

# Reaction of Substituted Anthracenes and a Butadiene with Nitric Oxide: Product Formation Determined by EPR Spectroscopy

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When nitric oxide (NO), generated from nitric acid and copper, was reacted with a series of 9,10-substituted anthracenes, only 9,10-dimethylanthracene gave EPR detectable nitroxide radicals, although the expected bicyclic nitroxide arising from cheletropic NO addition across the 9,10-positions was not observed. Purity of the NO is crucial as the presence of higher oxides of nitrogen leads to radicals by hydrogen abstraction which are trapped by NO and the resultant nitroso compounds produce stable nitroxides detectable by EPR. In contrast the acyclic system, 3,4-diphenyl-2,5-dimethyl-2,4-hexadiene gives rise to an EPR spectrum consistent with cheletropic NO addition, although higher oxides of nitrogen again mediate the formation of different nitroxides.

## INTRODUCTION

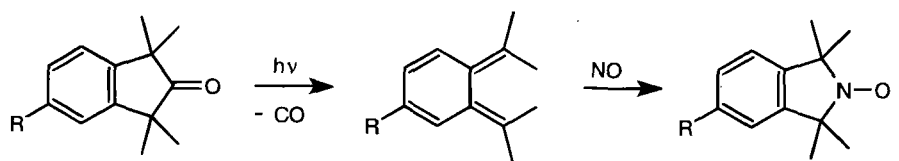
Nitric Oxide (NO) has been recognised during the last ten years as a molecule with immense biochemical significance.<sup>[1]</sup> Involvement of NO in physiological processes<sup>[2–5]</sup> includes neurotransmission, smooth muscle relaxation, immune response of macrophages and platelet

aggregation. Studies of NO in biological systems demand methods<sup>6</sup> of monitoring the dynamics of this species. Approaches used so far include chemiluminescence assays, methemoglobin spectrophotometry and spin trapping using Fe(mgd)<sub>2</sub> and hemoglobin.<sup>[7–10]</sup> One of the most promising concepts however represents the conversion of NO to nitroxide radicals by cheletropic spin traps,<sup>[11]</sup> as this method would allow *in vivo* imaging by very sensitive EPR techniques.

Ingold and Korth<sup>[12]</sup> have shown that *ortho*-quionidimethane-type systems, generated by photodecarbonylation of the corresponding 2-indanone derivatives, are able to add NO via cheletropic addition, thereby producing characteristic three line nitroxide EPR signals (Scheme 1).

Symons<sup>[13]</sup> also reported that nitroxides arise from cheletropic NO trapping by substituted butadiene systems, but Rockenbauer<sup>[14]</sup> later rationalised Symons' results as deriving from nitroso compounds which trap radicals pro-

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Scheme 1

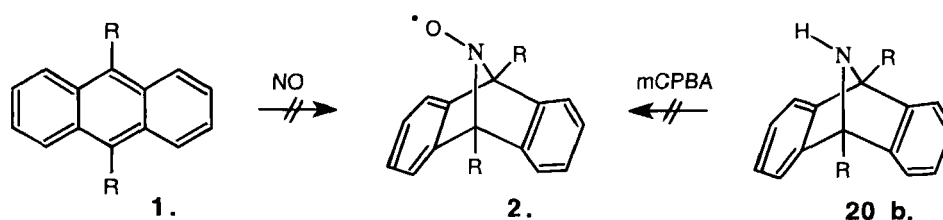
duced from  $\text{NO}_2$  radical additions. In an attempt to see if other unsaturated systems may act as effective probes for NO, we have investigated a range of substituted anthracenes as well as an appropriately substituted butadiene system. The data presented here confirms that the presence of adventitious traces of higher oxides of nitrogen in NO readily induce the formation of nitroxides, but as predicted by Rockenbauer, these do not arise from cheletropic trapping. EPR of reactions involving essentially  $\text{NO}_x$  free systems however, indicate cheletropic addition is not *impossible* with suitably reactive butadienes. Low reactivity, reversibility and ring strain appear to preclude the formation of useful concentrations of nitroxide NO adducts with anthracenes. Nevertheless, in the nitroxide formation reactions of 9,10-dimethylantracene it appears cheletropic trapping is involved in systems involving high purity NO which is effectively free from  $\text{NO}_x$ .

## RESULTS AND DISCUSSION

### Reaction of the anthracenes 1a-i with NO

Treatment of the 9,10-substituted anthracene **1a** dissolved in deoxygenated benzene with high purity NO at 70°C for 30 min in a sealed system followed by concentration to 50% under vacuum gave a complex EPR signal (Fig. 1a) arising from at least three distinct species which slowly disappeared after several hours.

A solution of **1a** in NO-saturated benzene gave an almost identical EPR spectrum upon photolysis ( $\lambda > 250$  nm), whereas simple stirring at room temperature did not produce any detectable EPR signals. No similar EPR signals could be detected with high purity NO from anthracenes **1b-i** according to the method described above, although **1i** produced a weak unresolved resonance around  $g = 2.00$ . Product based studies on **1a** detected largely unreacted starting mater-



	a	b	c	d	e	f	g	h	i
R =	Me	H	Br	CO <sub>2</sub> H	CO <sub>2</sub> Na	SiMe <sub>3</sub>	OMe	CH <sub>2</sub> CH <sub>2</sub> OH	Ph

Scheme 2

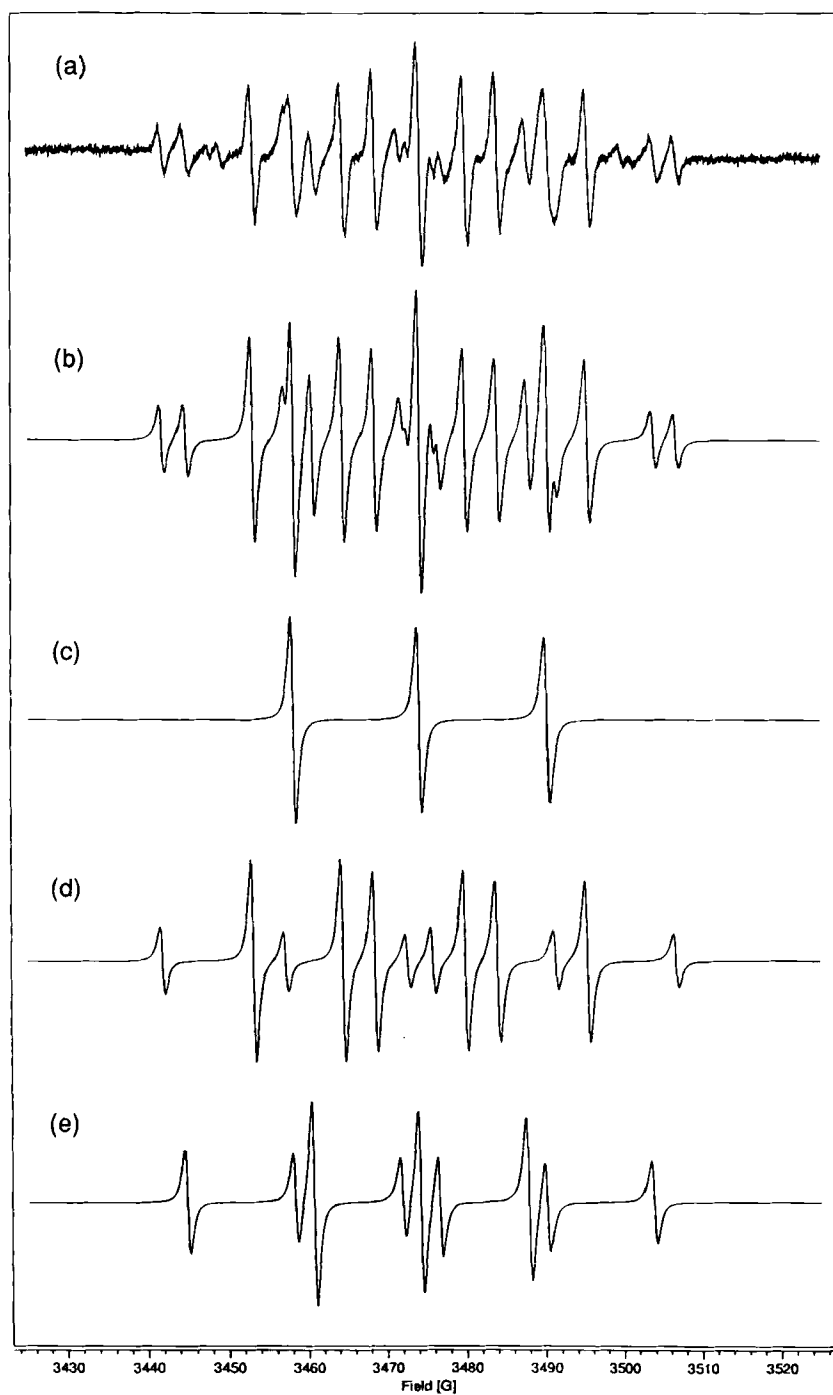
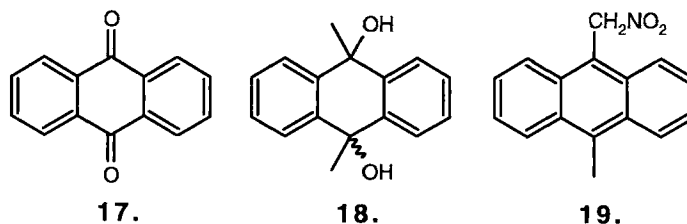


FIGURE 1 Reaction of **1a** with nitric oxide (NO). (a) Experimental spectrum,  $\nu = 9.75565$  GHz. (b) Computer simulation obtained by adding  $0.37 \cdot \mathbf{1c} + 0.37 \cdot \mathbf{1d} + 0.26 \cdot \mathbf{1e}$ . (c) Computer simulation of the spectrum arising from **4**. (d) Computer simulation of the spectrum arising from **5**. (e) Computer simulation of the spectrum arising from **7**.



ial along with anthraquinone **17**, the anthracene diol **18**, and nitroanthracene **19**.

The spectrum derived from **1a** and NO is consistent with three nitroxide signals two of which show additional coupling to hydrogen nuclei (Table I). Assignment of the structures **4**, **5** and **7** to the observed EPR spectrum was supported by comparison of the experimental result with a computer simulation derived from the addition of Figures 1c, 1d and 1e in the ratio of 0.37:0.37:0.26. Notably there is no indication of any large  $a_N$  nitroxide feature in this spectrum and therefore there is no support for the presence of a 9,10-bridged anthracene nitroxide (**2**) arising from the cheletropic addition of NO. Such a bicyclic nitroxide<sup>15</sup> should possess an unusually high  $a_N$  value ( $>20 \times 10^{-4} \text{ cm}^{-1}$ ) due to the strained pyramidal environment of the  $\text{sp}^3$  nitrogen atom. However it is very likely that the detected nitroxides derive originally from such a strained bicyclic species, as there is little evidence that NO will itself add to alkenes to generate radicals. Ring opening of **2** would give the carbon-centered radical **3** and subsequent dimerisation/oligomerisation cascades, based on intermolecular radical trapping by the nitroso group, would produce the observed persistent nitroxide signal (Scheme 3).

Support for this mechanism is given by the oxidation of anthracenimine **20b** with *m*CPBA,

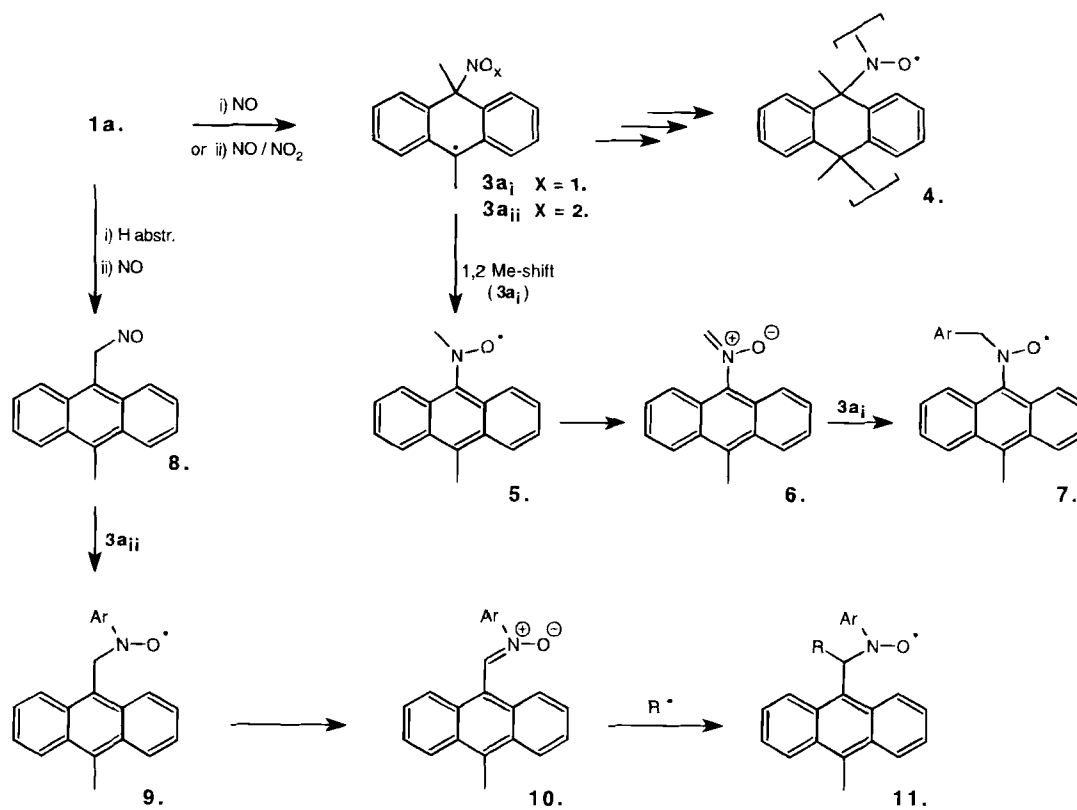
which also produces an EPR spectrum (Fig. 2a) arising from a standard nonbicyclic nitroxide. Computer simulation of this spectrum (with the spin Hamiltonian parameters  $g = 2.0053$ ,  $a_N = 14.35 \times 10^{-4} \text{ cm}^{-1}$ ,  $a_H = 0.99 \times 10^{-4} \text{ cm}^{-1}$ ,  $a_H = 1.77 \times 10^{-4} \text{ cm}^{-1}$ ) yields the spectrum shown in Figure 2b. The dissimilar proton splittings also argue for a non-bicyclic system with differing CH-NO torsion angles. The instability of 9,10-bridged anthracene nitroxides coupled with the reversibility of cheletropic NO addition probably indicates why no EPR signal is produced for compounds **1b-i** and why our attempts at cheletropic NO addition to the more "activated" anthracene analogues  $\text{Mg}(\text{anthracene})(\text{THF})_3$ <sup>[16]</sup> and the fullerene  $\text{C}_{70}$  also produced no signals.

The EPR spectrum (Fig. 1d) from the nitroxide **5** reveals the presence of three quartets (Table I) in the ratio of 1:3:3:1 which indicates a methyl substituted nitroxide. For comparison, *tert*-butylmethyl nitroxide<sup>[17]</sup> shows the values\*  $a_N = 14.24 \times 10^{-4} \text{ cm}^{-1}$ , and  $a_H = 10.58 \times 10^{-4} \text{ cm}^{-1}$ . Again the NO containing anthracene adduct (**3**) is implicated in the formation of **5** via a 1,2 methyl shift. Alternatively this species may arise from methyl radical scission, nitrosomethane formation and trapping with **3**, however we detected no evidence for the presence of dimethyl nitroxide,<sup>[18]</sup> or any other methyl nitroxides and therefore favour essentially *intra* over *inter* molecular trapping in this case. The rearrangement would be driven by the rearomatisation of the anthracene system and the increased radical stability of a nitroxide struc-

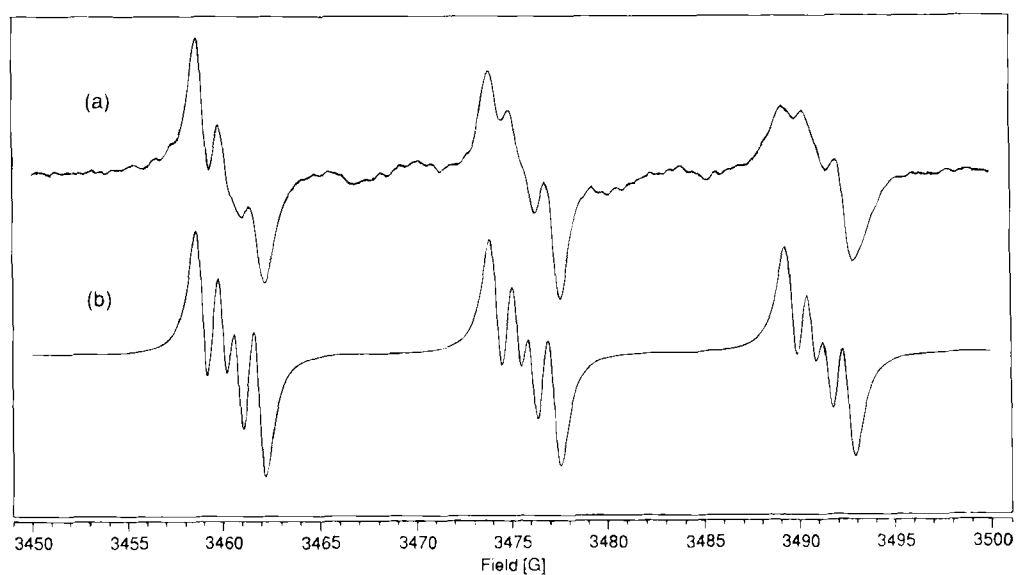
TABLE I Reaction of **1a** with NO at 70°C

nitroxide	$g$	$a_N (10^{-4} \text{ cm}^{-1})$	$a_H (10^{-4} \text{ cm}^{-1})$
<b>4</b> .	2.0062	14.99	—
<b>5</b> .	2.0062	14.43	10.62 (3H)
<b>7</b> .	2.0062	12.71	14.91 (2H)

\* Since the  $g$  value was not given by these authors, we have used the  $g$  value for **5** in the calculation of the isotropic  $a$  values for *t*-butyl methyl nitroxide.



Scheme 3

FIGURE 2 Oxidation of the anthracenimine **20b** with *m*CPBA. (a) Experimental spectrum,  $\nu = 9.7551$  GHz (b) Computer simulation

ture. Such free radical rearrangements are unusual, but cleavage of this carbon-carbon bond does occur in this reaction, as evidenced by the isolation from the reaction mixture of anthraquinone **17**.<sup>[18]</sup>

The third component (**7**) (Fig. 1e,  $a_N = 12.71 \times 10^{-4} \text{ cm}^{-1}$ ,  $a_H = 14.91 \times 10^{-4} \text{ cm}^{-1}$ , 2H) was present at 26% abundance and the presence of two equivalent proton splittings is consistent with a nitroxide containing an adjacent methylene group. This methylene nitroxide is most likely a decomposition product of the  $\alpha$ -hydrogen containing nitroxide **5**. Such species are not persistent and disproportionate to the EPR invisible nitrones (in this case **6**) and N-hydroxy compounds. Nitrones are themselves recognised radical scavengers and thereby generate EPR detectable nitroxides. Any carbon-centred radical (and especially the NO anthracene adduct) could react to give the methylene nitroxide **7**. Such large hydrogen hyperfine splitting constants are not unknown<sup>[19,20]</sup> and arise due to conformational restrictions with the bulky anthracene.

In order to investigate the relationship between product nature and NO purity, the reaction was

performed with NO that was deliberately contaminated with higher oxides of nitrogen. EPR analysis of the reaction of NO spiked with a small amount of oxygen revealed the formation of one major species (Fig. 3,  $g = 2.0064$   $a_N = 12.65 \times 10^{-4} \text{ cm}^{-1}$ , and  $a_H = 5.43 \times 10^{-4} \text{ cm}^{-1}$ , 2H) although much weaker unidentified features were also present. Higher oxides of nitrogen (mainly NO<sub>2</sub> radicals) would readily abstract hydrogen from **1a**<sup>[21–23]</sup> and the trapping of this allylic radical by NO (which remains in excess), would produce an EPR invisible nitroso compound—again a recognised radical scavenger. Reaction of this nitroso compound (**8**) with any radical, but most likely the NO<sub>2</sub> anthracene adduct **3a<sub>ii</sub>** would give rise to the observed nitroxide **9**. As NO<sub>2</sub> should add more rapidly to **1a** than NO<sup>12</sup>, the nitroso compound **8** is more likely to trap **3a<sub>ii</sub>** rather than the NO anthracene adduct **3a<sub>i</sub>**.

Additions of a larger amount of oxygen to the reaction vessel for longer periods in turn generated yet another EPR signal, a three line nitroxide pattern (Fig. 4,  $g = 2.0064$ ) with  $a_N = 6.89 \times 10^{-4} \text{ cm}^{-1}$  combined with a further small, *single*, proton splitting ( $a_H = 1.25 \times 10^{-4} \text{ cm}^{-1}$ ). This nitroxide is

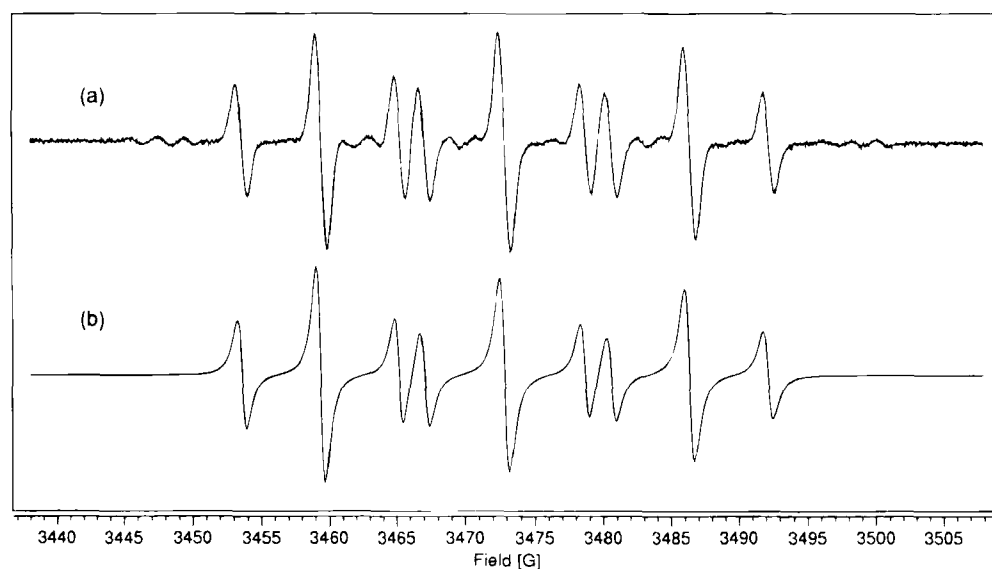


FIGURE 3 Reaction of **1a** with NO contaminated with dioxygen (20 sec). (a) Experimental spectrum,  $\nu = 9.7526 \text{ GHz}$  (b) Computer simulation

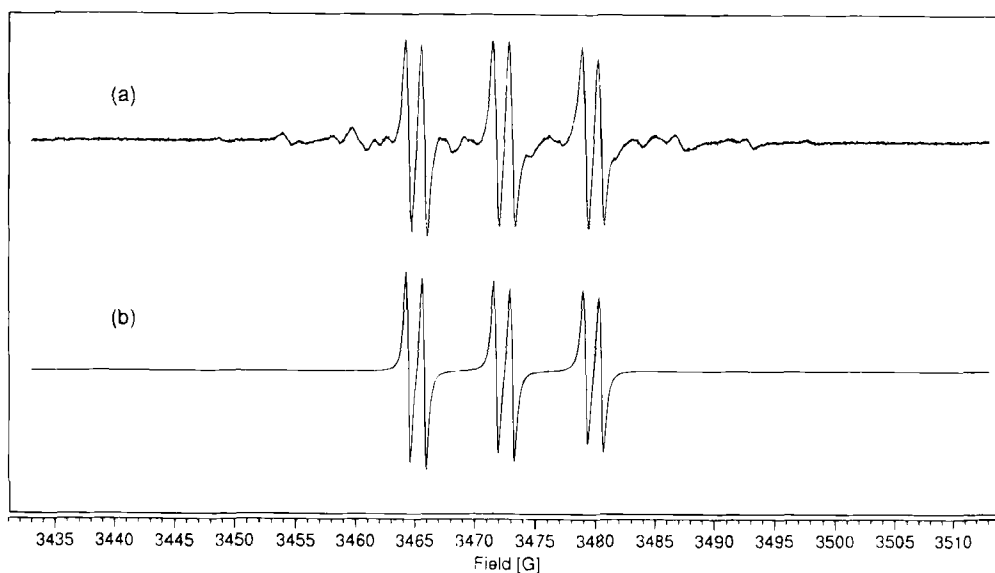


FIGURE 4 Reaction of **1a** with NO contaminated with dioxygen (180 sec). (a) Experimental spectrum,  $\nu = 9.7546$  GHz (b) Computer simulation

likely to have been derived from **9** via the nitron, as for the formation of **7\***. The resulting nitron (**10**) must trap an electronegative radical (possibly an  $\text{NO}_2$  radical) as the nitroxide **11** shows a relatively small  $a_N$  value—characteristic of such an electron withdrawing substituent effect. Additional experiments with **1a** and low purity NO produced EPR signals that consisted of mixtures of **9** and **11** in varying ratios.

#### Reaction of 3,4-diphenyl-2,5-dimethyl-2,4-hexadiene **12** with NO

When the open chain substituted butadiene-type system **12** was stirred in NO saturated benzene using a sealed reaction vessel at  $70^\circ\text{C}$ , two nitroxides were detected (Fig. 5) with  $g = 2.0058$ ,  $a_N = 25.64 \times 10^{-4} \text{ cm}^{-1}$ ; and  $g = 2.0062$ ,  $a_N = 13.54 \times 10^{-4} \text{ cm}^{-1}$ ,  $a_H = 0.22 \times 10^{-4} \text{ cm}^{-1}$ , 12H.

The spectrum with the large nitrogen hyperfine coupling (Fig. 5a, 5b) was assigned to the  $\text{NO}_2$

trapping product **14**. (Scheme 4). The  $a_N$  value is typical for such alkoxy nitroxide species which have been observed as by-products in other NO trapping reactions.<sup>[12,24]</sup> It is almost impossible to eliminate higher oxides of nitrogen from NO as the thermodynamically unstable NO forms  $\text{NO}_2$  via a slow disproportionation reaction and traces of oxygen convert NO in a very fast and efficient reaction to  $\text{NO}_2$  radicals. The presence of even minor amounts of  $\text{NO}_2$  gives rise to strong EPR signals, as  $\text{NO}_2$  reacts at least 500 times faster than NO with cheletropic spin traps.<sup>[12]</sup> Typically, however, these alkoxy nitroxides are not persistent and after three days this spectrum ( $a_N = 25.64 \times 10^{-4} \text{ cm}^{-1}$ ) disappeared, whereas the second component ( $a_N = 13.54 \times 10^{-4} \text{ cm}^{-1}$ ) remained stable. A close examination of the low field resonance from this second component (Fig. 5d) reveals additional hyperfine coupling. Computer simulation studies (Fig. 5e) showed that these resonances can be attributed to coupling from twelve magnetically equivalent protons arising from four methyl groups. The spectrum bandwidth of Figure 5c was used to establish the number of protons giving rise to these resonances. Thus this spectrum is

\* It is also possible that the nitrones arise via hydrogen abstraction from the radical adducts by the higher concentrations of  $\text{NO}_2$ .<sup>[21-23]</sup>

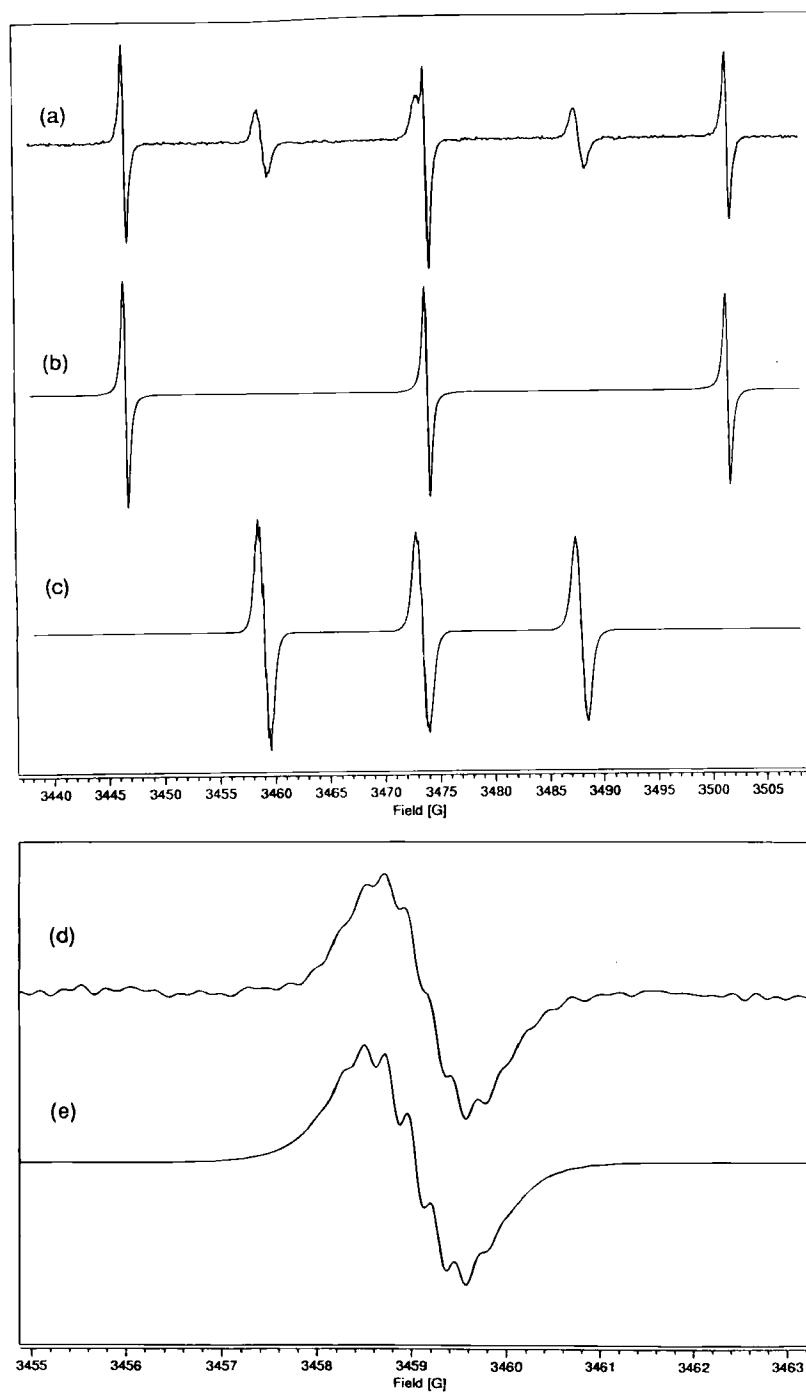
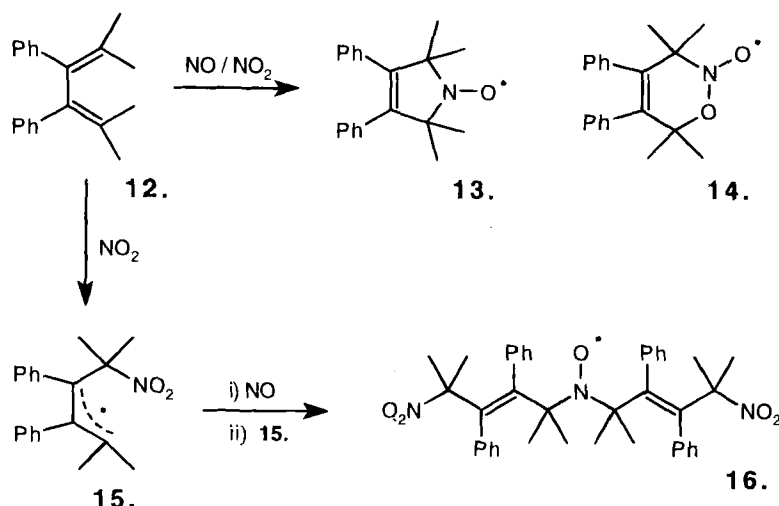


FIGURE 5 Reaction of **12** with high purity NO. (a) Experimental spectrum,  $\nu = 9.7532$  GHz (b) Computer simulation of the spectrum arising from **14**. (c) Computer simulation of the spectrum arising from **13**. (d) An expansion of the low field resonance in the spectrum arising from **13**. (e) Computer simulation of (d).





Scheme 4

consistent with the cheletropic addition of NO to **12** to yield the symmetric cyclic nitroxide **13**. Attempts to reproduce the EPR signal with the same procedure at lower temperature were ineffective, demonstrating the low favourability of this cheletropic trapping process. When this reaction was repeated using NO<sub>2</sub> contaminated NO as above, EPR showed a very strong three line signal with  $g = 2.0063$ ,  $a_N = 13.24 \times 10^{-4} \text{ cm}^{-1}$  (Fig. 6) which is consistent with Rockenbauer's<sup>[14]</sup> proposed NO<sub>2</sub> mediated pathway to nitroxides via combined NO<sub>2</sub> addition and NO trapping processes. The NO<sub>2</sub> reaction occurs readily at room temperature and produces a much stronger signal, which supports the involvement of a separate mechanism.

These results are in agreement with Rockenbauer's predicted mechanism for NO scavenging which is initiated by NO<sub>2</sub>, but also demonstrate the possibility of cheletropic conversion of NO to nitroxides with very reactive butadienes. However, the efficiency of the NO addition cannot be high, as evidenced by the weakness of the EPR signal, and the addition is likely to be reversible, as attempts to isolate **13** from large scale reactions and prolonged reaction times were unsuccessful even using very sensitive HPLC/MS-techniques.

For any substituted butadiene to be reactive towards NO it must favour cisoid conformation. Phenyl ring interactions produce this favourable orientation for **12** as demonstrated by simple MM2 and CVFF forcefield calculations. This is consistent with our unsuccessful attempts<sup>[25]</sup> of NO scavenging with 2,3-diphenylcyclobut-2-ene-1,4-diene, a very reactive transoid bisketene whereas a similar cisoid bisketene trapped NO. Additionally, significant "diradical character" is necessary for cheletropic NO trapping, which for **12** arises from conjugative effects with the phenyl rings. The cheletropic trapping systems which best possess these characteristics remain the *ortho*-quinodimethane systems of Ingold and Korth.<sup>[12]</sup>

## CONCLUSION

The results presented here demonstrate the general importance of NO purity on product formation and selectivity as the presence of even low amounts of higher oxides of nitrogen lead to abnormal by-products. Anthracenes generally do not add NO cheletropically whereas reactive butadienes with cisoid arrangement and sufficient diradical may trap NO to a minor extent.

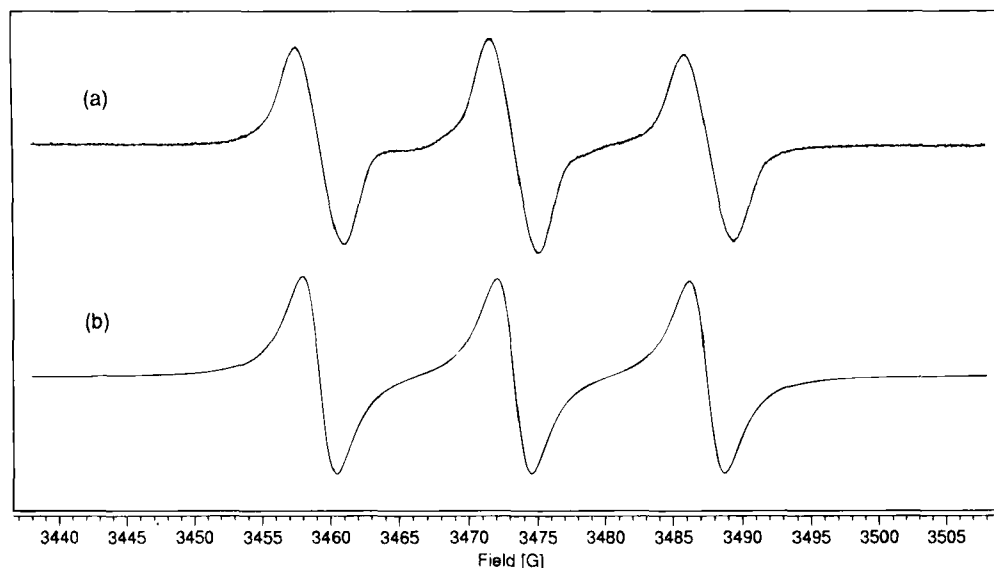


FIGURE 6 Reaction of **12** with NO contaminated with dioxygen. (a) Experimental spectrum  $\nu = 9.7532$  GHz. (b) Computer simulation.

## EXPERIMENTAL

X-band spectra were recorded on a Bruker ESP 300E EPR spectrometer as the first derivative of absorption. Calibration of the microwave frequency and the magnetic field were performed with an EIP 548B microwave frequency counter and a Bruker ER 035M gaussmeter. Computer simulations of the EPR spectra were refined using the program SOPHE<sup>[26,27]</sup> running on a Silicon Graphics Indigo<sup>II</sup> R10000 workstation.

The anthracenes **1c–h** and the butadiene **12** were synthesised as previously described.<sup>[17,28–32]</sup> The anthracenes **1a–b** and **1i** were purchased from Aldrich.  $C_{70}$  and  $Mg(\text{anthracene})\text{THF}_3$  were kindly provided by C.L. Raston, Griffith University and **20b** was provided by L.A. Carpino, University of Massachusetts.

NO was generated by slow reaction of 8M nitric acid with copper and purified by two consecutive washings with concentrated sodium hydroxide. The reaction apparatus was evacuated and flushed with dry, oxygen free nitrogen for at least 60 min before use. Although solvents were carefully deoxygenated according

to standard methods, all reaction solutions were additionally degassed by nitrogen bubbling and several freeze-pump-thaw cycles directly before use. The reaction of the anthracenes **1a–h** and the butadiene **12** with high purity NO was performed by the following procedure: The compound (0.1–0.5 mmole) was dissolved in dry benzene (30 mL) and deoxygenated as described above. NO was bubbled through the solution for 10 min. at room temperature, whilst a positive pressure of argon was maintained over the reaction solution in order to avoid contact with air. After sealing the system, the mixture was carefully heated at 70°C for at least 20 min. The volume of the solution was then reduced to 50% under high vacuum and the EPR measured without any further purification. For **1a** this gave a complex EPR (Fig. 1a) containing three nitroxides with  $a_N = 14.99 \times 10^{-4} \text{ cm}^{-1}$ ;  $a_N = 14.43 \times 10^{-4} \text{ cm}^{-1}$ , with  $a_H = 10.62 \times 10^{-4} \text{ cm}^{-1}$ , (3H); and  $a_N = 12.71 \times 10^{-4} \text{ cm}^{-1}$ , with  $a_N = 14.91 \times 10^{-4} \text{ cm}^{-1}$ , (2H); all of which were centred at  $g = 2.0062$ . For **12** this resulted in an EPR spectrum which showed two nitroxide signals with  $g = 2.0062$ ,

$a_N = 13.53 \times 10^{-4}$ ,  $\text{cm}^{-1}$ ,  $a_H = 0.29 \times 10^{-4}$   $\text{cm}^{-1}$  (12H); and  $g = 2.0058$ ,  $a_N = 25.64 \times 10^{-4}$   $\text{cm}^{-1}$ .

Reactions with low purity NO were done in a similar manner, except that during saturation of the mixture with NO, some atmosphere was allowed to enter the reaction vessel for varying periods. With a twenty second exposure of **1a** to atmosphere, an EPR spectrum with  $a_N = 12.65 \times 10^{-4}$   $\text{cm}^{-1}$  and  $a_H = 5.43 \times 10^{-4}$   $\text{cm}^{-1}$  centred at  $g = 2.0064$  was produced. When the exposure was increased to 180 seconds an EPR spectrum with  $a_N = 6.89 \times 10^{-4}$   $\text{cm}^{-1}$  and  $a_H = 1.25 \times 10^{-4}$   $\text{cm}^{-1}$  at  $g = 2.0071$  was generated. A similar procedure with **12** gave a strong signal with  $a_N = 13.24 \times 10^{-4}$   $\text{cm}^{-1}$  at  $g = 2.0063$ .

Oxidation of the anthracenimine **20b** (10 mg) was undertaken via the addition of three equivalents of *m*CPBA in an EPR tube under an inert atmosphere, the mixture dissolved in benzene and the resultant yellow solution immediately measured by EPR. The EPR spectrum showed a nitroxide with  $a_N = 14.35 \times 10^{-4}$   $\text{cm}^{-1}$  and  $a_H = 1.77 \times 10^{-4}$   $\text{cm}^{-1}$  and  $a_H = 0.99 \times 10^{-4}$   $\text{cm}^{-1}$  at  $g = 2.0053$ .

### Product-based Studies

9,10-Dimethylantracene (0.1 g, 0.5 mmole) dissolved in xylene (5 mL) was degassed by successive freeze/thaw cycles and NO bubbled through the mixture for 15 minutes. The reaction vessel was sealed and heated at 35°C for seven days. Separation of the unreacted starting material via crystallisation from xylene gave 9-nitromethyl-10-methylantracene **19** (0.01 g, 8%, m.p. 214–7°C dec. Lit.<sup>33</sup> 211–12°C). <sup>1</sup>H NMR ( $\text{CDCl}_3$ ):  $\delta$  8.39 (dd, 2x ArH), 7.62 (m, 2x ArH), 6.55 (s, 2H), 3.19 (s, 3H); <sup>13</sup>C NMR ( $\text{CDCl}_3$ ):  $\delta$  131.2 (s, ArC), 130.0 (s, ArC), 127.4 (d, ArC), 125.9 (d, ArC), 125.4 (d, ArC), 123.7 (d, ArC), 72.6 (t,  $\text{CH}_2$ ), 14.8 (q,  $\text{CH}_3$ ). High Resolution MS (EI)  $m/z$  251.0947 ( $\text{M}^+$ , 6.7%).

Similarly 9,10-dimethylantracene (0.05 g, 0.2 mmole) dissolved in xylene (4 mL) was degassed by successive freeze/thaw cycles and NO bubbled through the mixture for 5 minutes.

The reaction vessel was sealed and heated at 125°C for 5 hours. Chromatography gave two products: anthraquinone **17** (0.018 g, 36%, m.p. 285–6°C); <sup>1</sup>H NMR ( $\text{CDCl}_3$ ):  $\delta$  8.35 (m, 2 x ArH), 7.83 (m, 2 x ArH) MS (EI)  $m/z$  208 ( $\text{M}^+$ , 100%); and 9,10-dimethylantracene-9,10-diol **18** (0.021 g, 39%, m.p. 146–8°C dec.) <sup>1</sup>H NMR ( $\text{CDCl}_3$ ):  $\delta$  8.18 (d, 7.8 Hz, 2 x ArH), 7.94 (d, 7.8 Hz, 2 x ArH), 7.67 (t, 7.7 Hz, 2 x ArH); <sup>13</sup>C NMR ( $\text{CDCl}_3$ ):  $\delta$  148.8 (s, ArC), 133.9 (d, ArC), 129.7 (s, ArC), 128.1 (d, ArC), 127.2 (d, ArC), 125.9 (d, ArC), 70.2 (s, COHMe), 37.0 (q,  $\text{CH}_3$ ). MS (CI,  $\text{NH}_4^+$ )  $m/z$  242 ( $\text{M}^+ + 2$ , 25%), 225 (85,  $\text{M} - \text{CH}_3$ ), 207 (100,  $\text{M} - \text{CH}_3 - \text{H}_2\text{O}$ ).

### Acknowledgements

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