 1.25 equiv. of 1Br. The mixture was stirred for 45–60 min at RT, and then monitored by TLC (15% MeOH:H₂O). The residues were filtered off, washed with absolute ethanol (2x5 mL), and the solvents from the filtrate were rotor-evaporated (35°C; 20 Torr). Nitrones from the dry residues were separated by column chromatography as indicated SI.

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### Author Contributions
Both authors designed the study and performed the experiments. D.A.S. wrote the manuscript.

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