DOI: 10.1002/ejoc.200700545

The First Example of an Azaphenalene Profluorescent Nitroxide

James P. Blinco,[a] John C. McMurtrie,[a] and Steven E. Bottle*[a]

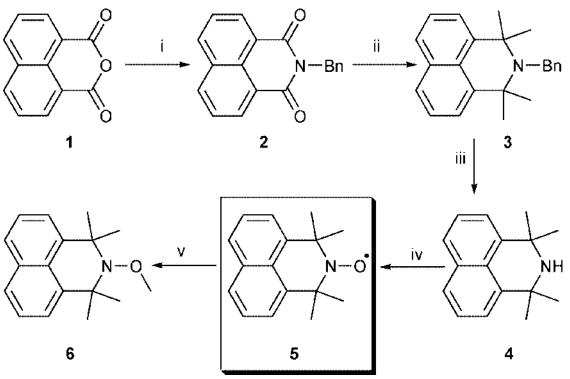
Keywords: Nitroxides / Fluorescence / Polymers / Degradation / Radicals

The synthesis of the first example of an azaphenalene-based fused aromatic nitroxide TMAO, [1,1,3,3-tetramethyl-2,3-dihydro-2-azaphenalen-2-yloxyl, (**5**)], is described. This novel nitroxide possesses some of the structural rigidity of the isoindoline class of nitroxides, as well as some properties akin to TEMPO nitroxides. Additionally, the integral aromatic ring imparts fluorescence that is switched on by radical scavenging reactions of the nitroxide, which makes it a sensitive probe for polymer degradation.

Introduction

Nitroxides are efficient excited-state quenchers, and they markedly reduce fluorescence through both inter- and intramolecular processes.[1–3] Intermolecular quenching may occur through chance collisions between an excited molecule and a nitroxide radical. A tether between the fluorophore and the radical moiety increases encounters between the fluorophore and the radical, which increases the efficacy of fluorescence quenching. Much work has been done on these tethered units, initially by Blough et al.[2–7] and more recently by Scaiano et al.[8–10] Both groups demonstrated that, in the presence of the nitroxide radical, fluorescence is substantially reduced. Loss of the spin by radical trapping, or redox activity, removes this quenching effect, and the fluorescence of the molecule can then be observed. The term profluorescence describes this capability, as in the paramagnetic form, such molecules are precursors to fluorescent systems. By using fluorescence spectroscopy, profluorescent nitroxides are sensitive probes for processes involving free radicals. Profluorescent probes synthesised to date, however, commonly link the fluorophore to the nitroxide through ester, amine, amide or sulfonamide groups. We recently showed that it is possible to combine phenanthrene[11] and stilbene[12] fluorophores with an isoindoline nitroxide in a C–C bond framework that is not susceptible to hydrolysis or enzymatic cleavage. These fused aromatic nitroxides also exhibit some advantages over less rigid five- and six-membered nitroxides, including superior thermal and chemical stability and narrower EPR linewidths.[13]

Herein we describe an entirely new class of nitroxide: 1,1,3,3-tetramethyl-2,3-dihydro-2-azaphenalene-2-yloxyl (**5**), to which we give the acronym TMAO. This unique nitroxide is the first to be based on an azaphenalene ring system (Scheme 1). The presence of a naphthalene ring within TMAO confers potent profluorescent properties. We further demonstrate the significance of TMAO by applying it to detect and protect against radicals formed during the photodegradation of polypropylene. As well as assessing the fluorescence properties of this novel nitroxide, we also compare some of the unique structural characteristics of TMAO with the related analogue 1,1,3,3-tetramethylbenzo[*f*]isoindolin-2-yloxyl (**7**),[14] by single-crystal X-ray diffraction structural analysis.



Scheme 1. Reagents and conditions: (i) $BnNH_2$, AcOH, reflux, >95%; (ii) MeMgI, xylenes, reflux, 15.5%; (iii) 50 psi H_2, 10% Pd/C, AcOH, 85%; (iv) H_2O_2, $Na_2WO_4{\cdot}2H_2O$, $NaHCO_3$/MeOH, 83%; (v) $FeSO_4{\cdot}7H_2O$, DMSO, H_2O_2, >95%.

Results and Discussion

A comparison of the fluorescence of nitroxides **5** and **7** with their diamagnetic methoxyamine derivatives **6** and **8** (Figures 1 and 2) demonstrated that the nitroxide quantum yields (**5** $\Phi_F = 9.2 \times 10^{-4}$ and **7** $\Phi_F = 4.5 \times 10^{-4}$) were several

---

[a] ARC Centre of Excellence for Free Radical Chemistry and Biotechnology, Queensland University of Technology,
GPO Box 2434, Brisbane Q4001, Australia
Fax: +61-7-38641804
E-mail: s.bottle@qut.edu.au

Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

magnitudes smaller than those recorded for the diamagnetic analogues (**6** $\Phi_F = 0.16$ and **8** $\Phi_F = 0.13$). This represents a significantly greater differential relative to other profluorescent nitroxides that all contain longer and more labile linkages.[7] Subtle differences can be observed in the spectra of these two ring systems, and TMBIO displays much sharper vibronics than TMAO, probably related to differences in the rigidity of the two structures. However, both nitroxides represent potent new examples of redox and radical probes with class-leading proximity between the spin system and the fluorophore, which importantly, are held together by a stable, noncleavable framework.

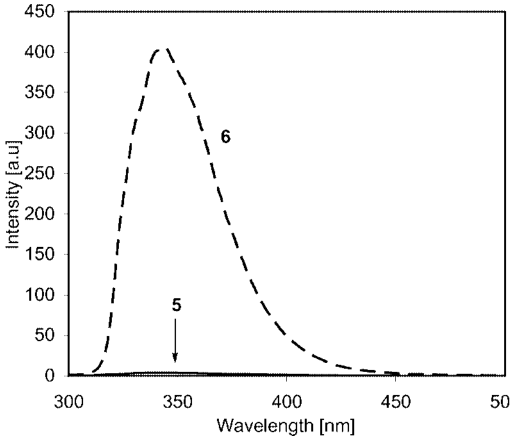


Figure 1. Fluorescence spectra of **5** (—) and **6** (---) excited at 290 nm in cyclohexane.

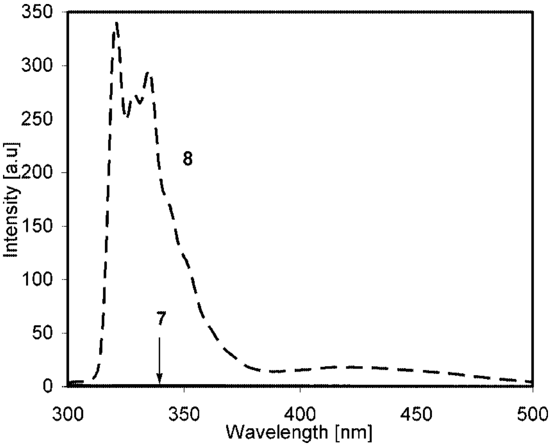
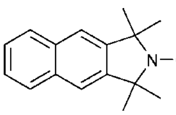
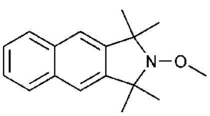


Figure 2. Fluorescence spectra of **7** (—) and **8** (---) excited at 290 nm in cyclohexane.



7



8

To demonstrate the application of TMAO as a probe, it was incorporated into polypropylene at low levels ($<0.05\%$) by using established methodology.[11] The polymer was irradiated in a Heraeus Sun Test CPS+ at an energy of 765 W m^{-2} and with a total dosage of 194400 kJ m^{-2}. Monitoring the fluorescence gave the plot shown in Figure 3. Notably after 30 h, significant fluorescence could be detected, yet the polymer displayed no visible indication of degradation. This mirrors the performance in thermooxidative degradation[11] where profluorescent nitroxides impart stability into the polymer matrix and signal the levels of radical degradation reactions occurring.

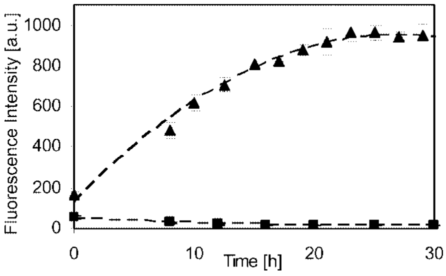


Figure 3. Spectrofluorimetry of UV-aged polypropylene doped with **5** (▲), compared with that of undoped polypropylene (■) monitored at 340 nm; excitation at 290 nm.

Notably there was no increase in fluorescence from polypropylene blanks photolysed under the same conditions. Equally cyclohexane solutions of TMAO showed little fluorescence change under these conditions.

As expected, the novel azaphenalene ring nitroxide displays properties falling somewhere between those of piperidines and isoindolines. X-ray crystallography reveals that, despite the structural constraints on the aza ring in TMAO that are imposed by the fused naphthalene, the steric characteristics of the molecule in the vicinity of the nitroxide group are similar to those in aliphatic TEMPO-like nitroxides. In the structure of TMAO (Figure 4), the sp^2-hybridised carbon atoms of the naphthalene ring hold the quaternary carbon atoms C(19) and C(20) almost coincident with the mean plane of the ring (0.079 Å, and –0.144 Å out of plane, respectively). By contrast, the carbon atoms in TEMPO adopt the classical chair configuration of aliphatic six-membered cyclic compounds. However, in TMAO the nitroxide moiety is displaced from the mean plane of the molecule, so two methyl groups on one face of the molecule are closer than their opposites. Analysis[15] of the structure of TMAO revealed that its methyl group arrangement and geometric parameters are typical for the analogous six-membered aliphatic nitroxides such as TEMPO.

The molecular structure of **7**, illustrated in Figure 5, displays very similar geometric parameters to the simple isoindoline nitroxide 1,1,3,3-tetramethylisoindolin-2-yloxyl, TMIO.[16,17] The five-membered isoindoline ring is almost coplanar with the mean plane of the naphthalene group (dihedral angle 0.60°) and the NO moiety is exactly coincident with the mean plane of the molecule. The methyl groups are symmetrically displaced ca. 1.35 Å above and below the mean plane of the molecule. This symmetry leads to narrower EPR line shapes (data not shown) and as expected, in contrast TMAO displays slightly broader EPR spectra.

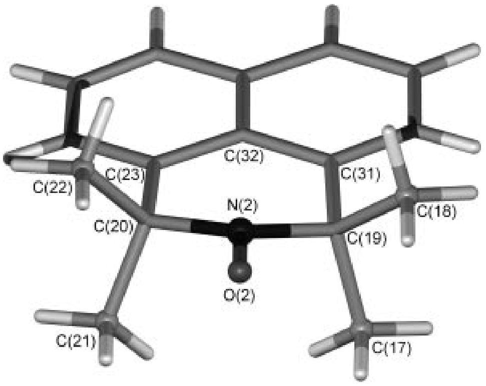


Figure 4. The molecular structure of one of five molecules in the symmetric unit of TMAO, **5** [N(1), O(1), C(17)–C(32)].

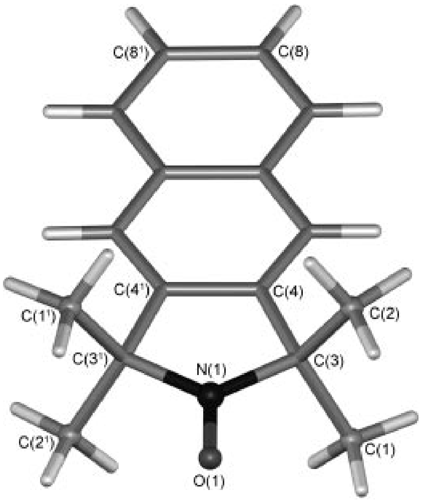


Figure 5. The molecular structure of **7**. The molecule has twofold symmetry [special positions occupied by N(1) and O(1) with the axis passing between C(8) and C(8¹)] (¹: *y* + 1, *x* – 1, –*z* + 1).

The two structures differ most in the greater degree of steric crowding around the TMAO nitroxide moiety relative to **7**. The methyl groups in **7** are held away from the N–O atoms (Me···O distances 2.997 and 3.010 Å). In TMAO, however, two of the methyl carbon atoms are ca. 0.25 Å closer to the nitroxide oxygen, thus increasing steric hindrance. This has implications for the use of TMAO in nitroxide-mediated living polymerisations where the fused structure may impart greater high-temperature stability over TEMPO analogues.

Conclusions

The novel azaphenalene-based nitroxide TMAO described here represents a new class of nitroxides. When present in a polymer this nitroxide protects the material by retarding oxidative damage as well as generating a fluorescent indicator for the degree of degradation to which the material has been exposed.

Experimental Section

The synthesis of **5** followed the established procedures for isoindoline nitroxides.[18] Anhydride **1** was heated at reflux (3 h) with benzylamine (1.6 equiv.) in CH_3COOH, poured onto ice and recrystallised from EtOH to give imide **2** (>95%, m.p. 198–200 °C.) This was suspended in xylenes and methylated with excess methylmagnesium iodide (6 equiv.). The product was extracted (hexanes) and then passed through Al_2O_3 (basic, activity II; EtOAc/hexane, 1:99). Evaporation and recrystallisation from MeOH yielded tetramethylazaphenalene **3** as a golden solid (15.5%, m.p. 150–3 °C). Hydrogenation of **3** (H_2, Pd/C, 50 psi, 4 h) gave secondary amine **4** as a low-melting solid (85%), which was difficult to crystallise, and this was oxidised by using hydrogen peroxide and Na_2WO_4 to give the target nitroxide, TMAO, **5**. This was recrystallised from heptane to yield long orange needles (83%; m.p. 163–5 °C; $C_{16}H_{18}NO$: calcd. C 80.0, H 7.55, N 5.8; found C 79.9, H 7.5, N 5.8). To confirm the structure of **5**, it was treated with methyl radicals generated from DMSO and H_2O_2 (3 equiv., 30 min) to produce methoxyamine derivative **6**, which readily recrystallised from EtOH (95%, m.p. 157–9 °C). Full synthetic details, NMR spectra and characterisation are supplied in the Supporting Information. By using similar methodology, starting from 2,3 naphthanoic anhydride it was also possible to synthesise 1,1,3,3-tetramethylbenzo[*f*]isoindolin-2-yloxyl (**7**; m.p. 228–229 °C, ref.[14] m.p. 228–230 °C). This represents a new synthetic route to this structural variant of **5**, to which we give the acronym TMBIO. TMBIO is also an analogue of the isoindoline class of nitroxides with the naphthalene-moiety imparting (quenched) fluorescent properties.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures for compounds **1**–**8** with full NMR spectroscopic data, ORTEP representations and discussion of X-ray data.

Acknowledgments

This work was produced with the support of the Australian Research Council under the ARC Centres of Excellence program, CE0561607.

---

[1] E. Lozinsky, A. I. Shames, G. I. Likhtenshtein, *Recent Res. Devel. Photochem. Photobiol.* **2001**, *5*, 41–55.
[2] S. A. Green, D. J. Simpson, G. Zhou, P. S. Ho, N. V. Blough, *J. Am. Chem. Soc.* **1990**, *112*, 7337–7346.
[3] S. E. Herbelin, N. V. Blough, *J. Phys. Chem. B* **1998**, *102*, 8170–8176.
[4] D. J. Kieber, N. V. Blough, *Anal. Chem.* **1990**, *62*, 2275–2283.
[5] D. J. Keiver, N. V. Blough, *Free Radical Res. Commun.* **1990**, *10*, 109–117.
[6] N. V. Blough, D. J. Simpson, *J. Am. Chem. Soc.* **1988**, *110*, 1915–1917.
[7] J. L. Gerlock, P. J. Zacmanidis, D. R. Bauer, D. J. Simpson, N. V. Blough, I. T. Salmeen, *Free Radical Res. Commun.* **1990**, *10*, 119–121.
[8] C. Coenjarts, O. Garcia, L. Llauger, J. Palfreyman, A. L. Vinette, J. C. Scaiano, *J. Am. Chem. Soc.* **2003**, *125*, 620–621.
[9] M. G. Ivan, J. C. Scaiano, *Photochem. Photobiol.* **2003**, *78*, 416–419.
[10] A. Aspee, O. Garcia, L. Maretti, R. Sastre, J. C. Scaiano, *Macromolecules* **2003**, *36*, 3550–3556.
[11] A. S. Micallef, J. P. Blinco, G. A. George, D. A. Reid, E. Rizzardo, S. H. Thang, S. E. Bottle, *Polym. Degrad. Stab.* **2005**, *89*, 427–435.
[12] D. J. Keddie, T. E. Johnson, D. P. Arnold, S. E. Bottle, *Org. Biomol. Chem.* **2005**, *3*, 2593–2598.

[13] D. G. Gillies, L. H. Sutcliffe, X. Wu, *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 2345–2349.
[14] G. Kulcsar, T. Kalai, J. Jeko, K. Hideg, *Synthesis* **2003**, *9*, 1361–1366.
[15] F. H. Allen, *Acta Crystallogr., Sect. B* **2002**, *58*, 380–388.
[16] W. K. Busfield, L. M. Engelhardt, P. C. Healy, I. D. Jenkins, S. H. Thang, A. H. White, *Aust. J. Chem.* **1986**, *39*, 357–365.
[17] R. Braslau, V. Chaplinski, *J. Org. Chem.* **1998**, *63*, 9857–9864.
[18] A. S. Micallef, R. C. Bott, S. E. Bottle, G. Smith, J. M. White, K. Mastuda, H. Iwamura, *J. Chem. Soc. Perkin Trans. 2* **1999**, 65–71.

Received: June 14, 2007