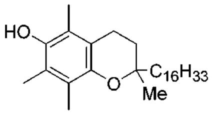
Neutron Diffraction Study of a Phenol·Nitroxide Radical Adduct: A Structural Model for Hydrogen Atom Abstraction by Peroxyl Radicals from Vitamin E and Related Phenolic Antioxidants

Birte Ahrens,[†] Matthew G. Davidson,*[,†] V. Trevor Forsyth,[‡,§]
Mary F. Mahon,[†] Andrew L. Johnson,[†] Sax A. Mason,[‡]
Richard D. Price,[†] and Paul R. Raithby[†]

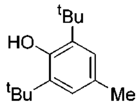
Department of Chemistry, University of Bath
Claverton Down, Bath BA2 7AY, UK
Physics Department, Keele University
Staffordshire, ST5 5BG, UK
Institut Laue Langevin, BP 156
38042 Grenoble, Cedex 9, France

Received March 20, 2001
Revised Manuscript Received June 13, 2001

Oxidation under ambient conditions is a major cause of hydrocarbon degradation in living organisms[1] and in many commercial products such as polymers,[2] lubricants,[3] and foodstuffs.[4] Low concentrations of so-called antioxidants that protect against this oxidative degradation are present naturally in aerobic organisms and are added to synthetic materials. The most prevalent and widely studied group of antioxidants is phenol-based. For example, in mammals, α-tocopherol, a major component of Vitamin E, is the most important lipid-soluble antioxidant,[5] and in synthetic materials, hindered phenols such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) find widespread application.[2,3]



α-tocopherol



BHT

The role of these phenolic antioxidants is to scavenge peroxyl radicals which otherwise propagate autoxidation in lipids and synthetic hydrocarbons. The relevant steps within a generally accepted mechanism (which may be simplistic for complex, nonhomogeneous systems such as liposomes and semicrystalline polymers) are shown below.[2,5] Following initiation, autoxidation can be propagated by rapid reaction of the hydrocarbon radical with oxygen (eq 1) followed by the rate-limiting hydrogen atom abstraction from the polymer (RH, eq 2). Phenolic antioxidants (ArOH) are able to inhibit this autoxidation by providing a hydrogen atom that is more easily abstracted (eq 3) to give an oxygen-centered phenoxy radical. This relatively stable $ArO^\bullet$ radical then gives nonradical products in preference to reacting further with RH.

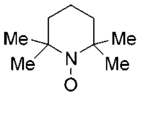
$$R^\bullet + O_2 \rightarrow ROO^\bullet \qquad \textit{autoxidation} \qquad (1)$$

$$ROO^\bullet + RH \rightarrow ROOH + R^\bullet \qquad \textit{autoxidation} \qquad (2)$$

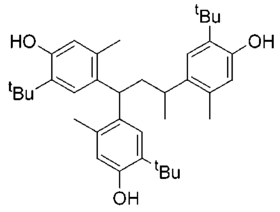
$$ROO^\bullet + ArOH \rightarrow ROOH + ArO^\bullet \qquad \textit{inhibition} \qquad (3)$$

Previous research into factors that affect the activity of phenolic antioxidants has focused on the key hydrogen atom abstraction step (reaction 3). DFT calculations suggest that this proceeds via an O−H···O hydrogen-bonded phenol···peroxyl transition state.[1i] Detailed kinetic studies have also yielded a number of important observations that relate hydrogen bonding to the activity of antioxidants. In particular, it has been shown that low O−H bond dissociation energies of phenolic antioxidants are related to high antioxidant activity,[1c] that intermolecular hydrogen bonding (e.g., from hydrogen bond acceptor solvents) generally inhibits hydrogen atom transfer,[1e] and that intramolecular hydrogen bonding within a phenol (e.g., from an *o*-methoxy group) enhances the rate of hydrogen atom transfer.[1f] Thus, an accumulation of indirect evidence suggests that a hydrogen-bonded radical·phenol adduct is the key intermediate in this biologically and commercially important function.

In this paper we report the synthesis and structural characterization by single-crystal neutron diffraction of the first such hydrogen-bonded complex. This system can be viewed as a structural model for the transition state in hydrogen atom transfer between a phenol and a peroxyl radical. We have chosen to investigate the structure of an adduct containing 2,2,6,6-tetramethylpiperidine-1-oxyl, TEMPO, and 1,1,3-tris(2-methyl-4-hydroxy-5-*tert*-butylphenyl)butane, H_3L. TEMPO is a stable aminoxyl radical that is structurally similar to (and isoelectronic with) peroxyl radicals. H_3L is typical of the class of hindered phenols that are commercially employed as antioxidants.



TEMPO



H_3L

Recrystallization of 3 equiv of TEMPO and 1 equiv of H_3L from toluene solution yielded orange crystals that were shown by NMR and elemental analysis to be a toluene solvate of H_3L·3TEMPO. A crystal structure, determined by X-ray diffraction, confirmed the isolated product to be a hydrogen-bonded adduct, via short O−H···O−N interactions between one trisphenol and three nitroxide molecules. Although phenol·nitroxide adducts have been investigated spectroscopically[6] and examples of the N−O group of nitroxide radicals functioning as hydrogen bond acceptors are known in the solid state,[7,8] a search of the Cambridge Structural Database[9] revealed no structural studies have been completed on other examples of phenol·nitroxide *adducts*.

Given the potential significance of the observed hydrogen bonding in H_3L·3TEMPO we have determined its structure by low-temperature (20 K) neutron diffraction, as well, to characterize

---

* To whom correspondence should be addressed. Fax +44 (0)1225 826231. E-mail: m.g.davidson@bath.ac.uk.
[†] University of Bath.
[‡] Institut Laue Langevin.
[§] Keele University.

[1] (a) Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1996**, *118*, 6790. (b) Antosiewicz, J.; Damiani, E.; Jassem, W.; Wozniak, M.; Orena, M.; Greci, L. *Free Radical Biol. Med.* **1997**, *22*, 249. (c) Valgimigli, L.; Lucarini, M.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 8095. (d) Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245. (e) Barclay, L. R. C.; Edwards, C. E.; Vinqvist, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 6226. (f) de Heer, M. I.; Korth, H. G.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 6969. (g) Lien, E. J.; Ren, S. J.; Bui, H. Y. H.; Wang, R. B. *Free Radical Biol. Med.* **1999**, *26*, 285. (h) Valgimigli, L.; Banks, J. T.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1999**, *64*, 3381. (i) de Heer, M. I.; Mulder, P.; Korth, H. G.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **2000**, *122*, 2355.

[2] Breese, K. D.; Lamethe, J. F.; DeArmitt, C. *Polym. Degrad. Stab.* **2000**, *70*, 89.

[3] Scott G. S., Ed. *Atmospheric Oxidation and Antioxidants*; Elsevier: Amsterdam, The Netherlands, 1993.

[4] Donnelly, J. K.; Robinson, D. S. *Free Radical Res.* **1995**, *22*, 147.

[5] Bowry, V. W.; Ingold, K. U. *Acc. Chem. Res.* **1999**, *32*, 27. Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194.

[6] Shenderovich, I. G.; Kecki, Z.; Wawer, I.; Denisov, G. S. *Spectrosc. Lett.* **1997**, *30*, 1515.

[7] Chion, B.; Lajzerowicz-Bonneteau, J. *Acta Crystallogr.* **1980**, *B36*, 998.

10.1021/ja015849+ CCC: $20.00

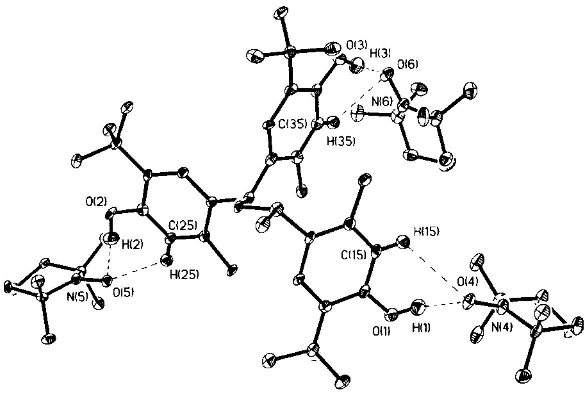


Figure 1. Neutron structure of $H_3L{\cdot}3TEMPO{\cdot}0.5C_7H_8$. Toluene and H atoms not involved in hydrogen bonding were omitted for clarity. Thermal ellipsoids are at the 60% probability level.

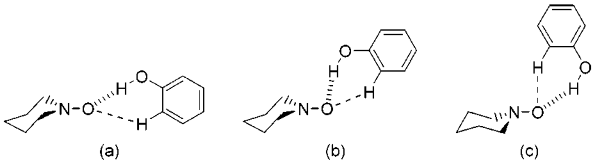


Figure 2. The three different hydrogen bond geometries in $H_3L{\cdot}3TEMPO$ involving (a) O(4), (b) O(5), and (c) O(6).

Table 1. Geometrical Parameters Associated with Intermolecular Interactions in the Neutron Structure of $H_3L{\cdot}3TEMPO$ (distances in Å, angles in deg)

parameter	interactions involving O(4)	interactions involving O(5)	interactions involving O(6)
O−H	0.968(11)	0.995(9)	0.974(10)
H···O	1.773(9)	1.691(8)	1.792(8)
O···O	2.723(5)	2.684(5)	2.764(5)
O−H−O	166.4(6)	175.4(6)	175.6(6)
N−O	1.276(4)	1.285(4)	1.282(4)
H−O−N	128.0(3)	104.9(3)	128.4(3)
H−O−C−C	−151.6(5)	−174.8(4)	170.8(5)
C−H	1.087(7)	1.088(7)	1.089(7)
H···O	2.826(7)	2.522(7)	2.549(7)
C···O	3.430(4)	3.323(4)	3.383(4)
C−H···O	115.1(4)	129.6(4)	132.6(5)

fully the intermolecular interactions (Figure 1).[10,11] The general structural features of $H_3L{\cdot}3TEMPO$ are unremarkable. All three hydroxyl hydrogen atoms are directed away from the *o-tert*-butyl substituents and all O−H···O−N distances are within the range anticipated. For all three such interactions, *o*-aryl C−H groups are also in close contact with nitroxide oxygen atoms and, although the geometries of these contacts are consistent with attractive C−H···O interactions,[12] their structural significance in the presence of the stronger O−H···O hydrogen bonds is unclear.[13] Most interestingly, close inspection of the structure reveals that the geometries and electronic nature of the three intermolecular interactions differ significantly from each other (Figure 2 and Table 1). The two hydrogen bonds from H(1) and H(3) interact with σ-type orbitals of O(4) and O(6), respectively, whereas that involving H(2) is directed toward a π-type orbital on O(5) (see H−O−N angles, Table 1). The weaker C−H···O interactions follow a similar but complementary pattern [σ for H(15)···O(4) and H(25)···O(5) and π for H(35)···O(6)]. A further notable difference is that one of the three phenolic hydrogen atoms [H(1)] lies significantly out of the plane of the aromatic ring to which it is attached, whereas the other two lie approximately in the respective equivalent planes (see H−O−C−C torsion angles, Table 1).[14] Despite these differences the H···O, C···O, and N−O distances of all interactions are surprisingly similar, suggesting that the strength of the three interactions is comparable. This implies that nitroxide (and isoelectronic peroxyl) radicals are versatile hydrogen bond acceptors over a wide range of geometries.

These results provide the first structural model for a hydrogen-bonded intermediate in the hydrogen atom abstraction from phenolic antioxidants by peroxyl radicals. Although observation of these interactions in a crystal environment is not ideal, the results are nonetheless significant given the difficulty in characterizing such interactions by other means. The observation of three geometrically very different but similarly short interactions suggests that the interaction of radicals with phenolic antioxidants is favorable over a wide range of steric and electronic environments. This is consistent with their widespread applicability in biological systems and commercial products. The observation of secondary *o*-aryl C−H···O interactions may influence design of new antioxidants. Further refinement of our model to include some of the more subtle steric and electronic features of biologically active antioxidants[5] is expected to shed further light on this important process.

Acknowledgment. We thank the University of Bath and ICI for Postdoctoral Fellowships (R.D.P. and A.L.J., respectively), the ILL for beam time and for the support of V.T.F. as a Senior Visiting Scientist, and the EPSRC (JREI grant for CCD area detector).

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR, and elemental analysis data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015849+

---

(8) Recent interest in the solid-state structures of nitroxide radicals has focused on their potential as organic-based molecular magnets. In this context, a number of hydrogen-bonded nitroxides have been characterized by X-ray crystallography. See for example: (a) Cirujeda, J.; Ochando, L. E.; Amigo, J. M.; Rovira, C.; Rius, J.; Veciana, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 55. (b) Park, J. G.; Paulsen, C.; Rey, P.; Rovira, C.; Veciana, J. *J. Chem. Soc., Chem. Commun.* **1995**, 709. (c) Cirujeda J.; Mas, M.; Molins, E.; Depanthou, F. L.; Laugier, J.; Matsushita, M. M.; Izuoka, A.; Sugawara, T.; Kobayashi, T.; Wada, N.; Takeda, N.; Ishikawa, M. *J. Am. Chem. Soc.* **1997**, *119*, 4369. (d) Pontillon, Y.; Akita, T.; Grand, A.; Kobayashi, K.; Lelievre-Berna, E.; Pecaut, J.; Ressouche, E.; Schweizer, J. *J. Am. Chem. Soc.* **1999**, *121*, 10126.

(9) Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, 1.

(10) Neutron data for $H_3L{\cdot}3TEMPO{\cdot}0.5C_7H_8$: $C_{67.5}H_{110}N_3O_6$, triclinic, $P\bar{1}$, orange blocks, $a = 12.6557(12)$ Å, $b = 15.2062(12)$ Å, $c = 18.5218(16)$ Å, $\alpha = 86.677(3)°$, $\beta = 83.451(3)°$, $\gamma = 67.714(3)°$, $T = 20(2)$ K, $Z = 2$, R_1-$[I > 2\sigma(I)] = 0.0521$, GOF($F^2$) = 1.093. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographc Data Centre as supplementary publication nos. CCDC 164444 (neutron data) and CCDC 164445. (X-ray data). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, ((fax) +44 1223 336033 or (e-mail) deposit@ccdc.cam.ac.uk).

(11) We note that an attempted single crystal neutron study has been reported previously for a hydrogen-bonded boronic acid·nitroxide adduct but a phase transition caused crystal splitting and no structure could be determined [ref 8d].

(12) Desiraju, G. R. *Acc. Chem. Res.* **1991**, *24*, 290.

(13) However, it is interesting to note that stabilization of the O−H···O(radical) interaction by an ortho aryl C−H group suggests that the presence of one rather than two substituents ortho to the OH group of a phenol may enhance antioxidant activity.

(14) In a DFT-calculated transition state for hydrogen atom abstraction by methoxyl radical from 2-methoxyphenol the phenolic H-atom lies significantly out of the aromatic plane [ref 1h].