Formation of aminoxyls by oxidative addition of *N-tert*-butylhydroxylamine to acceptor olefins

Lennart Eberson

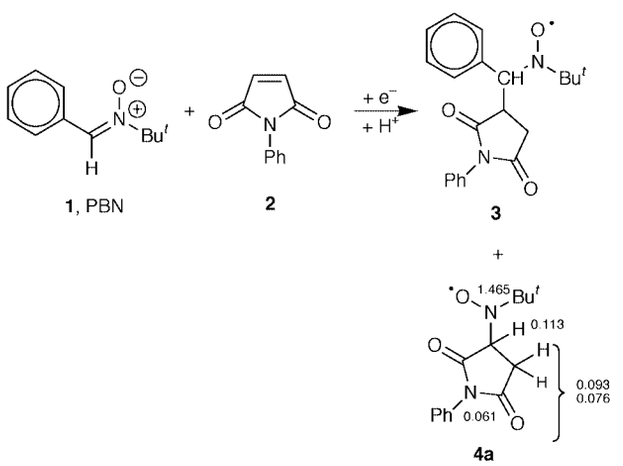
Department of Chemistry, Lund University, PO Box 124, S-221 01 Lund, Sweden

Received (in Cambridge, UK) 1st June 1999, Accepted 6th July 1999

The reaction between an acceptor olefin (symbolized as C=C and substituted by at least one conjugatively electron-withdrawing group) and *N-tert*-butylhydroxylamine in the presence of *t*-BuNO as an oxidant gives an aminoxyl which formally is a spin adduct of HC–C$^{\bullet}$ and *t*-BuNO and in the appropriate cases identical to the aminoxyl formed in the thermal or photochemical reaction between C=C and α-phenyl-*N-tert*-butylnitrone (PBN). The acceptor olefins studied were *N*-phenylmaleimide, maleimide, *N*-methylmaleimide, maleic anhydride, diethyl fumarate, diethyl 2,3-($^2H_2$)fumarate, diethyl maleate, trimethyl ethylenetricarboxylate, 1,4-benzoquinone, fumaronitrile, methyl acrylate, methyl methacrylate and acrylonitrile.

Introduction

The photochemical reaction between α-phenyl-*N-tert*-butylnitrone [**1**, PBN; IUPAC name: *N*-(benzylidene)-*tert*-butylamine *N*-oxide] and *N*-phenylmaleimide (**2**), a strongly activated olefin, gives a mixture of two persistent aminoxyls with characteristic EPR spectra (Fig. 1a). One was assigned the structure of **3** (Scheme 1) which is formally derived from a



Scheme 1

reductive coupling of PBN and **2**; alternatively one can view **3** as the spin adduct of PBN and *N*-phenyl-2-succinimidyl radical. The second aminoxyl, which was also formed in the thermal reaction between PBN and **2** (Fig. 1b), was assigned the structure of a reductive coupling product of 2-methyl-2-nitrosopropane (**5**, *t*-BuNO) and **2** on the basis of its EPR spectrum (**4a**, coupling constants in mT).[1] Also **4a** can be described as a spin adduct of the *N*-phenyl-2-succinimidyl radical, now with *t*-BuNO as the spin trap.

A number of other activated olefins, *viz*. maleimide, *N*-methylmaleimide, *N*-cyanomaleimide, maleic and methylmaleic anhydride, diethyl fumarate and diethyl maleate, underwent the same reaction.[1] Aminoxyls analogous to **3** and **4a** were formed, the latter (**4a**–**4g**) being assigned structures on the basis of their EPR spectra, one of which (**4g**) was identified previously.[2] Less reactive olefins, such as acrylonitrile and methyl acrylate, did not give any aminoxyls corresponding to **4a**–**4g**. Thus it was

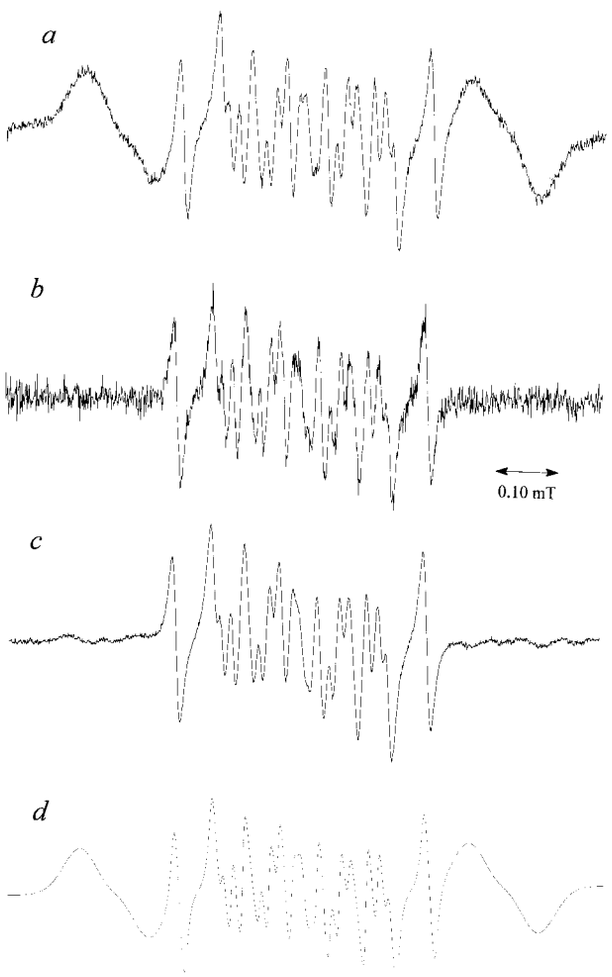
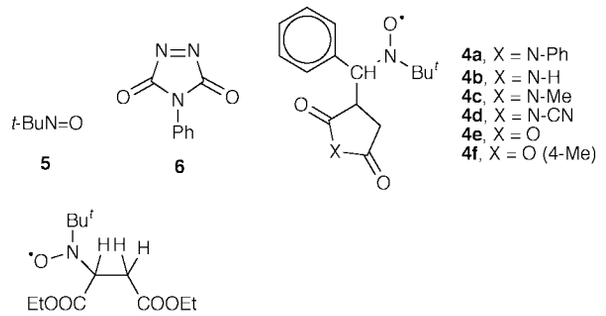


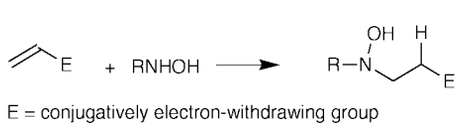
Fig. 1 Middle group of lines of the EPR spectrum recorded from a dichloromethane solution of (a) PBN (0.15 mol dm^{-3}) and *N*-phenylmaleimide (0.25 mol dm^{-3}) after irradiation by daylight for 10 h, (b) PBN (0.23 mol dm^{-3}) and *N*-phenylmaleimide (0.38 mol dm^{-3}) after being kept in the dark at 50 °C for 3 h and at 23 °C for 15 h, and (c) *t*-BuNHOH (0.050 mol dm^{-3}), *N*-phenylmaleimide (0.30 mol dm^{-3}) and *t*-BuNO (0.020 mol dm^{-3}) immediately after mixing. A simulation of the spectrum in (a) is shown in (d), using parameters given in Table 1 for **4a** and $a^{\alpha\text{-H}} = 0.629$ and $a^{\text{H}'} = 0.057$ mT for **3** (lit.[1] 0.625 and 0.060 mT, respectively).



inferred that there must exist a mechanism by which a sufficiently activated olefin can cleave PBN and give *t*-BuNO, presumably *via* the formation of a cycloadduct. Indirect support was obtained by allowing PBN to react with the extremely reactive dipolarophile, 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**6**) which in 5 min at 23 °C gave a 74% yield of *t*-BuNO. However, it was not clear how the final coupling between *t*-BuNO and the olefin might take place, except that it was established that mixtures of these compounds in themselves did not give **4** under thermal conditions. Photoactivation of such mixtures gave aminoxyl radicals of a different type, formed by *t*-Bu–*t*-BuNO addition across the carbon–carbon double bond and with different EPR spectral characteristics. This reaction mode has been demonstrated before.[3]

The identification of aminoxyls **4a–4g** was based on an analysis of their EPR spectra.[1] If the assignment is correct, these aminoxyls formally are generated by reductive coupling of *t*-BuNO and an activated olefin, some of them even under thermal conditions. This would be an unusual mechanism in the spin trapping context, and it is therefore important to establish the identity of **4a–4g** beyond doubt. In view of the widespread use of spin trapping, it is also desirable to try to establish a plausible mechanism for formation of **4**. If one judges the reactivity of activated olefins by their redox reactivity, the olefins promoting the cleavage reaction have redox potentials in the range of −0.5 to −1.6 V *vs*. saturated calomel electrode (SCE), a range which encompasses the class of quinones, ubiquitous in biochemical systems of interest for spin trapping studies.

It is known that *N*-alkylhydroxylamines undergo addition to activated olefins (Scheme 2).[4] In what follows, it is shown that



Scheme 2

N-*tert*-butylhydroxylamine can be added to various activated olefins and that the adducts in the appropriate cases can be oxidized to aminoxyls with EPR spectra identical to those of radicals **4a–4g**.

Results and discussion

Addition of *t*-BuNHOH to *N*-phenylmaleimide

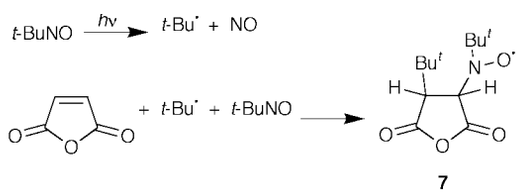
A deficit of tributylamine (40–70 mol%) was added to a stirred mixture of *N*-*tert*-butylhydroxylamine hydrochloride and **2** in dichloromethane. The mixture was stirred for a few min, transferred to an EPR tube and about 10 mol% *t*-BuNO added as the oxidant, a known method to oxidize hydroxylamines to aminoxyls.[5] The middle group of lines of the EPR spectrum (Fig. 1c) of the solution was identical to that shown for **4a** in Fig. 1a and b. The spectral parameters are given in Table 1. Any minor differences noted are presumably caused by a difference in evaluation method—visual comparison of experimental and simulated spectra[1] *vs*. computer optimization.

The same aminoxyl **4a** was obtained from a solution of **2** and *t*-BuNO by addition of a deficit (*c*. 20 mol%) of tetrabutylammonium borohydride (Table 1). Presumably *tert*-butylhydroxylamine is formed, followed by its addition to **2** and oxidation of the adduct. Alternatively, the known[6] capability of this reagent to produce radical anions from substrates with redox potentials for reduction above *ca*. −1.5 V *vs*. SCE might induce a reductive coupling reaction between **2** [$E(\mathbf{2}/\mathbf{2}^{\bullet -}) = -0.52$ V] and *t*-BuNO [$E(t\text{-BuNO}/t\text{-BuNO}^{\bullet -}) = -1.77$ V].

Addition of *t*-BuNHOH to other activated olefins

The reaction of some other activated olefins with *tert*-butylhydroxylamine and *t*-BuNO was investigated. The EPR spectra recorded are given in Table 1. *N*-Methylmaleimide gave a well resolved aminoxyl spectrum in contrast to that obtained in the PBN reaction, where the inferior resolution of the spectrum did not permit a reliable analysis. Both reactions gave well resolved and identical spectra from maleimide, as was also the case for diethyl fumarate (also in its 2,3-bisdeuteriated form), diethyl maleate and trimethyl ethylenetricarboxylate.[7]

Maleic anhydride did not give the expected spectrum by the *tert*-butylhydroxylamine method; only a weak spectrum of the photochemically produced *t*-Bu–*t*-BuNO adduct **7** was detected. This radical is formed according to Scheme 3 also



Scheme 3

upon very limited light exposure, and the reaction has been documented for a range of olefins with high reactivity toward radicals.[1,3a] The tetrabutylammonium borohydride method gave the expected spectrum, although it was weak. Presumably maleic anhydride is attacked by tributylamine and/or *tert*-butylhydroxylamine in fast ring-opening reactions giving products which do not sustain the addition reaction.

Fumaronitrile, methyl acrylate, methyl methacrylate and acrylonitrile did not react with PBN to give *t*-BuNO spin adducts.[1] However, they readily reacted with *tert*-butylhydroxylamine–*t*-BuNO to give aminoxyls **8a–8d** which in the case of the monosubstituted olefins had the large hyperfine splitting (hfs) constant (1–1.3 mT) expected for a methylene group attached to the N(O•)Bu′ group.

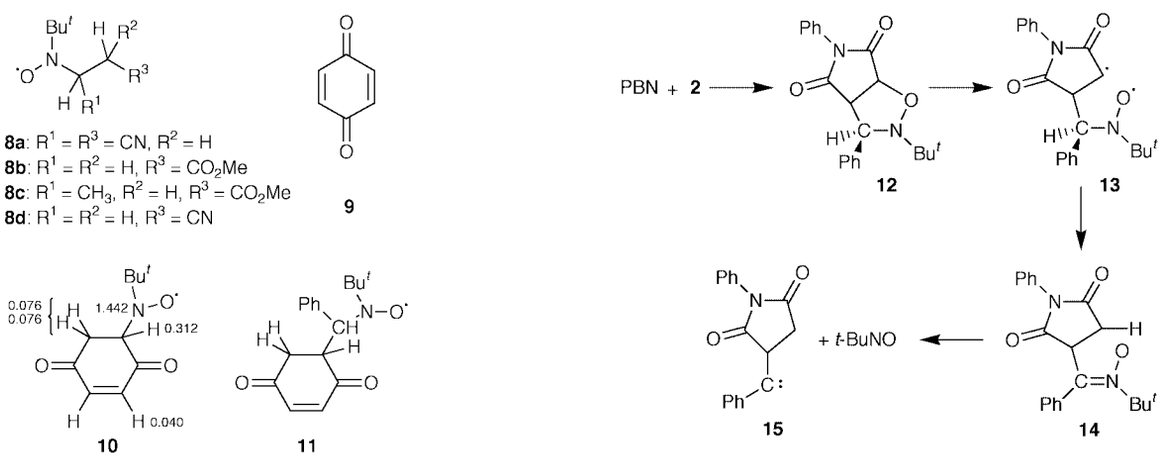
Benzoquinone **9** has the same redox reactivity as **2** [$E(\mathbf{9}/\mathbf{9}^{\bullet -}) = -0.52$ V]. It reacted with *tert*-butylhydroxylamine–*t*-BuNO to give a radical with a typical aminoxyl spectrum, assigned to **10** (coupling constants in mT). Surprisingly, this aminoxyl was not obtained from the **9**–PBN reaction, neither thermally nor photochemically. In the latter case, a 3 × 2 lines aminoxyl spectrum ($a^{\mathrm{N}} = 1.46$, $a^{\mathrm{H}} = 0.224$ mT) was detected, assigned to **11** analogously to **3**.

Styrene did not give any adduct with *N*-*tert*-butylhydroxylamine–*t*-BuNO, as expected in view of its electron donor properties. Instead, a weak EPR spectrum with a *g* value of 2.0035, typical of aminyl radicals, was recorded. It was best simulated with $a^{\mathrm{N}} = 0.732$, $a^{\mathrm{N}'} = 0.341$, $a^{\mathrm{H}} = 0.340$ and $a^{\mathrm{H}'} = 0.115$ (18 H). The same spectrum was detected in some of the experiments reported in Table 1, especially with the less reactive olefins. It was established that this spectrum is derived from a species formed in the reaction between *N*-*tert*-butylhydroxylamine and *t*-BuNO alone and thus was not dependent on any olefin being present.

Table 1 EPR spectral parameters[a] of aminoxyls formally derived by reductive coupling of an activated olefin and *t*-BuNO

Olefin	a^N/mT	$a^{\alpha\text{-H}}$/mT[b]	$a^{H'}$/mT	$a^{H''}$/mT	$a^{H'''}$/mT	$a^{N'}$/mT	Ref.
N-Phenylmaleimide[c]	1.466	0.114	0.093	0.076		0.062	
[d]	1.462	0.113	0.093	0.076		0.062	
[e]	1.458	0.116	0.094	0.077		0.063	1
N-Methylmaleimide[c]	1.467	0.114	0.095	0.074		0.060	
[e,f]	1.40	0.23	0.112	0.03	0.02		1
Maleimide[c]	1.470	0.114	0.095	0.076	0.061	0.058	
[e]	1.47	0.116	0.099	0.079	0.059	0.060	1
Maleic anhydride[c]		No	radical	formed			
[d,g]	1.448	0.116	0.087	0.081			
[e]	1.448	0.112	0.088	0.080			1
Diethyl fumarate[c]	1.440	0.270	0.059	0.048	0.029 (2) 0.014 (2)		
[e]	1.45	0.27	0.064 (2)	0.034 (2)	0.017 (2)		1
Diethyl 2,3-($^2H_2$)fumarate[c]	1.429	0.041 (D)	0.009 (D)	0.057	0.028 (2) 0.008 (2)		
Fumaronitrile[c]	1.451	0.196	0.056	0.053		0.025	
Diethyl maleate[c]	1.429	0.270	0.061	0.048	0.029 (2) 0.015 (2)		
[e]	1.45	0.27	0.064 (2)	0.034 (2)	0.017 (2)		1
Trimethyl ethylenetricarboxylate[c]	1.403	0.230	0.056	0.025 (6)	0.025 (3)		
[e]	1.408	0.231	0.057	0.023 (6)	0.029 (3)		7
Methyl acrylate[c]	1.568	1.267	1.267	0.056 (2)			
Methyl methacrylate[a]	1.550	1.233	1.263	0.053			
Acrylonitrile[c]	1.523	1.150 (2)	0.057 (2)				
1,4-Benzoquinone[a]	1.442	0.312	0.076 (2)	0.040			

[a] Multiplicity = 1, unless indicated by numbers in brackets. [b] The notation "α" refers to the hydrogen atom being located at the carbon atom α to the aminoxyl function. [c] The aminoxyl was obtained from *tert*-butylhydroxylamine–HCl, tributylamine, activated olefin and *t*-BuNO in dichloromethane. [d] The aminoxyl was obtained from activated olefin, *t*-BuNO and Bu_4NBH_4 in dichloromethane. [e] The aminoxyl was obtained from PBN and activated olefin in dichloromethane. [f] The spectrum was not maximally resolved. [g] The spectrum was weak and superimposed upon that of **7**.



Scheme 4

Mechanistic considerations

It was earlier[1] suggested that the reaction between PBN and a sufficiently activated olefin can proceed slowly in the thermal mode to produce a low concentration of *t*-BuNO. As indicated by the rapid thermal reaction between PBN and the extremely reactive dipolarophile **6**,[8] formation of *t*-BuNO is feasible in an analogous situation, and it is also possible to formulate a credible mechanism. This is exemplified in Scheme 4 by the reaction between PBN and **2**. It is suggested that the cycloadduct **12** is formed as an intermediate capable of undergoing homolytic C–O bond cleavage[1,9] to give diradical **13**. The next step, a 1,3-hydrogen shift to give **14**, followed by its cleavage to *t*-BuNO and a carbene **15**, is based on the analogy with PBN–**6** reaction.[1] Here the yield of *t*-BuNO was 74% and the tetrasubstituted olefin could be characterized.

One problem with Scheme 4 is that aminoxyls **4** are not formed thermally from *t*-BuNO and activated olefins and that the photochemical reaction leads to different aminoxyls. With the demonstration that *t*-BuNHOH can be added to activated olefins and the adducts oxidized to **4**, it appears likely[5] that *t*-BuNO can be reduced to *t*-BuNHOH under the prevailing reaction conditions and thus open a pathway to the formation of **4**. However, much work remains to establish this complex mechanism.

Experimental

Materials

All chemicals were of the highest commercial quality available and obtained either from Fluka AG or Aldrich. Dichloromethane was of Suprasolv® quality (Merck AG). Diethyl 2,3-($^2H_2$)fumarate was a gift from Dr H.-G. Korth, University of Essen,[3a] and trimethyl ethylenetricarboxylate was a gift from Drs H. K. Hall, Jr. and A. Padias, University of Arizona, Tucson.

Instruments and methods

EPR spectra were recorded by the Upgrade Version ESP 3220–200SH of a Bruker ER-200D spectrometer. The EPR spectra

were recorded as described before[1] (100 kHz modulation frequency, microwave effect 0.4–1.25 mW, modulation amplitude 0.01–0.04 mT). Simulations were carried out by the public domain programme WINSIM.[10] Photochemical reactions were carried out by irradiation with daylight from a north-facing window. This was a slow procedure but gave maximally resolved spectra.

Reaction between *t*-BuNHOH and activated olefins

A deficit of tributylamine (40–70 mol% of the *N*-*tert*-butylhydroxylamine hydrochloride) was added to a stirred mixture of *N*-*tert*-butylhydroxylamine hydrochloride (corresponding to 0.1–0.2 mol dm^{-3}) and **2** (0.3 mol dm^{-3}) in dichloromethane. The mixture was stirred for a few min, transferred to an EPR tube and *t*-BuNO (corresponding to 0.02–0.04 mol dm^{-3}) added as the oxidant. After 2 min of Ar bubbling, the tube was sealed and the EPR spectral recording started. Samples used for thermal reactions were prepared in a darkened room.

Reaction between *t*-BuNO, activated olefins and tetrabutylammonium borohydride

A solution of *t*-BuNO (as dimer, corresponding to 0.2 mol dm^{-3}) and the activated olefin (0.3 mol dm^{-3}) in dichloromethane was kept in the dark for 15–20 min to ensure that formation of the monomer was essentially complete. The blue solution was then transferred to an EPR sample tube and solid Bu_4N BH_4 added (2–4 mg). After 2 min of Ar bubbling, the tube was sealed and the EPR spectral recording started. Samples were prepared in a darkened room.

Acknowledgements

Financial support from the Swedish Natural Science Research Council and the Knut and Alice Wallenberg Foundation is gratefully acknowledged. I thank Dr H.-G. Korth, University of Essen for a gift of diethyl 2,3-($^2H_2$)fumarate and Drs H. K. Hall, Jr. and A. Padias, University of Arizona, Tucson, for a gift of trimethyl ethylenetricarboxylate.

References

1 L. Eberson and O. Persson, *Acta Chem. Scand.*, 1998, **52**, 1081.
2 T. Sato, M. Abe and T. Otsu, *J. Macromol. Sci., Chem.*, 1981, **A15**, 367.
3 (*a*) E. A. Mash, H.-G. Korth and S. M. DeMoss, *Tetrahedron*, 1997, **53**, 15297; (*b*) C. Chatgilialoglu and K. U. Ingold, *J. Am. Chem. Soc.*, 1981, **103**, 4833.
4 D. Niu and K. Zhao, *J. Am. Chem. Soc.*, 1999, **121**, 2456, and references cited therein.
5 For reviews, see H. G. Aurich, in *Nitrones, nitronates and nitroxides*, Wiley, New York, 1989, Chaps. 4 and 5.
6 M. Lucarini, G. F. Pedulli, A. Alberti, C. Paradisi and S. Roffia, *J. Chem. Soc., Perkin Trans. 2*, 1993, 2083.
7 L. Eberson, O. Persson, H. K. Hall, Jr., A. B. Padias and P. Steel, *Macromolecules*, to be submitted.
8 For a review, see S. Rádl, *Adv. Heterocycl. Chem.*, 1996, **67**, 199.
9 For a review, see C. J. Hawker, *Acc. Chem. Res.*, 1997, **30**, 373.
10 D. Duling, *Public EPR Software Tools*, National Institute of Environmental Health Sciences, 1996.

Paper 9/04368C