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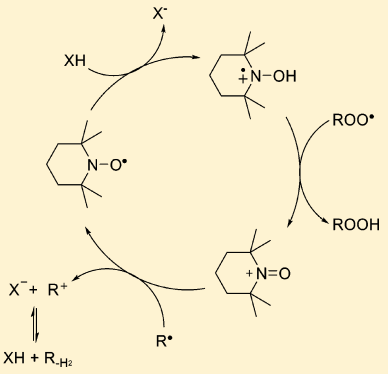
Acid Is Key to the Radical-Trapping Antioxidant Activity of Nitroxides

Evan A. Haidasz,[†] Derek Meng,[†] Riccardo Amorati,[‡] Andrea Baschieri,[‡] Keith U. Ingold,[§] Luca Valgimigli,*[,‡] and Derek A. Pratt*[,†]

[†]Department of Chemistry, University of Ottawa, Ottawa, Ontario K1N 6N5, Canada
[‡]Department of Chemistry "G. Ciamician", University of Bologna, Bologna I-40126, Italy
[§]National Research Council of Canada, Ottawa, Ontario K1A 0R6, Canada

Supporting Information

ABSTRACT: Persistent dialkylnitroxides (e.g., 2,2,6,6-tetramethylpiperidin-1-oxyl, TEMPO) play a central role in the activity of hindered amine light stabilizers (HALS)—additives that inhibit the (photo)oxidative degradation of consumer and industrial products. The accepted mechanism of HALS comprises a catalytic cycle involving the rapid combination of a nitroxide with an alkyl radical to yield an alkoxyamine that subsequently reacts with a peroxyl radical to eventually re-form the nitroxide. Herein, we offer evidence in favor of an alternative reaction mechanism involving the acid-catalyzed reaction of a nitroxide with a peroxyl radical to yield an oxoammonium ion followed by electron transfer from an alkyl radical to the oxoammonium ion to re-form the nitroxide. In preliminary work, we showed that TEMPO reacts with peroxyl radicals at diffusion-controlled rates in the presence of acids. Now, we show that TEMPO can be regenerated from its oxoammonium ion by reaction with alkyl radicals. We have determined that this reaction, which has been proposed to be a key step in TEMPO-catalyzed synthetic transformations, occurs with $k \sim 1-3 \times 10^{10}$ M^{-1} s^{-1}, thereby enabling it to compete with O_2 for alkyl radicals. The addition of weak acids facilitates this reaction, whereas the addition of strong acids slows it by enabling back electron transfer. The chemistry is shown to occur in hydrocarbon autoxidations at elevated temperatures without added acid due to the in situ formation of carboxylic acids, accounting for the long-known catalytic radical-trapping antioxidant activity of TEMPO that prompted the development of HALS.



INTRODUCTION

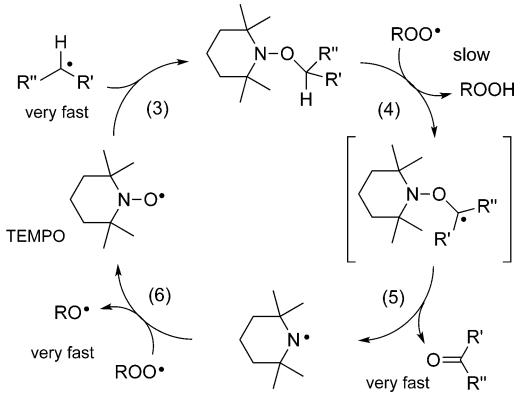
Radical-trapping antioxidants (RTAs) inhibit the autoxidation of hydrocarbons by trapping the peroxyl radicals (ROO•) that propagate the chain reaction.[1,2] Phenols and diphenylamines are the archetype RTAs (represented by A-H in eqs 1 and 2); they undergo efficient formal H atom transfer to peroxyl radicals to yield stable RTA-derived radicals that do not propagate the chain reaction (A•, eq 1). Instead, A• reacts with another peroxyl to yield nonradical products (eq 2). Thus, the overall stoichiometry of the ROO•/A-H reaction is 2.

$$\text{A-H} + \text{ROO}\bullet \rightarrow \text{A}\bullet + \text{ROOH} \quad (1)$$

$$\text{A}\bullet + \text{ROO}\bullet \rightarrow \text{nonradical products} \quad (2)$$

Nitroxides, such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, Scheme 1), have long been of interest as RTAs. Although early work by Brownlie and Ingold found TEMPO to be unreactive to peroxyl radicals at 65 °C,[3] later work showed that nitroxides were incredibly reactive at higher temperatures.[4,5] For example, a reaction stoichiometry of 510 was reported for the TEMPO-inhibited autoxidation of paraffin oil at 130 °C, making TEMPO (and related hindered nitroxides) the most efficacious RTA(s) ever reported.[5] This remarkable result coincided with the development of hindered amine light stabilizers (HALS)—technology now universally used to slow the (photo)oxidation of polymers and other petroleum-derived products. HALS generally comprise secondary or tertiary hindered amines that undergo in situ oxidation to nitroxides.[6] Related to this application, nitroxides have been explored as potential therapeutic and preventive agents against degenerative diseases in which lipid autoxidation (peroxidation) has been implicated.[7]

Scheme 1. Proposed Mechanism of Hindered Amine Light Stabilizer Activity



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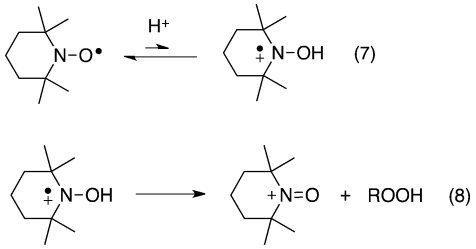
Although nitroxides do not react directly with peroxyl radicals,[3,8] they react very quickly with alkyl radicals (eq 3).[9] At low concentrations of O_2 and sufficiently high concentrations of nitroxide, this reaction competes with addition of O_2 to alkyl radicals (which propagates autoxidation) to break one chain reaction. To account for the apparent catalytic RTA activity of TEMPO (or HALS), it is widely accepted that TEMPO is regenerated from the alkoxyamine.[6] Among the various mechanisms proposed for regeneration,[10] the most reasonable starts with H atom abstraction from the alkoxyamine by a chain-carrying peroxyl radical (eq 4, Scheme 1).[10,11] This reaction produces an alkyl radical that rapidly undergoes β-fragmentation to yield a carbonyl compound and aminyl radical (eq 5), from which TEMPO can be regenerated following reaction with a peroxyl radical (eq 6). This series of reactions completes a catalytic cycle wherein the substrate undergoing autoxidation serves as the stoichiometric reductant, and each pass through the cycle traps two chain-carrying radicals.

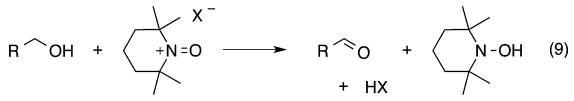
A short time ago, we found that the long-held dogma that nitroxides do not react with oxygen-centered radicals[12] must be applied with care. When autoxidations were carried out at ambient temperatures in the presence of added acid (e.g., acetic acid or trifluoroacetic acid), nitroxides were excellent radical-trapping antioxidants.[13] In our preliminary report, we showed that TEMPO, when protonated (eq 7), reacts with peroxyl radicals at rates approaching the diffusion-controlled limit (e.g., $k_{inh} \sim 1 \times 10^8$ M^{-1} s^{-1} with 10 mM *p*-TsOH) as in eq 8.[14]



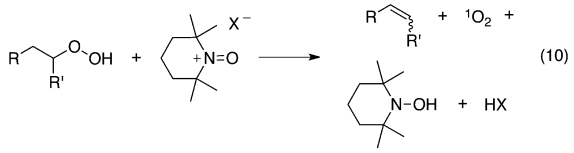
Furthermore, we showed that in the presence of weak carboxylic acids (e.g., acetic or benzoic acid), very long inhibited periods are observed, *during which the nitroxide is not consumed*—corresponding to massive stoichiometric numbers[13]—such as those observed in high-temperature autoxidations.[5] Thus, under weakly acidic conditions, TEMPO must be regenerated from its corresponding oxoammonium ion, $TEMPO^+$.[13] In sharp contrast, in the presence of strong acids (e.g., trifluoroacetic acid), only one peroxyl radical was trapped, suggesting that TEMPO could not be regenerated from $TEMPO^+$. At the time of our preliminary communication, the mechanism by which TEMPO was regenerated was elusive, as was the reason it occurred in the presence of weak acids but not stronger ones. Herein, we offer an explanation for these results and demonstrate that it accounts for the remarkable inhibition of autoxidation by nitroxides and, by extension, HALS.

RESULTS

Mechanistic Possibilities. The oxoammonium ion derived from TEMPO is best known for its role as the catalytic oxidant in the oxidation of alcohols to carbonyl compounds.[15,16] This is believed to occur via a hydride transfer in a noncovalent prereaction complex (eq 9). As such, at the conclusion of our preliminary work,[13] we wondered whether a (somewhat) similar reaction could occur with hydroperoxide products formed during

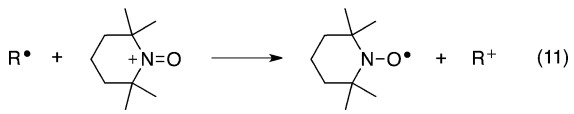


an autoxidation. This reaction would require hydride transfer from the β-carbon with concomitant formation of $^1O_2$ (eq 10):



The resultant hydroxylamine could then react with a peroxyl radical to regenerate TEMPO—known to proceed readily with $k = 5 \times 10^5$ to 3×10^6 M^{-1} s^{-1}.[3,13] No precedent exists in the literature for this mechanism. However, the reaction of hydrogen peroxide with $TEMPO^+$ was suggested some time ago by Denisov as a key step in the TEMPO-inhibited autoxidation of ethylbenzene.[17] More recently, Goldstein et al. investigated the kinetics of this reaction in water.[7b] They found that the reaction was only particularly facile at alkaline pH, where electron transfer from the peroxide anion was possible, for example, $k = 5 \times 10^4$ M^{-1} s^{-1} at pH 8 and 5.1 M^{-1} s^{-1} at pH 4.[7b] Given that the latter value must represent the upper bounds in an acidified organic solvent, this mechanism would appear to be irrelevant in the current context. Moreover, the reductant in the current context must be a hydroperoxide, which is less acidic and therefore less reactive as an electron transfer reagent. Indeed, we found that the reaction between the tetrafluoroborate salt of the TEMPO-derived oxoammonium ion (hereafter $TEMPO^+BF_4^-$) and *t*-BuOOH proceeds with a rate constant of only $(4.5 \pm 0.5) \times 10^{-3}$ M^{-1} s^{-1} (in acetonitrile at 25 °C, see Supporting Information for details). This value, in light of the modest amount of hydroperoxides that are formed in the early stages of an (inhibited) autoxidation, suggests that this cannot be the mechanism of TEMPO regeneration.

Further consideration of all the species present in the inhibited autoxidations left only one possible candidate to reduce the oxoammonium ion: the chain-carrying alkyl radical, R• (eq 11):[18]



Computations carried out at the CBS-QB3 level of theory[19] suggest that this electron transfer reaction is exergonic, with $\Delta G^\circ = -3.9$ and -6.1 kcal/mol in the gas phase and acetonitrile, respectively, for R = cumyl (cumene was one of the substrates that we autoxidized in our previous studies).[13]

Product Studies in a Model Reaction. Since inhibited autoxidations are inherently complex, evidence for the reaction in eq 11 was initially sought in a model system. Cumyl radicals were generated from the thermal decomposition of azocumene in acetonitrile at 50 °C in the presence of $TEMPO^+BF_4^-$ and Me_4NOAc. The latter was included to produce the same $TEMPO^+AcO^-$ species that is expected to form in a TEMPO-inhibited autoxidation in the presence of acetic acid (as in our previous studies[13]). The reaction products were analyzed by HPLC with UV detection. The results are shown in Figure 1.

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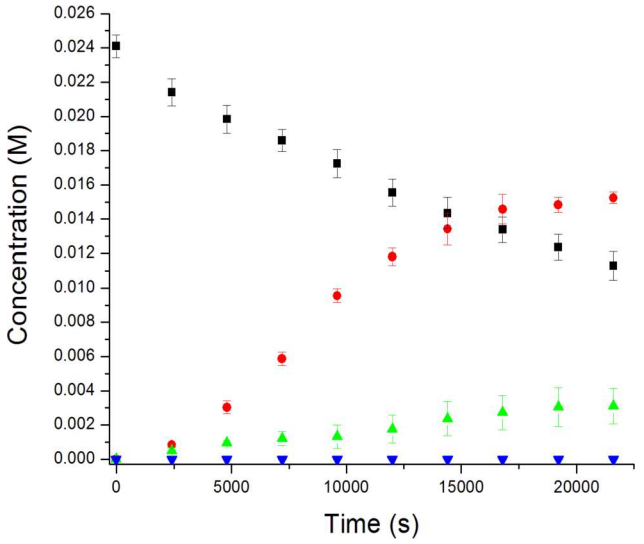
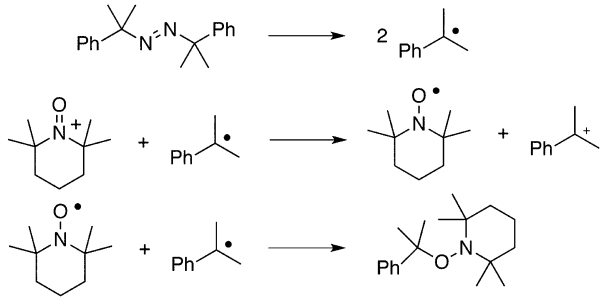


Figure 1. Decomposition of azocumene (black) and formation of the cumyl-TEMPO adduct in the presence of $TEMPO^+BF_4^-$ (25 mM) and $Me_4N^+AcO^-$ (25 mM) in acetonitrile at 50 °C under an atmosphere of argon (red), air (green) or O_2 (blue).

In the absence of O_2 (via sparging the solutions extensively with argon), the cumyl-TEMPO adduct was the sole product formed and appeared at a rate roughly coinciding with the rate at which azocumene decomposed.[20] This is consistent with the expected reaction sequence shown in Scheme 2. Thus,

Scheme 2. Formation of the Cumyl-TEMPO Adduct from Azocumene and $TEMPO^+BF_4^-$



decomposition of azocumene proceeds to yield two cumyl radicals—one of which reduces the oxoammonium ion to TEMPO, and the other reacts with TEMPO to give the observed alkoxyamine product. The same profile was observed in chlorobenzene (see Supporting Information). Similar results were obtained in experiments where azo(phenylethane), which yields secondary 1-phenylethyl radicals, was used in lieu of azocumene (see Supporting Information).

In the presence of air, the cumyl-TEMPO adduct was also formed, but at a much lower level, whereas when the reaction was carried out under an atmosphere of O_2, no adduct was observed. The lower yields of alkoxyamine in the presence of air were expected given the rapid reaction of cumyl radicals with O_2 ($k \sim 3 \times 10^9$ M^{-1} s^{-1}),[21] which outcompetes the reaction of cumyl radicals with TEMPO ($k = 1.2 \times 10^8$ M^{-1} s^{-1}).[9] This is underscored by the complete lack of alkoxyamine formed when the reaction was carried out in the presence of O_2. The addition of acetic acid (25 mM) had no effect on the reaction (see Supporting Information).[22]

Inhibited Autoxidations. If TEMPO is formed from $TEMPO^+$ in an autoxidation, the oxoammonium ion should inhibit the autoxidation similarly to the nitroxide from the outset. Thus, matched styrene autoxidations were carried out where either TEMPO or $TEMPO^+$ was added with or without acetic acid. The results are shown in Figure 2. Similar results were obtained in autoxidations of cumene (see Supporting Information).

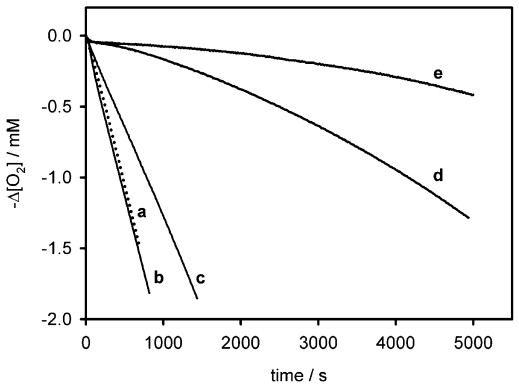


Figure 2. O_2 consumption during the autoxidation of styrene (4.3 M) in acetonitrile initiated by AIBN (0.05 M) at 30 °C (a, dotted line) and corresponding experiments carried out in the presence of 13 μM of either $TEMPO^+BF_4^-$ (b,d) or TEMPO (c,e) with (d,e) or without (b,c) acetic acid (43 mM).

As we reported in our preliminary communication,[13] TEMPO + AcOH gave rise to a lengthy inhibited period corresponding to a reaction stoichiometry of $n \gg 1$. When $TEMPO^+BF_4^-$ was used in place of TEMPO, the initial rate of autoxidation was not suppressed to the same extent as with TEMPO, but significant inhibition was still observed. Each of the TEMPO-inhibited and $TEMPO^+$-inhibited autoxidations could be modeled using the standard kinetic scheme for the inhibited autoxidation of styrene,[23] including the proposed inhibition reactions in eqs 7, 8, and 11, and fit by numerical integration to yield the unknown rate constant $k_{11} = (2.4 \pm 0.4) \times 10^{10}$ M^{-1} s^{-1} (see Supporting Information for details). The magnitude of this rate constant accounts for the successful competition of $TEMPO^+$ with O_2 for alkyl radicals necessary for this mechanism to be viable.

The combination of TEMPO and AcOH was also effective at inhibiting the autoxidation of styrene in chlorobenzene, but no significant inhibitory activity was observed past $n = 1$, implying that oxidation by $TEMPO^+$ cannot effectively compete with O_2 for alkyl radicals. Indeed, when used directly, $TEMPO^+BF_4^-$ had only a small effect on the autoxidation (Figure 3). Modeling the data as above yields the rate constant $k_{11} = 1.5 \times 10^9$ M^{-1} s^{-1}, which is similar to the rate constant for the competing reaction of the styryl radicals with O_2 ($\sim 3 \times 10^9$ M^{-1} s^{-1}). However, since $[O_2] = 2$ mM $\gg$ $[TEMPO^+] = 13$ μM, this reaction is not competitive and no catalytic activity is observed.

Electron Paramagnetic Resonance (EPR) Spectroscopy. To corroborate the foregoing product studies and inhibited autoxidation data, we sought to directly demonstrate that TEMPO is produced from $TEMPO^+$ under the conditions of a typical autoxidation. In fact, upon addition of $TEMPO^+BF_4^-$ to an air-saturated solution of either cumene or styrene in acetonitrile containing AIBN as the radical initiator, the formation of TEMPO could be observed directly by EPR (Figure 4A).

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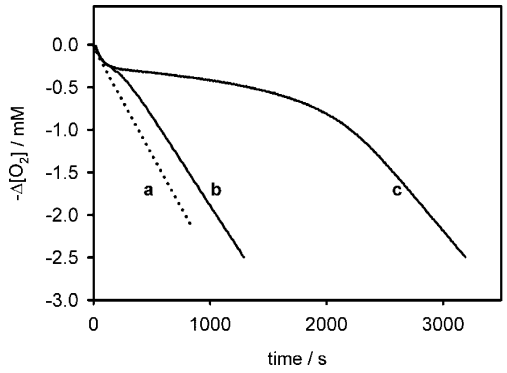


Figure 3. O_2 consumption during the autoxidation of styrene (4.3 M) in chlorobenzene initiated by AIBN (0.05 M) at 30 °C (a, dotted line) and corresponding experiments carried out in the presence of 13 μM of either $TEMPO^+BF_4$ (b) or TEMPO (c) and AcOH (44 mM).

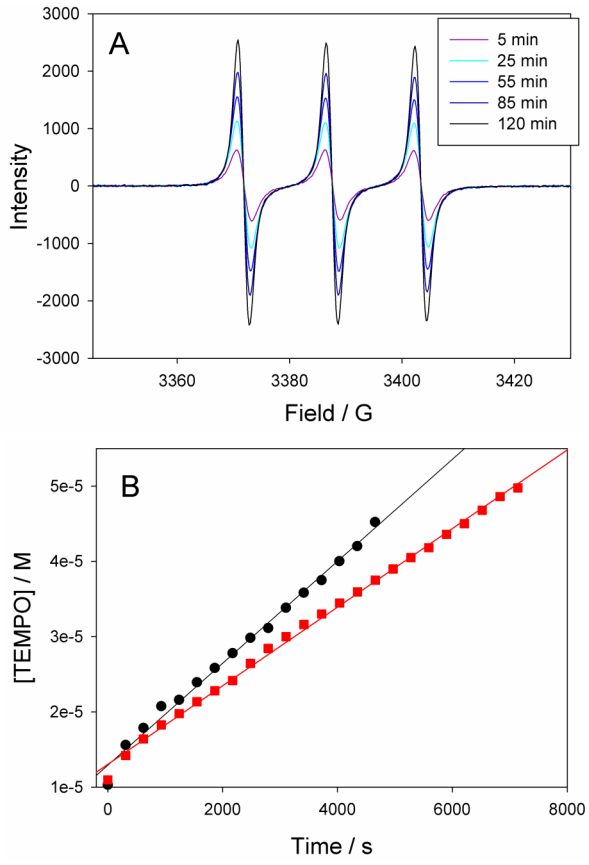


Figure 4. TEMPO formation during the autoxidation of styrene (4.3 M) in acetonitrile initiated by AIBN (50 mM) at 30 °C in the presence of $TEMPO^+BF_4^-$ (0.66 mM). Top: Representative EPR spectra. Bottom: Rate with (black) and without (red) added acetic acid (35 mM).

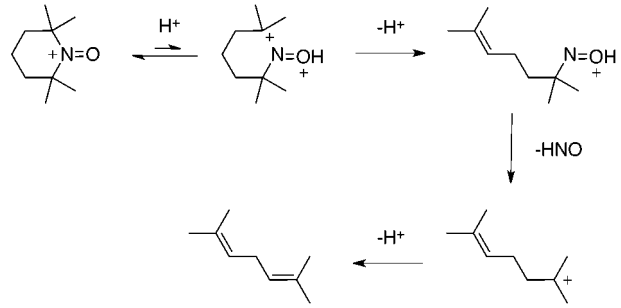
The evolution of the spectra revealed a rate of TEMPO formation (3.5×10^{-9} M s^{-1}) that was only slightly lower than the rate of radical initiation from AIBN decomposition ($R_i = 6.1 \times 10^{-9}$ M s^{-1}).[24] (The rate determined in a cumene autoxidation was 5.0×10^{-9} M s^{-1}; see Supporting Information.) As a result, since the rate constant for O_2 addition to the alkyl radicals derived from AIBN and styrene (or cumene) is $k \sim 3 \times 10^9$ M^{-1} s^{-1}, $[O_2] \sim 2$ mM and $[TEMPO^+ BF_4^-] = 0.66$ mM, we can estimate that under these conditions $k_{11} \sim 1 \times 10^{10}$ M^{-1} s^{-1}. Interestingly, when acetic acid (35 mM) was added to the reaction mixture, the formation of TEMPO was accelerated (compare data sets in Figure 4B), yielding an observed rate that was indistinguishable from the rate of radical initiation and implying that the rate constant for electron transfer had increased to $k_{11} \sim 3 \times 10^{10}$ M^{-1} s^{-1}, in excellent agreement with the rate constant derived from fitting the inhibited autoxidation data (vide supra). It is important to note that no TEMPO was observed in the absence of AIBN. Moreover, in the absence of either cumene or styrene, the formation of TEMPO due to reduction of $TEMPO^+$ by AIBN-derived radicals was determined to be much slower ($k_{11} \sim 1 \times 10^8$ M^{-1} s^{-1}; see Supporting Information).

In chlorobenzene, the rate of formation of TEMPO from $TEMPO^+BF_4^-$ in the presence of the same amount of acetic acid enables derivation of a rate constant of $k_{11} = 2.6 \times 10^9$ M^{-1} s^{-1} for the electron transfer, which is just over an order of magnitude slower than that in acetonitrile and in excellent agreement with the kinetic data from the inhibited autoxidations.[25]

Addition of Strong Acids. Each of the three foregoing experiments were also carried out with TFA in place of AcOH. The data are presented in the Supporting Information. To summarize the results, (1) significantly lower yields of the cumyl-TEMPO adduct were observed when azocumene was decomposed in the presence of $TEMPO^+BF_4^-$ and TFA instead of AcOH, (2) the combination of $TEMPO^+BF_4^-$ and TFA did not inhibit the autoxidation of styrene in acetonitrile, and (3) no TEMPO was observed by EPR spectroscopy when AIBN was decomposed in the presence of $TEMPO^+BF_4^-$ and TFA instead of AcOH.

The simplest explanation for the lack of regeneration of TEMPO from $TEMPO^+$ in the presence of a strong acid is that it is destroyed under these conditions. Indeed, Ma and co-workers have suggested that $TEMPO^+$ is unstable in the presence of H_2SO_4 at elevated temperatures (100 °C, monitored by UV–vis spectroscopy),[26] where it is believed to eliminate HNO, eventually yielding unsaturated aliphatic products (Scheme 3). However, when we subjected $TEMPO^+BF_4^-$ (400 μM) to 10 mM TFA in acetonitrile at 50 °C, no change was observed in the UV–vis spectrum over the course of 1 h.[27]

Scheme 3. Proposed Mechanism for the Decomposition of $TEMPO^+$ in the Presence of Strong Acid



Since the oxoammonium ion was stable under the reaction conditions, we next considered the possibility that the key electron transfer reaction (eq 11) was reversible. If so, the strength of the acid and/or the nucleophilicity of its conjugate base are expected to influence the position of the key redox equilibrium in Scheme 4.

Thus, the more acidic the medium, the less favorable the loss of a proton from the carbocation and/or the trapping of the carbocation by the less nucleophilic conjugate base. Indeed, if a

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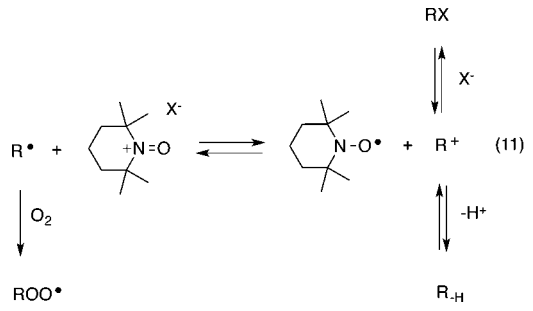
Scheme 4. Reactions Influencing the Reversibility of the Electron Transfer between TEMPO$^+$ and an Alkyl Radical



strong acid (e.g., HBF_4) is added to a TEMPO/AcOH-inhibited autoxidation, the catalytic effect disappears (Figure 5).[28]

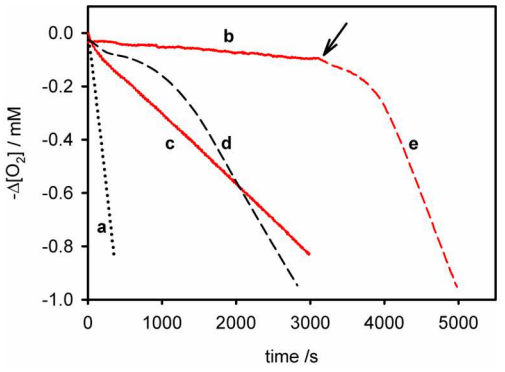
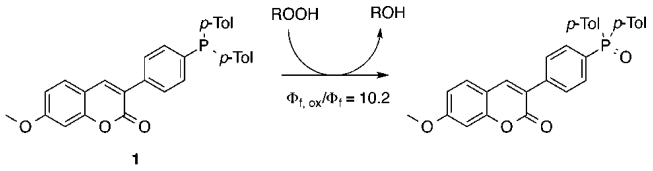


Figure 5. O_2 consumption during the autoxidation of styrene (4.3 M) in acetonitrile containing 1% H_2O initiated by AIBN (0.05 M) at 30 °C (a) and corresponding experiments carried out in the presence of TEMPO (13 μM) and acetic acid (43 mM) (b), acetic acid (43 mM) and Oct_4NBF_4 (0.13 M) (c), acetic acid (43 mM) and HBF_4 (43 mM) (d), and acetic acid (43 mM) with HBF_4 (43 mM) added at the time indicated by the arrow (e).

Likewise, if an excess of the conjugate base of the strong acid (e.g., Oct_4NBF_4) is added, the catalytic effect decreases substantially (Figure 5). The latter result suggests that the oxidation potential of TEMPO$^+$ is also dependent on the identity of its counterion.

Autoxidations at Elevated Temperatures. Given the effect of weak acids on the RTA activity of nitroxides at ambient temperatures, we wondered whether the addition of a weak acid could bolster the activity of nitroxides at elevated temperatures, as well. Consequently, we examined the effect of a nitroxide/acid combination on the autoxidation of paraffin oil in a stirred flow reactor at 160 °C.[29,30] The reaction was initiated with a small amount of tetralin hydroperoxide (5 mM), and a dispersed stream of O_2 was continuously passed through the solution to stir the medium and prevent mass transfer of O_2 from becoming rate-limiting. Aliquots were removed at regular time intervals, and the hydroperoxide concentration in each was determined using our previously described profluorescent phosphine (**1**).[31]



1

Since TEMPO is somewhat volatile at 160 °C, a higher molecular weight analogue (**2**) was investigated, along with palmitic acid in lieu of the acetic acid used at ambient temperatures.[32] The results are shown in Figure 6A.

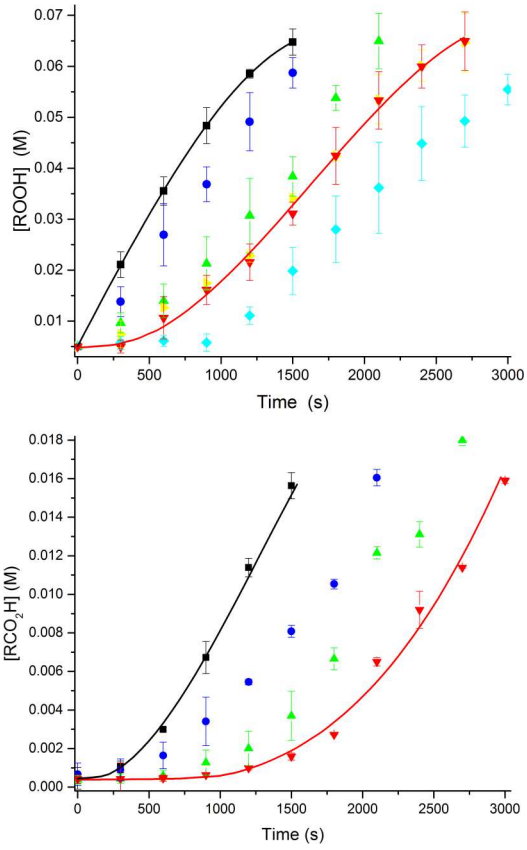
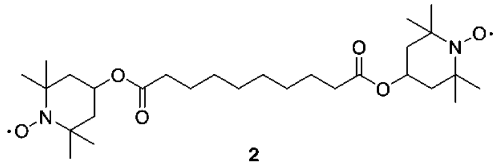


Figure 6. Hydroperoxide (top) and acid (bottom) formation in the autoxidation of light paraffin oil at 160 °C initiated by 5 mM tetralin hydroperoxide (black) and inhibited by 40 μM **2** (red) with 4 mM palmitic acid (yellow), 40 mM palmitic acid (light blue), 4 mM 2,4,6-(*t*-Bu)$_3$pyridine (green), or 40 mM 2,4,6-(*t*-Bu)$_3$pyridine (dark blue).



2

Addition of the bis-nitroxide **2** to the paraffin autoxidation yielded the expected sigmoidal profile of hydroperoxide production in an inhibited autoxidation at elevated temperatures.[33] Although inclusion of 4 mM palmitic acid to the reaction mixture did not significantly improve the inhibitory activity of **2**, a higher loading (40 mM) produced a significant increase in the inhibited period. At first glance, the lack of effect of the lesser amount of acid and the fact that **2** is capable of inhibiting the autoxidation in the absence of added acid suggested that the acid-catalyzed reaction mechanism accounts for only a fraction of the activity of nitroxides at elevated temperatures. However, the autoxidation of paraffinic hydrocarbons is known to produce carboxylic acids (in addition to hydroperoxides) from the very early stages of the reaction.[34,35] Therefore, acids formed in situ may activate the nitroxide to react with peroxyl radicals. To probe this possibility, we added 4 and

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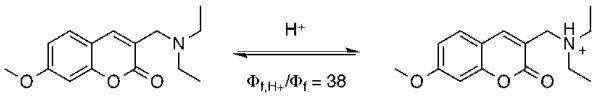
40 mM of the nonvolatile, non-nucleophilic base 2,4,6-tri-*tert*-butylpyridine (TTBP) to autoxidations inhibited by **2** and found that it progressively diminished the RTA activity of the bis-nitroxide. Importantly, the addition of either acid or base had no effect on the rate of the uninhibited autoxidation, suggesting that these additives play no role other than modulating the pH of the reaction (see Supporting Information for more data).

To confirm that carboxylic acids were present in the paraffin autoxidations, they were determined using the aminated coumarin derivative **3**, whose fluorescence is greatly enhanced (38-fold) upon protonation (see Supporting Information for details).[36] The results are shown in Figure 6B.



3

The commercially sourced light paraffin oil contained 0.14 mM carboxylic acid, and upon equilibration of the sample under a N_2 atmosphere and then heating to 160 °C, this increased to 0.5 mM.[37] Addition of the initiator and changing the atmosphere to O_2 led to a rapid accumulatation of acid, reaching 15 mM within 1500 s. In the inhibited autoxidations, the production of carboxylic acids mirrored the formation of hydroperoxides (albeit at lower absolute levels), consistent with the potent antioxidant activity of **2** and its diminution upon addition of base to the autoxidation.

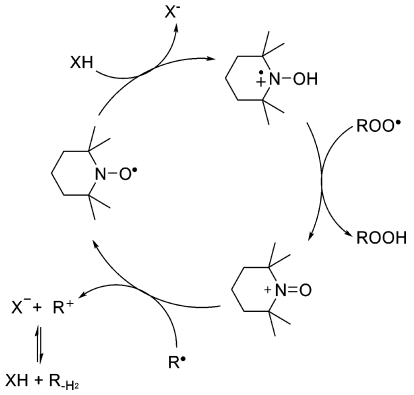
DISCUSSION

Despite the widespread use of HALS, their mechanism has remained a mystery since the suggestion that nitroxides must be the key intermediate in a catalytic radical-trapping cycle.[6] The commonly presented mechanism (Scheme 1) requires the nitroxide to compete with O_2 for alkyl radicals, but it is well known that the reaction of R• with TEMPO is 20−30-fold slower than the reaction of R• with O_2.[9,21] This is irrelevant if the TEMPO/O_2 concentration ratio is large, but in many of the experiments that established the unique reactivity of HALS, this condition is not fulfilled (likewise for the conditions under which HALS-containing materials are manipulated and/or used). For example, in the pioneering experiments carried out by Bolsman, Blok, and Frijns,[5] which showed a stoichiometric number of 510 for the inhibition of paraffin oil autoxidation, only 1−4 μM TEMPO was used. Given that [O_2] ∼ 2 mM,[38] *the rate of alkoxyamine formation must be at least 10000 times slower than the rate of peroxyl radical formation.*

Nevertheless, if alkoxyamines are indeed formed in these reactions, they must decompose to regenerate the nitroxide to complete the catalytic cycle. Recent computations and a reinterpretation of literature data led to the conclusion[10] that it must occur via the sequence of eqs 4, 5, and 6 in Scheme 1: H atom abstraction from the position adjacent the O atom in the alkoxyamine, followed by β-fragmentation of the resultant alkyl radical to give an aminyl radical, and then oxidation to give the nitroxide—as suggested earlier by Bolsman, Blok, and Frijns.[11] While it seems quite clear that this is the mechanism f an alkoxyamine with a peroxyl radical, it is unlikely to be kinetically relevant in an inhibited autoxidation. In fact, we have attempted to measure the rate constant for the reaction of a model alkoxyamine (*O*-allyl-TEMPO) with peroxyl radicals using the radical clock approach and found that it proceeds with $k \leq 1$ M^{-1} s^{-1} at 37 °C, expectedly similar to H atom abstraction from the α-CH_2 group of an ether.[39] Assuming log A = 8 for this H atom transfer[50] suggests that the rate constant could be as big as ∼70 M^{-1} s^{-1} at 130 °C, but given that the alkoxyamine can be present at only 1−4 μM at most (assuming all of the TEMPO added in the first place is converted to the alkoxyamine), this means that *this reaction must be ca. 6 orders of magnitude too slow to compete with chain propagation* (which has k[substrate] ∼ 90 s^{-1})[11,40] in the pioneering experiments of Bolsman, Blok, and Frijns.

Given our observation that TEMPO becomes a catalytic RTA in the presence of weak acid at ambient temperatures, it seemed reasonable to consider this as an alternative to the mechanism in Scheme 1. Indeed, the addition of acid to a paraffin oxidation at 160 °C improved the already catalytic RTA activity of bis(nitroxide) **2**, but more importantly, the addition of base was able to wipe it out in a dose-dependent manner (i.e., the activity of the nitroxide correlated with the amount of acid present). This must rule out the mechanism in Scheme 1 or any mechanism which invokes H atom abstraction from the alkoxyamine in the turnover-limiting step since it cannot account for these observations. Moreover, the bis(oxoammonium) derived from **2** inhibited the paraffin oxidation similarly to **2** itself. Therefore, we suggest that the unique reactivity of nitroxides as RTAs (and HALS, in general) is better accounted for by the mechanism shown in Scheme 5.

Scheme 5. Proposed Mechanism of Acid-Catalyzed RTA Activity of Nitroxides



Although this mechanism still requires the participation of an alkyl radical in the catalytic cycle, the reaction it undergoes is an electron transfer (to regenerate the nitroxide from the oxoammonium ion), which has been shown to compete effectively with its combination with O_2 (vide supra).

Diarylamines are also common additives to petroleum-derived products, but because their oxidation products are highly colored, they are generally not used in applications where color changes are undesirable (e.g., in lightly colored plastics). Given that diarylamines are secondary amines whose catalytic activity also depends on the formation of a nitroxide intermediate (cf. Scheme 6),[41] it is possible that the mechanism in Scheme 5 could also contribute to their activity.[42,43] However, it is expected that (1) alkoxyamine formation will be slightly faster for Ar_2NO• + R• than for TEMPO• + R• due to reduced steric hindrance, (2) unimolecular decomposition of the resultant Ar_2NOR to regenerate Ar_2NH has a lower barrier than the return of the nitroxide,[42] (3) the diaryl nitroxide will be less basic than TEMPO, and (4) the diaryloxoammonium ion will be a weaker oxidant than $TEMPO^+$. Moreover, in related work, we found that acid formation diminishes the activity of some Ar_2NH.[30]

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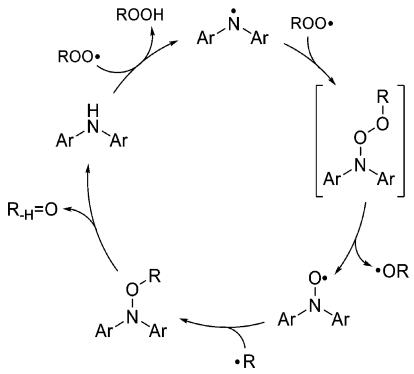
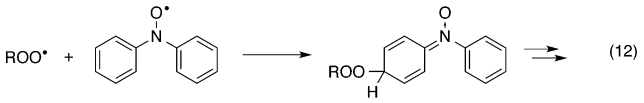
Scheme 6. Proposed Mechanism of Catalytic Activity of Diarylamine RTAs



Although the secondary amines found in HALS are far less reactive toward peroxyl radicals than diarylamines, HALS have the distinct advantage that the nitroxide intermediate in their catalytic cycle is persistent and does not undergo deleterious reactions with peroxyl radicals. The same cannot be said for the nitroxides derived from diarylamines, which undergo competing reactions with peroxyl radicals at ring carbon atoms,[3] leading to complex mixtures of products[44] and precluding continuation of the cycle in Scheme 5.



This fact underscores the unique reactivity of HALS but also prompts the question: what eventually leads to exit from the nitroxide's catalytic cycle? Why are nitroxides not infinitely reactive? The answer to this question may provide the key to the design of the ultimate hindered amine light stabilizers.

CONCLUSIONS

For the past 40 years, there has been widespread agreement that nitroxides are key intermediates in the catalytic activity of hindered amine light stabilizers, but the precise mechanism has been elusive. The formation of an alkoxyamine, and its subsequent decomposition to re-form a nitroxide, was believed to comprise the catalytic cycle. However, for the reasons discussed above, this cannot account for the reactivity of nitroxides as autoxidation inhibitors under most conditions. Instead, we have advanced the more plausible proposal that protonation of the nitroxide creates a potent formal H atom donor which reacts with a peroxyl radical[14] and the resultant oxoammonium ion oxidizes an alkyl radical, regenerating the nitroxide. The latter electron transfer has been shown to be competitive with O_2 addition in both model systems and authentic autoxidations (k_{11} = 1−3 × 10^{10} M^{-1} s^{-1}). This pathway provides a more plausible explanation for the catalytic activity of nitroxides as RTAs and also supports a role for this electron transfer reaction in TEMPO-mediated synthetic transformations. The ability of nitroxides to inhibit the autoxidation of hydrocarbons at high temperature is shown to depend on acid formation in situ. We have shown that the proposed catalytic cycle is also fully operative at ambient temperatures, suggesting that it may be of biological relevance and may contribute to the biological activity of TEMPO and related nitroxides.[7]

EXPERIMENTAL SECTION

Reagents and solvents were purchased from commercial sources and used without further purification unless otherwise indicated. TEMPO$^+BF_4^-$,[45] azocumene,[46] bis(nitroxide) **1**,[47] phosphine **2**,[31] and BODIPY **3**[36] were synthesized by literature precedent. Oxidizable substrates (cumene, styrene, paraffin oil) were carefully purified from stabilizers and hydroperoxides before use and were stored refrigerated under nitrogen.

Model Reactions. TEMPO$^+BF_4^-$ (12 mg, 50 μmol) and tetramethylammonium acetate (6.7 mg, 50 μmol) were added to a 3 mL vial. The contents were dissolved in acetonitrile (sparged with either argon or oxygen as necessary) and placed under the appropriate atmosphere. To this, azocumene (13 mg, 50 μmol) was added. The contents were heated and stirred at 50 °C. Aliquots (100 μL) were removed every 40 min and diluted to 1 mL with methanol containing 2.8 mM hexylbenzene. Samples were analyzed on a Waters Acquity H-Class UPLC equipped with a XTerra RP-18 column (5 μM × 4.6 mm × 150 mm) using 20% H_2O in methanol at a flow rate of 0.4 mL/min and detection at 216 nm.

Inhibited Autoxidations. Experiments were performed in a two-channel oxygen uptake apparatus, based on a Validyne DP 15 differential pressure transducer.[48] In a typical experiment, an air-saturated solution of either styrene or cumene containing AIBN was equilibrated with an identical reference solution containing excess 2,2,5,7,8-pentamethyl-6-hydroxychromane (PMHC) (25 mM). After equilibration, and when a constant O_2 consumption was reached, a stock solution of TEMPO or TEMPO$^+BF_4^-$ (final concentration = 5−50 μM) and a stock solution of the desired acid were injected in the sample flask. After calibration of the apparatus, the oxygen consumption in the sample was measured from the differential pressure recorded with time between the two channels. Rates of initiation, R_i, were determined for each condition in preliminary experiments by the inhibitor method using PMHC as the reference antioxidant: $R_i = 2\,[PMHC]/\tau$, where τ is the length of the induction period. Kinetic traces were analyzed by numerical fitting using GEPASI software.

EPR Measurements. EPR spectra were recorded with a X-band spectrometer with the following settings: microwave power = 6.3 mW, time constant and conversion time = 20.48 ms, modulation amplitude = 1.0 G. Typical samples contained TEMPO$^+BF_4^-$ (0.5−5 mM), AIBN (0.05 M), and styrene or cumene (40−50% v/v) in MeCN or PhCl and were air-saturated. Samples were transferred in a capillary glass tube and were placed in the thermostated instrument cavity at 303 K to cover the entire sensitive area. CH_3COOH and CF_3COOH (30−50 mM) were added to the sample as indicated. The absolute concentration of TEMPO formed in the sample was determined upon calibration with standard solutions in the corresponding solvent mixture. Time evolution of the EPR signal was monitored by an automated acquisition routine and analyzed using either the intensity of the first spectral line or the double integration of the whole spectrum.

Paraffin Autoxidations. Paraffin autoxidations were carried out using an analogous procedure to hexadecane autoxidations previously carried out by our group.[30,31,43] Light paraffin oil (100 mL) was thoroughly degassed with N_2 and then heated to 160 °C in a stirred flow reactor. Once the temperature stabilized, 0.04 mmol of bis(2,2,6,6-tetramethylpiperidin-1-oxyl-4-yl) decanedioate (**2**), the appropriate amount of either palmitic acid or 2,4,6-tri-*tert*-butylpyridine, and 82 mg (0.5 mmol) of tetralin hydroperoxide[49] were added to the solution. The flow of N_2 was replaced with 1 L/min O_2. Aliquots (0.5 mL) were removed every 5 min and allowed to cool to room temperature for analysis.

Four duplicates (30 μL) of each sample were loaded into a 96-well microplate.[50] Each well was read sequentially following manipulation as follows: an automated reagent dispenser was used to dilute the sample with *tert*-amyl alcohol (200 μL), and the plate was stirred for 28 s, after which a solution of fluorogenic phosphine **1** (20 μL of a 250 μM stock solution in acetonitrile) was injected and the plate stirred for an additional 8 s and then allowed to rest for 2 more seconds. The fluorescence of each well was measured every 1.3 s for 30 s (excitation = 340 nm; emission = 425 nm). The concentration of hydroperoxide was

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determined from the rate of phosphine oxidation using the rate constant for the reaction of the dye with secondary hydroperoxides in *tert*-amyl alcohol (1.2 M^{-1} s^{-1}) assuming pseudo-first-order kinetics.[31]

In tandem, four duplicates (1.2 μL) of each sample were loaded into separate wells of a 96-well microplate; the automated reagent dispenser of the microplate reader was used to dilute each sample with 25% isopropyl alcohol in methanol (280 μL), and the plate was stirred for 15 s. Afterward, a solution of fluorogenic amine **3** (20 μL of a 630 μM stock in methanol) was added. The plate was stirred for 8 s, and the fluorescence of each well was measured every second for 10 s (excitation = 315 nm; emission = 395 nm) and the acid concentration was determined from the average fluorescence reading.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00677.

Synthetic details and results of model studies, inhibited autoxidations, EPR experiments, and paraffin autoxidations referred to, but not included in, the article (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*luca.valgimigli@unibo.it

*dpratt@uottawa.ca

Notes

The authors declare no competing financial interest.

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