Pergamon

Tetrahedron, Vol. 53, No. 50, pp. 17221-17234, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10202-2

The Addition of Nitric Oxide to 1,5-Dimethylhexa-2,4-diene; X-ray Crystal Structure Determination of the Major Product, (*E*)-2,5-dimethyl-2,5-dinitrohex-3-ene

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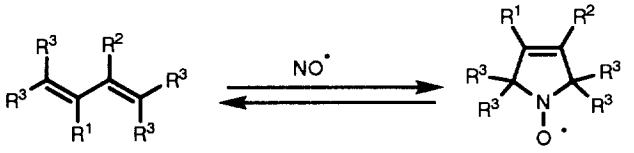
Abstract. The reaction of nitric oxide with 1,5-dimethylhexa-2,4-diene **1a** gives (*E*)-2,5-dimethyl-2,5-dinitrohex-3-ene **7** as the major product. The structure was confirmed by X-ray crystallography. 2,2,5,5-Tetramethylpyrroline-1-oxyl **2a**, which has been claimed to be formed in this reaction could not be isolated. The minor products were (*E*)-2,5-dimethyl-5-nitrohexa-1,3-diene **7**, (*E*)-2,5-dimethyl-6-nitrohexa-2,4-diene **8** (which interconvert *via* a unique 1,5-rearrangement), (*rac*)-2,5-dimethyl-4,5-dinitrohexa-2-ene **11**, and (*E*)-2,5-dimethyl-5-hydroxy-2-nitrohexa-2-ene **13**.

Nitric oxide is as an important biological messenger molecule with vital immune, cardiovascular and neurological functions[1]. It is formed biosynthetically from L-arginine by a family of nitric oxide synthase (NOS) enzymes, consisting of three isoforms[2]. The neuronal and endothelial forms are constitutively expressed (cNOS) whereas the inducible form (iNOS) is found in inflammatory cells[3]. The interaction of NO with protein heme groups and thiols can either activate or deactivate target enzymes. For example the heme-dependent activation of soluble guanylate cyclase by NO leads to increased intracellular cGMP and results in vascular relaxation and neurotransmission in the central nervous system[4]. However, the *S*-nitrosylation of glyceraldehyde-3-phosphate dehydrogenase[5] and the NO-Fe interaction in the iron-sulphur clusters of enzymes such as aconitase and NADH:ubiquinone oxidoreductase[6] results in inactivation of enzymatic activity. This is the mechanism by which NO is thought to fulfil its microbicidal and anti-tumour functions. Stimulation of iNOS by endotoxin and host cytokines such as interferon-γ and tumour necrosis factor (TNFα) causes increased production of NO, resulting in tissue damage and vasodilation[7] (eg septic shock). Regulators of NO or iNOS are being investigated as therapeutic agent and the rapid measurement of *in vivo* levels of NO has become an important objective[8].

Nitric oxide is a highly stable free radical which shows no tendency to dimerise or disproportionate, it does not abstract hydrogen or add to unactivated double bonds. In many ways its chemistry is similar to the triplet ground state of dioxygen[9]. However under physiological conditions the mean half life of nitric oxide is only 4-50 seconds[10] and consequently until recently it has proved difficult to quantify. The usual solution to this problem is to add a diamagnetic spin trap and measure the concentration of the spin adduct, however nitric oxide does not react with the conventional nitrone and nitroso spin traps[11]. Iron(II) complexes react with nitric oxide to give paramagnetic adducts that are sufficiently stable that ESR imaging is possible[12]; indeed haemoglobin may act as a natural nitric oxide scavenging system[13]. Never the less there are circumstances under which it would be useful to have metal-free spin traps. Some success has been achieved with quinodimethanes[14], *aci*-nitromethane[15] and phenols[16], but none of these are suitable for use under physiological conditions.

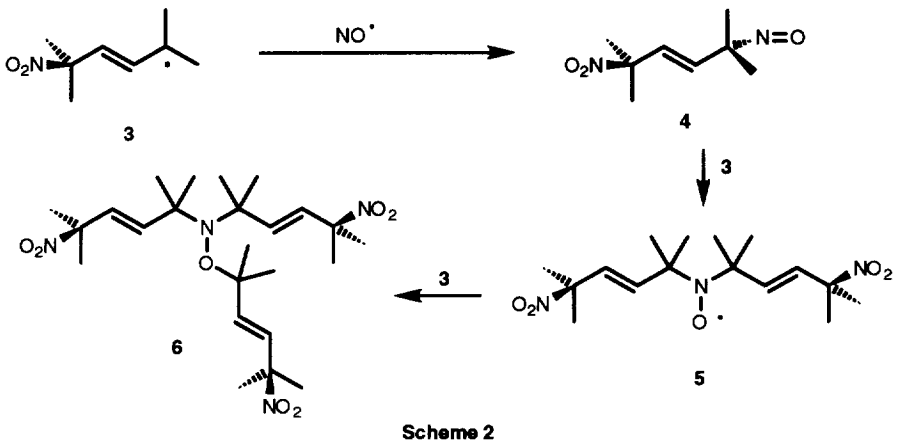


1 **2**

	R^1	R^2	R^3
a	H	H	CH_3
b	$CONH_2$	H	CH_3
c	Ph	Ph	CH_3
d	CH_3	CH_3	H

Scheme 1

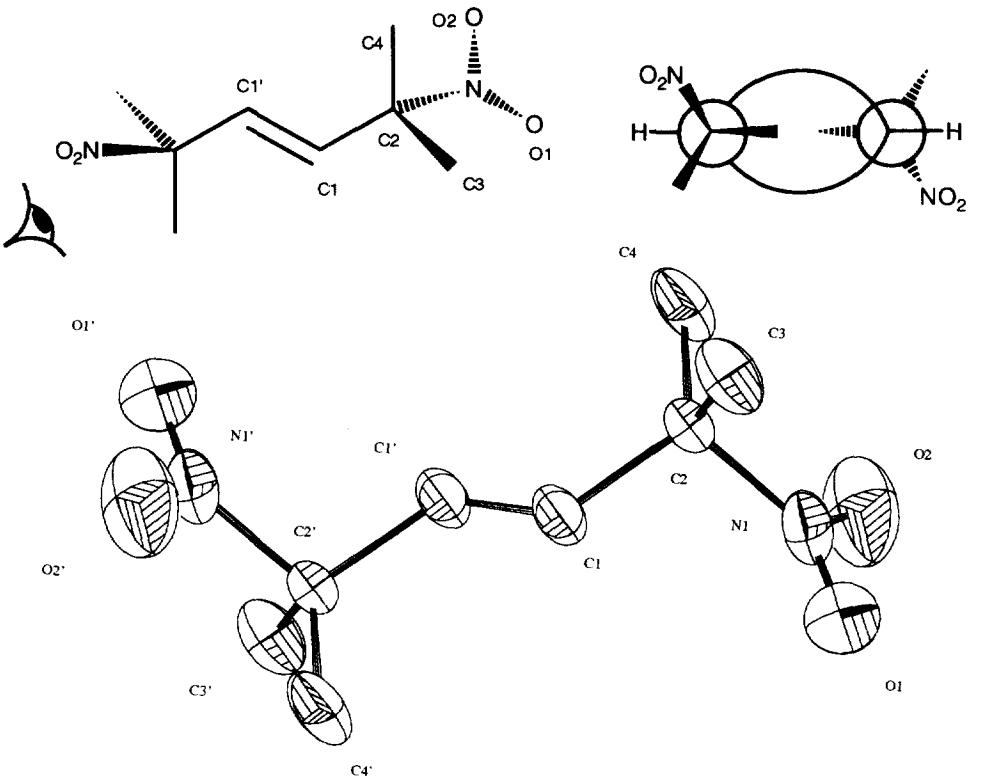
We were attracted by a report from Gabr, Rai and Symons that simple dienes (eg **1a**, Scheme 1) undergo chelotropic addition of nitric oxide to give nitroxides **2a**[17]. The credibility of this reaction was supported by an earlier report of the corresponding elimination by photolysis of the nitroxide **2b**[18]. In principle this would have been an ideal way to spin label a wide range of substrates. For example there is a continuing need for the preparation of spin labelled Lipid A[19] the terminal disaccharide unit of endotoxin which is the causative agent of septic shock. Replacement of a natural (*R*)-3-hydroxy-myristate side chain of Lipid A with a substituted *trans,trans*-diene analogue[20] would enable the spin label to be introduced late in the synthesis. The ESR spectrum obtained for the supposed adduct **2d** was challenged, because the hydrogen hyperfine couplings were smaller than expected[21] and the assigned structure was withdrawn[22]. This also cast doubt on the structure assignments of analogues such as **2a**. It was argued that traces of oxygen, oxidised nitric oxide to nitrogen dioxide which underwent addition to the alkene (eg **1a**) to give an allylic radical **3** which trapped nitric oxide (Scheme 2). The nitroso compound **4** (and/or the allylic regioisomer) so formed would then react further with the allylic radical **3** to give a plethora of products, including **6**, **7** (Scheme 3) and regioisomeric compounds formed by trapping on the secondary rather than the tertiary radical centre[21]. In support of this a tris(*t*-butylnitro)hydroxylamine was the major product isolated from the reaction of nitric oxide with isobutylene[23].



Scheme 2

Attempted addition of nitric oxide to the diphenyldiene **1c** (which plausibly should be more reactive than the diene **1a**) in the absence of oxygen gave products with ESR spectra consistent with NO and NO_2 cycloaddition adducts, whereas in the presence of a trace of oxygen the ESR spectra were similar to those obtained by Gabr *et al.*[17]. However in neither case could the products be isolated or identified (except by ESR)[24]. The debate over the structure of the nitric oxide/diene adducts was conducted solely using ESR data. It seemed plausible that the conflicting data might be resolved by isolating the adducts[25].

Nitric oxide undergoes very facile oxidation in air to give nitrogen dioxide[26] and other higher oxides of nitrogen[27]. These are appreciably more reactive than nitric oxide and may react preferentially with the diene despite being present in only trace amounts[14]. Accordingly carefully purified nitric oxide[28], in a stream of argon was passed through a solution of 2,5-dimethylhexa-2,4-diene **1a** in hexane. After 30 minutes the reaction mixture was pale blue (possibly indicating nitroso compounds) and after a further two hours the flow of nitric oxide was terminated. The crude reaction mixture was blue/green and gave ESR spectra with a strong three line feature indicative of a nitroxide type radical (a_N = 1.525mT in hexane) and signals due to ^{13}C satellites which were complex and poorly resolved[29]. This is consistent with the data and deductions of Gabr *et al* that two nitroxide species (a_N 1.45 and 1.50mT in CCl_4 or C_6D_6) are present with different ^{13}C splittings (a_C 1.05 and 0.60mT respectively). The species with the smaller ^{13}C splittings is favoured in dilute solutions and the data are consistent with the ESR spectrum (a_N 1.434, a_C 0.556mT in toluene) of the nitroxide radical **2a** produced by an unambiguous method[30]. ^1H NMR spectra of the crude reaction mixture indicated that the predominant constituent (>95%) was the starting material **1a**. Evaporation of solvent and residual diene **1a** gave a bluish oil which deposited fine white crystals (2% yield). These were removed by filtration and gave no ESR signal, whereas the filtrate gave ESR spectra identical to those measured previously. ^1H-NMR spectra of the crystals showed only two singlets (δ 6.18, 1.74) which integrated in the ratio 1:6 and the ^{13}C-NMR spectrum three signals: δ 132.4 (CH), 87.1 (C) and 25.8 (CH_3), indicating a plane or a C_2 axis of symmetry. The presence of a nitro group(s) was indicated by an IR band[31] at 1536 cm^{-1}, but the only substantial peak in the mass spectrum was *m/z* 110 which corresponds to the molecular weight of the diene starting material **1**.



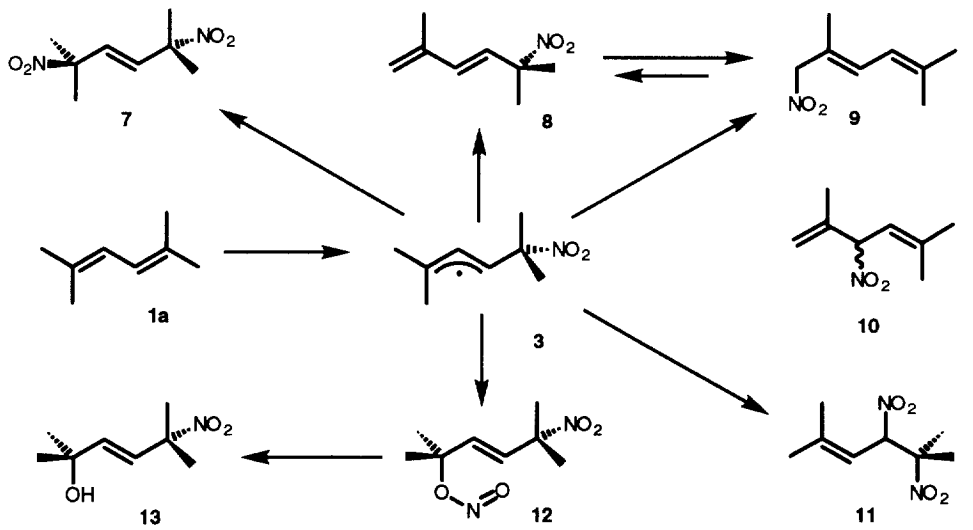
Bond lengths C1-C1' 1.301(4), C1-C2 1.490(4), C2-N1 1.552(4), N1-O1 1.197(3), N1-O2 1.192Å; Bond angles C1'-C1-C2 127.1(4), C1-C2-N1 104.6(2), C2-N1-O1 117.1(4), C2-N1-O2 119.8(3), O1-N1-O2 123.2(4)°; Torsion angles C1'-C1-C2-N1 -118.7(4)°, C1'-C1-C2-C3 126.9(4)°; C1'-C1-C2-C4 -0.5(4)°; C1-C2-N1-O1 112.9(3)°, C1-C2-N1-O2 -62.3(4)°

Figure 1 Molecular structure of *trans*-2,5-dimethyl-2,5-dinitrohex-3-ene 7. Thermal ellipsoids are drawn at the 30% probability level.

The structure was finally established as the dinitroalkene **7** by an X-ray crystal structure determination using a small crystal which had poor diffracting power. Nevertheless the final R factor was only 0.0413. The crystal structure and representative bond lengths and angles are shown in Figure 1. A substructure search for allylic nitro compounds in the Cambridge Crystallographic database revealed 44 structures. With one exception[32] all of these structures are from the work of Hartshorn on the addition of nitrogen dioxide to phenols and ring contraction of the adducts to cyclopentenes[33]. There are no reports of acyclic allylic nitro compounds. Thus this is the first structure in which the conformation of an allylic nitro group is unconstrained by a ring closure. The C2-C4 bond is virtually eclipsed with respect to a line joining the alkene carbons (C1, C1') and hence six of the eight carbon atoms and the two vinylic hydrogen atoms lie in the same plane. The

C2-N1 and C2-C3 bonds are staggered relative to the proximal vinylic hydrogen. If the alkene linkage is modelled as a *tau* bond, this arrangement minimises interactions of the bonds to heavy atoms as shown in the Newman projection (Figure 1)[34].

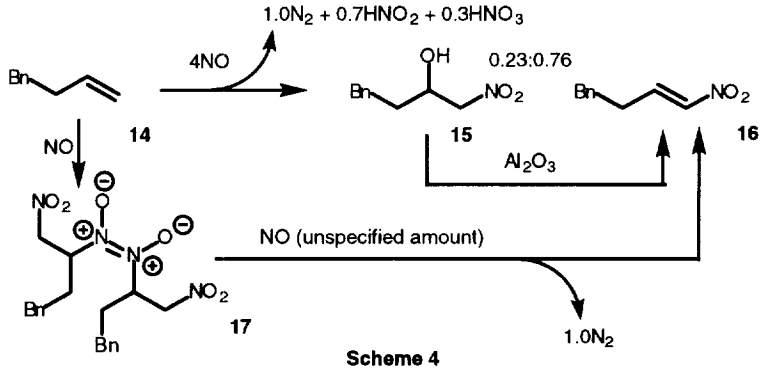
A Chemical Abstracts search for the 1,4-dinitro-adduct **7** revealed a similar preparation to that reported above, but with benzene as the solvent. As in the current study, the dinitroalkene **7** was the major characterised product, but another product which may have been a nitroso dimer was isolated but not identified[35]. Examination of the mother liquors of the crystallisation of the dinitroalkene **7** by ^{1}H-NMR or GC-MS indicated that the residual soluble material consisted of approximately 50% of the dinitroalkene **7**, plus at least four other components in roughly comparable amounts. There were variable amounts of insoluble polymers, which increased with time. Chromatographic separation of these components was bedevilled by their occurrence in trace amounts and their lability. Identification by GC-MS (EI+) was thwarted by their tendency to eliminate to give peaks at *m/z* 110 and 109 and the lack of an appreciable chromophore discouraged the use of HPLC. We were thus forced to optimise the preparative procedure. After considerable experimentation it was found that substantial amounts of products could be obtained if a large amount of the diene **1a** at 0°C was treated with a large excess of nitric oxide, generated slowly over 24 hours. Excess diene was easily removed by evaporation to give an oil, which gave ESR spectra identical to those seen before. The oil was subjected to flash column chromatography over silica gel (eluant petrol: diethyl ether or benzene), to give four main fractions, each of which was repurified several times. However none of these or any of the other fractions investigated, showed appreciable ESR spectra. Other than during chromatography or spectroscopic measurements all materials were stored at in a freezer at -20°C. We routinely separate substituted TEMPO radicals by column chromatography without incident and hence the "nitroxide radicals" produced in this reaction must be unusually labile.



Scheme 3

The least polar column fraction consisted of a circa 50:50 mixture of the nitrodienes **8**, **9** which were inexplicably difficult to separate (Scheme 3). Repeated chromatography gave a small sample of the tertiary nitrodiene **8** and mixtures **8**, **9**. These samples were stable in the freezer (-20°C) for 6 months, however when they were left at room temperature in benzene-d_6 they both isomerised to a 20:80 mixture (**8**:**9**) of the nitrodienes, plus small amounts of polymeric material. The residual C_6D_5H signal acted as a convenient internal standard for monitoring losses of material due to polymerisation. Repeated column chromatography gave a pure sample of the nitrodiene **9** which again isomerised at room temperature, although in this case the onset of polymerisation made accurate estimation of the ratio (**8**:**9**) more difficult. The half life of the isomerisation was about 3 days and the reactions could be monitored for about 14 days before polymerisation made the results unreliable. The data are consistent with an equilibrium rather than an irreversible process. Several 1,3-rearrangements of allylic nitrocompounds have been reported[36], but we were not able to find evidence for the presence of the regioisomer **10**. Thus this reaction either consists of two 1,3-rearrangements with kinetics such that the secondary nitrodiene **10** does not accumulate, or a single 1,5-rearrangement. We are not aware of any prior reports of the latter possibility.

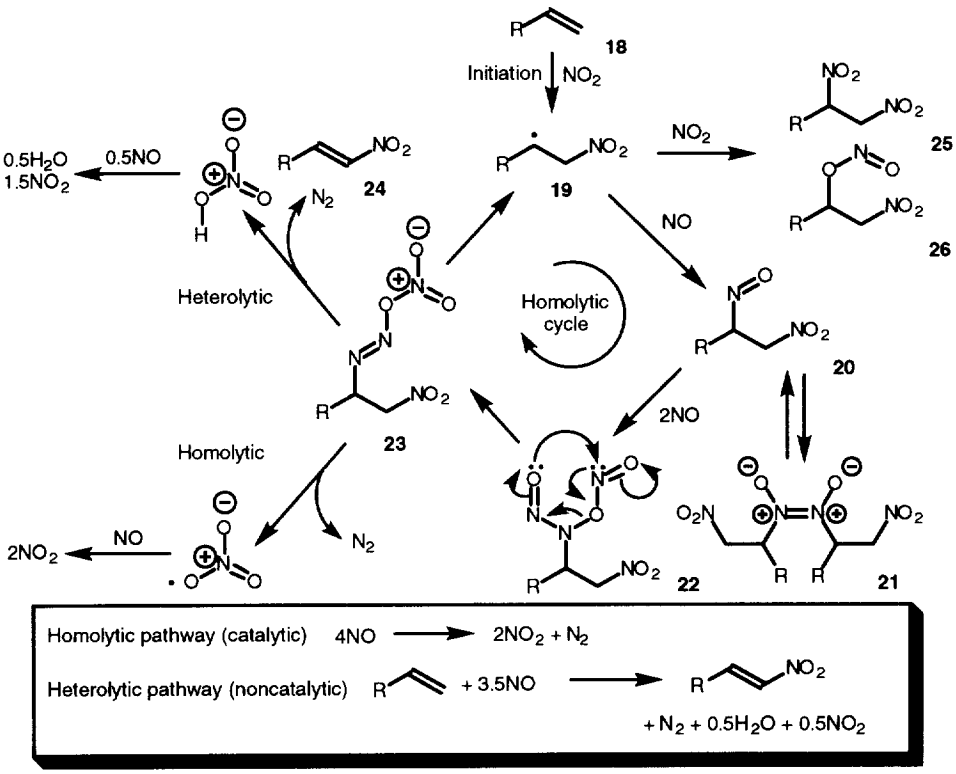
The remaining fractions were repurified by repeated column chromatography (petrol:diethyl ether and petrol:benzene) to give (in order of elution) the 1,2-dinitro- **11** and the 1,4-dinitro- **7** adducts plus the 1,4-nitroalcohol **8** which results from hydrolysis of the nitrite **12** (Scheme 3). Comparison of the products isolated with crude ^{1}H-NMR and GC-MS data showed that all the major components had been identified, although there was also a plethora of minor components. The data and the principal arguments for the assignment of the structures shown above are described in the experimental section. $^4J_{H,H}$ Allylic couplings (circa 1.5Hz) proved to be essential for linking methyl groups to vinyl protons, and where possible structures were deduced from connectivity data (^{1}H-^{1}H J-COSY and ^{13}C-^{1}H TOCSY) rather than from chemical shift arguments[37].



Scheme 4

The abundance of nitro groups in the products from these reactions pose a significant problem, where is all the oxygen coming from? It is inconceivable that "traces of oxygen" could stoichiometrically generate the products observed and oxidation during work up can be excluded because all the components were observed in the crude reaction mixture. The answer to the "oxygen question" was deduced from the work of Mukiayama (which was reported during the course of our studies) and from some of the earliest papers on the

addition of nitric oxide to alkenes. Mukiayama showed that the addition of nitric oxide to alkenes eg **14** gave mixtures of nitroalcohols **15** and nitroalkenes **16** (Scheme 4). Refluxing the crude reaction with alumina gave exclusively the nitroalkenes **16** in excellent yield[38]. He also showed that 4 equivalents of nitric oxide were required for complete conversion of one equivalent of alkene and that one equivalent of nitrogen and a total of one equivalent of nitrous and nitric acid were produced as by-products. By using only 1.1 equivalents of nitric oxide, the nitroso dimer **17** was isolated in low yield. When this was reacted with further nitric oxide, equal amounts of the nitroalkene **16** and nitrogen were formed[39]. Birchall *et al.* showed that analogous perfluoronitroso dimers react readily with nitric oxide, but not dinitrogen tetroxide (and presumably not nitrogen dioxide)[40]. The stoichiometry and co-production of nitrogen was noted quantitatively by Tuaillon and Perrot[41] and semiquantitatively by Bloomfield and Jeffrey[42] and an explanation was proposed by Brown[43]. The various pathways are assembled into Scheme 5.

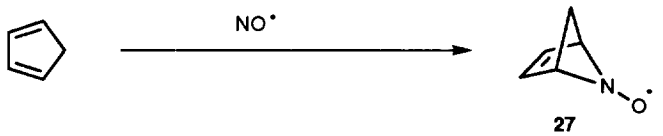


Scheme 5

The homolytic catalytic cycle is initiated by nitrogen dioxide, or some radical species capable of adding to an alkene **18**. The carbon radical **19** so formed then reacts with nitric oxide to give a nitroso adduct **20** which is in equilibrium with the dimer **21**. Addition of two equivalents of nitric oxide to the nitroso group

gives an *N*-nitroso-*N*-nitrite **22** which rearranges to the diazonium nitrate **23**[44]. In the homolytic pathway this decomposes to nitrogen trioxide which in turn reacts with nitric oxide to give two equivalents of nitrogen dioxide. In the heterolytic pathway (which was considered a less likely possibility by Birchall *et al*[40]), the alkene **24** and nitric acid are produced and the latter reacts further with nitric oxide to give nitrogen dioxide. Once either pathway is traversed more nitrogen dioxide is produced than consumed and the rate of reaction increases. When sufficient levels of nitrogen dioxide have built up the carbon radical **19** will start to be trapped by nitrogen dioxide to give dinitro compounds **25** or nitronitrites **26**. Both the heterolytic pathway and elimination of nitrous acid from the dinitro compounds **25** or nitronitrites **26** are viable routes to the nitroalkenes **24**. The participation of the allylic radical **3** in this pathway, in place of the generalised radical **19**, would generate the products **7**, **8**, **9**, **11**, **13** observed in the current work.

The failure of 1,5-dimethylhexa-2,4-diene **1a** to undergo chelotropic addition of nitric oxide (or any other species) is due to the low reactivity of nitric oxide with alkenes and because the terminal methyl groups prevent of the diene prevent attainment of the *s-cisoid* conformation. If one or more of these methyl groups is replaced by a hydrogen (which would favour the *s-cisoid* conformation) the resultant nitroxide is susceptible to disproportionation to nitrones and hydroxylamines. One solution to this conundrum is to place the nitroxide in a bicyclic system **27** which is unable to form a nitrone unless it violates Bredt's rule. Accordingly nitric oxide was generated as before and passed through a solution of cyclopentadiene. A brown oil was deposited but it was insoluble in all common solvents and this approach was abandoned.



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Conclusion The low reactivity of nitric oxide with alkenes (and dienes), its rapid reaction with traces of oxygen and catalytic conversion to nitrogen dioxide by nitroso compounds place severe limits on methods for the analysis of nitric oxide using alkene traps.

Experimental

NMR spectra were run on Bruker WM-360 or UX-400 instruments at 360 or 400MHz for protons and 90MHz or 100MHz for carbon-13 unless noted otherwise. ^{1}H NMR coupling constants reported to one decimal place of accuracy were calculated using the computer program; Multiplet (release NMRUC51.1) and have a digital resolution of 0.3Hz unless indicated otherwise. Spin simulations were performed using RACCOON. Electron spin resonance (ESR) spectra were recorded on a Varian E-109 spectrometer, operating at 100KHz field modulation (in X-Band mode), 9.21GHz microwave frequency at 298K. GC-MS were run on a HP5890 gas chromatograph fitted with a capillary column (SGE BPX5, 12m, 0.22mm id, 0.1μm film thickness) and temperature programmed, 60°C (1min), x10°C/min to 260°C (50min). The detector was a VG Trio-1 mass spectrometer running Lab-Base 3.0, with an EI source at 70eV or a CI+ (NH_3) source at 60eV. Other low resolution EI mass spectra were run on a VG-Platform II spectrometer with EI or CI+ (CH_4) sources. TLCs were run on aluminium plates precoated with silica gel (Merck $60F_{254}$) and the spots were

visualised using UV and/or dodecaphosphomolybdic acid (3% in ethanol) followed by heating. FT-IR spectra were run on a Perkin Elmer 1600 and UV spectra on a Perkin Elmer Lambda 2 instruments.

The Addition of Nitric Oxide to 1,5-Dimethylhexa-2,4-diene

Small Scale: Nitric oxide was generated according to the method of Blanchard[45] or obtained from a cylinder (Matheson, 99%[46]). Stock solutions were prepared consisting of acidified ferrous sulfate; $FeSO_4$ (278g) added to conc. H_2SO_4 (55ml) in water (1L) and sodium nitrite (69g) in water (1L). Acidified ferrous sulfate (50ml) was added to sodium nitrite solution (50ml; 50mmoles, 3 equivalents) which was stirred vigorously in an argon purged flask. The gas evolved was passed through NaOH solution (6M) to remove impurities, NaOH pellets to dry it and finally through an acetone/cardice trap to remove NO_2 (bp. 21.15°C). The purified gas was bubbled through a previously degassed stirred solution of 2,5-dimethylhexa-2,4-diene **1a** (1.65g; 2.1ml; 15mmol) in hexane (150ml). A constant flow of argon was maintained through the apparatus during the experiment. After 30mins the solution turned pale blue and after 2 hours the hexane was evaporated to yield a blue oil (2.06g). On standing for 10 minutes a precipitate was formed which was filtered off and washed with hexane to yield a crystalline solid **3** (0.0591g; 0.29mmol; 2%; yield based on recovered starting material 20%). The mother liquors from the crystallisation were chromatographed over silica gel, (eluted with a petrol:ether gradient) but no pure materials could be isolated.

Large Scale: The reaction above was repeated using 2,5-dimethylhexa-2,4-diene **1a** (50g) in hexane (1L) and nitric oxide (50equiv) bubbled through the solution over 24 hours. The reaction was repeated on this scale five times. Percentage yields for this work are not meaningful because many semi-purified fractions were discarded and material from separate runs was combined when advantageous. The mixture was separated by repeated flash column chromatography over silica gel, eluting with petroleum ether/diethyl ether or petroleum ether/benzene gradients. Fractions containing complex mixtures and/or large amounts of saturated hydrocarbons were discarded. The components identified in order of elution on TLC were:

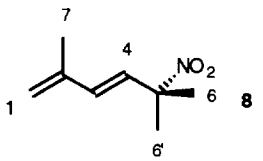
Fraction 1 a complex mixture of hydrocarbons which were discarded.

Fraction 2 initially consisted of a circa 50:50 mixture of two components: 2,5-dimethyl-5-nitrohexa-1,3-diene **8** and (4*E*)-2,5-dimethyl-6-nitrohexa-2,4-diene **9** as judged by ^{1}H-NMR (360Mhz). Repeated chromatography gave a small sample (9 mg) of the primary nitrodiene **8**. The remainder of the material (480mg) was stable in the freezer (-20°) for 6 months. Upon standing at room temperature for two weeks it isomerised to a 20:80 mixture (**8**:**9**), a portion was separated by column chromatography as described above to give pure primary nitrodiene **9** (30mg).

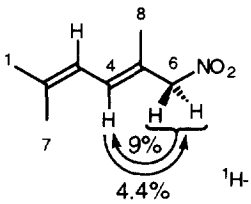
Fraction 3: (*rac*)-2,5-Dimethyl-3,5-dinitrohex-2-ene **11** (total 319mg).

Fraction 4: (*E*)-2,5-Dimethyl-2,5-dinitrohex-3-ene **7** (total 2.5g).

Fraction 5: (*E*)-2,5-Dimethyl-5-hydroxy-2-nitrohexa-2-ene **13** (total 43mg)



2,5-Dimethyl-5-nitrohexa-1,3-diene 8 Clear oil; ν_{max} (thin film)/cm^{-1} 2988, 1542 (str), 1458, 1346, 972; δ_H C_6D_6 (360 MHz) 6.24 (1H, d *J* 16.0, 4-H), 5.87 (1H, d *J* 16.0, 3-H), 5.0 (1H, br s, 1-H), 4.97 (1H, br s, 1'-H), 1.67 (3H, br s, 7-H_3), 1.37 (6H, br s, 6-H_3, 6'-H_3); δ_H $CHCl_3$ (400 MHz) 6.37, 5.93, 5.11, 5.08, 1.86, 1.74 (all couplings, integrations and assignments as in C_6D_6); coupling pathways were confirmed by ^{1}H-^{1}H decoupling; δ_C (90 MHz) $CDCl_3$ 140.5 (C, 2-C), 134.4 (CH, 4-C), 129.1 (CH, 3-C), 119.5 (CH_2, 1-C), 87.9 (C, 5-C), 26.0 (CH_3, 6-C, 6'-C), 18.4 (CH_3, 7-C); *m/z* (CI+, CH_4) 109 (100% $C_8H_{13}^+$).



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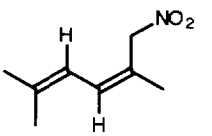
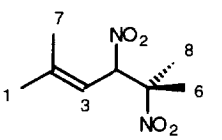
^{1}H-^{1}H nOe irradiations



28

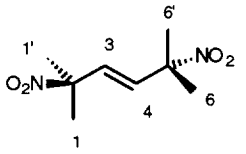
(4*E*)-2,5-Dimethyl-6-nitrohexa-2,4-diene 9 Clear oil; ν_{max} (thin film)/cm^{-1} 2980, 1682, 1651, 1554 (str), 1445, 1372, 974; δ_H $CHCl_3$ (400 MHz) 6.35 (1H, br d, *J* 10.9, 4-H), 6.0 (1H, d heptets *J* 10.9 and 1.3, 10 lines detected, 3-H), 4.88 (2H, s, 6-H_2), 1.84 (6H, s, 7-H_3, 8-H_3), 1.80 (3H, d *J* 1.1, 1-H_3); ^{1}H-^{1}H J-COSY 1-H_3 to 3-H (weak); 3-H to 4-H; 3-H to 7-H; 4-H to 8-H; δ_C (100 MHz, DEPT) $CDCl_3$ 140.1 (C, 2-C), 132.2 (CH, 4-C), 123.7 (C, 5-C), 120.5 (CH, 3-C), 85.2 (CH_2, 6-C), 26.5 (CH_3, 1-C), 18.8 (CH_3, 8-C), 15.3 (CH_3, 7-C); ^{1}H and ^{13}C assignments were correlated with a TOCSY spectrum; *m/z* (CI+, CH_4) 109 (100%, $C_8H_{13}^+$); *m/z* (GC-MS, CI+, NH_3) 124 (7), 109 (100); GC retention time 10.9min (BPX5). The key assignments in this structure are 3-H and 4-C. The higher frequency vinylic proton (δ 6.35) is a broadened doublet, whereas the lower frequency vinylic proton (δ 6.0) shows the same doublet splitting plus distinct fine structure, which is at least a quintet and is most likely a heptet. Hence these are assigned as 4-H and 3-H respectively. Both the ^{1}H and ^{13}C shifts concur with chemical shift arguments based on the electron withdrawing ability of the nitro group. nOe experiments link 4-H to 6-H_2 which indicates structure **9** rather than the (4*Z*)-stereoisomer **28**.



11

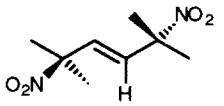
(*rac*)-2,5-Dimethyl-4,5-dinitrohexa-2-ene 11 White waxy solid; ν_{max} (thin film)/cm^{-1} 2984, 1555 (str), 1455, 1400, 1346, 1134, 1047, 852; δ_H $CDCl_3$ (400 MHz) 5.93 (1H, d *J* 10.4, 4-H), 5.39 (1H, d heptets *J* 10.5 and 1.4, 3-H), 1.95 (3H, d *J* 1.3), 1.89 (3H, d *J* 1.4), 1.71 (3H, s), 1.61 (3H, s); coupling pathways were confirmed by ^{1}H-^{1}H decoupling; δ_C (100 Mhz, DEPT) $CDCl_3$ 145.6 (C, 2-C), 112.4 (CH, 3-C), 87.6 (C, 4-C or 5-C), 87.5 (CH, 4-C or 5-C), 26.3 (CH_3, C-1, correlation δ_H 1.95), 24.4 (CH_3, correlation δ_H 1.61), 21.5 (CH_3, correlation δ_H 1.71), 18.1 (CH_3, 7-C, correlation δ_H 1.89); ^{1}H and ^{13}C spectra were correlated with a TOCSY experiment. Correlations are only reported for potentially ambiguous

assignments; *m/z* (CI+, CH_4) 156 (1), 111 (50), 110 (100, $C_8H_{14}^+$), 109 (27); *m/z* (GC-MS, CI+, NH_3) 220 (12, M + NH_4^+), 173 (3, M + NH_4^+-HNO_2), 144 (10), 127 (80), 111 (55), 110 (100, $C_8H_{14}^+$), 109 (70), 95 (60), 83 (68), 58 (39); GC retention time 12.4min (BPX5).



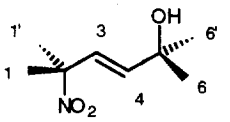
7

(*E*)-2,5-Dimethyl-2,5-dinitrohex-3-ene 7 Clear crystals, mpt. 97-99°C; lit 131-133°C (from DSC[34]) calculated for $C_8H_{14}N_2O_4$ C 47.52, H 6.98, N 13.85 found C 48.00 H 7.07 N 13.83; ν_{max} (nujol mull)/cm^1 1536, 1346, 1133 (w); δ_H $CDCl_3$ (400 MHz) 6.18 (2H, s, 3-H, 4-H), 1.74 (12H, $4CH_3$); δ_C (90 Mhz) $CDCl_3$ 132.4 (d, 3-C, 4-C), 87.1 (s, 2-C, 5-C), 25.8 (q, $4CH_3$); *m/z* (GC-MS, EI+) 156 (1, M-NO_2) 126 (2) 111 (15) 110 (100, $C_8H_{14}^+$) 95 (65); GC: 30m DB17, 30°C (5min) x10°/min to 245° (20min), retention time 18.40min; X-Ray Structure Crystal data for $C_8H_{14}N_2O_4$, Mr = 202.21, monoclinic, space group P21/n, a = 9.0721(7), b = 6.151(3), c = 10.085(4), β = 109.87(4)°, (by least squares refinement of the setting angles for 250 reflections within θ = 2.61 - 24.98°). V = 529.3(4)Å^{-3}, Z = 2, Dc = 1.269 gcm^{-3}, T = 298K, μ(Mo-Kα) = 10.2 cm^{-1}, F(000) = 216, crystal size = 0.035 x 0.014 x 0.21 mm. Data was collected on a FAST TV Area detector diffractometer following previously described methods[47]. From the ranges scanned, 1952 data were recorded ($2.61 \leq \theta \leq 24.98°$; index ranges $-10 \leq h \leq 10$, $-5 \leq k \leq 6$, $-9 \leq l \leq 11$) and merged to give 779 unique [R(int) = 0.0572]. The structure was solved via direct methods[48] and refined on Fo^2 by full matrix least squares[49] using all unique data corrected for Lorentz and polarisation factors. All non-hydrogen atoms were anisotropic. The hydrogen atoms were inserted in idealised positions with Uiso set at 1.5 times the Ueq of the parent. The weighting scheme used was $w=1/[\sigma^2(Fo)^2 + (0.034P)^2]$, where $P = [Max(Fo)^2 + 2(Fc)^2]/3$; this gave satisfactory agreement analyses. Final R_1 (on F) and wR_2 (on Fo^2) values were 0.1155 and 0.0907 for all 1952 data and 66 parameters. The corresponding R-values were 0.0413 and 0.0793 for 778 data with $I > 2\sigma(I)$. It should be noted that the data was unusually weak as a result of the small crystal and its poor diffracting power. Sources of scattering factors as in ref. 47. Additional material available from the Cambridge Crystallographic Data Centre comprises full crystal data and details of data collection and refinement, H-atom co-ordinates and thermal parameters.



7 Lowest energy conformer from molecular mechanics calculation

The bond lengths and geminal bond angles of the structure were satisfactorily reproduced by molecular modelling (PC Model, V3.2, Serena software and Cerius 2, V1.6, Molecular Simulations Incorp.), however the conformation was not. Despite prolonged randomisation and/or using the crystal structure geometry as a starting structure, the structure minimised to a rotamer in which the C-C bond of one of the methyl groups was virtually eclipsed (dihedral angle, 0-10°) with respect to the proximal vinylic hydrogen.



13

(*E*)-2,5-Dimethyl-5-hydroxy-2-nitrohex-2-ene 13 wax, ν_{max} (nujol mull)/cm^{-1} 3356 (br, O-H), 2978, 1643 (w), 1537 (str), 1346, 1216 (str), 758 (str); δ_H $CDCl_3$ (400 MHz) 6.05 (1H, d *J* 15.8, 2-H), 5.91 (1H, d *J* 15.9, 4-C), 1.71 (6H, s, 6-H_3, 6'-H_3), 1.34 (6H, s, 1-H_3, 1'-H_3); δ_C (90 Mhz, DEPT) $CDCl_3$ 140.5 (CH, 3-C), 127.8 (CH, 4-C), 87.9 (C, 2-C), 71.0 (C, 5-C), 30.0 (CH_3, 1-C), 26.4 (CH_3, 6-C); *m/z* (CI+, CH_4) 127 (100, M-NO_2), 111 (10), 110 (22), 109 (30); *m/z* (GC-MS, CI+, NH_3) 144 (13, M + NH_4^+-HNO_2), 127 (100, M-NO_2), 109 (66), 83 (18); GC retention time 10.53min (BPX5).

Attempted synthesis of 5-azabicyclo[2.1.1]hex-2-en-5-oxy. free radical

Nitric oxide was generated as above and the purified gas bubbled through a previously degassed stirred solution of freshly cracked cyclopentadiene (0.99g, 1.0ml, 0.015mol) in hexane (150ml). A constant flow of argon was maintained through the apparatus during the experiment. After 30 minutes the solution turned cloudy, and a brown oil was deposited over a further 2 hours. Evaporation of the hexane gave a brown oil, which did not dissolve in any of the usual NMR solvents. TLC analysis showed no mobile components.

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(*Received in UK* 22 *September* 1997; *revised* 10 *October* 1997; *accepted* 16 *October* 1997)