JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Incorporation of Ring Nitrogens into Diphenylamine Antioxidants: Striking a Balance between Reactivity and Stability

Jason J. Hanthorn,[†] Luca Valgimigli,*[,‡] and Derek A. Pratt*[,†,§]

[†]Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6
[‡]Department of Organic Chemistry "A. Mangini", University of Bologna, 40126 Bologna, Italy
[§]Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

Supporting Information

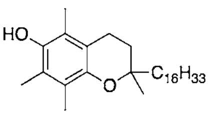
ABSTRACT: The incorporation of nitrogen atoms into the aryl rings of conventional diphenylamine antioxidants enables the preparation of readily accessible, air-stable analogues, several of which have temperature-independent radical-trapping activities up to 200-fold greater than those of typical commercial diphenylamines. Amazingly, the nitrogen atoms raise the oxidation potentials of the amines without greatly changing their radical-trapping (H-atom transfer) reactivity.

Diarylamines (Ar_2NH) and phenols (ArOH) constitute the bulk of radical-trapping antioxidant (RTA) additives to petroleum-derived products because of their ability to slow hydrocarbon autoxidation through the following rate-controlling inhibition reactions:[1]

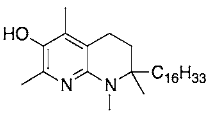
$$Ar_2N{-}H + ROO\cdot \xrightarrow{k_1} Ar_2N\cdot + ROOH \qquad (1)$$

$$ArO{-}H + ROO\cdot \xrightarrow{k_2} ArO\cdot + ROOH \qquad (2)$$

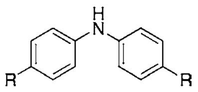
Of the two parent structures, the N−H bond in diphenylamine [bond dissociation energy (BDE) = 84.7 kcal/mol[2]] is weaker than the O−H bond in phenol (87.2 kcal/mol[3]), which is believed responsible for its faster radical-trapping kinetics (k_1[4] = 2.0×10^4 M^{-1} s^{-1} vs k_2[5] = 2.9×10^3 M^{-1} s^{-1} in styrene at 65 °C). Regardless, phenols are commonly viewed as the quintessential antioxidants since their reactivities are more easily manipulated. Nature has optimized the substitution of phenol in its evolution of α-tocopherol (α-TOH, **1**), the key lipophilic antioxidant in vivo, which has an O−H BDE of 77.3 kcal/mol[6] and $k_2 = 3.2 \times 10^6$ M^{-1} s^{-1}.[7] Furthermore, on the basis of known structure−activity relationships, related synthetic compounds with reactivities up to 90-fold higher than that of **1** (e.g., **2**) have been developed.[8−10] In contrast, optimization of diarylamines has been difficult.[11] The industry standards are 4,4′-dialkyldiphenylamines (**3**), which have N−H BDEs of ~82 kcal/mol[2] and $k_1 = 1.8 \times 10^5$ M^{-1} s^{-1} in PhCl at 37 °C (see below).



1



2

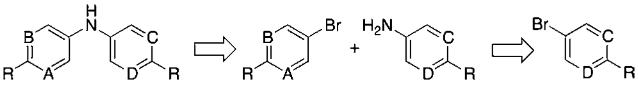


3

Not long ago, we showed that when diphenylamine is substituted with increasingly electron-donating groups at the 4- and 4′- positions, the N−H BDE is predictably weakened (e.g., by 4.0 and 6.3 kcal/mol for alkoxy and dialkylamino groups, respectively).[2] This suggested that diarylamines with improved RTA activity relative to **3** should be accessible. However, 4,4′-bis(*N*,*N*-dimethylamino)diphenylamine and analogous compounds are unstable under typical autoxidation conditions (hydrocarbon, O_2, radical initiator), precluding a determination of their inhibition kinetics (k_1) and implying they would be useless as antioxidants. Since then, we have found that the incorporation of N atoms into the aromatic ring of phenols allows them to be substituted with highly electron-donating groups (e.g., **2**), substantially weakening their O−H bonds and dramatically accelerating their rates of reactions with radicals, but not at the expense of their stability toward oxidation by air or hydroperoxides.[8−10] In view of these results, it was our supposition that this approach could be extended to the development of highly reactive diarylamine RTAs. Preliminary results are reported here.

The (novel) diarylamines described here were prepared using Buchwald−Hartwig Pd-catalyzed amination chemistry with the XPhos ligand.[12] The modular synthetic strategy employed commercially available or readily synthesized[13] aryl bromides, which were used in the construction of both the diarylamines and the precursor amines, as shown in Scheme 1.[14] For this transformation, the electron-rich aryl bromides were converted to the amines by a two-step sequence involving benzylamine intermediates,[13] while the electron-poor aryl bromides were reacted directly with aqueous NH_3.[15] We note that these reactions were enabled by the use of an "unconventional" precatalyst, $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$.[16] In fact, for many of the aminations performed here, the most often used precatalyst, $Pd_2(dba)_3$, gave substantially lower yields or required long reaction times and/or excessive heating,

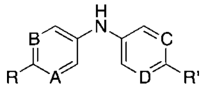
Scheme 1. Synthetic Approach to Substituted Diarylamines (A−D = CH or N; R = Alkyl or *N*,*N*-Dialkylamino)



Received: January 12, 2012
Published: February 27, 2012

dx.doi.org/10.1021/ja300086z | J. Am. Chem. Soc. 2012, 134, 8306−8309

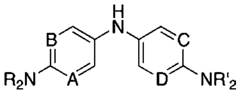
Table 1. Reactivities of Alkylated Diarylamines toward Peroxyl Radicals and the Associated One-Electron Oxidation Potentials



	A	B	C	D	R, R′[a]	$10^5 k_1$[b]	E_{pa}[c]
3	CH	CH	CH	CH	C_8, C_8	1.8 ± 1.1	1.02
4	N	CH	CH	CH	C_6, C_4	1.5 ± 1.1	0.95
5	N	N	CH	CH	C_7, C_4	1.3 ± 0.1	1.13
6	N	CH	N	CH	C_6, C_6	0.9 ± 0.3	1.12
7	N	N	N	CH	C_7, C_6	0.8 ± 0.1	1.50
8	N	N	N	N	C_7, C_7	0.3 ± 0.1	1.55

[a] Linear alkyl chains with the indicated lengths. [b] Values in $M^{-1}\ s^{-1}$ determined at 37 °C in PhCl using the peroxyl radical clock methodology.[17] [c] Anodic peak potentials in V vs NHE determined at 25 °C by differential pulse voltammetry in CH_3CN.

Table 2. Reactivities of *N*,*N*-Dialkylaminated Diarylamines toward Peroxyl Radicals and the Associated One-Electron Oxidation Potentials



	A	B	C	D	R, R′	$10^7 k_1$[a]	$E°$[b]
9	CH	CH	CH	CH	Me, Me	–[c]	0.34
10	N	CH	CH	CH	Me, Me	–[c]	0.37
11	N	N	CH	CH	Me, Me	3.7 ± 1.0	0.44
12	N	CH	N	CH	Me, Me	3.4 ± 1.1	0.44
13	N	N	N	CH	Me, Et	3.1 ± 1.2	0.50
14	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.[17] [b] Values in V vs NHE determined at 25 °C by cyclic voltammetry in acetonitrile. [c] Compound was unstable under the reaction conditions.

leading to competing reactions, including catalyst decomposition.

The incorporation of N atoms into the aryl rings of the alkylated diarylamine scaffold gave rise to compounds that retained their facile H-atom transfer chemistry to peroxyl radicals but had significantly increased one-electron oxidation potentials (Table 1). For instance, in going from diphenylamine **3** to the amines **7** and **8**, the peak potential determined by differential pulse voltammetry (cyclic voltammagrams were irreversible) increased by ~0.5 V (~12 kcal/mol), but k_1 decreased only 2–6-fold.

These exciting results prompted us to attempt to stabilize the labile *N*,*N*-dialkylamine-substituted diphenylamines next. Upon preparation, we found that diarylamines containing ring nitrogens were significantly more stable and easier to prepare, isolate, and purify. For example, while **9** and **10** became intensely colored immediately upon exposure to air or hydroperoxides,[18] the pyridyl and pyrimidyl analogues **11–14** could be manipulated without obvious degradation. Furthermore, these diarylamines were highly effective peroxyl RTAs under ambient conditions, as indicated by the values of the rate constant k_1, which were 100–200-fold higher than that of the industry standard **3** (Table 2). Similar to our results with amines **3–8**, the k_1 values we measured for **11–14** were within a factor of 2 of each other regardless of the number of N atoms in the aromatic rings. This clearly demonstrates that the introduction of N atoms into the aryl rings imparts greater stability to the amines but does not lead to significant differences in their radical-trapping activities—an ideal outcome.

To provide a thermodynamic rationale for the observed kinetics, the radical-equilibration electron paramagnetic resonance (EPR) technique was used to determine the N–H BDEs of diarylamines **9–14**. Thus, the diarylaminyl radicals were generated via reaction of the corresponding diarylamines with *t*-BuO· (generated in situ by photolysis of di-*tert*-butyl peroxide), and equilibrium constants for their H-atom exchange reactions with tri-*tert*-butylphenol (Ar′O–H BDE = 80.1 kcal/mol[3]) (eq 3) were determined from the resulting spectra (e.g., Figure 1). The spectra were highly reproducible for all of the radicals except those derived from **13**.

$$\mathrm{Ar_2N\cdot + HOAr' \rightleftarrows Ar_2N{-}H + \cdot OAr'} \qquad (3)$$

The BDEs of **9**, **12**, and **14**, which were the most easily determined because of the molecular symmetry, increased systematically with increasing N-atom incorporation into the aryl rings: 78.4 ± 0.6, 78.8 ± 0.8, and 79.2 ± 0.5 kcal/mol, respectively. However, it should be pointed out that these differences are within the experimental error of the measurements. This was further reinforced by the N–H BDEs of the unsymmetrical compounds **10** and **11**, which fell in the middle of the range: 78.8 ± 0.3 and 79.0 ± 0.5 kcal/mol, respectively. While these results parallel the observed kinetics, the differences in the N–H BDEs are much smaller than the differences in the $E°$ values, consistent with the expectation that N-atom incorporation into the aryl rings destabilizes the diarylamine radical cation formed by one-electron oxidation much more than it destabilizes the corresponding diarylaminyl radicals formed from H-atom abstraction. Furthermore, the changes in N–H BDE and k_1 upon N-atom incorporation into the aryl rings are much smaller than those observed in phenolic compounds (ca. 1.2–1.5 kcal/mol per N atom).[8,9] This is likely due to the fact that the diphenylaminyl radical is inherently less electron-poor than the phenoxyl radical and therefore is less

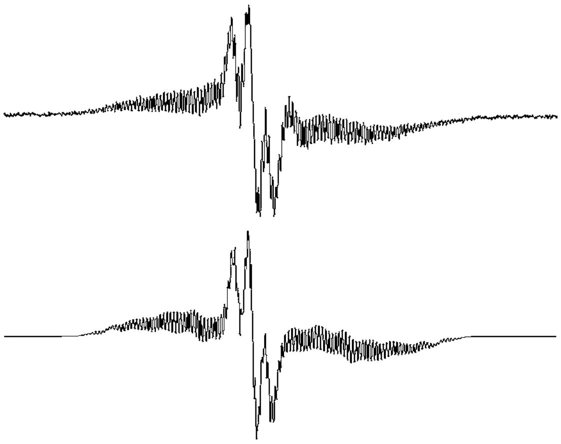
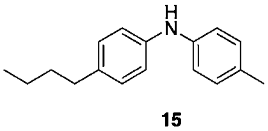


Figure 1. (top) EPR spectrum of an equilibrated mixture of the diarylaminyl radical derived from **12** and 2,4,6-tri-*tert*-butylphenoxyl radical in benzene at 298 K and (bottom) the associated simulated spectrum for a 100:15 ratio of the two equilibrating radicals.

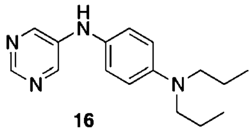
destabilized by the introduction of the N atoms into the aryl rings. This clearly shows that diphenylamines are better platforms for manipulation by this strategy in comparison with phenols.

While we were delighted with the properties of these new compounds, the results were confounded by the fact that the magnitude of the rate constants in Table 2 (log k_1 > 7) are at odds with the only reported pre-exponential factor determined for the reaction of peroxyl radicals with diarylamines (log A = 5.1 ± 0.5 for the reaction of *N*-α-naphthyl-*N*-phenylamine with *tert*-butylperoxyl radical).[19] This implied that the mechanism of the reactions of **11**−**14** with peroxyl radicals must be different and that perhaps an electron transfer mechanism intervenes for these more reactive diarylamines. However, when we measured rate constants for the reactions of a representative compound (**12**) in a variety of solvents, we found that increasing the polarity of the medium did not accelerate the rate but rather decreased it. Instead, the kinetic data yielded an excellent correlation with the H-bond-accepting ability of the solvent (given by its β_2^{H} value;[20] see the Supporting Information for details), supporting a H-atom transfer mechanism[21] akin to that long-accepted for the less reactive diarylamines.

As a result of this apparent contradiction, we measured the temperature dependence of k_1 for reactions of diarylamines **15** and **16** with peroxyl radicals at six temperatures between 37 and 95 °C. While this is admittedly a small range, the data for



15



16

diarylamine **15** yielded E_a = 2.5 ± 0.3 kcal/mol and log A = 6.9 ± 0.2, while the rate constants for diarylamine **16** were found to be invariant with temperature [k_1 = (1.3 ± 0.3) × 10^7 M^{-1} s^{-1}], implying that this reaction proceeds with a negligible activation energy (i.e., $E_a \approx 0$) and that log $A \approx$ log k_1 = 7.1 ± 0.1 (see the Supporting Information for further details).[22] From these data, a pre-exponential factor of log $A \approx 7$ seems more appropriate for these reactions than the previously reported value that is 2 orders of magnitude lower.

The foregoing results yielded an unexpected insight: reactions of diarylamines with peroxyl radicals are clearly faster than reactions of phenols with peroxyl radicals that proceed with comparable thermodynamics. For example, while all of the diarylamines in Table 2 have N−H BDEs that are 1.3−1.9 kcal/mol greater than the O−H BDE of α-TOH (77.3 kcal/mol, measured the same way by the same laboratory under the same conditions),[6] they have inhibition rate constants that are 2.5−5.2-fold greater than that of α-TOH under the same conditions (k_2 = 7.1 × 10^6 M^{-1} s^{-1}, which was used to calibrate the peroxyl radical clock).[17b] This implies that the entropic demand of the reactions of phenols with peroxyl radicals must be greater. However, the peroxyl radical clock method described above, which provided log A = 6.9 and 7.1 for the reactions of **15** and **16**, respectively, with peroxyl radicals, was calibrated using log A = 8.0 for the reaction of α-TOH with peroxyl radicals,[17b] meaning that the entropic demand is in fact smaller for phenols and that the difference in reactivity must originate in E_a.

We surmise that the origin of this difference in reactivity can be explained upon consideration of the transition state (TS) structure for the formal H-atom transfer reaction between peroxyl radicals and diarylamines (e.g., Ph_2NH in Figure 2). As for the reactions of phenols with peroxyl radicals,[23,24] the calculated TS structure for the reaction of diphenylamine with peroxyl radicals is best described as a proton-coupled electron transfer (PCET) reaction, wherein the proton moves from the amine to the peroxyl radical via two nominally nonbonding orbitals (roughly in the plane of the page) while an electron moves from the π-HOMO of the amine to the π-SOMO of the peroxyl radical (roughly perpendicular to the page; see Figure 2b). From this structure it follows that a diarylamine with a given N−H bond strength should have a lower activation energy for reaction with a peroxyl radical than does a phenol whose O−H bond has a similar strength, since the π-MOs of the diarylamine are higher in energy than those of the phenol,[25] thereby providing better orbital overlap with the π-SOMO of the peroxyl radical.

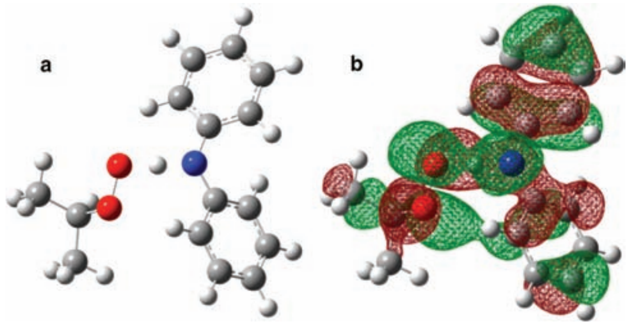


Figure 2. (a) Calculated (B3LYP/CBSB7) TS structure for the reaction of diphenylamine with *iso*-propylperoxyl radical, yielding E_a = 3.7 kcal/mol and log A = 6.9, which give k_1 = 3.2 × 10^4 M^{-1} s^{-1} at 65 °C, in good agreement with the literature value (k_1 = 2.0× 10^4 M^{-1} s^{-1} at 65 °C). (b) The highest (doubly) occupied MO.

Diarylamines such as **3** 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.[26] In contrast, the compounds described here also provide excellent antioxidant activity at ambient temperatures—*comparable to or better than* *those of the best phenolic antioxidants*—suggesting that they will be useful in a far broader range of applications. This is currently under more detailed investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete characterization data for amines **3−16** and experimental data for peroxyl radical kinetics, electrochemical, and EPR studies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

luca.valgimigli@unibo.it; dpratt@uottawa.ca

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the support of NSERC of Canada, the Ontario Ministry of Research and Innovation, and the Canada Research Chairs Program for grants to D.A.P. and to the MIUR (Rome) and the University of Bologna for grants to L.V.

■ REFERENCES

(1) Ingold, K. U. *Chem. Rev.* **1961**, *61*, 563−589.
(2) Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2002**, *124*, 11085−11092.
(3) Mulder, P.; Korth, H.-G.; Pratt, D. A.; DiLabio, G. A.; Valgimigli, L.; Pedulli, G. F.; Ingold, K. U. *J. Phys. Chem. A* **2005**, *109*, 2647−2655.
(4) Brownlie, I. T.; Ingold, K. U. *Can. J. Chem.* **1966**, *44*, 861−868.
(5) Howard, J. A.; Ingold, K. U. *Can. J. Chem.* **1963**, *41*, 1744−1751.
(6) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Cabiddu, S.; Cipollone, M. *J. Org. Chem.* **1996**, *61*, 9259−9263. The data were revised downward by 1.1 kcal/mol, as described in ref 3.
(7) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194−201.
(8) Pratt, D. A.; DiLabio, G. A.; Brigati, G.; Pedulli, G. F.; Valgimigli, L. *J. Am. Chem. Soc.* **2001**, *123*, 4625−4626.
(9) Wijtmans, M.; Pratt, D. A.; Valgimigli, L.; DiLabio, G. A.; Pedulli, G. F.; Porter, N. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4370−4373.
(10) Nam, T.-g.; Rector, C. L.; Kim, H.-y.; Sonnen, A. F.-P.; Meyer, R.; Nau, W. M.; Atkinson, J.; Rintoul, J.; Pratt, D. A.; Porter, N. A. *J. Am. Chem. Soc.* **2007**, *129*, 10211−10219.
(11) Lucarini, M.; Pedrielli, P.; Pedulli, G. F.; Valgimigli, L.; Gigmes, D.; Tordo, P. *J. Am. Chem. Soc.* **1999**, *121*, 11546−11553.
(12) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523−6527.
(13) Nara, S. J.; Jha, M.; Brinkhorst, J.; Zemanek, T. J.; Pratt, D. A. *J. Org. Chem.* **2008**, *73*, 9326−9333.
(14) Complete details will be provided in a forthcoming manuscript.
(15) Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052−3054.
(16) Murrall, N. W.; Welch, A. J. *J. Organomet. Chem.* **1986**, *301*, 109−130. Norton, D. M.; Mitchell, E. A.; Botros, N. R.; Jessop, P. G.; Baird, M. C. *J. Org. Chem.* **2009**, *74*, 6674−6680.
(17) (a) Jha, M.; Pratt, D. A. *Chem. Commun.* **2008**, 1252−1254. (b) Hanthorn, J. J.; Pratt, D. A. *J. Org. Chem.* **2012**, *77*, 276−284.
(18) For example, **9**, **12**, and **14** have half-lives of 30 min, 7 h, and 41 h when exposed to 1 equiv of *tert*-butyl hydroperoxide in dichlorobenzene (200 mM) under air at 80 °C (see the Supporting Information).
(19) Howard, J. A.; Furimsky, E. *Can. J. Chem.* **1973**, *51*, 3738−3745.
(20) Abraham, M. H.; Grellier, P. D.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1989**, 699−711.
(21) Litwinienko, G.; Ingold, K. U. *Acc. Chem. Res.* **2007**, *40*, 222−230.
(22) Furthermore, DFT calculations predicted that log $A = 6.9$ for the reaction of diphenylamine with *iso*-propylperoxyl radical (see Figure 2).
(23) DiLabio, G. A.; Johnson, E. R. *J. Am. Chem. Soc.* **2007**, *129*, 6199−6203.
(24) Valgimigli, L.; Amorati, R.; Petrucci, S.; Pedulli, G. F.; Hu, D.; Hanthorn, J. J.; Pratt, D. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8348−8351.
(25) Diphenylamine has a gas-phase ionization energy of 7.19 eV, while that for *p*-methylphenol, whose O−H BDE is essentially the same as the N−H BDE in diphenylamine, is 8.34 eV. See: Lias, S. G. In *NIST Chemistry WebBook*; Linstrom, P. J.; Mallard, W. G., Eds.; NIST Standard Reference Database 69; National Institute of Standards and Technology: Gaithersburg, MD.
(26) Jensen, R. K.; Korcek, S.; Zinbo, M.; Gerlock, J. L. *J. Org. Chem.* **1995**, *60*, 5396−5400. We recently presented an alternative (see: Amorati, R.; Pedulli, G. F.; Pratt, D. A.; Valgimigli, L. *Chem. Commun.* **2010**, *46*, 5139−5141). The greater access to stable but electronically distinct diarylamines described here should aid in the design of experiments aimed at distinguishing which mechanism is responsible for this highly relevant catalytic activity.