Diels–Alder trapping of an *o*-dinitroso intermediate in the 1-oxide/3-oxide interconversion of a 2,1,3-benzoxadiazole derivative

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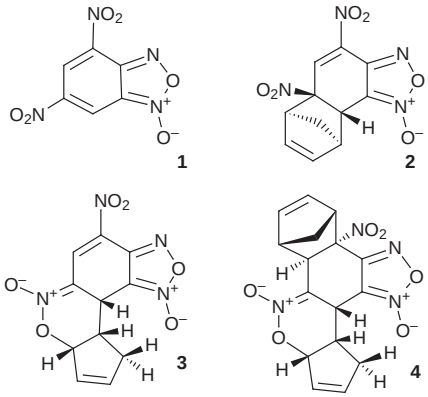
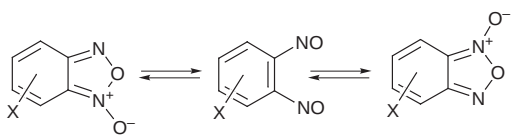
Convincing evidence is presented that the *o*-dinitroso intermediate involved in the exchange of the 1-oxide and 3-oxide tautomers of 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine 1-oxide 5 is the precursor of the Diels–Alder diadduct 7 isolated upon treatment of this compound with cyclohexadiene in $CHCl_3$.

The high susceptibility of the nitro-substituted 2,1,3-benzoxadiazoles to undergo covalent nucleophilic addition or substitution processes has attracted considerable attention over the two last decades, leading to numerous synthetic, analytical and biological applications.[1–8] A most significant finding has been, however, our recent discovery that the carbocyclic ring of these strongly electron-deficient heteroaromatics can also be involved in a variety of Diels–Alder type reactions.[9] As a prototype example, 4,6-dinitro-2,1,3-benzoxadiazole 1-oxide **1**



has been found to act as a dienophile in normal electron demand Diels–Alder (NEDDA) processes or as a heterodiene in inverse electron demand Diels–Alder (IEDDA) processes to give the monoadducts **2** and **3**, respectively, upon treatment with cyclopentadiene at −20 °C in $CHCl_3$. In the presence of excess cyclopentadiene at 0 °C, the IEDDA–NEDDA diadduct **4** is quantitatively formed with high stereoselectivity at the expense of **2** and **3**.[9]

Here we report our finding of another Diels–Alder reactivity pattern that we have identified in the reaction of 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine 1-oxide **5**[10] with cyclohexadiene. This new pattern provides convincing evidence in support of the long standing belief that the mechanism of the interconversion of the 1-oxide/3-oxide tautomers (Scheme 1) proceeds through formation of an *o*-dinitroso intermediate.[7,11,12] So far, it is only through photolysis of unsubstituted 2,1,3-benzoxadiazole and *o*-nitrophenyl azide in Ar matrices at 14 K that the existence of such an unstable species could be demonstrated by IR and UV spectroscopy.[13]



Scheme 1

Treatment of **5** with cyclohexa-1,3-diene (5 equiv.) in $CHCl_3$† affords a 2 : 1 mixture of two products which were readily separated by column chromatography and isolated as pale yellow solids. Although it has been obtained with a crystal of poor quality, the ORTEP view in Fig. 1 leaves no doubt that the major product is the diadduct **7**‡§ whose formation can only be accounted for in terms of two NEDDA processes, in which the N=O double bonds of the *o*-dinitroso intermediate **6** play the role of the dienophile contributors (Scheme 2). Such behaviour of N=O fragments is well known.[14] Based on a detailed analysis *via* COSY, HETCOR and *J* modulation experiments, the NMR data agree with the stereochemistry assigned to **7** in the solid state. The recovery of a pyridine ring on formation of **7** from **5** is supported by the disappearance in the ^{13}C NMR spectra of the

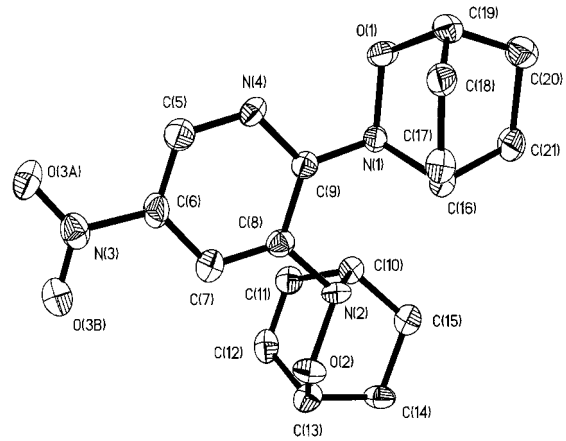
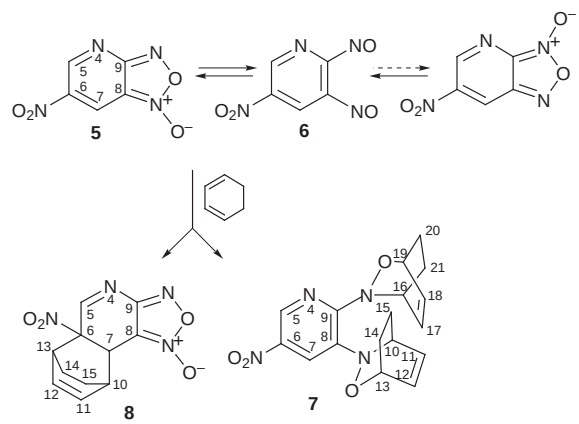


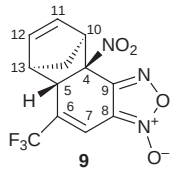
Fig. 1 ORTEP view of **7**, as derived from a partial structure solution (only one enantiomer is represented).



Scheme 2

resonance typical for the C_8 carbon of a 2,1,3-benzoxodiazole structure (δ_C 108.79 in **5**)[10,11] and its replacement by a resonance at δ_C 137.59 for **7**, a classical value for a pure aromatic carbon.

In view of the ^1H and ^{13}C NMR spectra also recorded in $CDCl_3$, the minor product can be formulated as the cycloadduct **8** in its racemic form. This adduct, which is not very stable in the solid state, results from a regioselective and diastereoselective NEDDA process involving the C_6–C_7 double bond of **5** as the dienophile contributor. It should be noted that the related *endo* cycloadduct **9** was recently isolated as the only product of the reaction of cyclopentadiene with 4-nitro-6-trifluoromethyl-2,1,3-benzoxadiazole.[15]



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In the literature, many examples of 2,1,3-benzoxadiazole structures undergoing the tautomeric exchange shown in Scheme 1 have been reported,[10–12] but no firm Diels–Alder support for the transient formation of the postulated *o*-dinitroso intermediate along the reaction coordinate has been obtained so far. The isolation and characterization of the diadduct **7** *in a thermal process* is therefore of great relevance to the rearrangement shown in Scheme 1, especially because this equilibrium has been shown to be strongly shifted toward the 1-oxide tautomer in the case of the 6-nitro[2,1,3]oxadiazolo[4,5-*b*]-pyridine 1-oxide system.[10]

Notes and references

† *Synthetic procedure* for **7** and **8**: 1.3 ml of cyclohexa-1,3-diene (13.75 mmol) were added to a solution of 0.5 g of **5** (2.75 mmol) in $CHCl_3$. The solution turned rapidly orange.The mixture was maintained under stirring at room temperature for 2 d. Evaporation of $CHCl_3$ under reduced pressure gave a mixture of 7 and **8** as a red semi-solid (0.8 g). The product was purified by chromatography on silica gel using a gradient of EtOAc–pentane as eluent; **7** and **8** were obtained in a 2:1 ratio as yellow crystals.

‡ *Selected data* for **7**: δ_H(300.13 MHz, acetone-d_6) (1.40, 1.60 and 2.21 (m, H-14, H-15, H-20, H-21), 4.88 (dt, 2 H, H-10, H-16, *J* 1.47, 5.88), 5.06 (m, 1 H, H-13 or H-19), 5.67 (m, 1 H, H-13 or H-19), 6.01 (ddd, 1H, H-11 or H-17, *J* 1.47, 6.24, 7.71), 6.16 (ddd, 1H, H-11 or H-17, *J* 1.47, 6.24, 8.07), 6.62 (ddd, 1 H, H-12 or H-18, *J* 1.85, 5.88, 8.07), 6.74 (ddd, 1 H, H-12 or H-18, *J* 1.47, 5.88, 6.27), 7.88 (d, 1 H, H-7, J_{5-7} 2.58), 8.62 (d, 1 H, H-5); δ_C (75.47 MHz, acetone-d_6) 21.36, 21.82, 24.40 and 24.96 (C-14, C-15, C-20, C-21), 50.45 and 51.43 (C-10, C-16), 70.72 and 71.24 (C-13 , C-19), 121.41 (C 7), 129.91 and 130.35 (C-11, C-17), 132.95 and 133.27 (C-12, C-18), 137.59 (C 8), 138.20 (C 5), 140.78 (C 6), 156.52 (C 9); mp 147–150 °C; *m*/*z* (EI) 342 ($M^{+\cdot}$), 262 [$M - C_6H_8^{+\cdot}$]), 232 ($M - C_6H_8 - NO^{+\cdot}$]) (Found: C, 59.63; H, 5.43; N, 16.04 . $C_{17}H_{18}N_4O_4$ requires C, 59.65; H, 5.26; N, 16.37%). For **8**: δ_H(300.13 MHz, acetone-d_6) 1.15–1.60 (m, 4 H, H-14, H-15), 3.43 (dd, 1 H, H-10, J_{7-10} 2.94 , J_{10-11} 6.27), 4.07 (dd, 1 H, H-7 , J_{5-7} 1.83), 3.79 (m, 1 H, H-13), 6.35 (dd, 1 H, H-12, J_{11-12} 7.35), 6.65 (dd, 1 H, H-11), 8.48 (s, 1 H, H-5); δ_C (75.47 MHz, acetone-d_6) 19.00 and 20.36 (C-14, C-15), 30.54 (C-10), 35.62 (C-7), 38.41 (C-13), 91.38 (C-6), 102.15 (C-8), 130.95 (C-12), 136.51 (C-11), 157.26 (C-9), 166.95 (C-5); mp 185 °C; *m*/*z* (EI) 234 [$M + H_2O–NO_2^{+\cdot}$]), 216 ([$M - NO_2^{+\cdot}$]).

§ *Crystal data* for **7**: $C_{17}H_{18}N_4O_4$, M = 342.35, monoclinic, space group $P2_1/n$, a = 6.418(8), b = 10.010(11), c = 24.850(3) Å, β = 91.95(6)°, U = 1595(3) Å^3, Z = 4, D_c = 1.425 mg cm^{-3}, μ(Mo-Kα) = 1.04 cm^{-1}, λ = 0.71073 Å, graphite monochromator, crystal dimensions: 0.08 × 0.32 × 0.40 mm. The data were collected up to 2θ = 60° on a Siemens SMART three-circle diffractometer equipped with a bidimensional CCD detector. The poor quality of the data prevents the structure from being published in full.

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