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The Reactivity of Air-Stable Pyridine- and Pyrimidine-Containing Diarylamine Antioxidants

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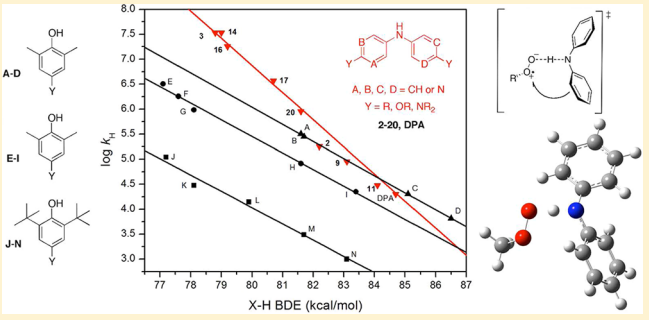
Supporting Information

ABSTRACT: We recently reported a preliminary account of our efforts to develop novel diarylamine radical-trapping antioxidants (Hanthorn et al. *J. Am. Chem. Soc.* **2012**, *134*, 8306−8309), wherein we demonstrated that the incorporation of ring nitrogens into diphenylamines affords compounds that display a compromise between H-atom transfer reactivity to peroxyl radicals and stability to one-electron oxidation. Herein, we report the results of thermochemical and kinetic experiments on an expanded set of diarylamines (see the accompanying paper, DOI: 10.1021/jo301013c), which provide a more complete picture of the structure−reactivity relationships of these compounds as antioxidants. Nitrogen incoporation into a series of alkyl-, alkoxyl-, and dialkylamino-substituted diphenylamines raises their oxidation potentials systematically with the number of nitrogen atoms, resulting in overall increases of 0.3−0.5 V on going from the diphenylamines to the dipyrimidylamines. At the same time, the effect of nitrogen incorporation on their reactivity toward peroxyl radicals was comparatively small (a decrease of only 6-fold at most), which is also reflected in their N−H bond dissociation enthalpies. Rate constants for reactions of dialkylamino-substituted diarylamines with peroxyl radicals were found to be $>10^7$ M^{-1} s^{-1}, which correspond to the pre-exponential factors that we obtained for a representative trio of compounds ($\log A \sim 7$), indicating that the activation energies (E_a) are negligible for these reactions. Comparison of our thermokinetic data for reactions of the diarylamines with peroxyl radicals with literature data for reactions of phenols with peroxyl radicals clearly reveals that diarylamines have higher inherent reactivities, which can be explained by a proton-coupled electron-transfer mechanism for these reactions, which is supported by theoretical calculations. A similar comparison of the reactivities of diarylamines and phenols with alkyl radicals, which must take place by a H-atom transfer mechanism, clearly reveals the importance of the polar effect in the reactions of the more acidic phenols, which makes phenols comparatively more reactive.



INTRODUCTION

Diarylamines and phenols are widely used radical-trapping antioxidant additives that slow the oxidative degradation of oils, lubricants, polymers, plastics, and fine chemicals.[1] Phenolic antioxidants are generally regarded as the most important of the two types, due to their prominence in vivo and the relative ease with which their reactivity can be manipulated by substitution of the aromatic ring. The introduction of electron-donating substituents (e.g., alkyl, alkoxyl) weakens the phenolic O−H bond by stabilizing the inherently electron-poor phenoxyl radical that results from H-atom transfer to autoxidation chain-carrying peroxyl radicals (eq 1):

$$\mathrm{ArO{-}H + ROO^{\bullet} \rightarrow ArO^{\bullet} + ROOH} \qquad (1)$$

A well-established Evans−Polanyi relationship relates the O−H bond strength of the phenol to the rate constant for the reaction in eq 1, established largely by the drive to understand why α-tocopherol (**1**), the most potent form of vitamin E, is such an effective peroxyl-radical-trapping antioxidant. The substituents on the phenolic ring of **1** weaken the O−H bond by 10 kcal/mol relative to phenol itself (77.2 vs 87.2 kcal/mol), enabling it to react much more quickly with peroxyl radicals (k_1 = 3.2 × 10^6 vs 2.9 × 10^3 M^{-1} s^{-1} in benzene and styrene, respectively).[2]

In contrast, optimization of the reactivity of diarylamine antioxidants to peroxyl radicals (eq 2)

$$\mathrm{Ar_2N{-}H + ROO^{\bullet} \rightarrow Ar_2N^{\bullet} + ROOH} \qquad (2)$$

has lagged behind their phenolic counterparts. The industry standards are 4,4′-dialkyldiphenylamines (**2**, N−H BDEs of ∼82 kcal/mol and $k_2 \sim 2 \times 10^5$ M^{-1} s^{-1}), which have rate constants only marginally higher than those of unsubstituted diphenylamine (N−H BDE of 84.7 kcal/mol and $k_2 \sim 4.4 \times 10^4$ M^{-1} s^{-1}). Similar to phenols, it is known that addition of electron-donating groups at the para positions relative to the

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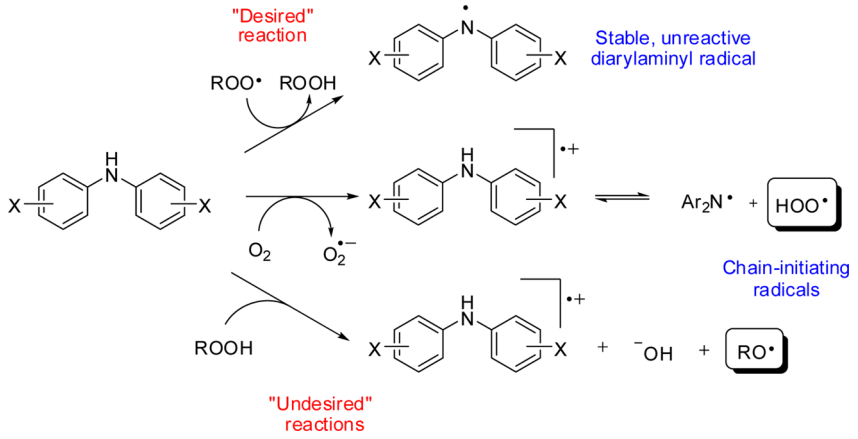
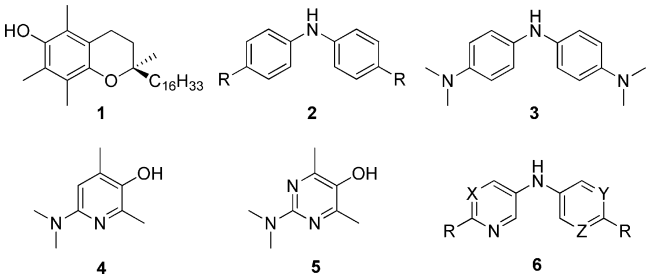
Scheme 1. Competing Antioxidant and Proantioxidant Reactions of Electron-Rich Diphenylamines



aminic N−H weakens the bond (e.g., 4,4′-(*N*,*N*-dimethylamino)-diphenylamine (**3**) has an N−H BDE of 78.4 kcal/mol),[3] but these compounds are generally not employed as antioxidants since they are sufficiently electron-rich to undergo direct reactions with O_2 and product hydroperoxides, rendering them pro-oxidants as opposed to antioxidants (Scheme 1).

Over the past decade, we have described the development of phenolic-like antioxidants, 3-pyridinols and 5-pyrimidinols, that have rate constants for reactions with peroxyl radicals that are up to 88-fold higher than that of α-tocopherol, making them the most effective peroxyl-radical-trapping antioxidants described to date. The design strategy centered on the incorporation of nitrogen atoms in the phenolic ring, which raises the oxidation potentials of the phenols, allowing them to be substituted with stronger electron-donating groups (i.e., *N*,*N*-dialkylamino) as in **4** and **5**, further weakening the O−H bond compared to compounds such as **1**, but not at the expense of their one-electron oxidation by O_2.[4−7]



In a recent communication,[8] we described preliminary results of our attempts to improve the activity of diphenylamine antioxidants using the same strategy. We showed that analogues of diphenylamine **2** bearing either ring carbons or nitrogens at the positions indicated by X, Y, and Z in **6** were characterized by oxidation potentials that increased systematically with the number of N atoms from less than 1 V to >1.5 V (vs NHE), while their reactivity to peroxyl radicals decreased only 6-fold at most (from 1.8×10^5 M^{-1} s^{-1} for **2** to 3.0×10^4 M^{-1} s^{-1} for **6** with X = Y = Z = N in chlorobenzene at 37 °C). This permitted the design of pyridyl and pyrimidyl analogues of the very electron-rich diphenylamine **3** that were stable in air and reacted with peroxyl radicals with temperature-independent rate constants up to 200-fold greater than those measured for **1** under the same conditions. These exciting results prompted us to carry out a thorough study of the structure−reactivity relationships in these compounds, which we describe here.

RESULTS

Theoretical Calculations. Quantum chemical calculations using the complete basis set approach at the CBS-QB3 level[9] were carried out in order to predict the effects that heteroatom incorporation would have on the N−H BDE and IP of diphenylamine. We first considered all of the possible positions of attachment of either a pyridine or a pyrimidine ring to the diphenylamine nitrogen in place of one of the phenyl rings (Table 1). The incorporation of each of the 2-, 3-, and 4-pyridyl substituents resulted in increases in both the calculated N−H BDE and the IP, with the 2-pyridyl substituent giving rise to the largest increase in BDE (+3.7 kcal/mol), but the smallest increase in IP (+2.7 kcal/mol). The largest increase in IP was predicted for the 4-pyridyl substituent (+10 kcal/mol), which was accompanied by an increase in the BDE of 2.5 kcal/mol. The best compromise between a negligible effect on BDE (0.4 kcal/mol), but significant increase in IP (6.4 kcal/mol), was predicted for the 3-pyridyl substituent. The same trends were predicted when each of 2-, 4-, and 5-pyrimidyl substituents were incorporated in place of one of the phenyl rings.

The foregoing results make it clear that incorporation of nitrogen atoms at the 3- and 5-positions strikes the best compromise between maximally increasing the IP while minimally increasing the N−H BDE. Since both phenyl rings in diphenylamine could be replaced with pyridyl and/or pyrimidyl rings, we expanded our calculations to include the corresponding dipyridylamines and dipyrimidylamines as well as the unsymmetric pyridyl pyrimidyl amines (Table 2). The results suggest that the N−H BDEs in diarylamines are almost invariant with nitrogen incorporation at the 3- and/or 5-positions relative to the amine nitrogen (predicted to be within 0.6 kcal/mol of each other) and that ionization potentials increase systematically by roughly 6 kcal/mol per nitrogen atom.

Synthesis. A small library of diarylamines with the core structures shown in Table 2 were prepared as described in detail in the accompanying manuscript.[10] Briefly, the syntheses were accomplished by a modular approach that utilized Buchwald−Hartwig Pd-catalyzed amination chemistry as the ultimate step. The approach was modular in that the aryl bromides used in the construction of the diarylamines (which were easily prepared from the common starting materials 2-aminopyridine and 2-aminopyrimidine) also served as precursors to their arylamine coupling partners (Scheme 2).

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Table 1. Calculated (CBS-QB3) Gas-Phase N−H Bond Dissociation Enthalpies (BDEs) and Ionization Potentials (IPs) for a Series of Heteroatom-Containing Diphenylamines in kcal/mol

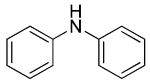
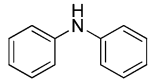
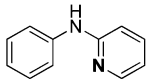
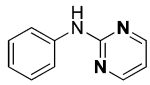
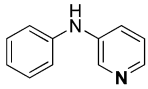
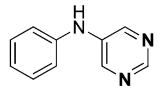
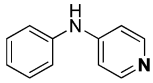
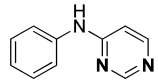
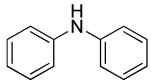
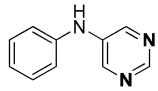
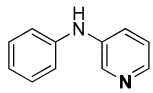
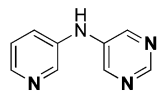
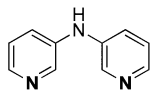
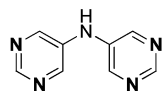
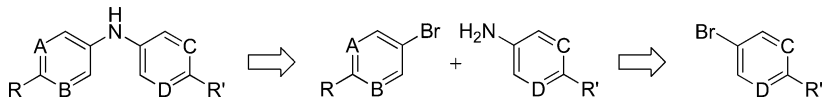
Structure	BDE	IP	Structure	BDE	IP
	86.4	168.3		86.4	168.3
	90.1	171.0		96.0	175.4
	86.8	174.7		86.4	179.3
	88.9	178.3		92.8	181.0

Table 2. Calculated (CBS-QB3) Gas-Phase N−H Bond Dissociation Enthalpies (BDEs) and Ionization Potentials (IPs) for a Series of Diphenylamines Incorporating Heteroatoms at the 3- and 5-Positions in kcal/mol

Structure	BDE	IP	Structure	BDE	IP
	86.4	168.3		86.4	179.3
	86.8	174.7		86.6	186.0
	87.0	180.2		86.5	193.0

Scheme 2. Synthetic Approach to Substituted Diarylamines (A−D = CH or N; R = H, Alkyl, Alkoxyl, or *N*,*N*-Dialkylamino)



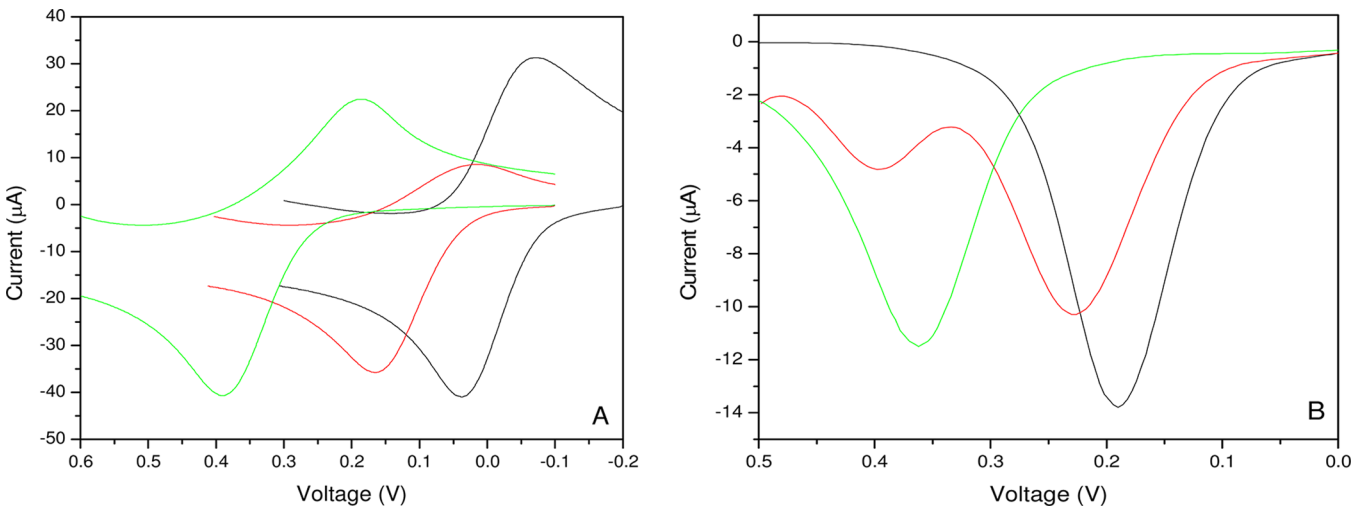


Figure 1. (A) Cyclic voltammograms obtained for **20** (black), **21** (red), **22** (green) in MeCN at 25 °C vs $Ag/AgNO_3$. (B) Differential pulse voltammograms obtained for **17** (black), **18** (red), **19** (green) in MeCN at 25 °C vs $Ag/AgNO_3$. For both (A) and (B), only the first oxidations are shown for clarity.

Through our modular approach, we were able to prepare a series of substituted diarylamines varying in heteroatom distribution and substitution. Symmetric and unsymmetric compounds were prepared, with respect to both heteroatom incorporation and/or substituents, and in the case of

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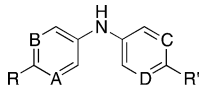
unsymmetrical compounds, the substituent was appended to either a phenyl or a heterocyclic ring.

Electrochemistry. To quantitatively determine the propensity of the diarylamines to undergo one-electron oxidation, we utilized electrochemical techniques. For compounds having reversible or quasi-reversible redox chemistry, we turned to cyclic voltammetry to measure standard potentials (E°), while differential pulse voltammetry was used to measure anodic peak potentials (E_{pa}) for compounds with irreversible redox chemistry. A representative set of cyclic voltammograms are shown in Figure 1A (vs $Ag/AgNO_3$), a representative set of differential pulse voltammograms is shown in Figure 1B (vs $Ag/AgNO_3$), and the measured potentials of all compounds are summarized in Tables 3–6 (vs NHE).

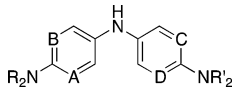
Table 3. Reactivity of Disubstituted Alkylated Diarylamines toward Peroxyls and Corresponding Oxidation Potentials



	A	B	C	D	R, R′[a]	k_2 (×10^5)[b]	E_{pa}[c]
2	CH	CH	CH	CH	C_8, C_8	1.8 ± 1.1	1.02
7	N	CH	CH	CH	C_6, C_4	1.5 ± 1.1	0.95
8	N	N	CH	CH	C_7, C_4	1.3 ± 0.1	1.13
9	N	CH	N	CH	C_6, C_6	0.9 ± 0.3	1.12
10	N	N	N	CH	C_7, C_6	0.8 ± 0.1	1.50
11	N	N	N	N	C_7, C_7	0.3 ± 0.1	1.55

[a]Linear alkyl chain of indicated lengths. [b]Values in M^{-1} s^{-1} determined at 37 °C in PhCl using the peroxyl radical clock methodology. [c]Anodic peak potentials in V vs NHE determined at 25 °C by differential pulse voltammetry in CH_3CN.

Table 4. Reactivity of Disubstituted *N,N*-Dialkylaminated Diarylamines toward Peroxyls and Corresponding Oxidation Potentials



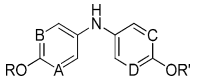
	A	B	C	D	R, R′	k_2 (×10^7)[a]	E°[b]
3	CH	CH	CH	CH	Me, Me	[c]	0.34
12	N	CH	CH	CH	Me, Me	[c]	0.37
13	N	N	CH	CH	Me, Me	3.7 ± 1.0	0.44
14	N	CH	N	CH	Me, Me	3.4 ± 1.1	0.44
15	N	N	N	CH	Me, Et	3.1 ± 1.2	0.50
16	N	N	N	N	Et, Et	1.8 ± 1.9	0.65

[a]Values in M^{-1} s^{-1} determined at 37 °C in PhCl using the peroxyl radical clock methodology. [b]Values in V vs NHE determined at 25 °C by cyclic voltammetry in acetonitrile. [c]Compounds were unstable under reaction conditions.

The redox chemistry was reversible or quasi-reversible for all of the *N,N*-dialkylamino-substituted compounds (be they symmetrical, **3** and **12**–**16**, or unsymmetrical, **22**–**26**) and irreversible for nearly all of the alkyl- and alkoxy-substituted compounds up to a scan rate of 5 V/s (see the Supporting Information for more details).

Peroxyl Radical Kinetics. To determine the kinetics of H-atom abstraction from the diarylamines by peroxyl radicals, we turned to a peroxyl radical clock approach.[11,12] The method used here[13] relies on the competition between the β-fragmentation of the nonconjugated 2-napthyl allylperoxyl

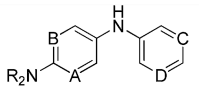
Table 5. Reactivity of Disubstituted Alkoxylated Diarylamines toward Peroxyls and Corresponding Oxidation Potentials



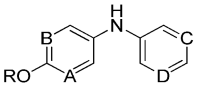
	A	B	C	D	R, R′[a]	k_2 (×10^6)[b]	E_{pa}[c]
17	CH	CH	CH	CH	Me, Me	3.7 ± 0.4	0.70
18	N	CH	CH	CH	Me, Me	1.4 ± 1.0	0.74
19	N	N	CH	CH	PhEt, Bu	nd	0.88
20	N	CH	N	CH	Me, Me	0.9 ± 0.2	0.95
21	N	N	N	CH	PhEt, Bu	0.6 ± 0.1	1.03

[a]Linear alkyl chain of indicated lengths. [b]Values in M^{-1} s^{-1} determined at 37 °C in PhCl using the peroxyl radical clock methodology. [c]Anodic peak potentials in V vs NHE determined at 25 °C by differential pulse voltammetry in CH_3CN.

Table 6. Reactivity of Monosubstituted Diarylamines toward Peroxyl Radicals and Associated One-Electron Oxidation Potentials



	A	B	C	D	R	k_2 (×10^7)[b]	E°[c]
22	CH	CH	CH	CH	Me	1.3±1.6	0.51
23	N	CH	CH	CH	Me	1.1±0.8	0.60
24	N	N	CH	CH	Me	0.3±0.1	0.81
25	CH	CH	N	CH	Me	0.8±0.2	0.53
26	CH	CH	N	N	Bu	0.8±0.1	0.56



	A	B	C	D	R[a]	k_2 (×10^5)[b]	E_{pa}[d]
27	CH	CH	CH	CH	Me	3.0±0.5	0.94
28	N	CH	CH	CH	Me	2.9±0.6	1.02
29	N	N	CH	CH	C_7	0.6±0.1	1.17
30	CH	CH	N	CH	Bu	2.1±0.4	0.90
31	CH	CH	N	N	C_{12}	*nd*	1.34

[a]Linear alkyl chain of indicated lengths. [b]Values in M^{-1} s^{-1} determined at 37 °C in PhCl using the peroxyl radical clock methodology. [c]Values in V vs NHE determined at 25 °C by cyclic voltammetry in acetonitrile. [d]Anodic peak potentials in V vs NHE determined at 25 °C by differential pulse voltammetry in CH_3CN.

radical (k_β = 5.7 × 10^5 s^{-1} in PhCl) and the bimolecular H-atom transfer reaction of interest, with the unknown rate constant (k_2), as shown in Scheme 3.

By measuring the ratio of conjugated/nonconjugated products, we can determine the rate constant for H-atom transfer (k_2) using eq 3:

$$\frac{[\text{conjugated}]}{[\text{nonconjugated}]} = \frac{k_\beta}{k_2[\text{Ar}_2\text{NH}]}\left(\frac{1-\alpha}{\alpha}\right) + \frac{1-\alpha}{\alpha} \qquad (3)$$

Using this technique, inhibition rate constants (k_2) were measured for five sets of diarylamine antioxidants, those substituted with alkyl, alkoxyl, and *N,N*-dialkylamino groups symmetrically (i.e., the same para substituents on both aromatic rings) and those substituted with alkoxy and *N,N*-dialkylamino

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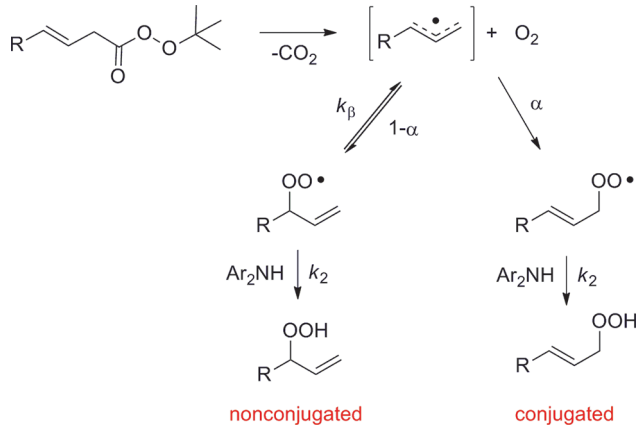
Scheme 3. Reaction Scheme Illustrating the Application of the Peroxyl Radical Clock Methodology[a]



[a]R = 2-naphthyl.

groups unsymmetrically (i.e., para substituents on only one aromatic ring). A representative data set used to determine k_H for **18** and **30** is shown in Figure 2, and the inhibition rate constants obtained at 37 °C are given in Tables 3–6.

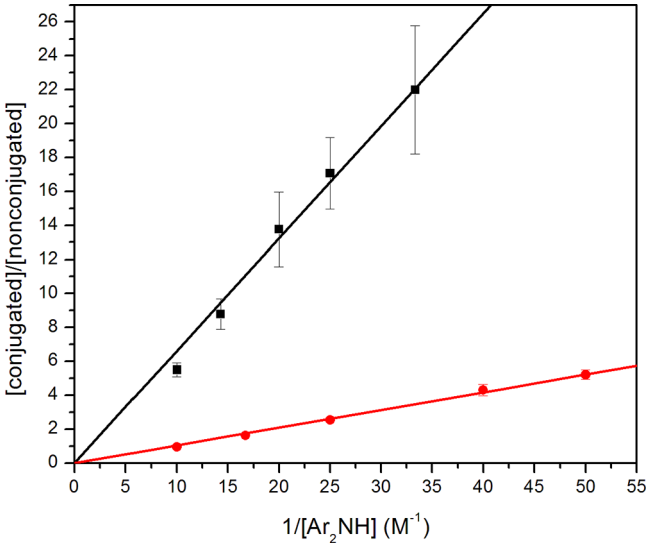


Figure 2. Double reciprocal plot of clock product ratios (Scheme 3) vs 1/[**18**] (black squares) and 1/[**30**] (red circles) in chlorobenzene at 37 °C used to obtain $k_2 = 2.1(\pm0.4) \times 10^5$ M^{-1} s^{-1} and $k_2 = 1.4(\pm1.0) \times 10^6$ M^{-1} s^{-1}, respectively.

The same trends are observed for each subset of compounds: oxidation potentials increase upon nitrogen atom incorporation (as little as 0.3 V and as much as 0.53 V for max number of N atoms), and the inhibition rate constants decrease ca. 2–6 fold upon incorporation of N atoms, depending on the para substituents.

Inhibited Autoxidations. Although peroxyl radical clocks offer a convenient method for determining rate constants for reactions of H-atom donors with peroxyl radicals, as shown in the preceding section, the method does not directly demonstrate the inhibition of hydrocarbon autoxidation by antioxidants, and they do not account for the number of peroxyl radicals trapped per molecule of antioxidant (i.e., the so-called stoichiometric factor, n).[14] Therefore, we carried out autoxidations of styrene to which small amounts of representative diarylamines were added (see eqs 4–9), and the reaction progress was followed by oxygen consumption (Figure 3), such that n and k_{inh} (=k_2 by the peroxyl radical clock

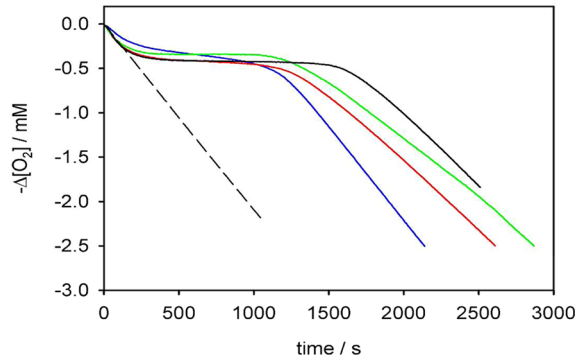


Figure 3. Representative oxygen consumption traces for the oxidation of styrene (6.5 M) in chlorobenzene initiated by AIBN (25 mM) at 30 °C without inhibitors (dashed line) or in the presence of PMHC (1.9 μM, blue), **12** (1.3 μM, green), **14** (1.9 μM, black), and **16** (1.4 μM, red).

method) could be determined as described in the Experimental Section.[14]

$$\text{initiator} \xrightarrow{R_i} R^\bullet \quad (4)$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet \quad (5)$$

$$ROO^\bullet + RH \xrightarrow{k_p} ROOH + R^\bullet \quad (6)$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2k_t} \text{nonradical products} \quad (7)$$

$$ROO^\bullet + Ar_2NH \xrightarrow{k_{inh}} ROOH + Ar_2N^\bullet \quad (8)$$

$$ROO^\bullet + Ar_2N^\bullet \rightarrow \text{products} \quad (9)$$

The results reveal pronounced inhibited periods in the presence of the diarylamines (**12**, **14**, and **16**), similar to those observed when the well-studied 2,2,5,7,8-pentamethyl-6-hydroxychroman (PMHC, an analogue of **1** differing simply in that the $C_{16}H_{33}$ chain is replaced with CH_3) is used as an inhibitor, which yield stoichiometric factors of ~2.8. These values are slightly larger than that for PMHC (n = 2), indicating that the products formed in eq 9 still have some antioxidant activity.[15] Furthermore, in accordance with the peroxyl radical clock data, the inhibition rate constants obtained from the slopes of these inhibited periods are within a factor of 2 (**12**, $1.0 \pm 0.2 \times 10^7$ M^{-1} s^{-1}; **14**, $1.0 \pm 0.2 \times 10^7$ M^{-1} s^{-1}; **16**, $0.74 \pm 0.05 \times 10^7$ M^{-1} s^{-1}), regardless of the number of N atoms incorporated into the aryl rings.

N–H Bond Dissociation Enthalpies. To understand the effect of nitrogen incorporation on the thermodynamics of H-atom transfer reactions of the diarylamines, the N–H BDEs of a representative set of compounds were measured using the radical-equilibrium electron paramagnetic resonance (EPR) technique.[3,16,17] The diarylaminyl radicals were generated in situ by photolysis of solutions of the diarylamine in benzene containing di-*tert*-butylperoxide and were allowed to reach equilibrium with a hindered phenol of similar O–H bond strength compared to the diarylamine of interest (eqs 10–12). Representative EPR spectra of equilibrated mixtures are shown

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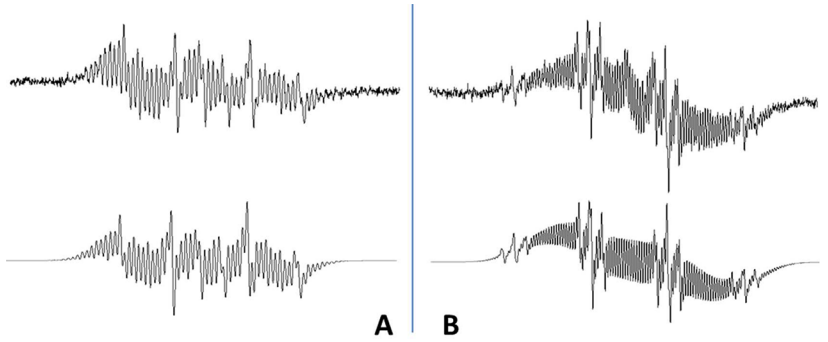


Figure 4. (A) (top) EPR spectrum of an equilibrated mixture of the diarylaminyl radical derived from **16** and 3,5-di-*tert*-butylphenoxyl radical in benzene at 298 K and (bottom) the associated simulated spectrum for a 100:6.3 ratio of the two equilibrated radicals. (B) (top) EPR spectrum of an equilibrated mixture of the diarylaminyl radical derived from **14** and 3,5-di-*tert*-butylphenoxyl radical in benzene at 298 K and (bottom) the associated simulated spectrum for a 100:1 ratio of the two equilibrated radicals.

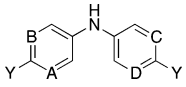
in Figure 4 (more are given in the Supporting Information), and the N–H BDEs we obtained are provided in Table 7.

$$(t\text{-BuO})_2 \rightarrow 2t\text{-BuO}^{\bullet} \quad (10)$$

$$t\text{-BuO}^{\bullet} + Ar_2NH \rightarrow t\text{-BuOH} + Ar_2N^{\bullet} \quad (11)$$

$$Ar_2NH + ArO^{\bullet} \leftrightarrows Ar_2N^{\bullet} + ArOH \quad (12)$$

Table 7. N–H Bond Dissociation Enthalpies of Representative Diarylamines Measured by the Radical Equilibration EPR Technique in Benzene at 298 K[b]



	A	B	C	D	Y	N–H BDE
32	CH	CH	CH	CH	H	84.7 ± 0.7[a]
33	N	CH	N	CH	H	85.0 ± 0.5
34	CH	CH	CH	CH	CH_3	82.2 ± 0.6[a]
35	N	CH	N	CH	CH_3	83.1 ± 0.4
11	N	N	N	N	C_7H_{16}	84.1 ± 0.5
17	CH	CH	CH	CH	OCH_3	80.7 ± 0.3[a]
20	N	CH	N	CH	OCH_3	81.6 ± 0.5
3	CH	CH	CH	CH	$N(CH_3)_2$	78.4 ± 0.5[a]
12	N	CH	CH	CH	$N(CH_3)_2$	78.8 ± 0.3
14	N	CH	N	CH	$N(CH_3)_2$	78.8 ± 0.8
13	N	N	CH	CH	$N(CH_3)_2$	79.0 ± 0.5
16	N	N	N	N	$N(Et)_2$	79.2 ± 0.5

[a]Taken from ref 3. [b]Values in kcal/mol.

The incorporation of nitrogen into the aromatic rings of the substituted diphenylamines leads to a small increase in the N–H bond strength; this is clearly evident upon comparing dphenylamines and 3,'3-dipyridylamines with no substitution (0.3 kcal/mol), alkyl substitution (0.9 kcal/mol), alkoxy substitution (0.9 kcal/mol) and dialkylamino substitution (0.4 kcal/mol).

The persistence of the diarylaminyl radicals with *N,N*-dimethylamino substitution suggested that they would serve as the best candidates to study the effect of nitrogen incorporation in each of the four positions. Indeed, five of the six possibilities were characterized by N–H BDEs that varied little incorporation of nitrogen atoms in the aryl rings at the 3- and/or 5-positions (<0.8 kcal/mol).

Mechanistic Studies. The peroxyl radical clock methodology easily affords the ability to measure solvent effects on the reaction of the diarylamines with peroxyl radicals,[11,13] which provides insight on the mechanism of the reaction.[18] We measured the rate constants for reactions of peroxyl radicals with diarylamines **14** and **16** in five different solvents (chlorobenzene, benzene, anisole, acetonitrile, and ethyl acetate) and found an excellent correlation with the hydrogen-bond-accepting (HBA) ability of the solvent when plotted versus Abraham's solvent HBA scale β_2^H (Figure 5),[16] but no obvious correlation with common solvent polarity parameters.[19]

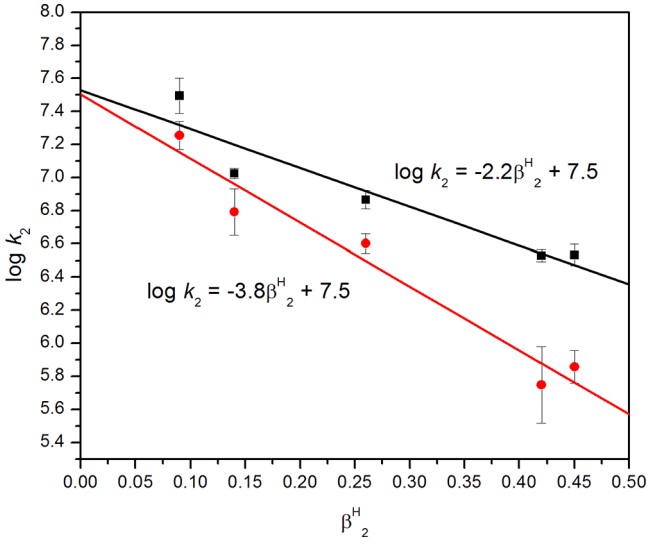


Figure 5. Rate constants for the reaction of diarylamines **14** (black squares) and **16** (red circles) with peroxyl radicals as a function the H-bond-accepting ability (β_2^H) of the solvent. Solvents used in the correlation (and their corresponding β_2^H parameter) are chlorobenzene (0.09), benzene (0.14), anisole (0.26), MeCN (0.42), and EtOAc (0.45). The correlation coefficients are R^2 = 0.89 and 0.95, respectively.

The temperature dependence on the rate of hydrogen-atom abstraction by peroxyl radicals from representative diarylamines was also studied for a representative set of diarylamines using the peroxyl radical clock methodology, where the temperature-dependence of the β-fragmentation of the secondary (non-conjugated) peroxyl radical has been determined (log A = 12.8

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s^{-1} and E_a = 9.6 kcal/mol) in the temperature range of 37−95 °C.[13] The data are shown in Figure 6, and the associated Arrhenius parameters are given in Table 8.

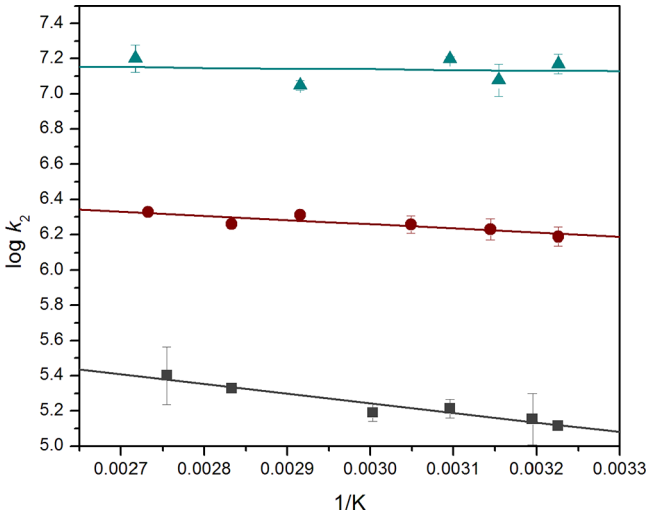


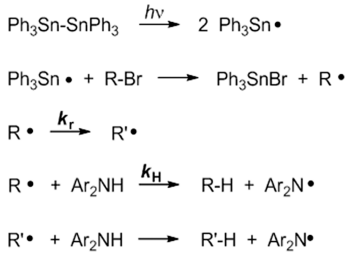
Figure 6. Temperature dependence of the rate constants for reactions of diarylamines **2** (blue ■), **20** (red ●), and **26** (green ▲) with peroxyl radicals in chlorobenzene in the range of 37−95 °C.

Table 8. Arrhenius Parameters for the Reactions of Selected Diarylamines with Secondary Peroxyl Radicals Derived from Rate Constants Measured Between 37 and 95 °C in Chlorobenzene

Ar_2NH	log A	E_a (kcal/mol)
2	6.9 ± 0.2	2.5 ± 0.4
20	7.0 ± 0.1	1.1 ± 0.3
26	7.1 ± 0.1	~0

Alkyl Radical Kinetics. The kinetics of the reactions of alkyl radicals with a representative series of diarylamines (i.e., those for which we measured N−H BDEs) were determined using the radical clock technique. Similar to the peroxyl radical clock methodology described above, the alkyl radical clock approach involves the kinetic competition between a unimolecular process with a known rate constant (k_r) and the bimolecular reaction under investigation (k_H). We utilized the 1,2-aryl migration of the 2-methyl-2-(2-naphthyl)-1-propyl (MNP) radical, having $k_r = 1.4 \times 10^4$ s^{-1} at 298 K[20] as the unimolecular process, and generated the radicals by photolysis of a deoxygenated solution of MNP-Br in the presence of hexaphenyldistannane, according to the reactions given in Scheme 4.

Scheme 4. Reaction Scheme Illustrating the Application of the Alkyl Radical Clock Methodology



The alkyl radicals react with the diarylamine under investigation, which is present in varying concentrations, with concentration ranges chosen to maintain pseudo-first-order kinetics. Under these conditions, the product ratios (determined by GC) can be used to determine the rate of H-atom transfer (k_H) to the primary alkyl radical, calculated according to eq 13. The results are shown in Table 9.

$$k_H[Ar_2NH] = k_r\frac{[RH]}{[R'H]} \quad (13)$$

Table 9. Second-Order Rate Constants for the Reactions of Selected Diarylamines with Primary Alkyl Radicals in Chlorobenzene at 25 °C

Ar_2NH	k_H (M^{-1} s^{-1})
11	(2.3 ± 0.9) × 10^5
14	(1.5 ± 0.2) × 10^5
16	(1.4 ± 0.1) × 10^5
17	(2.5 ± 0.1) × 10^4
20	(1.9 ± 0.2) × 10^4
2	(1.3 ± 2.9) × 10^3
9	(9.7 ± 2.3) × 10^2

■ DISCUSSION

The design of synthetic radical-trapping antioxidants and the identification and characterization of natural products with antioxidant properties have long been objectives of academic and industrial researchers around the globe. Compounds with increased reactivity are desirable not only because they ensure that chain-carrying or chain-transfer reactions in the radical-mediated autoxidation of hydrocarbons are less competitive, but also because, by increasing the reactivity, the amounts of antioxidant required to achieve a desired performance level can be decreased. This has the potential benefits of lowering cost and lessening undesirable properties of the antioxidant (interactions with other constituents) or oxidation products derived therefrom (color).

Over the past decade, we established that the incorporation of nitrogen atoms into the aromatic ring of phenolic antioxidants leads to compounds that are much more stable to electron-transfer reactions (to O_2 and hydroperoxides) due to higher inherent IPs, but which remain highly reactive to H-atom transfer reactions (to peroxyl and alkyl radicals) since they still possess relatively low O−H BDEs.[4−7] The success of this approach to stabilize the one-electron reactivity of highly electron-rich phenols, such as those substituted with dialkylamino groups, leads to the development of the most effective peroxyl-radical-trapping antioxidants ever described. This prompted us to extend the approach to diarylamines.

Our work with phenols revealed that the maximum benefits of heteroatom incorporation (minimal increase in O−H BDE and maximum increase in IP) are achieved when the nitrogen atoms are incorporated in the 3- and 5-positions relative to the reactive phenolic O−H moiety. Incorporation of nitrogen atoms at either the 2- and/or 4-positions or the 2- and/or 6-positions results in isomerization of the aryl alcohols to the corresponding pyridinone and/or pyrimidinone tautomers, which predominate at equilibrium and decrease the antioxidant activity since the N−H bonds are stronger. In contrast with phenolic antioxidants, a number of possibilities exist for the incorporation of nitrogen atoms into diarylamines, not just

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because there are two aromatic rings that can be modified but also because tautomers of heteroarylamines are not likely to be relevant as they are higher-energy species compared with their heteroaryl alcohol counterparts. To pare down the number of compounds to be studied in detail, we carried out CBS-QB3 calculations on a series of unsubstituted diarylamines incorporating N atoms in all of the possible positions. The results of these calculations suggested that the 3- and 5-positions were optimal for maximizing the ionization potentials of the compounds while maintaining a minimal perturbation on the N−H BDE (cf. Table 1). When considering the patterns that incorporate N atoms in the 3- and/or 5-positions (cf. Table 2), calculations suggested that N−H BDEs should be almost invariant with N-atom incorporation and that IPs were predicted to increase systematically by ca. 6 kcal/mol per nitrogen atom.

On the basis of these calculations, a series of symmetrical (with respect to the reactive amine N−H) alkyl- and *N*,*N*-dialkylamino-substituted diarylamines that incorporated nitrogen atoms in the 3- and/or 5-positions were prepared. The alkylated compounds are representative of the scaffold of the industry standard (**2**), and the *N*,*N*-dialkylamino-substituted compounds represent a very electron-rich scaffold that is difficult to prepare, isolate, store, and use in an air atmosphere. We were pleased to see that, while both series of compounds had increased one-electron oxidation potentials that correlated systematically with N-atom content (between 1.02 and 1.55 V for the alkyl-substituted series and 0.34 and 0.65 V for the *N*,*N*-dialkylamino-substituted series), they maintained their reactivities toward peroxyl radicals ($k_2 \sim 10^5$ M^{-1} s^{-1} for the former and $k_2 \sim 10^7$ M^{-1} s^{-1} for the latter; cf. Tables 3 and 4). In fact, the *N*,*N*-dialkylamino-substituted compounds are excellent peroxyl-radical-trapping antioxidants, having rate constants ca. 200-fold higher than that of the industry standard **2**. Delighted with these results, we sought to expand the structure/reactivity understanding of symmetrically substituted heterocyclic diarylamines by preparing and characterizing the corresponding alkoxyl-substituted compounds, which were predicted to have a reactivity between the *N*,*N*-dialkylamino- and alkyl-substituted compounds.

Indeed, we found that the oxidation potentials for the series of symmetrically substituted alkoxylated diarylamines systematically increased with N-atom incorporation and spanned the gap in between the symmetrical alkyl- and *N*,*N*-dialkylamino-substituted compounds (0.7−1.03 V), as did the peroxyl-trapping rate constants ($k_2 \sim 10^6$ M^{-1} s^{-1}; cf. Table 5).

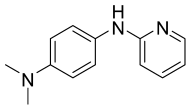
In addition to the foregoing symmetrically substituted series of diarylamines, we also examined two series of monosubstituted compounds having either alkoxy or *N*,*N*-dialkylamino substituents on either an aryl or a heteroaryl ring (Table 6). Interestingly, the substituent effects on the one-electron oxidation potential and rate constants for peroxyl trapping appear to be greater when the substituent group was placed on the heteroaryl ring. At first glance, it is unclear as to why this may be the case. Combining these data with the data for the symmetrically substituted compounds, we correlated the reactivity of each diarylamine toward peroxyl radicals on the basis of N-atom incorporation by plotting log k_2 vs $\sum\sigma_p^+$ for the para substituents.[3,21] Each subset afforded an excellent linear correlation with ρ^+, indicating that the substituent effects on the two aryl rings of the diarylamines are approximately additive. The reaction constants and correlation coefficients are shown in Table 10.

Table 10. Reaction Constants (ρ^+) from Plots of log k_H vs $\sum\sigma_p^+$ for the Reactions of Substituted Diarylamines Containing Either Phenyl, 3-Pyridyl, or 5-Pyrimidyl Rings

Ar−NH−Ar′	compounds	ρ^+ (r^2)
Ph−NH−Ph	**2**, **3**, **17**, **22**, **27**	−1.59 ± 0.17 (0.98)
Pyr−NH−Ph	**7**, **12**, **18**, **23**, **28**, **25**, **30**	−1.51 ± 0.27 (0.93)
Pym−NH−Ph	**8**, **13**, **19**, **24**, **29**, **26**	−1.00 ± 0.17 (0.86)
Pyr−NH−Pyr	**9**, **14**, **20**	−0.94 ± 0.05 (0.99)
Pym−NH−Pyr	**10**, **15**, **21**	−0.91 ± 0.07 (0.94)

The negative reaction constants in Table 10 imply that the reaction center becomes more electrophilic in the transition state compared to the starting material. This follows the established trend that the N−H bond dissociation enthalpies of diphenylamines correlate with $\sum\sigma_p^+$ because EDGs stabilize the electron-poor diarylaminyl radical (and destabilize the electron-rich diarylamine). Interestingly, the magnitudes of the ρ^+ values *decrease* with increasing heteroatom incorporation into the aryl rings. This can be attributed to the electronegative nitrogen atoms inductively counteracting the effects of the EDGs, thereby reducing their effect on the reactivity of the diarylamines. It should be noted that these reaction constants are of similar magnitude to that determined from limited data on reactions of substituted diphenylamines with peroxyl radicals at 65 °C (−0.89)[23] and also for the reactions of substituted phenols with peroxyl radicals under the same conditions (−1.6).[14,24]

To verify that the substitution patterns predicted by the calculations are indeed optimal for reactivity/oxidative stability, we prepared the monosubstituted 2-pyridyl and 2-pyrimidyl derivatives **36** and **37** and compared their reactivities to the 3-pyridyl and 5-pyrimidyl compounds **25** and **26**.



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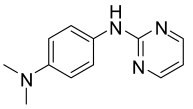

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We found $k_2 = (6.4 \pm 0.8) \times 10^6$ M^{-1} s^{-1} and $E^\circ = 0.57$ V for **36**, and $k_2 = (1.5 \pm 0.4) \times 10^5$ M^{-1} s^{-1} and $E^\circ = 0.64$ V for **37**. Although these compounds have only slightly higher one-electron oxidation potentials than their counterparts having nitrogen atoms in the 3- and 5-positions (**25**, $E^\circ = 0.53$ V, and **26**, $E^\circ = 0.56$ V), their inhibition rate constants are depressed 1.3-fold and 53-fold, respectively, for reactions with peroxyl radicals. Although it is indeed the case that the 2-pyridyl and 2-pyrimidyl analogues are less effective as radical-trapping antioxidants than their 3-pyridyl and 5-pyrimidyl counterparts, the difference is less obvious than was expected from the results of our calculations on the unsubstituted compounds (cf. Table 1) when comparing the pyridyl derivatives. Nevertheless, the scaffolds containing N atoms in the 2- and/or 6-positions were not further pursued.

To provide a thermodynamic rationale for the trends in the kinetics of the radical-trapping reactions of the diarylamines, the N−H BDEs of selected examples were measured using the radical-equilibrium EPR spectroscopy approach (Table 7). We found that the changes in the N−H BDEs are much smaller than the differences in the E° (or E_{pa}) values, consistent with the expectation that N-atom incorporation into the aryl rings destabilizes the radical cations formed by one-electron oxidation of the diarylamines more than it destabilizes the

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corresponding diarylaminyl radicals formed by H-atom abstraction. It was also interesting to note that the magnitude of the changes in N−H BDEs and rate constants for reactions of the diarylamines with peroxyl radicals upon N-atom incorporation is much smaller than those observed for phenolic compounds (ca. 1.2−1.5 kcal/mol per N atom).[4,6] We attribute this difference to the fact that the diphenylaminyl radicals are inherently less electron-poor than the phenoxyl radicals, and therefore, are less destabilized by the incorporation of electronegative nitrogen atoms into the aryl rings.

The rate constants determined for reactions of the diarylamines with peroxyl radicals afforded a good correlation with their corresponding N−H BDEs (cf. Figure 7).

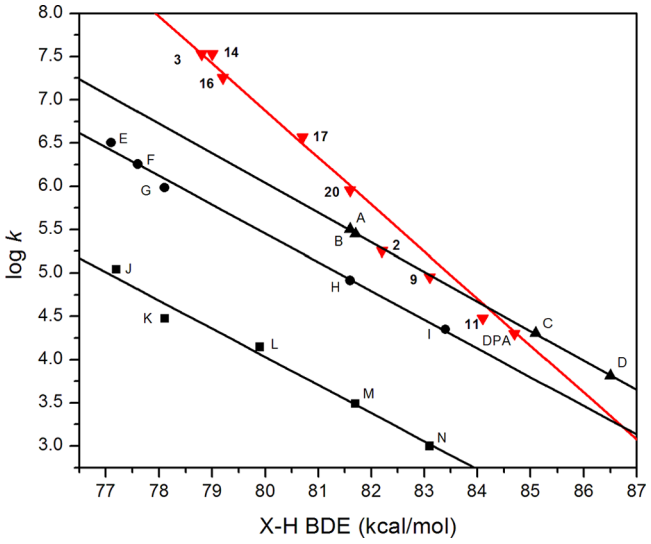


Figure 7. Correlations of log k (reaction with peroxyl radicals) and either the N−H BDEs of diarylamines (red ▼) or the O−H BDEs of some 4-substituted phenols (black ▲), 2,6-dimethyl-4-substituted phenols (black ●), and 2,6-di-*tert*-butyl-4-substituted phenols (black ■).[5,6] Legend: A = 4-(methylselanyl)phenol; B = 4-methoxyphenol; C = 4-methylphenol; D = phenol; E = α-TOH; F = 2,6-dimethyl-4-(methylselanyl)phenol; G = 2,6-dimethyl-4-methoxyphenol; H = 2,4,6-trimethylphenol; I = 2,6-dimethylphenol; J = 2,6-di-*tert*-butyl-4-methoxyphenol; K = 2,6-di-*tert*-butyl-4-thiomethylphenol; L = 2,6-di-*tert*-butyl-4-methylphenol; M = 2,6-di-*tert*-butylphenol; N = 2,6-di-*tert*-buty-4-cyanophenol; DPA = diphenylamine.

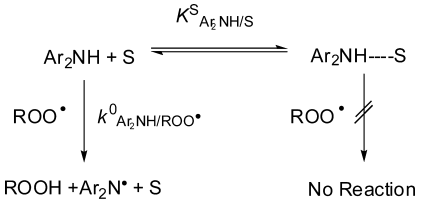
Interestingly, when the data relating the kinetics of the reactions of phenols with peroxyl radicals to their corresponding O−H BDEs were included in the same plot,[22−25] it became obvious that the reactions of diarylamines were faster when the thermodynamics of the reactions were comparable (i.e., for reactions of diphenylamines and phenols whose N−H and O−H BDEs, respectively, were similar).

The difference was most striking for the most electron-rich compounds; the rate constants for the *N*,*N*-dialkylamino-substituted compounds, **11**, **12**, and **14**, were 2−5 fold faster than the rate constant for α-TOH established under the same conditions (k_1 = 7.1 × 10^6 M^{-1} s^{-1}) despite the fact that the N−H BDEs of these diarylamines were measured to be 1.3−1.9 kcal/mol greater than the O−H BDE of α-TOH (77.3 kcal/mol). We can be confident in the relative accuracy of these measurements since the peroxyl radical clock approach used to obtain the inhibition rate constants (k_2) for the diarylamines was calibrated (k_β) using α-TOH and the X−H BDEs were measured by the same laboratory using the same technique (radical equilibrium EPR, vide supra) under the same conditions. At first glance, these results imply that the entropic demand for the reaction of phenols with peroxyl radicals must be greater. However, the only reported pre-exponential factor for a diarylamine reacting with peroxyl radicals was reported as log A = 5.1 ± 0.5 by Howard and Furimsky[26] (*N*-α-naphthyl-*N*-phenylamine with *tert*-butylperoxyl radical) versus values of log A ∼ 8 commonly ascribed to the reactions of phenols with peroxyl radicals.[27]

This prompted us to measure the temperature dependence of k_2 for representative diarylamines **2**, **20**, and **26** (Figure 6, Table 8) using the peroxyl radical clock method (which was calibrated using a log A = 8 for α-TOH),[13,27] and from these data, we obtained pre-exponential factors of log A = 7.0 ± 0.1 for each reaction and E_a values that correlated with the strength of the N−H bonds (**2** > **20** > **26**). In fact, the rate constants for the reactions of **26** with peroxyl radicals were invariant with temperature, implying $E_a \approx 0$. Thus, from these data, we can conclude that the high reactivity of diarylamines **13**−**16** compared to α-TOH (and other similarly reactive phenols) does not originate from decreased entropic demand (log $A \approx 8$ for α-TOH and log $A \approx 7$ for diarylamines), but rather from inherently lower activation energies.

To confirm that the reactions of the most electron-rich diarylamines were not simply electron-transfer reactions, which would mean that their kinetics would not be directly comparable with the reactions of phenols, we measured solvent effects on the inhibition rate constants for compounds **14** and **16**. While there were no obvious correlations of the kinetics with the polarity of the medium, which would be expected if an electron-transfer mechanism was operative, there were excellent (negative) correlations with the H-bond-accepting strength of the medium (cf. Figure 5). This solvent effect follows the trends observed for phenols and can be explained by a simple predissociation model (Scheme 5), wherein only the non-H-bonded diarylamine is reactive to peroxyl radicals, and is fully consistent with a formal H-atom transfer, as for phenols.

Scheme 5. Kinetic Solvent Effect on the Reaction of Diarylamines with Peroxyl Radicals



Ingold and co-workers have shown that the rate constants for reactions of phenols with alkoxyl and hydrazyl radicals in a given solvent (k^S) are a function of the hydrogen-bond-accepting ability of the solvent (β_2^H) and hydrogen-bond-donating ability of the substrate (α_2^H), as in eq 14.[28,29]

$$\log k^S = \log k^0 - 8.3\alpha_2^H\beta_2^H \quad (14)$$

Furthermore, some of us subsequently showed that this extends to the reactions of phenols with peroxyl radicals.[11] The results above point to the same relationship holding for diarylamines. Furthermore, they clearly show how the incorporation of nitrogen into the aromatic rings can result in much stronger H-bonding interactions, since the slope of the line of best fit for the dipyrimidineamine **16** is almost twice as

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large (−3.8) as that for the dipyridineamine **14** (−2.2), which is similar to that for diphenylamine (−2.5)[11] for which α_2^H = 0.324.[19] Thus, the replacement of two phenyl rings with two pyridyl rings is mostly offset by the presence of the two *N*,*N*-dimethylamino groups on comparing the H-bond-donating ability of **14** with diphenylamine. However, the introduction of two more nitrogen atoms as in the bis-pyrimidyl **16** leads to a much better H-bond donor, and it displays a much larger kinetic solvent effect.

Confident that the reactions between peroxyl radicals and diarylamines are indeed formal H-atom transfer reactions analogous to the reactions between peroxyl radicals and phenols, we looked to the calculated transition-state structures for these reactions for insight as to why diarylamines are inherently more reactive. As for the reaction of phenol with peroxyl radicals,[30,31] the calculated transition-state structure for the reaction of diphenylamine with peroxyl radicals is best described as a proton-coupled electron-transfer (PCET) reaction,[8] wherein the proton moves between the diphenylamine and peroxyl radical via two nominal lone pairs on the N atom and terminal oxygen atom, respectively, while an electron moves from the π-HOMO of the amine to the π-SOMO of the peroxyl radical (drawn schematically as its charge-separated resonance structure in Figure 8). On the basis of these

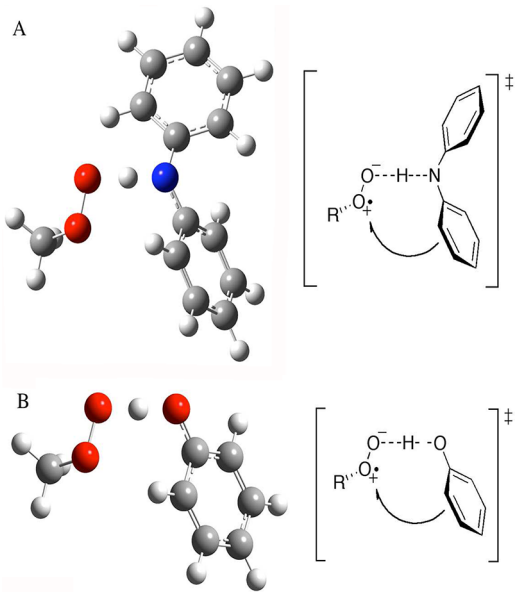

Figure 8. Calculated transition-state structures for the formal H-atom transfer from diphenylamine (A) and phenol (B) to the methylperoxyl radical.

structures, it follows that reactants with higher HOMO energies should have lower activation energies since they will provide better orbital overlap with the π-SOMO of the peroxyl radical and facilitate proton-coupled electron transfer. Indeed, diphenylamines have much higher HOMO energies when compared to phenols that possess similar X−H BDEs; for example, while α-TOH has E° = 0.97 V (vs NHE),[33] the values given above for **13**−**16** are comparatively lower (0.44−0.65 V).

The transition-state structures in Figure 8 may also provide some insight into the trends we observed in the monosubstituted diarylamines in Table 6. Consider the *N*,*N*-dialkylamino-substituted diarylamines, which differ in whether nitrogen(s) are incorporated into the substituted ring or the unsubstituted ring. When two nitrogens are incorporated in the aryl ring bearing the substituent, the rate constant for reaction with peroxyl radicals drops 4.3-fold, whereas when they are incorporated in the aryl ring that does not contain the substituent, the rate constant drops only 1.6-fold. This is consistent with the preferred interaction of the peroxyl radical with the more electron-rich aryl ring of the two (in a transition-state structure analogous to that in Figure 8A), which would be the same for **21**, **24**, and **26** (and the disubstituted diarylamine **13**, which may have slightly higher reactivity simply due to the 2-fold symmetry of the molecule, resulting in a slightly higher log *A* value). This observation merits further investigation.

The kinetics of the reactions of these new diarylamines with alkyl radicals were also examined. This reactivity is relevant since diarylamines can act as antioxidants via their reactions with chain-carrying alkyl radicals in autoxidations that take place at low partial pressures of oxygen, and also in the application of diarylamines as polymerization inhibitors (monomer stabilizers). Indeed, we found that the diarylamines reacted very rapidly with primary alkyl radicals (cf. Table 9) and that the rate constants correlated nicely with the strength of the N−H bond (Figure 9). Interestingly, when this

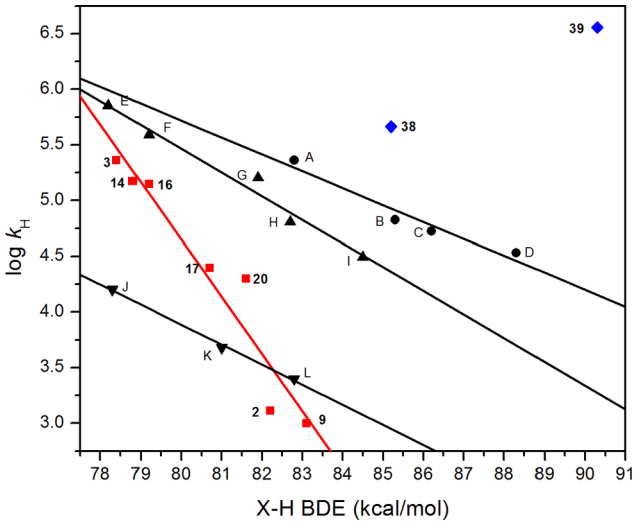

Figure 9. Correlations of log k_H (for reactions with alkyl radicals) and either the N−H BDEs of diarylamines (red ■) or the O−H BDEs of some phenols (black ●), *ortho*-methylated phenols (black ▲), *ortho*-*tert*-butylated phenols (black ▼), and pyrimidinols (blue ◆). Legend: A = 4-methoxyphenol; B = 4-*tert*-butylphenol; C = 4-methylphenol; D = phenol; E = 2,2,5,7,8-pentamethyl-6-chromanol ; F = 4-methoxy-2,3,6-trimethylphenol; G = 4-methoxy-2,3,5,6-tetramethylphenol; H = 2,4,6-trimethylphenol; I = 2,6-dimethylphenol; J = 2,6-di-*tert*-butyl-4-methoxyphenol; K = 2,6-di-*tert*-butyl-4-methylphenol; L = 2,6-di-*tert*-butylphenol.

relationship was plotted alongside literature data for the reactions of phenols with primary alkyl radicals[34] (also obtained by competition kinetics using the radical clock methodology), the trend opposed that which we observed with peroxyl radicals; that is, diarylamines with a given N−H BDE react slower than phenols with comparable O−H BDEs (with the exception of the 2,6-di-*tert*-butylated phenols, which react more slowly due to steric hindrance). This result implies that the two reactions have different mechanisms.

Since alkyl radicals cannot H-bond the diarylamines/phenols and do not possess an adjacent lone pair, their reactions

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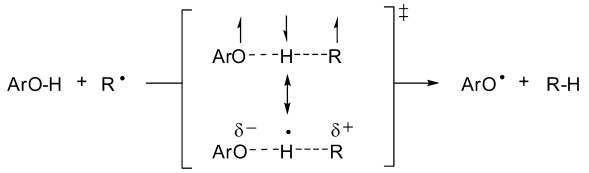
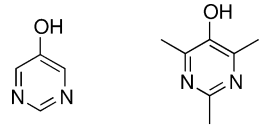
necessarily take place by a H-atom transfer mechanism as opposed to the PCET mechanism described above for their reactions with peroxyl radicals. As such, the inherently higher reactivity of diarylamines that we see in reactions with peroxyl radicals is not observed here. The high reactivities of phenols toward alkyl radicals has been explained on the basis of a polar effect in the transition state of the HAT reaction. This can be conceptualized by the contribution of the charge-separated resonance form shown in Scheme 6, which lowers the energy of the transition state, accelerating the rate of reaction.

Scheme 6. Polar Effect in the Reaction of Phenols with Alkyl Radicals

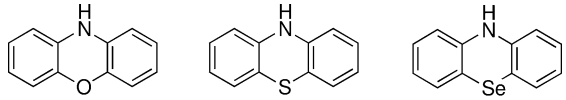


As such, the contribution of the polar effect in HAT reactions with alkyl radicals is most obvious for compounds that can best accommodate a partial negative charge on the atom from which the H atom is being abstracted, i.e., those with lower pK_a's. Perhaps the best examples are in reactions of pyrimidinols, such as **38** and **39**, which have O−H BDEs of 90.3 and 85.2 kcal/mol, but rate constants for reactions with alkyl radicals of 3.6×10^6 and 4.6×10^5 M^{-1} s^{-1}, respectively (which deviate significantly from the correlations in Figure 9).[4,5] The polar effect makes reactions of phenols having higher O−H BDEs (they are not substituted with strong EDGs and, therefore, have lower pK_a's) much faster than those of diarylamines with comparable N−H BDEs.



38 **39**

The only other extensive structure−reactivity study on the reactions of aromatic amines with alkyl and peroxyl radicals was carried out by one of us and others some time ago.[35] Diphenylamine, as well as the analogues that featured a second connection between the two aryl rings: phenoxazines (**40**), phenothiazines (**41**), and phenoselenazines (**42**) were examined.



40 **41** **42**

When the data for **40**−**42** and a series of substituted phenothiazines were plotted alongside the current data for the reactions of the diarylamines with both alkyl and peroxyl radicals (cf. Figure 10), two excellent correlations are obtained: one relating the rate constants for the reactions of both sets of amines with alkyl radicals and the other relating the rate constants of both sets of amines with peroxyl radicals. The correlations are (incidentally) almost perfectly parallel, but are separated in the vertical dimension by 2 orders of magnitude. Therefore, while the reactions of diarylamines with primary

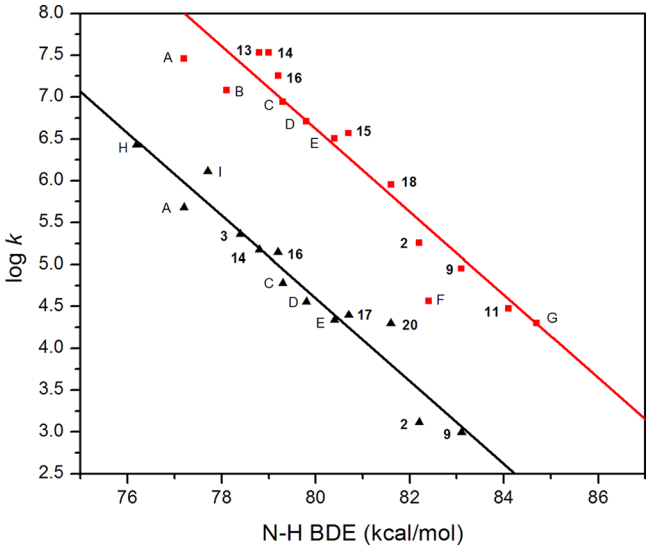


Figure 10. Correlation between N−H BDEs and log k for reaction of diarylamines, phenothiazines, and phenoxazines for reaction with primary alkyl radicals (black ▲) and peroxyl radicals (red ■).[35,40] Data for diarylamines were obtained at 298 K, whereas phenothiazines/phenoxazines were measured at 298 K (alkyl radicals) and 323 K (peroxyl radicals). Legend: A = phenoxazine; B = 1,9-di-*tert*-butylphenothiazine; C = phenothiazine; D = 3,7-dichlorophenothiazine; E = phenoselenazine; F = 5*H*-dibenz[b,f]azepine; G = diphenylamine; H = 3,7-dimethoxyphenothiazine; I = 1,9-dimethylphenothiazine. Correlations are log $k = -0.495x + 46.2$ ($r^2 = 0.92$) and log $k = -0.495x + 44.2$ ($r^2 = 0.94$), respectively. Note that phenothiazine and phenoxazine N−H BDEs were revised downward by 1.1 kcal/mol, as suggested by Mulder et al.[40]

alkyl radicals at least ca. 13 kcal/mol *more exothermic* than their reactions with peroxyl radicals (the RCH_2−H BDE is 101 kcal/mol, whereas the ROO−H BDE is 85−88 kcal/mol),[32] the reactions are *2 orders of magnitude slower*. This has been explained[35] on the basis of lesser triplet repulsion in the transition state for H-atom transfer between a nitrogen atom and an oxygen compared to a nitrogen atom and a carbon, a concept first advanced by Zavitsas.[38]

However, in light of the different reactivities of phenols and diarylamines toward peroxyl radicals (vide supra),[39] it would appear that the trends in Figure 10 would be better explained by the simple fact that the reactions of diarylamines with alkyl radicals and peroxyl radicals proceed by two different mechanisms: H-atom transfer for the former and proton-coupled electron transfer for the latter.

■ CONCLUSIONS

We have prepared a series of heterocycle-containing diarylamine antioxidants and demonstrated that incorporation of nitrogen atoms affords compounds with increased one-electron oxidation potentials while not compromising their H-atom transfer reactivity, quantified kinetically via rate constants of their peroxyl-radical-trapping reactions and thermodynamically via determination of their N−H bond dissociation enthalpies. Rate constants for the reactions of the most reactive compounds (mono- or di-*N*,*N*-dialkylamino-substituted) with peroxyl radicals were shown to be 100−200-fold greater than the industry standard dialkylated diphenylamine and shown to proceed with pre-exponential values of log $A \sim 7$ and negligible activation energies. Additionally, we have shown the substituent effects on diarylamine radical trapping to be additive, but for

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N,*N*-dialkylamino-substituted compounds, the difference between mono- and disubstituted compounds is very small, meaning that monosubstituted diarylamines, which are more easily prepared (and inexpensive), may be better options for applications.

Diarylamines, such as **2**, are most effective as antioxidants at higher temperatures (>120 °C), such as those commonly attained by the lubricants of operating combustion engines. Under these conditions, they exhibit catalytic radical-trapping antioxidant activity that is believed to be the result of reactions of nitroxide radicals formed in situ from the diarylamines via a mechanism that remains unresolved.[36,37] Our inhibited autoxidation studies reveal stoichiometric factors approaching 3, which is highly surprising given the temperatures at which they were carried out (30 °C) and certainly merits further investigation. Indeed, we are currently carrying out inhibited autoxidation at different temperatures to explore the efficacy of these new compounds under industrially relevant conditions, and also to attempt to shed further light on the origins of the catalytic activity of diarylamine antioxidants.

EXPERIMENTAL SECTION

General. Diarylamines were prepared according to the procedures in the accompanying manuscript.[10] Solvents for kinetic studies were purified according to the procedures given in "*Purification of Laboratory Chemicals*".[41] All other commercially available reagents were used without further purification, unless otherwise specified.

Electrochemistry. Standard potentials (CV) and anodic peak potentials (DPV) were measured using a potentiostat with a glassy-carbon working electrode, a platinum counter electrode, and a Ag/$AgNO_3$ (0.005 M) reference electrode. Voltammagrams were obtained in dry acetonitrile using $Bu_4N{\cdot}PF_6$ (0.1 M) as an electrolyte at 25 °C. For compounds displaying reversible redox chemistry, cyclic voltammograms were obtained using a scan rate of 100 mV/s. For compounds displaying irreversible redox chemistry, differential pulse voltammograms were obtained using a scan rate of 20 mV/s.

Peroxyl Radical Kinetics. Peroxyl radical clock experiments to determine inhibition rate constants, kinetic solvent effects, Arrhenius parameters, and deuterium kinetic isotope effects were performed according to the procedures given in our previous reports.[8,13]

Inhibited Autoxidations. The chain-breaking antioxidant activity was evaluated by studying the inhibition of the thermally initiated autoxidation of either styrene or cumene in chlorobenzene. Autoxidation experiments were performed in a two-channel oxygen uptake apparatus. In a typical experiment, an air-saturated chlorobenzene solution of styrene containing azobisisobutyronitrile was equilibrated with an identical reference solution containing also an excess of PMHC (1×10^{-3} M) in the same solvent at 303 K. When a constant oxygen consumption was observed, the antioxidant was injected into the sample flask, and oxygen consumption was measured, after calibration of the apparatus, from the differential pressure recorded with time between the two channels. The stoichiometric factor of antioxidants was obtained by eq 15, where τ is the length of the inhibition period. The value of k_{inh} was determined from the oxygen consumption during the inhibition period by using eq 16, where k_p is the propagation rate constant of the oxidizable substrate (41 M^{-1} s^{-1} for styrene).[42−44]

$$n = \frac{R_i\tau}{[Ar_2NH]} \tag{15}$$

$$-\Delta[O_2]_t = \frac{k_p[RH]}{k_{inh}} \ln(1 - t/\tau) \tag{16}$$

N−H Bond Dissociation Enthalpies. Radical equilibration experiments (REqEPR) were performed by continuous irradiation in the cavity of the EPR spectrometer of benzene solutions (containing 10% v/v di-*tert*-butylperoxide) of the diarylmine under investigation (1−50 mM) with 2,4,6-tri-*tert*-butylphenol (BDE = 80.1 kcal/mol), 2,4,6-trimethoxyphenol (BDE = 78.9 kcal/mol), or 2,6-di-*tert*-butyl-4-methylphenol (BDE = 79.9 kcal/mol) as reference compounds (2−20 mM) in variable ratios. To verify that the system was at equilibrium, spectra were also recorded under different irradiation intensities by intercepting the UV beam with calibrated metal sectors. The relative amount of the two equilibrating radical species was determined by interactive fitting of simulated to experimental spectra. The equilibrium constant K_{eq} was then determined according to eq 17 and used to determine the reaction ΔG, which yielded ΔH under the assumption that the entropy change is negligible (eq 18).[45−47] The quality of such an assumption had previously been verified in the equilibration of structurally related diphenylmines and phenothiazines with phenols.

$$K_{eq} = \frac{[Ar_2N^{\bullet}]}{[ArO^{\bullet}]} \times \frac{[ArOH]}{[Ar_2NH]} \tag{17}$$

$$\Delta G = \Delta H - T{\cdot}\Delta S = RT \ln K_{eq} \tag{18}$$

Alkyl Radical Kinetics. Rate constants for trapping alkyl radicals were obtained by alkyl radical clock techniques. A 100 μL sample containing diarylamine (0.02−0.25 M, depending on k_H), bis-(triphenylstannane) (0.01 M), and 2-(2-bromo-1,1-dimethylethyl)-naphthalene[20] (0.01 M) in chlorobenzene was degassed by sparging with argon for 2 min. The sample was then irradiated for 20 min in a photoreactor equipped with UVC germicidal lamps (strong line at 254 nm). The samples were transferred to GC vials and diluted with acetonitrile (300 μL) for analysis. GC analysis was carried out using an Agilent DB-5 column (30 m × 0.32 μm × 0.25 μm) with the following temperature profile: 70 °C, hold 0.5 min; 1 °C/min to 82 °C; 20 °C/min to 280 °C; hold 5 min. Preparation of GC standards: 2-*tert*-butylnaphthalene and 2-*iso*-butyl-naphthalene were prepared by treating 2-(2-bromo-1,1-dimethylethyl)-naphthalene with $AgClO_4$ and $LiAlH_4$ (obtained as a 16:1 mixture by ^{1}H NMR).[49] 2-(2-Methyl-1-propen-1-yl)-naphthalene was prepared via the Wittig reaction.[49]

ASSOCIATED CONTENT

Supporting Information

Raw kinetic data for reactions of diarylamines with peroxyl and alkyl radicals via competition methods, voltammograms, and sample EPR spectra used for determining N−H BDEs. 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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