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Unprecedented Inhibition of Hydrocarbon Autoxidation by Diarylamine Radical-Trapping Antioxidants

Ron Shah,[†] Evan A. Haidasz,[†] Luca Valgimigli,[‡] and Derek A. Pratt*,[†]

[†]Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5
[‡]Department of Chemistry "G. Ciamician", University of Bologna, Bologna I-40126, Italy

Supporting Information

ABSTRACT: The reactivities of novel heterocyclic diarylamine radical-trapping antioxidants (RTAs) are profiled in a heavy hydrocarbon at 160 °C, conditions representative of those at which diphenylamine RTAs are used industrially. While carboxylic acids produced during the autoxidation are shown to deactivate these more basic RTAs, the addition of a sacrificial base leads to efficacies that are unprecedented in the decades of academic and industrial research in this area.

Diarylamine (Ar_2NH) radical-trapping antioxidants (RTAs) are key additives to many types of petroleum-derived products because of their high inherent reactivities toward peroxyl radicals (eq 1) and the persistence of the resultant

$$Ar_2NH + ROO^{\bullet} \xrightarrow{k_1} Ar_2N^{\bullet} + ROOH \quad (1)$$

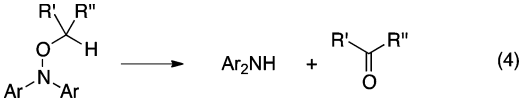
radicals toward both O_2 and nonradical species.[1,2] Instead, the diarylaminyl radical reacts with another peroxyl radical to yield a nitroxide (eq 2), which can either react with a peroxyl radical on

$$Ar_2N^{\bullet} + ROO^{\bullet} \xrightarrow{\text{very fast}} Ar_2NO^{\bullet} + RO^{\bullet} \quad (2)$$

one of the aryl rings or combine with an alkyl radical to give an alkoxyamine (eq 3). Either way, a single Ar_2NH molecule inhibits the propagation of two autoxidative chain reactions and gives rise to a so-called stoichiometric factor of 2.

$$Ar_2NO^{\bullet} + R^{\bullet} \xrightarrow{\text{very fast}} Ar_2NOR \quad (3)$$

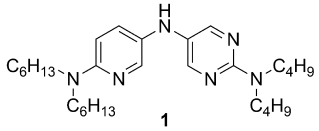
At elevated temperatures, such as those to which engine lubricants are exposed and at which polymers are processed, much greater stoichiometric factors have been reported. For example, a remarkable stoichiometric factor of 52 was determined for a 4,4′-dialkyldiphenylamine in paraffin oil at 130 °C.[4] The apparent catalytic antioxidant behavior of diphenylamines results from regeneration of the diphenylamine from the *N*,*N*-diarylalkoxyamine (eq 4), as first suggested by Korcek[5] and recently investigated by our group.[6] This transformation, which occurs either by N−O dissociation and in-cage disproportionation or a retro-carbonyl−ene reaction, is believed to underlie the unique efficacy of diphenylamine RTAs in high-temperature applications.



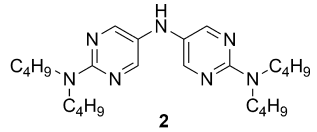
(4)

Over the years we have shown that the incorporation of nitrogen atoms into the aromatic rings of phenolic[7−11] and diphenylamine[12−14] RTAs enables the design of compounds with outstanding reactivities toward peroxyl radicals (i.e., $\Delta H_1^{\ddagger} \approx 0$). Herein we report preliminary results of the reactivity of these heterocyclic diarylamine RTAs at 160 °C, a temperature more representative of their potential "real world" applications and at which the reaction in eq 4 may be expected to occur. The compounds in Chart 1 were selected for study on the basis of their reactivity toward peroxyl radicals (high k_1, i.e., **1**−**3**),

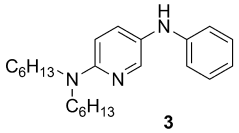
Chart 1. Some Diarylamines and Their Relevant Properties[27]



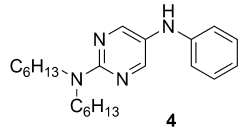
1
k_1(37°C) = 3.1x10^7 M^{-1}s^{-1}
E^0 = 0.50 V



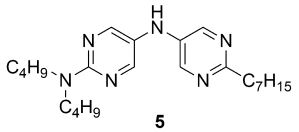
2
k_1(37°C) = 1.8x10^7 M^{-1}s^{-1}
E^0 = 0.65 V



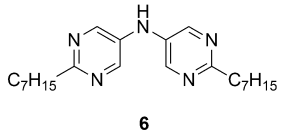
3
k_1(37°C) = 1.1x10^7 M^{-1}s^{-1}
E^0 = 0.60 V



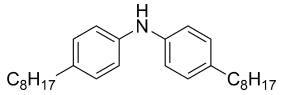
4
k_1(37°C) = 3.0x10^6 M^{-1}s^{-1}
E^0 = 0.81 V



5
k_1(37°C) = 2.4x10^6 M^{-1}s^{-1}
E^0 = 0.84 V



6
k_1(37°C) = 3.0x10^4 M^{-1}s^{-1}
E_{pa} = 1.55 V



7
k_1(37°C) = 1.8x10^5 M^{-1}s^{-1}
E_{pa} = 1.02 V

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stability toward oxidation (high E^0, i.e., **6**), or a balance of these two characteristics (i.e., **4** and **5**). In fact, they are similar to the compounds we initially reported,[12−14] but are substituted with longer alkyl chains in order to ensure their solubility in heavy hydrocarbons and low volatility at elevated temperatures (see the Supporting Information for details of their preparation). Diarylamine **7** is representative of industry-standard alkylated diphenylamines, therefore providing a basis for comparison.

To evaluate the high-temperature RTA activities of **1**−**7**, autoxidations of *n*-hexadecane were carried out at 160 °C in a stirred-flow reactor, where a constant positive pressure of O_2 was used to stir the medium and prevent mass transfer from becoming rate-limiting, which is otherwise a problem at this temperature.[3,15] Tetralin hydroperoxide (10 mM) was used as a radical initiator since inhibited autoxidations in the absence of an initiator were *very* slow (see Supporting Information). At regular intervals, aliquots of the reaction mixture were removed and cooled, and the concentration of hydroperoxide products were determined by reaction with a fluorogenic phosphine developed in our laboratory.[16] The autoxidations were followed for the first 2% of the reaction (based on hydroperoxide formation), since beyond ca. 3% conversion the hydroperoxide yield begins to decrease and highly complex mixtures of ketones, alcohols, carboxylic acids, and esters arise.[15] The results are shown in Figure 1.

In the absence of an RTA additive, the rate of hydroperoxide formation increases with time because of the autocatalytic nature of the reaction: the product hydroperoxides undergo O−O cleavage, leading to radicals that initiate new chain reactions.[15] The industry standard **7** inhibits the autoxidation for ca. 900 s, after which a profile roughly identical to that for the uninhibited autoxidation is observed, while the heterocyclic diarylamines **1**−**6** show varied behavior. The data obtained with the most reactive compounds (**1**, **2**, and **3**) are shown in the top panel of Figure 1. Of them, only the bis(pyrimidine) **2** inhibits the autoxidation more effectively than **7**, and the difference seems inconsistent with the 100-fold difference in k_1 determined at 37 °C (cf. Chart 1). Although the pyridine-containing diarylamines **1** and **3** display poor inhibitory activity in the early going, they appear to slow the rate of autoxidation with time, suggesting that one or more of their oxidation products are inhibitors. The data obtained with the less reactive compounds (**4**, **5**, and **6**) are shown in the bottom panel of Figure 1. Compound **4** has a similar effect on the autoxidation as bis(pyrimidine) **2**, both of which exhibit superior activity compared with the industry standard **7**; in contrast, bis(pyrimidine) **5** starts off well but appears to be entirely consumed in the first 1500 s, and bis(pyrimidine) **6** is ineffective, consistent with its lower k_1.

Beyond the results obtained with bis(pyrimidine) **6**, the data in Figure 1 are impossible to reconcile in light of the values of k_1 given in Chart 1. Since the reactions have very small activation enthalpies, raising the temperature has only a small effect on the magnitude of k_1 (e.g., in the case of **7**, for which $\log A = 6.9$ and E_a = 2.5 kcal/mol,[14] $k_1 = 4.4 \times 10^5$ M^{-1} s^{-1} at 160 °C, which is only 2.4-fold higher than at 37 °C). On this basis it was expected that the significant differences in the reactivities of **1**−**6** and **7** found at ambient temperature (37 °C) should translate to elevated temperatures (160 °C). Moreover, the rate of regeneration of the diarylamine from the corresponding alkoxyamine (i.e., eq 4) should increase with the stability of the diarylaminyl radicals derived from **1**−**5** (e.g., N−H bond dissociation energy (BDE) = 79.2 kcal/mol for **2**) compared with that derived from **7** (N−H BDE = 82.2 kcal/mol).[14]

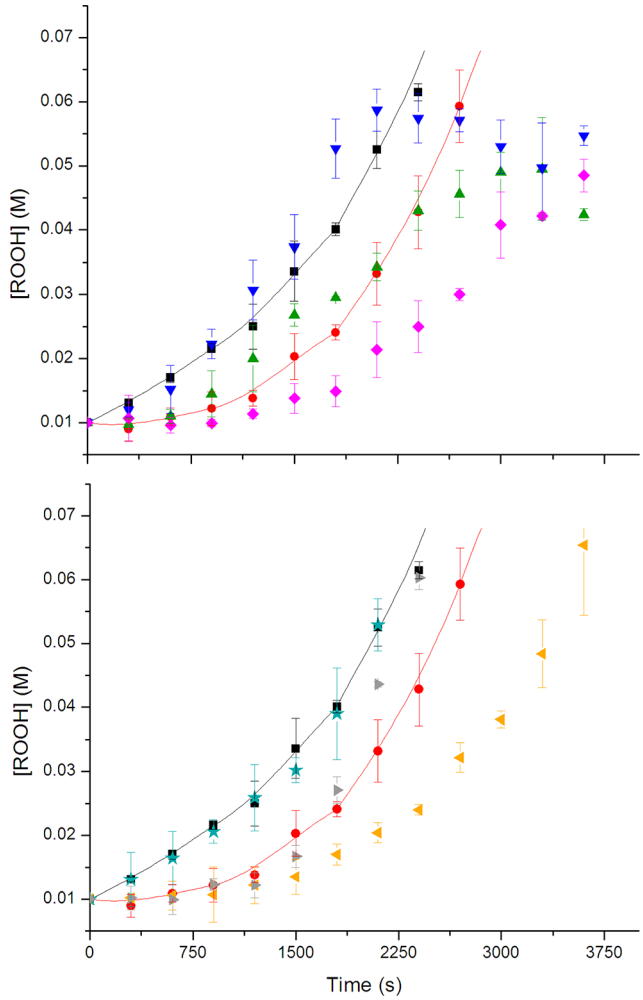

Figure 1. Hydroperoxide formation in the autoxidation of *n*-hexadecane at 160 °C initiated by 10 mM tetralin hydroperoxide in the absence of an RTA (black ■) or in the presence of 40 μM **1** (blue ▼), **2** (magenta ◆), **3** (green ▲), **4** (gold ◀), **5** (gray ▶), **6** (aqua ★), or **7** (red ●).

Given the foregoing, we wondered whether the heterocyclic diarylamines, while stable toward O_2 at ambient temperatures, were not so at elevated temperatures. In fact, when each of **1**−**6** was heated to 160 °C in *n*-hexadecane under O_2 in the absence of an initiator, the most oxidizable compounds (**1**, **2**, and **3**; E^0 = 0.5−0.65 V) decomposed steadily over 1 h ($t_{1/2}$ = 19, 24, and 22 min, respectively) while compounds **4**, **5**, and **6** ($E^0 > 0.8$ V) did not decompose to any significant extent, similarly to **7** (see the Supporting Information for the data). Therefore, the poor reactivity of the pyridine-containing compounds as RTAs at 160 °C can be readily explained by the fact that they autoxidize under the reaction conditions. However, since the pyrimidine-containing compounds are stable toward O_2, something else must account for their poorer-than-expected RTA activities.

We next considered whether the heterocyclic diarylamines were sufficiently basic to interact with carboxylic acids that are formed in the autoxidation. Hydrocarbon autoxidation is known to produce carboxylic acids from the very early stages of the reaction in addition to hydroperoxides. Korcek and co-workers suggested that they arise primarily from fragmentation of γ-hydroperoxy ketones by a concerted mechanism recently investigated by Green, Truhlar, and co-workers (cf. Scheme 1).[17] In fact, when acid formation was monitored over the initial

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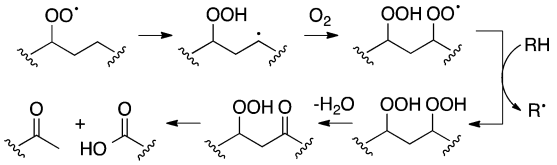
Scheme 1. Proposed Mechanism of Acid Formation in the Early Stages of Hydrocarbon Autoxidations



period (the first 2400 s) of an autoxidation of *n*-hexadecane directly by electrospray ionization mass spectrometry, the total acid concentration was already roughly 25% of the hydroperoxide concentration (~15 mM vs ~60 mM; see the Supporting Information). Protonation of the diarylamines by these acids would lead to much poorer RTAs since the diarylaminyl radicals are already inherently electron-poor.[18,19] For example, the N–H BDE of **4** (calculated using the reliable CBS-QB3 method)[20] increases from 81.8 to 86.0 kcal/mol upon protonation of the ring.[21]

To assess whether acid suppresses the reactivity of the heterocyclic diarylamines, palmitic acid, a nonvolatile saturated carboxylic acid, was added to an autoxidation inhibited by **4**. In the event, as little as 1 mM acid was found to disrupt the inhibitory activity of **4**, while that of the expectedly less basic diphenylamine **7** was unchanged, as was the course of the uninhibited oxidation (see the Supporting Information for the data). In light of these results, a base was added to an autoxidation inhibited by **4** in an attempt to "rescue" its RTA activity. Gratifyingly, in the presence of the nonvolatile nonnucleophilic base 2,4,6-tri-*tert*-butylpyridine (TTBP) (1 mM), an unprecedented inhibited period was observed (Figure 2).

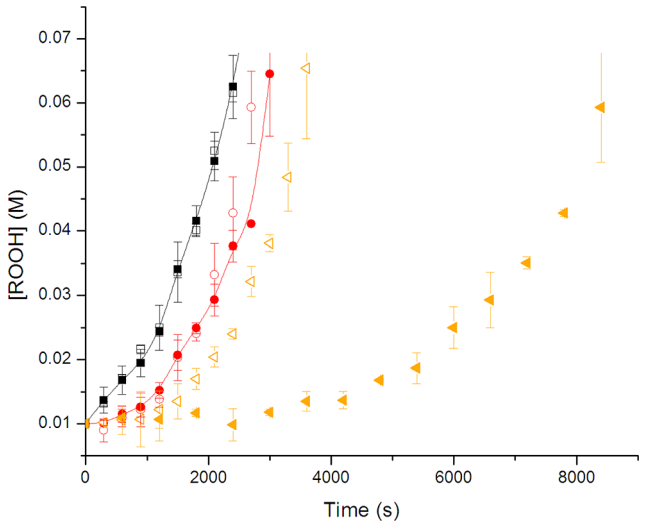


Figure 2. Hydroperoxide formation in the autoxidation of *n*-hexadecane at 160 °C initiated by 10 mM tetralin hydroperoxide in the absence of RTA (black ■) or inhibited by 40 μM **4** (gold ◀) or **7** (red ●) in the presence of TTBP (1 mM). Open symbols correspond to the data in Figure 1 (i.e., in the absence of TTBP).

Importantly, the addition of base had no effect on the activity of diphenylamine **7** (or the uninhibited rate of oxidation), suggesting that the acid produced early in the autoxidation was sufficient to deactivate heterocyclic diarylamine **4**, but not diphenylamine **7**. The activity of **4** could also be rescued using cesium carbonate or the *tert*-alkylated primary amine Primene 81-R, underscoring that the inactivation of **4** is due to protonation (see the Supporting Information for the data).[22]

Consistent with the foregoing, the pK_a of the conjugate acid of **4** was determined to be almost 4 units greater than that of the conjugate acid of **7** (8.2 ± 0.2 vs 4.6 ± 0.3 in 4:1 CH_3CN/H_2O; see the Supporting Information for the data). In fact, each of the reactive heterocyclic diarylamines (**1**–**5**) were found to be significantly more basic than the diphenylamine, with pK_a's of the corresponding conjugate acids of 9.8 ± 0.1 (**1**), 8.8 ± 0.1 (**2**), 8.4 ± 0.1 (**3**), and 8.3 ± 0.1 (**5**).[23] Accordingly then, autoxidations were much better inhibited by these compounds in the presence of added base (Figure 3).[24] Interestingly, even the pyridine-

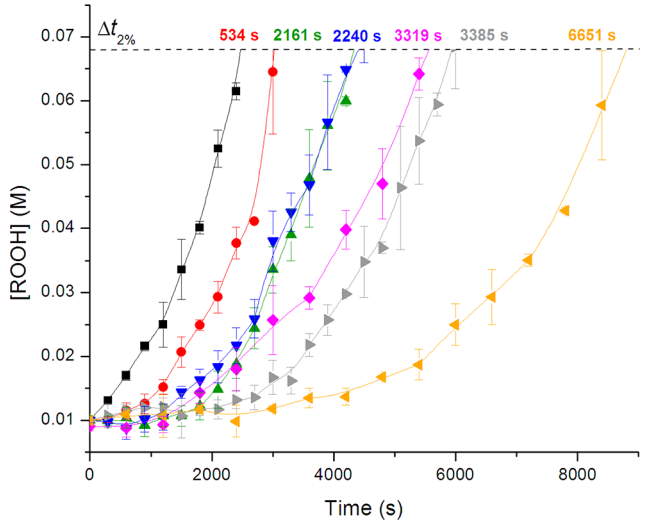


Figure 3. Hydroperoxide formation in the autoxidation of *n*- hexadecane at 160 °C initiated by 10 mM tetralin hydroperoxide in the absence of RTA (black ■) or inhibited by 40 μM **1** (blue ▼), **2** (magenta ◆), **3** (green ▲), **4** (gold ◀), **5** (gray ▶), or **7** (red ●) in the presence of TTBP (1 mM). The delay in the time required to reach [ROOH] = 68 mM (=2%) in the presence of each of **1**–**5** or **7** is given as $\Delta t_{2\%}$.

containing compounds **1** and **3**, which were found to be relatively unstable toward O_2 at 160 °C, were superior to **7**. This is presumably because the balance of either **1** or **3** remains over the course of the autoxidation is highly potent. The pyrimidine-containing compounds **2**, **4**, and **5** are much better overall, presumably because of a compromise between stability and reactivity, which is best demonstrated by **4**.

The unprecedented inhibited periods observed for the heterocyclic diarylamines *in the presence of base* must result from increased stoichiometric factors for the reactions of these amines with peroxyl radicals,[25] arising from one or both of the following: faster/more efficient regeneration of the diarylamine from its corresponding alkoxyamine and/or fewer deleterious off-cycle reactions. We recently investigated the mechanism of diphenylamine regeneration,[6] which revealed that either a retro-carbonyl–ene reaction or N–O dissociation/disproportionation pathway operates depending on the structure of the diarylamine and/or substrate. Those studies were enabled by the synthesis of authentic alkoxyamines derived from diphenylamine and 4,4′-di-*tert*-butyldiphenylamine. Unfortunately, attempts to prepare authentic alkoxyamines derived from **1**–**5** have not been successful, precluding determination of the kinetics of diarylamine regeneration for these compared with **7**. However, CBS-QB3 computations[20] of the N–O BDEs in model (O–CH_3) alkoxyamines derived from **4** and **7** suggest that the regeneration

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of diarylamine **4** requires 2.3 kcal/mol less energy than the regeneration of **7**, which corresponds to a 14-fold increase in rate at 160 °C — in good agreement with the observed 12.5-fold difference in $\Delta t_{2\%}$ (moreover, in the presence of **4**, the maximum oxidation rate has still not been reached at 2% conversion; cf. Figure 3).[26]

The foregoing results provide a clear path forward for the development of more effective additives for preserving petroleum-derived products than those that are currently in use. Although we have demonstrated that carboxylic acids that are produced in the autoxidation of hydrocarbons can mask the greater efficacy of the heterocyclic diarylamines, this can be easily unmasked by addition of base to the autoxidizing hydrocarbon. In practice, bases are universally added to petroleum-derived products that come into contact with metal surfaces in order to minimize corrosion. Of the wide variety of applications wherein the compounds described above may have a significant impact, the most tangible would be increasing maintenance intervals on automobile and jet engines and enabling the development of more efficient combustion engines, which necessarily run at higher temperatures and require lubricants containing more effective RTAs.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and NMR spectra for **1**−**6**; stabilities of **1**−**7** toward O_2 and tetralin hydroperoxide at 160 °C; hexadecane autoxidations inhibited by **4** and **7** in the presence of palmitic acid, cesium carbonate, and Primene 81-R; pK_a measurements for **1**−**7**; k_1 and E^0 measurements for **5**; and Cartesian coordinates and energetics of computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*dpratt@uottawa.ca

Notes

The authors declare no competing financial interest.

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(21) Protonation of the ring would also be expected to slow the regeneration of the amine from the corresponding alkoxyamine (i.e., eq 4) via N−O bond homolysis/disproportionation, since the same diarylaminyl must be formed, or via the retro-carbonyl−ene reaction, since the highest-occupied molecular orbital of the aryl ring will decrease in energy (cf. ref 6). In fact, the O−C BDE in a O-methyl alkoxyamine derived from **4** calculated using CBS−QB3 increases from 39.0 to 43.2 kcal/mol upon protonation of the ring.
(22) Addition of more base did not further extend the inhibited period.
(23) For reference, the pK_a of diphenylamine in water is 0.79. See: Pankratov, A. N.; Shchavlev, A. E. *J. Anal. Chem.* **2001**, *56*, 123.
(24) Addition of base did not improve the activity of bis(2-alkylpyrimidine)amine **6**, consistent with the fact that its conjugate acid (pK_a = 4.2 ± 0.1) is stronger than the conjugate acid of **7** (pK_a = 4.6 ± 0.3).
(25) Unfortunately, it is not possible to accurately determine the stoichiometry of the reaction of the diarylamines with peroxyl radicals at this temperature since the autocatalytic nature of the reaction means that R_i changes as the reaction proceeds. As a result, we have "quantified" the efficacy of the inhibition of the heterocyclic diarylamines relative to the industry standard **7** simply by comparing the times required for 2% of the substrate to be autoxidized ($\Delta t_{2\%}$).
(26) We acknowledge that this may be entirely fortuitous, as it assumes that the off-cycle reactions of the intermediate diarylaminyl and diarylnitroxide radicals are essentially the same for **4** and **7**, which may not be the case.
(27) The data shown are from ref 14 and were obtained with the analogous compounds with shorter alkyl side chains, except for the data for **5**, which are reported for the first time here (see the Supporting Information).

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