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The Catalytic Mechanism of Diarylamine Radical-Trapping Antioxidants

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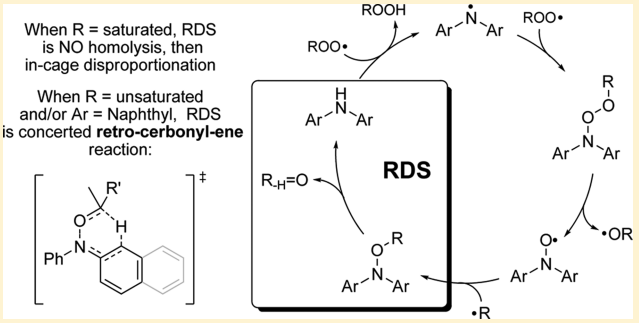
Supporting Information

ABSTRACT: Diarylamine radical-trapping antioxidants are important industrial additives, finding widespread use in petroleum-derived products. They are uniquely effective at elevated temperatures due to their ability to trap multiple radicals per molecule of diarylamine. Herein we report the results of computational and experimental studies designed to elucidate the mechanism of this remarkable activity. We find that the key step in the proposed catalytic cycle—decomposition of the alkoxyamine derived from capture of a substrate-derived alkyl radical with a diarylamine-derived nitroxide—proceeds by different mechanisms depending on the structure of both the substrate and the diarylamine. *N*,*N*-Diarylalkoxyamines derived from saturated substrates and diphenylamines decompose by N−O homolysis followed by disproportionation. Alternatively, those derived from unsaturated substrates and diphenylamines, or saturated substrates and *N*-phenyl-*β*-naphthylamine, decompose by an unprecedented concerted retro-carbonyl-ene reaction. The alkoxyamines that decompose by the concerted process inhibit hexadecane autoxidations at 160 °C to the same extent as the corresponding diarylamine, whereas those alkoxyamines that decompose by the N−O homolysis/disproportionation pathway are much less effective. This suggests that the competing cage escape of the alkoxyl radicals following N−O homolysis leads to significantly less effective regeneration of diarylamines and implies that the catalytic efficiency of diarylamine antioxidants is substrate-dependent. The results presented here have significant implications in the future design of antioxidant additives: diarylamines designed to yield intermediate alkoxyamines that undergo the retro-carbonyl-ene reaction are likely to be much more effective than existing compounds and will display catalytic radical-trapping activities at lower temperatures due to lower barriers to regeneration.



INTRODUCTION

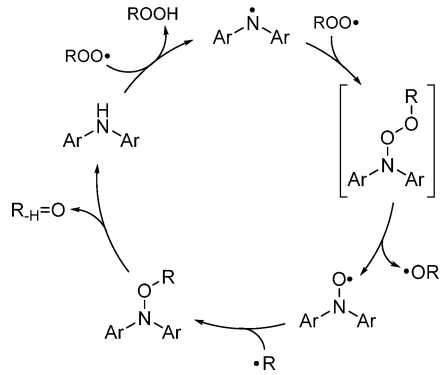
Diarylamines are among the most commonly used radical-trapping antioxidants (RTAs); compounds which inhibit the free radical chain oxidation of hydrocarbons by trapping chain-carrying peroxyl radicals (eqs 1 and 2).[1,2]

$$Ar_2NH + ROO\bullet \rightarrow Ar_2N\bullet + ROOH \quad (1)$$

$$Ar_2N\bullet + ROO\bullet \rightarrow \text{nonradical products} \quad (2)$$

While diarylamines display similar efficacies to more prolific phenolic RTAs at ambient temperatures (typical k_1 values of 10^4−10^5 M^{-1} s^{-1} and stoichiometric coefficients, n, of 2 based on eqs 1 and 2),[3] they have uniquely high efficacies at elevated temperatures (>120 °C), where 1 equiv of diarylamine can trap several chain-carrying peroxyl radicals. For example, as early as 1978 an unbelievable stoichiometry of n = 41 was reported from a diphenylamine-inhibited autoxidation of paraffin oil at 130 °C.[4] Some time ago, Korcek and co-workers proposed a mechanism accounting for these dramatic observations, shown in Scheme 1.[5] The large stoichiometric coefficients were ascribed to the observed regeneration of the diarylamine *in situ* during hexadecane autoxidation at 160 °C inhibited by the corresponding diarylnitroxide. Furthermore, the nitroxide proved to be as powerful an RTA as its parent amine. The amine was believed to be formed from a substrate-derived alkoxyamine—therefore *making use of the substrate as a stoichiometric reductant*.[6] Elevated temperatures were presumed necessary to cleave the N−O bond of the alkoxyamine, which

Scheme 1. Proposed Mechanism of Catalytic Activity of Diarylamine RTAs



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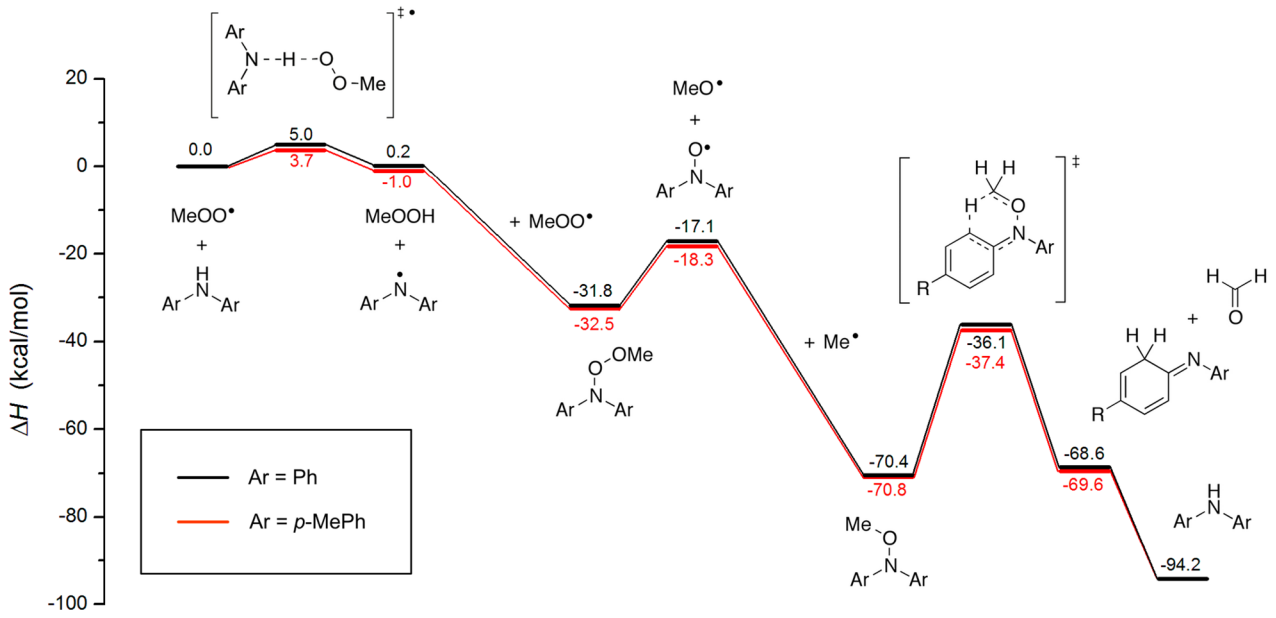

Figure 1. CBS-QB3-calculated enthalpies (at 25 °C) for relevant structures in Scheme 1.

would lead to the diarylamine upon in-cage disproportionation of the diarylaminyl and alkoxyl radicals.[7] This idea was supported by the observation that heating of a mixture of alkoxyamines generated *in situ* from decomposition of *tert*-butyl peroxy-2-ethylhexanoate in hexadecane in the presence of crude bis(*p*-octylphenyl)nitroxide gave 64% bis(*p*-octylphenyl)amine (among other products).[5] No further scrutiny of this mechanism is evident in the literature and no significant improvement in the chemistry behind diarylamine RTA technology has emerged since the 1950s.

In recent years we have reported on the design and development of novel heterocyclic diarylamines,[8−10] some of which react up to 2 orders of magnitude faster with peroxyl radicals than conventional compounds at ambient temperatures (i.e., $k_1 > 10^7$ M^{-1} s^{-1}) due to their comparatively weaker N−H bonds (ca. 6 kcal/mol relative to diphenylamine). We anticipated that they would also be more efficient than conventional compounds at elevated temperatures since homolysis of the N−O bond in the intermediate alkoxyamines would also be much more facile. However, before setting out to investigate the properties of the new compounds any further, we sought more information about the mechanism proposed by Korcek and co-workers and present the results of our computational and experimental studies here.

RESULTS AND DISCUSSION

Computations. The structures and energetics of the participants in the proposed catalytic cycle shown in Scheme 1 were computed at the CBS-QB3 level of theory[11] for the reaction between either diphenylamine (**1**) or 4,4′-dimethyldiphenylamine (**2**) and a model peroxyl radical, methylperoxyl (MeOO•). The former was chosen as it is the parent diarylamine, and the latter was chosen as a model for the industry-standard dialkylated diphenylamines. The key stationary points and their relative enthalpies were determined at 25 °C and are shown in Figure 1.

The initial step, abstraction of the labile H-atom of diphenylamine by a peroxyl radical (eq 1), proceeds through a transition state characterized by proton transfer (roughly) within the plane of the aromatic rings, and simultaneous electron transfer from the π-system to the radical, consistent with its description as a proton coupled electron transfer (PCET) reaction.[8,12,13] The TS structure is shown in Figure 2

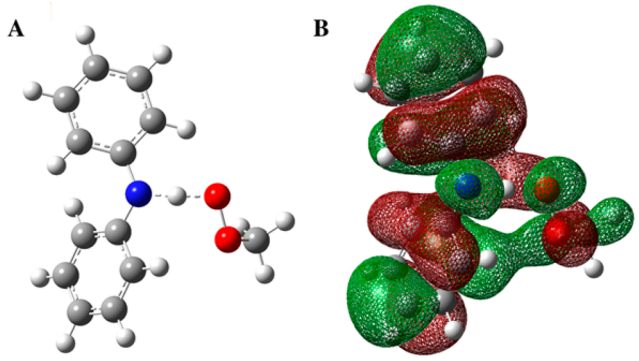

Figure 2. (A) Calculated TS structure for the reaction between diphenylamine and a methylperoxyl radical, and (B) the highest (doubly) occupied molecular orbital.

along with the highest (doubly) occupied molecular orbital, which clearly shows electron delocalization from the π-HOMO of diphenylamine to the π*-LUMO of the methylperoxyl radical. The enthalpic barrier to the reaction was calculated to be 5.0 kcal/mol, and the corresponding free energy barrier ($\Delta G^{\ddagger}$ = 16.2 kcal/mol) yields a rate constant of 1.8×10^4 M^{-1} s^{-1} by application of transition state theory (at 25 °C), in good agreement with the experimental result of 1.5×10^4 M^{-1} s^{-1} (at 50 °C).[3] It should be pointed out that the TS is preceded by a H-bonded prereaction complex and followed by a H-bonded postreaction complex with enthalpies of −4.2 and −9.0 kcal/mol, respectively, relative to the separated starting materials (not shown in Figure 1). The phenyl rings in both the TS and product diphenylaminyl radical are oriented to maximize the delocalization of the radical throughout the π-system, although repulsion between the *ortho* hydrogens precludes complete planarization of the two rings.[14] Addition of *p*-methyl substituents to the rings drops the barrier 1.3 kcal/mol,

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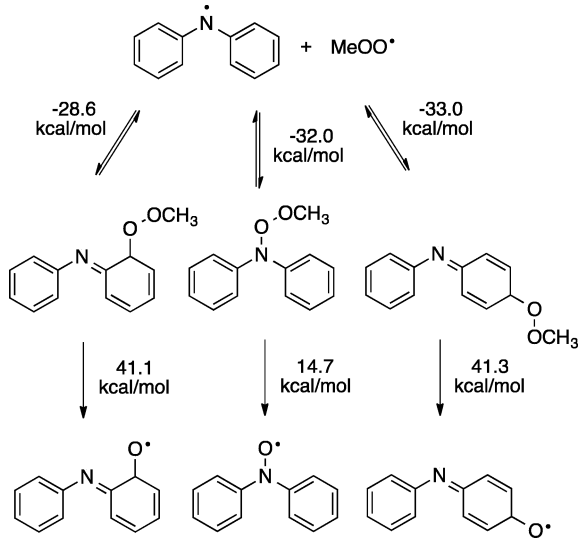
corresponding to a 10-fold increase in the rate constant at 25 °C (k = 1.5 × 10^5 M^{-1} s^{-1}), in good agreement with experiment (k = 1.8 × 10^5 M^{-1} s^{-1} for 4,4′-dioctyldiphenylamine at 37 °C).[8,9] The substituent effect can be understood on thermodynamic grounds by the greater stability of the diarylaminyl radical,[15,16] and on kinetic grounds by the reduced energy gap between the higher energy π-HOMO of the substituted diphenylamine and π^*-LUMO of the peroxyl radical.

Coupling of the diphenylaminyl radical to a methylperoxyl to yield an alkylperoxyamine is 32.0 kcal/mol downhill (enthalpically) and expected to be diffusion-controlled. N−O bond formation must compete with addition of the peroxyl radical to the aryl ring (the preferred pathway for reactions of peroxyl radicals with phenoxyl radicals[17]) as is shown in Scheme 2. The

Scheme 2. Competing Pathways (and Associated ΔH Values) for $Ph_2N^{\bullet}$ + $^{\bullet}OOMe$

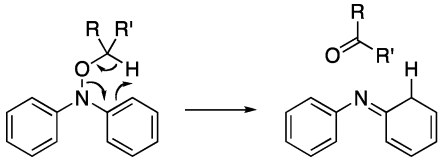


para and *ortho* adducts have C−O BDEs of 33.0 and 28.6 kcal/mol, respectively. While, at first glance, it would seem that the preferred reaction of peroxyl radicals with diphenylaminyl radicals should therefore follow the *para*-coupling pathway, the follow-up reactions need to be considered. In the alkylperoxyamine intermediate the O−O bond is much weaker than the N−O bond (14.7 vs 32.0 kcal/mol), cleaving to yield the nitroxide and alkoxyl radical, whereas in the *para*-coupled adduct, the C−O bond is much weaker than the O−O bond (33.0 vs 41.3 kcal/mol), suggesting that, at elevated temperatures, the intermediates will be funneled toward the thermodynamic product: the nitroxide. (Should the O−O bond in the *para*- or *ortho*-coupled adduct be cleaved, in-cage disproportionation of the two oxygen-centered radicals is likely to proceed to give an *N*-phenyl iminoquinone. Alternatively, tautomerization of the adduct may occur, followed by very rapid O−O dissociation and in-cage disproportionation, to afford the same products.)[30]

The structure of the diphenylnitroxide is similar to that of the diphenylaminyl radical. Nitroxides can have up to ca. 30% of their spin density on the nitrogen atom,[18] and the aromatic rings in the diphenylnitroxide are oriented to maximize delocalization of the radical while minimizing the repulsion associated with planarizing the rings. Though the nitroxides derived from **1** and **2** are comparatively stable (the corresponding hydroxylamines have O−H BDEs of 71.4 and 70.8 kcal/mol, respectively), they can potentially react with peroxyl radicals via their aryl rings. (The *para* and *ortho* adducts from coupling diphenylnitroxide and methylperoxyl have C−O BDEs of 20.9 and 19.6 kcal/mol, respectively. While they are expected to fragment back to the nitroxide at elevated temperatures, competing tautomerization and subsequent O−O bond cleavage will yield *N*-oxides of the same *N*-phenyl iminoquinone products that arise from addition of peroxyl radicals to the rings of diphenylaminyl radicals, *vide supra*.)

Combination of an alkyl (methyl) radical to the diphenylnitroxide is exothermic (53.3 kcal/mol),[19] and the N−O bond dissociation enthalpy in the resultant alkoxyamine is 42.1 kcal/mol (ΔG = 29.5 kcal/mol),[31] making it the rate-determining step in the regeneration of the diarylamine from its diarylaminyl radical upon disproportionation. Interestingly, we were able to locate a transition state for concerted N−O dissociation and disproportionation. The enthalpic cost to reach the transition state ($\Delta H^{\ddagger}$ = 39.4 kcal/mol) was slightly less than the N−O bond dissociation enthalpy and, given the small entropic cost associated with the process ($T\Delta S^{\ddagger} \sim 0$ kcal/mol at 298 K), suggested that the concerted pathway may be accessible. However, we subsequently found that this stationary point was unstable with respect to RHF → UHF transformation,[20] and while a stable UHF wave function could be obtained corresponding to the singlet biradical, no concerted TS structure could be located on this surface, with the structure collapsing directly to products.

While struggling with the foregoing calculations, we wondered whether another concerted process could intervene: a concerted six-electron pericyclic process—an unprecedented retro-carbonyl-ene (hereafter RCE) reaction—which would give the same carbonyl product and an imino-tautomer of diphenylamine:



(3)

Indeed, we were able to find a transition state structure corresponding to this process (cf. Figure 3), and its enthalpic barrier, $\Delta H^{\ddagger}$ = 34.3 kcal/mol, was almost 8 kcal/mol lower than the N−O BDE. The HOMO of the TS structure is a

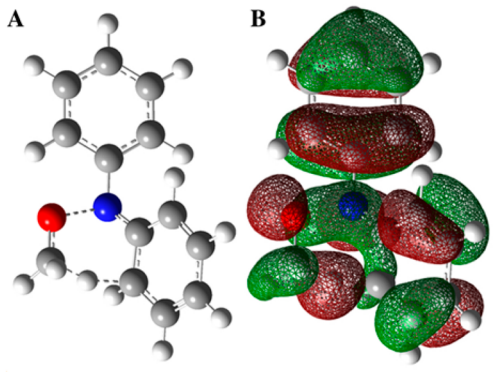


Figure 3. (A) Calculated TS structure for the retro-carbonyl-ene reaction of *O*-methyl *N*,*N*-diphenylhydroxylamine and (B) its HOMO.

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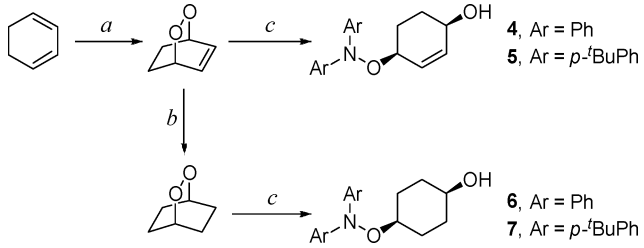
mixture of the π-HOMO of the imino-tautomer of diphenylamine and the π^*-LUMO of formaldehyde, the expected frontier MOs in the six-electron RCE pericyclic process. The low entropy of activation of $T\Delta S^{\ddagger}$ = 1.4 kcal/mol at 298 K suggests that this process could be competitive with N−O bond homolysis.

Since the RCE mechanism involves concerted C−H cleavage, the ease with which it occurs should be dependent on the identity of the alkyl moiety. Indeed, when we replaced the methyl group with an isopropyl or allyl group, we found that the calculated N−O BDEs increased slightly (44.5 and 42.6 kcal/mol, respectively, compared to 42.1 kcal/mol), but the RCE reaction became more facile by 1.8 (32.5) and 4.0 (30.3) kcal/mol, respectively.

While the alkoxyamine derived from the 4,4′-dimethyldiphenylamine had an expectedly weaker N−O bond than in the diphenylamine-derived alkoxyamine owing to the ability of the electron-donating methyl substituents to better stabilize the electron-poor aminyl radical[15,16] (N−O BDE = 41.3 kcal/mol), a concerted RCE TS was also found for this reaction ($\Delta H^{\ddagger}$ = 33.4 kcal/mol), and again, it was lower in enthalpy than that for bond dissociation. These results suggest that the RCE reaction may be an accessible pathway for decomposition of diarylamine-derived alkoxyamines.[32]

Experiments. Despite the proposed central role of *N*,*N*-diarylalkoxyamines in the catalytic activity of diarylamine radical-trapping antioxidants, there are only a handful of examples of their preparation and characterization and only one study of their reactivity—the seminal work of Korcek and coworkers relayed above.[5] We felt that our understanding of this reaction would be greatly bolstered by experiments employing authentic *N*,*N*-diarylalkoxyamines. As such, following Kelly's work,[21] we were able to prepare saturated and unsaturated alkoxyamines derived from diphenylamine and 4,4′-di-*tert*-butyldiphenylamine (**3**) as shown in Scheme 3. Briefly, the

Scheme 3[a]



[a](a) O_2, $h\nu$, Rose Bengal, MeOH/CH_2Cl_2, 0 °C, 6 h, 46%; (b) $N_2(CO_2)_2K_2$, AcOH, MeOH, 0 °C, 2 h, 46%; (c) Ar_2NH, BuLi, Et_2O, −78°C, 10 min, 30% (**4**), 22% (**5**), 20% (**6**), 15% (**7**).

endoperoxide formed from photosensitized oxygenation of 1,3-cyclohexadiene[22] was treated with lithium diarylamide to prepare the unsaturated alkoxyamines **4** and **5**, and the corresponding saturated alkoxyamines **6** and **7** were obtained by the same chemistry, but following the precedented diimide reduction of the 1,3-cyclohexadiene-derived endoperoxide.[23] With these compounds in hand, we set out to determine the kinetics and mechanism of their decomposition by HPLC.

In the event, the unsaturated alkoxyamine decomposed smoothly (cf. Figure 4A), and roughly six times faster than the saturated alkoxyamine at 120 °C, as monitored directly by HPLC (k = 2.4 × 10^{-4} s^{-1} vs k = 4.1 × 10^{-5} s^{-1}). Product analysis revealed near-quantitative formation of diphenylamine

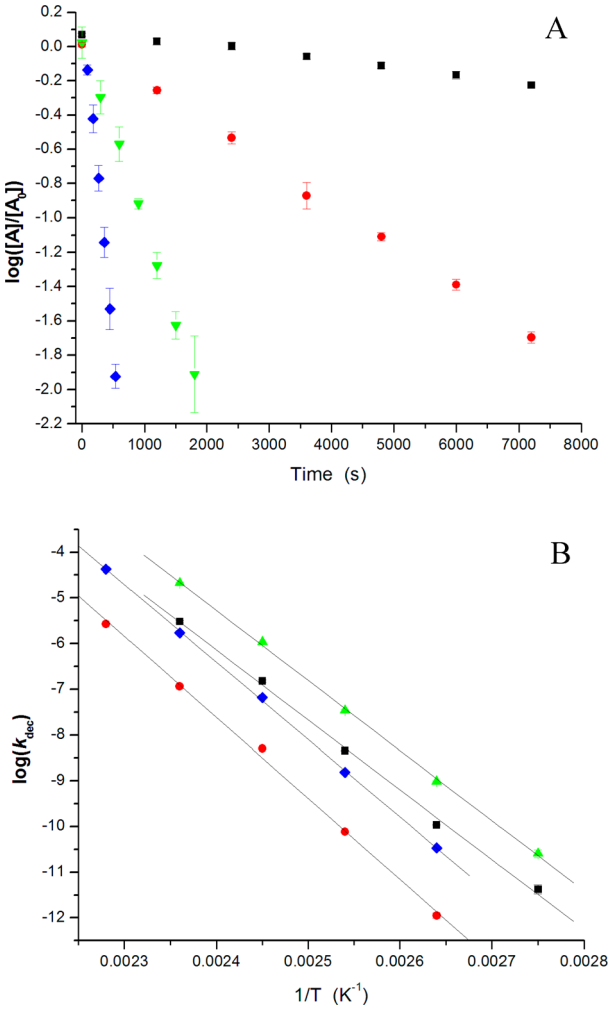


Figure 4. (A) Decomposition of **4** monitored by HPLC between 105 and 150 °C. (B) Temperature dependence of the decomposition of **4** (■), **5** (●), **6** (▲), and **7** (◆).

in both cases. However, subsequent experiments carried out at a variety of temperatures between 75 and 165 °C revealed markedly different Arrhenius parameters for the two substrates (cf. Figure 4B). The decomposition of the saturated alkoxyamine **6** was characterized by E_a = 35.1 ± 0.7 kcal/mol and log A = 15.1 ± 0.4, whereas the unsaturated alkoxyamine **4** decomposed with E_a = 30.2 ± 0.7 kcal/mol and log A = 13.2 ± 0.4. These results hint at different processes: the larger log A is consistent with a simple (N−O) bond dissociation in the transition state,[24] and the smaller log A is consistent with more organization in the transition state, perhaps due to concerted C−H cleavage such as in the computed RCE reaction. The alkoxyamines derived from the 4,4′-di-*tert*-butyldiphenylamine, **5** and **7**, decomposed faster than their diphenylamine-derived counterparts, **4** and **6**, by 2.4- and 3.7-fold at 120 °C, respectively. The activation energies for the substituted compounds (30.3 ± 0.3 kcal/mol for **5** and 33.5 ± 0.2 kcal/mol for **7**) were comparatively lower and also showed that the unsaturated alkoxyamine **5** had a significantly lower log A (13.6 ± 0.2) than the saturated compound alkoxyamine **7** (14.8 ± 0.1), indicating that regardless of the substitution of the diphenylamine, both unsaturated alkoxyamines decomposed through a pathway distinct from the saturated compounds.

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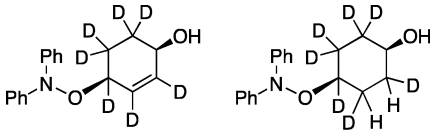
To provide further insight on the lower log *A* value for **4** compared to **6**, we synthesized the octadeuterated compounds **4**-d_8 and **6**-d_8 as in Scheme 3 (using ca. 94% perdeuterated 1,3-cyclohexadiene[25] as starting material) and measured their decomposition kinetics at 120 °C. These experiments revealed a kinetic isotope effect of 1.8 for **4** and 1.2 for **6**, which correspond to values of 2.1 and 1.3 at 25 °C—a primary kinetic isotope effect for **4**, suggesting some C−H bond cleavage in the transition state of the decomposition reaction, and a secondary kinetic isotope effect for **6**.

Direct evidence for the RCE mechanism was obtained upon examination of the products derived from the decomposition of **4**-d_8 and **6**-d_8; deuterium incorporation was observed in the *ortho* position of one of the phenyl rings of the diphenylamine derived from **4** (49% at 90 °C and decreasing with increasing temperature to 28% at 150 °C, as judged by the diminished integration of the signal in the ^{1}H NMR spectra relative to the *meta* and *para* proton signals), whereas the diphenylamine derived from decomposition of **6** contained no deuterium (see Supporting Information). These results, taken alongside the kinetic isotope effects and the Arrhenius parameters, suggest a change in mechanism upon going from an "unactivated" (i.e., saturated) to "activated" (i.e., unsaturated) substrate. Incorporating the insights from the computations, our view is that "unactivated" alkoxyamines undergo N−O homolysis and disproportionation to yield diarylamines,[33] whereas suitably "activated" substrates can access the RCE pathway to yield the same products. Furthermore, a switch from the high-enthalpy/low-entropy N−O homolysis to the low-enthalpy/high-entropy RCE pathway with changing temperature is evident from the changing deuterium incorporation in the diphenylamine product.



4-d_8 **6**-d_8

With the authentic alkoxyamines in-hand, we also evaluated their ability to inhibit the autoxidation of a hydrocarbon at elevated temperature relative to the corresponding diarylamines. We selected hexadecane because Korcek's suggested mechanism in Scheme 1 was derived largely from experiments carried out with this hydrocarbon.[5,26,27] Moreover, we employed the same temperature (160 °C) and the same type of stirred flow reactor as originally used by Korcek.[26] The stirred flow reactor makes use of a constant flow of O_2 to stir the reaction mixture and ensure that it is continuously oxygenated; a necessity at this temperature, otherwise, mass transfer of O_2 becomes rate-limiting.[26,27] In principle, since the half-lives of the unsaturated and saturated alkoxyamines at 160 °C (derived from the Arrhenius parameters given above) are only ca. 100 and 200 s, respectively, they should decompose largely to the diphenylamines in the first few minutes of the reaction, giving rise to inhibited autoxidations indistinguishable from those inhibited by the corresponding diphenylamines. The data, presented as the concentration of hydroperoxide determined as a function of time (using our previously described pro-fluorescent phosphine[28]), are shown in Figure 5. Interestingly, while the data from autoxidations inhibited by the unsaturated alkoxyamines **4** and **5** were fully consistent with

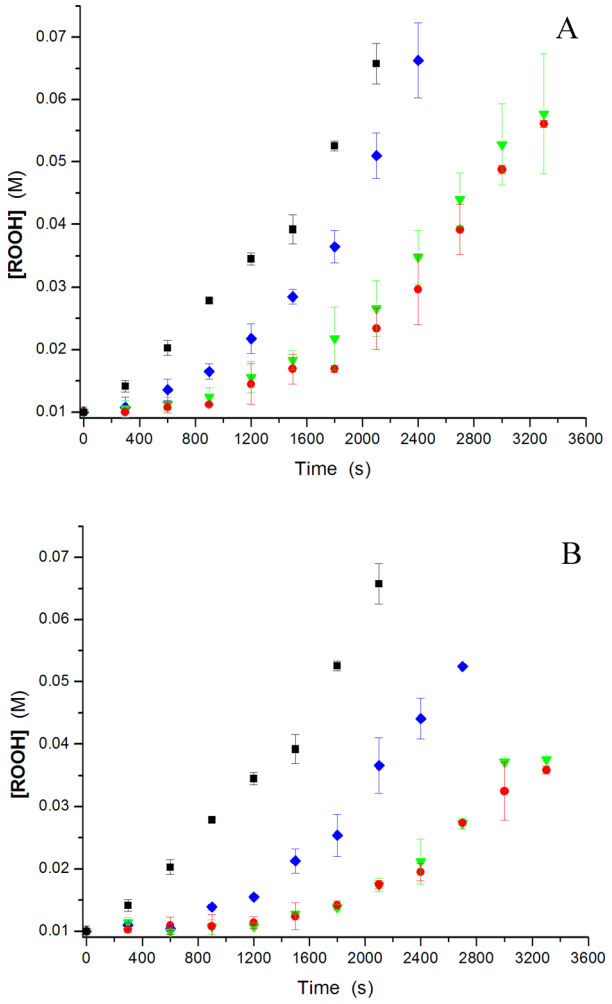


Figure 5. Hydroperoxide formation in the autoxidation of hexadecane at 160 °C initiated by 10 mM tetralin hydroperoxide (■) and inhibited by 100 μM of (A): diphenylamine **1** (●) n = 8.4, unsaturated alkoxyamine **4** (▼) n = 8.2, or saturated alkoxyamine **6** (◆) n = 5.8; (B): 4,4′-di-*tert*-butyldiphenylamine **3** (●) n = 9.5, unsaturated alkoxyamine **5** (▼) n = 9.1, or saturated alkoxyamine **7** (◆) n = 6.3.

our expectations, the saturated alkoxyamines **6** and **7** were found to be less effective than either the unsaturated alkoxyamines or authentic diphenylamines.

These results imply that while the unsaturated alkoxyamines decompose to give diphenylamine quantitatively in hexadecane at 160 °C, the same cannot be said of the saturated alkoxyamines. This was hinted at in Korcek's original experiment, where he found that heating of a mixture of alkoxyamines generated *in situ* from decomposition of *tert*-butyl peroxy-2-ethylhexanoate in hexadecane in the presence of bis(*p*-octylphenyl)nitroxide gave 64% bis(*p*-octylphenyl)-amine.[5] If we consider this in the context of the foregoing mechanistic studies, the results highlight the competition that exists between disproportionation of the initially formed diphenylaminyl-alkoxyl radical pairs and other possible reactions, e.g. H-atom abstraction from hexadecane by the alkoxyl radical, which can initiate autoxidation. In contrast, the unsaturated alkoxyamines yield the same extent of inhibition as the corresponding diphenylamines because no radicals are formed in the RCE reaction, and the diphenylamines are produced quantitatively. This leads to the somewhat surprising conclusion that *the catalytic radical-trapping antioxidant activities*

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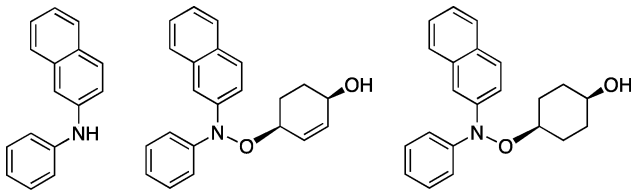
of diarylamines are likely to be highly substrate-dependent. That is, while unsaturated hydrocarbons may be more oxidizable than saturated ones, when oxidized at elevated temperatures in the presence of diarylamines, they should give rise to alkoxyamines which are more efficiently converted back to the starting diarylamines, which will be characterized by higher stoichiometric numbers.

While the foregoing results certainly provide insight into the mechanism of diarylamine regeneration and show that the efficacy of the diarylamine as an RTA is likely to be dependent on the substrate that is undergoing oxidation, it would arguably be more useful to know if the structure of the diarylamine could instead be altered to favor decomposition by the RCE reaction in lieu of N−O homolysis/disproportionation. We surmised that replacement of one of the phenyl rings in the diphenylamine-derived alkoxyamine with a naphthyl ring may decrease the enthalpic barrier for the RCE reaction sufficiently that an activated (i.e., unsaturated) alkyl element would no longer be required for the reaction to proceed in this way. CBS-QB3 calculations suggested that this would indeed be the case, predicting that the $\Delta H^{\ddagger}$ for the RCE reaction of the *O*-methyl alkoxyamine derived from *N*-phenyl-*β*-naphthylamine (**8**)[35] would be 6 kcal/mol lower than the corresponding alkoxyamine derived from diphenylamine. Gratifyingly, we were able to prepare the two corresponding *N*-phenyl-*β*-naphthylamine-derived alkoxyamines **9** and **10** as in Scheme 3.



8 **9** **10**

The *β*-naphthyl-containing alkoxyamines **9** and **10** decomposed rapidly compared with the corresponding diphenylamine-derived compounds (at 120 °C, $k = 2.1 \times 10^{-3}$ and 6.4×10^{-4} s^{-1}, respectively). More interestingly, the temperature dependence of the rate constants for their disappearance yielded Arrhenius parameters of log $A = 13.0 \pm 0.3$ and $E_a = 28.2 \pm 0.4$ kcal/mol for **9** and log $A = 12.9 \pm 0.2$ and $E_a = 29.0 \pm 0.4$ kcal/mol for **10**, implying that both compounds decompose via the RCE pathway. Moreover, hexadecane autoxidations at 160 °C inhibited by **9** and **10** were indistinguishable from each other, and from hexadecane autoxidations inhibited by *N*-phenyl-*β*-naphthylamine[35] (cf. Figure 5). Thus, by lessening the energetic penalty paid by the group on the amine to undergo the concerted process (the aromatic stabilization of the "second" ring of naphthalene is estimated to be 10−12 kcal/mol less than that in benzene),[29] we can favor this pathway even for "unactivated" (i.e., saturated) alkoxyamines.

Despite the greater reactivity of *N*-phenyl-*β*-naphthylamine[35] toward peroxyl radicals compared to diphenylamine ($k = 1.1 \times 10^5$ M^{-1} s^{-1} (**8**) vs 4.2×10^4 M^{-1} s^{-1} (**1**) at 65 °C),[34] and significantly more favorable regeneration from its saturated alkoxyamine (*vide supra*), it is not as effective an inhibitor of hexadecane autoxidation (compare Figures 5A and 6 and stoichiometric factors derived from the data of $n = 8.4$ for the former and 5.2 for the latter). The likely explanation is that addition of peroxyl radicals to the *α*-position of the naphthyl ring of the *N*-phenyl-*β*-naphthylaminyl radical intermediate will also be made easier compared to the diphenylaminyl radical due to the reduced aromaticity of the naphthyl ring. Indeed, the CBS-QB3-calculated C−O BDE of the adduct is 41.7 kcal/mol, which is 13.1 kcal/mol stronger than the analogous adduct of the diphenylaminyl radical (see Scheme 1), which makes peroxyl radical addition to the ring 9.7 kcal/mol more favorable than N−O bond formation (see Scheme 4). Although this reaction is reversible, it must compete with subsequent O−O bond homolysis (or tautomerization followed by homolysis), which requires roughly the same amount of energy as the reverse reaction (41.1 kcal/mol). Moreover, O−O bond homolysis is likely to be irreversible under the reaction conditions, as the resultant radicals can disproportionate to the iminoquinone and alcohol, products from which the diarylamine cannot be regenerated.

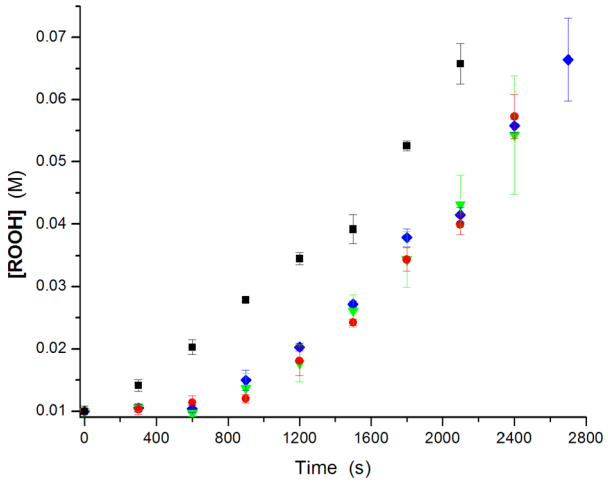
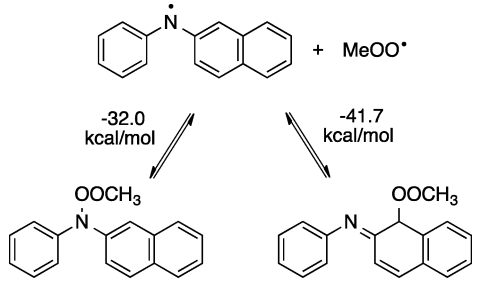


Figure 6. Hydroperoxide formation in the autoxidation of hexadecane at 160 °C initiated by 10 mM tetralin hydroperoxide (■), and inhibited by 100 μM of either *N*-phenyl-*β*-naphthylamine **8** (●) $n = 5.2$, unsaturated alkoxyamine **9** (▼) $n = 5.2$, or saturated alkoxyamine **10** (◆) $n = 5.2$.

Scheme 4. Key Competing Pathways (and Associated ΔH Values) for Phenyl *β*-Naphthylaminyl + ·OOMe



The foregoing results have important implications with respect to the design of improved diarylamine radical-trapping antioxidants. They suggest that while optimization of the stability of the diarylaminyl radical may promote the initial H-atom transfer (proton-coupled electron transfer, eq 1) from the diarylamine to the peroxyl radical, this may not be helpful for promoting regeneration of the amine, since it could promote N−O bond homolysis and may facilitate cage escape. Instead, it would appear that diarylamines which are good H-atom donors and whose corresponding alkoxyamines preferentially follow the retro-carbonyl-ene route to regenerate the diarylamine

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would be ideal radical-trapping antioxidants. We are currently exploring these ideas.

CONCLUSIONS

The synthesis of a series of *N*,*N*-diarylalkoxyamines has enabled kinetic and mechanistic experiments that clarify the mechanism of the catalytic behavior of diarylamine radical-trapping antioxidants. The determination of Arrhenius parameters, deuterium kinetic isotope effects, and isotope incorporation experiments confirm computational predictions that alkoxyamines derived from diphenylamines and saturated substrates decompose by N−O homolysis followed by disproportionation, whereas those derived from either diphenylamines and unsaturated substrates or *N*-phenyl-β-naphthylamine[35] and saturated substrates decompose by a concerted retro-carbonyl-ene reaction. This change in mechanism has significant implications in the use of diarylamine radical-trapping antioxidants, since they are expected to be comparatively better inhibitors of the autoxidation of unsaturated substrates owing to the more efficient regeneration of the diarylamine from its corresponding alkoxyamine. Moreover, it provides important insight into the design of the next generation of diarylamine radical-trapping antioxidants: compounds which turnover via the retro-carbonyl ene pathway will be far more effective than those that turnover via N−O homolysis and in-cage disproportionation, as do the industry-standard alkylated diphenylamines. While substitution of one of the phenyl rings for a naphthyl ring achieves this, it also makes deleterious (off-cycle) reaction pathways more accessible. Limiting these reactions, while preserving the RCE pathway for diarylamine regeneration, should be the focus of future research.

EXPERIMENTAL SECTION

General. Reagents were purchased from commercial suppliers and used without further purification. 2,3-Dioxabicyclo[2.2.2]oct-5-ene was synthesized from the reaction of 1,3-cyclohexadiene with singlet oxygen according to the procedure of Ziegert and Brase.[22] The diimide reduction of the unsaturated endoperoxide was carried out according to the procedure of Coughlin, Brown, and Salomon.[23] Cyclohexadiene-d_8 was produced as a mixture of isomers via the procedure of Mugridge, Bergman, and Raymond,[25] and the crude mixture was subjected directly to singlet oxidation. Column chromatography was carried out using flash silica gel (40−63 μm, 230−400 mesh). ^{1}H and ^{13}C NMR were recorded on a Bruker AVANCE spectrometer at 400 and 100 MHz, respectively, unless specified otherwise. High-resolution mass spectra were obtained on a Kratos Concept Tandem mass spectrometer.

General Procedure for the Synthesis of Diarylalkoxyamines. In a dry Schlenk flask under an inert atmosphere, 2.2 mmol of the appropriate diarylamine was dissolved in 15 mL of dry Et_2O (0.13 M) and cooled to −78 °C. Once cooled, 0.90 mL of *n*-BuLi in hexanes (2.5 M, 2.2 mmol) was added dropwise to the diarylamine solution, after which it was allowed to stir for 15 min at −78 °C. Endoperoxide (2.0 mmol) was dissolved in 1−2 mL of dry Et_2O and was added rapidly to the cooled reaction (over *ca.* 20 s; the color of the solution typically became a dark green). The reaction was allowed to stir for 10 min before an excess of water was added to quench the reaction, and the solution was allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted with Et_2O twice. The combined organic phases were washed with brine, then dried with $MgSO_4$, filtered, and concentrated in vacuo. The alkoxyamines were purified by silica gel chromatography with 40% to 70% Et_2O/petroleum ether, typically yielding a viscous oil which was crystallized from a small amount of Et_2O in hexanes at −20 °C overnight.

4-[*N*,*N*-Diphenyl(aminoxy)]-2-cyclohexen-1-ol (4). Yield: 30%. Off-white solid. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31 (dd, J = 8.5, 7.4 Hz, 4H), 7.17−7.14 (m, 4H), 7.13−7.08 (m, 2H), 6.01−5.94 (m, 2H), 4.34 (m, 1H), 4.17 (br, 1H), 2.09−2.02 (m, 1H), 1.87−1.75 (m, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 149.4, 134.3, 128.9, 128.8, 124.4, 121.1, 74.8, 66.0, 28.4, 24.1. HRMS m/z: calcd $C_{18}H_{19}NO_2$, 281.1416; found, 281.1427.

4-[*N*,*N*-Di(4-*tert*-butylphenyl)aminooxy]-2-cyclohexen-1-ol (5). Yield: 22%. Off-white solid. ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.34 (d, J = 8.8 Hz, 4H), 7.01 (d, J = 8.8 Hz, 4H), 5.86 (dd, J = 10.2, 1.7 Hz, 1H), 5.79 (dd, J = 10.5, 2.9 Hz, 1H), 4.86 (d, J = 5.5 Hz, 1H), 4.19 (m, 1H), 3.97 (m, 1H), 1.97−1.91 (m, 1H), 1.68−1.56 (m, 3H), 1.26 (s, 18H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 147.04, 146.95, 134.0, 129.2, 125.6, 120.7, 74.4, 66.0, 34.3, 31.4, 28.5, 24.1. HRMS m/z: calcd $C_{26}H_{35}NO_2$, 393.2668; found, 393.2667.

4-[*N*,*N*-Diphenyl(aminooxy)]cyclohexanol (6). Yield: 20%. White solid. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.35−7.30 (m, 4H), 7.20−7.17 (m, 4H), 7.14−7.09 (m, 2H), 3.97 (m, 1H), 3.83−3.78 (m, 1H), 2.07−1.99 (m, 2H), 1.76−1.62 (m, 6H), 1.36 (br, 1H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 149.7, 128.8, 124.2, 121.0, 77.5, 68.1, 30.8, 26.7. HRMS m/z, calcd $C_{18}H_{21}NO_2$, 283.1572; found, 283.1551.

4-[*N*,*N*-Di(4-*tert*-butylphenyl)aminooxy]-cyclohexanol (7). Yield: 15%. White solid. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.30 (d, J = 8.8 Hz, 4H), 7.08 (d, J = 8.8 Hz, 4H), 3.91 (m, 1H), 3.80−3.75 (m, 1H), 2.01 (m, 2H), 1.72−1.62 (m, 6H), 1.30 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.8, 125.6, 120.5, 68.2, 34.3, 31.4, 30.8, 26.8. HRMS m/z: calcd $C_{26}H_{37}NO_2$, 395.2824; found, 395.2849.

4-[*N*,*N*-Diphenyl(aminooxy)]-2-(1,2,3,4,5,5,6,6-d_8)-cyclohexen-1-ol (4-d_8). Yield: 29%. Off-white solid. Ca. 94% D. ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.31 (dd, J = 8.4, 7.2 Hz, 4H), 7.16 (dd, J = 8.7, 1.2 Hz, 4H), 7.13−7.08 (m, 2H), 5.97 (d, J = 9.7 Hz, 0.15H), 4.33 (s, 0.07H), 4.18−4.15 (m, 0.06H), 2.01 (s, 0.07H), 1.78 (d, J = 12.7 Hz, 0.21H), 1.51 (s, 1H). ^{13}C NMR (76 MHz, $CDCl_3$) δ 149.3, 128.9, 124.3, 121.1. HRMS m/z: calcd $C_{18}H_{19}NO_2$, 289.1924; found, 289.1918.

4-[*N*,*N*-Diphenyl(aminooxy)]-2-(1,2,3,4,5,5,6,6-d_8)-cyclohexanol (6-d_8). Yield: 14%. White solid. Ca. 93% D. ^{1}H NMR ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.30 (dd, J = 8.5, 7.2 Hz, 4H), 7.16 (d, J = 8.7 Hz, 4H), 7.09 (t, J = 7.3 Hz, 2H), 3.94−3.92 (m, 0.07H), 3.78−3.76 (m, 0.07H), 3.40 (t, J = 6.6 Hz, 0.06H), 1.97 (br, 1H), 1.66 (br, 1H), 1.31 (s, 1H). ^{13}C NMR (76 MHz; $CDCl_3$): δ 149.7, 128.8, 124.1, 121.0. HRMS m/z: calcd $C_{18}H_{21}NO_2$, 291.2074; found, 291.2096.

4-[*N*-2-Naphthyl-*N*-phenyl(aminooxy)]-2-cyclohexen-1-ol (9). Yield: 13%. Off-white solid. ^{1}H NMR (400 MHz; DMSO-d_6): δ 7.86 (m, 3H), 7.61 (d, J = 2.0 Hz, 1H), 7.47 (td, J = 13.6, 5.8 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.27 (dd, J = 8.8, 2.2 Hz, 1H), 7.16 (m, 3H), 5.92−5.84 (m, 2H), 4.89 (d, J = 5.6 Hz, 1H), 4.33 (m, 1H), 3.99 (m, 1H), 2.04−1.98 (m, 1H), 1.75−1.56 (m, 3H). ^{13}C NMR (100 MHz; DMSO-d_6): δ 149.0, 146.3, 136.9, 133.2, 130.4, 129.0, 128.8, 127.39, 127.37, 126.4, 125.8, 125.0, 124.4, 121.1, 120.7, 116.8, 74.4, 64.3, 27.7, 24.1. HRMS m/z: calcd $C_{26}H_{37}NO_2$, 331.1572; found, 331.1555.

4-[*N*-2-Naphthyl-*N*-phenyl(aminooxy)]cyclohexanol (10). Yield: 11%. Off-white solid. ^{1}H NMR (300 MHz; DMSO-d_6): δ 7.87 (m, 3H), 7.60 (s, 1H), 7.51−7.33 (m, 4H), 7.26 (d, J = 8.9 Hz, 1H), 7.18−7.11 (m, 3H), 4.44 (d, J = 3.6 Hz, 1H), 3.91 (m, 1H), 3.57 (m, 1H), 1.90 (m, 2H), 1.67−1.43 (m, 6H). ^{13}C NMR (76 MHz; DMSO-d_6): δ 149.2, 146.6, 133.2, 130.3, 128.9, 128.7, 127.4, 127.3, 126.4, 124.9, 124.2, 121.1, 120.7, 116.6, 77.9, 65.5, 30.4, 26.2. HRMS m/z: calcd $C_{26}H_{37}NO_2$, 333.1729; found, 333.1731.

Alkoxyamine Decomposition Experiments. *n*-Hexadecane (1.0 mL) was added to 0.015 mmol of alkoxyamine that was weighed into a glass vial. A magnetic Teflon coated stir bar was added, and the vial was capped with a rubber septum. The vial was then placed in a heating block at the appropriate temperature and allowed to stir for 30 s before the first sample was taken. Samples (100 μL) were taken at regular intervals and added to 900 μL of a 2.2 mM solution of benzyl alcohol in 2% isopropanol/hexanes (HPLC grade). Samples were analyzed using a Waters 2695 Alliance HPLC (gradient: 1−4 min:1.2% *i*PrOH/hexanes, 0.8 mL min^{-1}; 5 min, 1.4% *i*PrOH/hexanes, 0.8 mL min^{-1}; 10 min 1.6% *i*PrOH/hexanes, 1.2 mL min^{-1}; 15−16 min:2.0%

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*i*PrOH/hexanes, 0.6 mL min^{-1}; 30 min; Sunfire Silica column (5 μm, 4.6 mm × 250 mm)) and analyzed by UV absorbance at 215 nm.

Hexadecane Autoxidations. *n*-Hexadecane (100 mL) was thoroughly degassed with argon and then heated to 160 °C while argon was continuously bubbled through the liquid. Once the temperature stabilized, 0.10 mmol of inhibitor (**1**, **3**−**10**) and 164 mg (1.0 mmol) of tetralin hydroperoxide were added to the solution, and the flow of argon was replaced with O_2. Aliquots (1.5 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 separate wells of a 96-well microplate, and the automated reagent dispenser of a Biotek Synergy H1 microplate reader was used to dilute each sample with *tert*-amyl alcohol (200 μL) and a solution of a fluorgenic phosphine dye solution (20 μL of a 250 μM stock solution in acetonitrile) immediately before reading. The plate was stirred for 8 s and allowed to rest for 2 s more, and the fluorescence of each well was measured every second for 60 s (excitation = 340 nm; emission = 425 nm). The concentration of hydroperoxide was determined from the rate of phosphine oxidation using the rate constant for the reaction of the dye with secondary hydroperoxides in *tert*-amyl alcohol (k = 1.2 M^{-1} s^{-1}) assuming pseudo-first-order kinetics.[28]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete kinetic data, NMR spectra for isotope labeling studies, NMR spectra of synthesized alkoxyamines, and Cartesian coordinates and energetics of computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(32) It is difficult to determine $\Delta S^{\ddagger}$ for the N−O bond dissociation/in-cage disproportionation pathway for direct comparisons to the concerted process, or for comparison to our solution-phase experiments (*vide infra*).
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