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The Cheletropic Trapping of Nitric Oxide by the *bis*-Ketene 1,2-Dicarbonylcyclohexa-3,5-diene and the Diene 3,4-Diphenyl-2,5-dimethyl-2,4-hexadiene.

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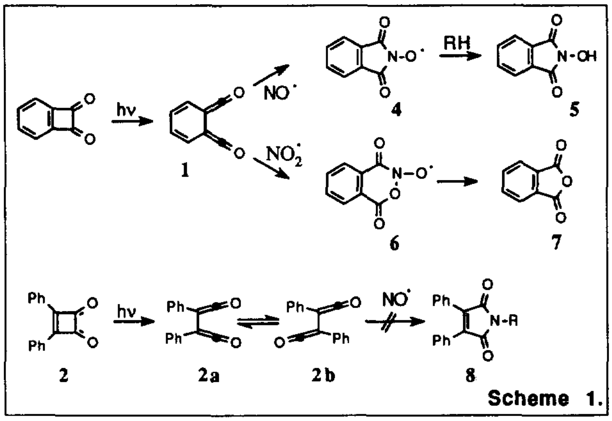
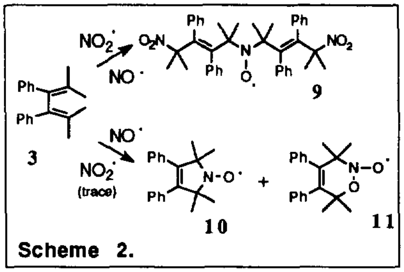
Abstract: *We report the first example of the cheletropic trapping of nitric oxide with a bis-ketene. In the presence of nitric oxide the bis-ketene 1,2-dicarbonylcyclohexa-3,5-diene (1), generated from photolysis of benzocyclobutenedione, gave N-hydroxyphthalimide (5) and phthalic anhydride (7); additionally, cheletropic NO trapping with 3,4-diphenyl-2,5-dimethyl-2,4-hexadiene (3) gave strong persistent ESR signals, the nature of which was dependent on the purity of the NO.*

One of the most significant discoveries in the last few years has been the mediation of nitric oxide (NO) in a variety of biochemical pathways,[1] including muscle relaxation,[2] macrophage activation[3] and neurotransmission.[4] With these developments has come renewed interest in methods of trapping and monitoring this highly reactive molecule. Ingold and Korth *et al.*[5] used an *ortho*-quinodimethane system to cheletropically trap nitric oxide, thereby generating stable paramagnetic nitroxides readily detected by ESR. Symons[6] appeared to have replicated these results with simple substituted butadienes, generating typical three-line nitroxide ESR spectra which he ascribed to cyclic nitroxides. However, this was disputed by Rockenbauer,[7] who explained the results via the mediation of higher oxides of nitrogen, namely NO_2 radicals. In order to further our understanding of the surprisingly complex chemistry of this simple molecule, we have undertaken the cheletropic trapping of NO with appropriate *bis*-ketenes **1** and **2**; as well as a substituted hexadiene **3** which upon cheletropic NO trapping would produce a *stable* nitroxide, isolable by standard chemical techniques.



Scheme 1.

The cyclic *bis*-ketene **1**, produced *in situ* following the literature method[8] from the photolysis ($\lambda > 295$ nm) of a solution of benzocyclobutenedione (100 mg, 0.1 mmol) in 25 ml of dry, deoxygenated benzene, successfully trapped NO (generated from the reduction of 8M nitric acid with copper powder and purified via several aqueous NaOH washes), as evidenced by the production of N-hydroxyphthalimide (5). ^{1}H and ^{13}C NMR spectroscopy of the reaction mixture after removal of the solvent, showed a very clean mixture of only three components: N-hydroxyphthalimide (5) and phthalic anhydride (7) in a ratio of 15:85 and a small amount of starting material. Apart from a weak and very broad structureless feature, no ESR signal could be detected for the diacyl nitroxide precursor **4**, even with experiments measured *in situ*, which indicates no steady-state build up of this compound. It is likely that hydrogen abstraction (from the solvent) by **4** to give N-hydroxyphthalimide (5) would be very rapid, given the high reactivity of this acyl nitroxide species,[9] especially under the effect of the photolytic excitation used to generate the *bis*-ketene.[10] We propose[11] the phthalic anhydride (7) arises from the extrusion of NO from the unstable alkoxy/alkyl nitroxide **6** produced from the reaction of **1** with nitrogen dioxide radicals (Scheme 1). Although the reaction was very clean as evidenced by nmr spectroscopy, TLC etc., work up gave only low yields (**5**, 5 mg, 4.0% and **7**, 50 mg, 44.6%), presumably due to hydrolysis and irreversible binding of these polar materials during preparative silica chromatography. Both **5** and **7** were characterised by comparison of their IR, MS (EI), ^{1}H and ^{13}C NMR spectra to those of authentic material.



Scheme 2.

Reaction of the *bis*-ketene, 2,3-diphenyl-1,3-butadien-1,4-dione (2), produced from 2,3-diphenylcyclobut-2-ene-1,4-dione (200 mg, 0.9 mmol), with NO in an analogous manner[12] led to a brown/yellow oily residue unamenable to further separation by chromatography. NMR showed only broad peaks commensurate with high molecular weight materials. An ESR spectrum of this product showed only a weak complex signal without ordinary couplings. It is known[12] that unlike **1** the *bis*-ketene **2** favours a transoid structure which would preclude cheletropic trapping and allow only the formation of oligomeric and polymeric condensation products.

The concept of preferred conformation was not addressed by Symons[6], but it is probable that, like the *bis*-ketene **2**, simple butadienes would also adopt a transoid arrangement which would hinder the cheletropic trapping process. Simple calculations[13] however, indicate that the diene 3,4-diphenyl-2,5-dimethyl-2,4-hexadiene (3) (Scheme 2) should favour a *cisoid* arrangement because of advantageous phenyl ring interactions. As the resultant cheletropic trapping product **10** would be a persistent nitroxide with increased conjugative stabilisation, **3** represents a very good test to determine if cheletropic NO trapping is possible with simple dienes. Therefore **3** (200 mg, 0.8 mmol) in 80 ml of dry, NO saturated benzene was heated at 70 $^{\circ}$C for 20 min in a sealed vessel. The reaction mixture was concentrated to ~ 60% to remove residual NO and the ESR spectrum measured. The ESR (microwave frequency 9.753084 GHz) gave two clear three-line features (Figure 1) with g = 2.0063, a_N = 14.4 G and g = 2.0059, a_N = 27.4 G. The reaction was repeated, this time being deliberately spiked with oxygen to produce high concentrations of oxides of higher oxides of nitrogen (including NO_2 radicals). ESR (microwave frequency 9.753223 GHz) of this solution showed only one much stronger and different three-line feature (Figure 2) with $g = 2.0060$, $a_N = 14.2$ G. In both cases, despite the strong ESR signals, work-up gave only unreacted starting material as the major component of the reaction mixture.

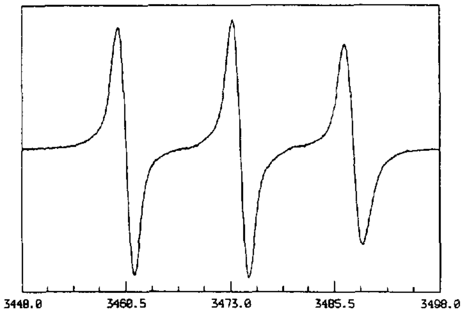


Figure 1. (Magnetic Field * 10^{-4} Tesla)
ESR spectrum of the reaction of 3,4-diphenyl -2,5-dimethyl-2,4-hexadiene (3) with NO in the presence of a trace amount of oxygen.

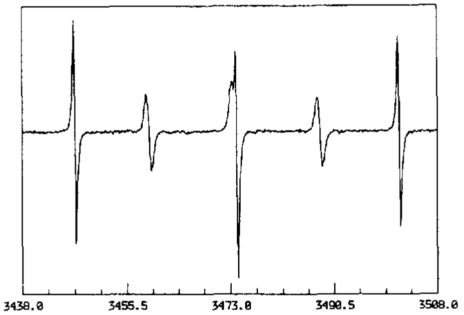


Figure 2. (Magnetic Field * 10^{-4} Tesla)
ESR spectrum of the reaction of 3,4-diphenyl -2,5-dimethyl-2,4-hexadiene (3) with NO.

Clearly the fate of the diene is very dependent on the purity of the NO used and there appears to be at least three reaction pathways involved. Strong contamination with higher oxides of nitrogen gives a nitroxide ESR spectrum (Figure 1) commensurate with Rockenbauer's addition / trapping / addition pathway[7] (Scheme 2, nitroxide **9**). Hydrogen abstraction however appears less significant with more highly purified sources of NO. When samples contain only traces of NO_2 (and no other higher oxides) a mixture of two different nitroxides arises (Scheme 2, nitroxides **10** and **11**) comensurate with *two* different cheletropic additions (Figure 2). The strongest signal has a large a_N value of 27.4 G which correlates with known[5] NO_2-derived alkoxy/alkyl nitroxide addition by-products generated in NO cheletropic trapping reactions with *o*-quinodimethanes.[14] The other nitroxide signal may then be assigned to the pentacycle **10**. However product analysis of this reaction mixture, even by very sensitive HPLC/MS techniques, could not confirm the presence of **10**. As this nitroxide should be persistent and isolable (and related nitroxides are known[15]) this indicates that the addition can, at best, only be a minor pathway. ESR is a very sensitive probe for stable radicals, but the species detected are not necessarily present in isolable quantities. Our results indicate that even the most favourable simple dienes do not represent efficient means of monitoring the presence of NO by ESR. Nitric oxide will react cheletropically with conformationally appropriate and chemically aggressive *bis*-ketenes and *ortho*-quinodimethanes, but not with unactivated simple dienes.

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