# A new feature in the chemistry of nitrobenzofuroxans: ambident reactivity in Diels–Alder condensations

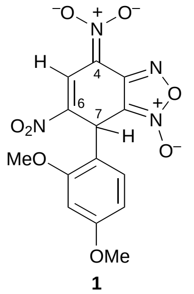
**Dominique Vichard,**[a]† **Jean-Claude Hallé,***[a]‡ **Boris Huguet,**[a] **Marie-José Pouet,**[a] **Didier Riou**[b] **and François Terrier***[a]§

[a] *Laboratoire SIRCOB, CNRS EP 102, Université de Versailles-Saint Quentin, Bâtiment Lavoisier, 45 Avenue des Etats-Unis, 78035 Versailles Cedex, France*

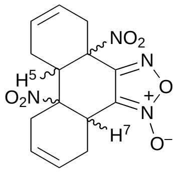
[b] *Laboratorie IREM, CNRS CO173, Université de Versailles-Saint Quentin, Bâtiment Lavoisier, 45 Avenue des Etats-Unis, 78035 Versailles Cedex, France*

**The 4,6-dinitrobenzofuroxan (DNBF) structure is shown to act both as a dienophile and a heterodiene upon treatment with 1-trimethylsilyloxybuta-1,3-diene and vinyl ethyl ether, providing in two steps a highly functionalised stereoselective compound.**

In recent years, a large body of evidence has been accumulated showing that 4,6-dinitro-2,1,3-benzoxadiazole 1-oxide, commonly known as 4,6-dinitrobenzofuroxan (DNBF), is a neutral 10π-electron heteroaromatic substrate which, in many processes, exhibits extremely high electrophilic character.[1–5] In fact, recent studies have shown that DNBF is a stronger electrophile than the 4-nitrobenzenediazonium cation.[2] This makes DNBF a remarkable probe to assess the reactivity of such weak carbon nucleophiles as benzenoid aromatics or π-excessive heteroaromatics with large negative $\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ values, *e.g.* 1,3-dimethoxybenzene ($\mathrm{p}K_\mathrm{a}^\mathrm{CH} = -9$) or 3-methoxythiophene ($\mathrm{p}K_\mathrm{a}^\mathrm{CH} = -6.5$).[6,7] In all of the above processes, covalent addition of the carbon nucleophile takes place at C(7) of the carbocyclic ring of DNBF to give stable anionic σ-complexes, *e.g.* **1**.[6] The same principle applies in all reported interactions of DNBF with oxygen, nitrogen or sulfur nucleophiles.[1,3,4,8–10]



**1**

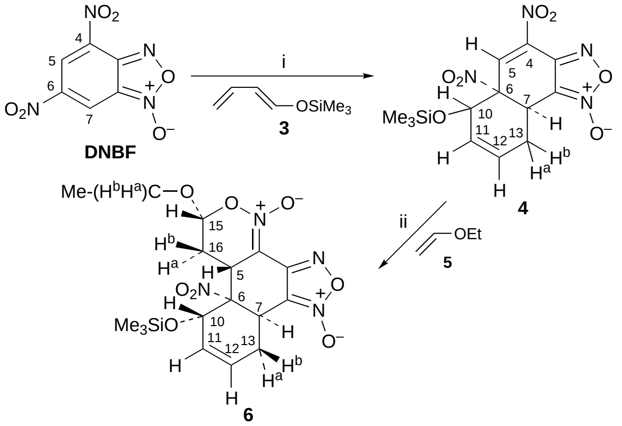


**2**

Interestingly it has been argued that the low aromatic character of the benzofuroxan system should be one of the major factors responsible for the exceptional electrophilic reactivity of DNBF and nitrobenzofuroxans in general.[1,2,9] Should this be true, the idea that these compounds might be involved in Diels–Alder type reactions under some experimental conditions could not be excluded. In 1973, Kresze and Bathelt reported the very slow formation of the diadduct **2** upon reaction of DNBF with butadiene.[11] Although the most reasonable explanation for the formation of this adduct was in terms of a Normal Electron Demand Diels–Alder (NEDDA) mechanism, this finding did not lead to further investigation and the stereochemistry was not investigated. Here we present the first evidence that the DNBF structure can in fact exhibit an ambident Diels–Alder reactivity, acting as a dienophile in NEDDA reactions or as a heterodiene in Inverse Electron Demand Diels–Alder (IEDDA) reactions, depending upon the experimental conditions and the reaction partners employed.

Treatment of DNBF with 1-trimethylsilyloxybuta-1,3-diene **3** (used as the solvent at room temperature) (Scheme 1) results in the rapid and nearly quantitative formation of a product which we readily isolated as a pale yellow solid. Based on $^1H$ NMR and electrospray mass spectroscopy data,¶ this product can be formulated as the cycloadduct **4** in racemic form, resulting from a regioselective NEDDA process involving the C(6)=C(7) double bond of DNBF as the dienophile contributor. Strong support for the regioselectivity of the condensation comes from $^{15}N$ labelling of the 4- and 6-$NO_2$ groups in **4**. In this instance, only the H(5) proton appears to be coupled with both $^{15}N$ atoms [$J_{N(4)H(5)} = 3.1$ and $J_{N(6)H(5)} = 0.7$ Hz]. Interestingly, the $^1H$ NMR spectra of **4**, recorded in $CDCl_3$, consisted of only one set of signals, indicating that the reaction is also diastereoselective and affords only the cycloadduct resulting from an *endo* condensation, as will be confirmed in the second step. In contrast with Kresze and Bathelt's finding that the addition of butadiene to DNBF eventually afforded the diadduct **2** within a few weeks at low temperature,[11] further reaction of **3** with **4** to give the related bis-NEDDA adduct did not occur in our case.

Most interestingly, we found that a second cycloaddition process takes place readily on treatment of **4** with vinyl ethyl ether **5** (Scheme 1). In this cycloaddition process, the DNBF moiety does not act as a dienophile but clearly as a heterodiene, according to an IEDDA process, to give the dihydrooxazine *N*-oxide **6**‖ in 92% yield. As found for the formation of **4**, the reaction is highly stereoselective, affording only the diastereomer **6**, shown in Scheme 1, whose stereochemistry could be safely attributed *via* $^1H$ NMR and NOE experiments in solution. A determination of the crystallographic structure of **6** by X-ray analysis** confirmed the consecutive NEDDA and the IEDDA



**Scheme 1** *Reagents and conditions*: i, 1-trimethylsilyloxybuta-1,3-diene **3** (50 equiv., no solvent), 84%; ii, vinyl ethyl ether **5** (50 equiv., no solvent), 92%

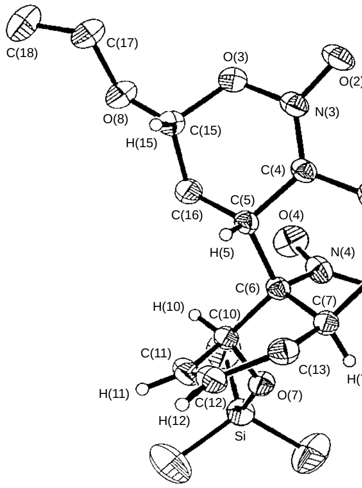
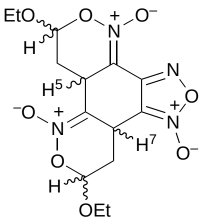


**Fig. 1** ORTEP view of **6** (only one enantiomer is represented). Bond lengths (Å): C(4)–N(3) 1.321(3), C(6)–N(4) 1.544(3), C(15)–O(3) 1.476(3), C(15)–O(8) 1.360(3), N(3)–O(2) 1.245(2), N(3)–O(3) 1.404(3), N(4)–O(4) 1.215(3), N(4)–O(5) 1.208(3).

additions as well as the stereochemistry assignment in the solid state (Fig. 1). This ORTEP view shows that H(7), the 6-$NO_2$ group and the $OSiMe_3$ substituent are located on the same side of the molecule, *trans* to both H(5) and H(15). This clearly indicates that both Diels–Alder condensations proceed through *endo* processes which take place *via* consecutive *trans* addition.

Such nitro group participation has previously been observed in the reaction of DNBF with indene.[12] Recently, we found that direct treatment of DNBF with **5** affords the bis(dihydrooxazine *N*-oxide) adduct **7**.[13] In this instance, both experimental and theoretical studies indicated that **7** was the result of two consecutive IEDDA processes involving the 4-$NO_2$ and 6-$NO_2$ heterodienyl moieties of DNBF, respectively.[13,14] In the present work we extend considerably the scope of the reactivity of DNBF by showing that this compound may also be consecutively involved in NEDDA and IEDDA cycloadditions to give a functionalised diadduct which is formed with high stereoselectivity. Interestingly, this ambident reactivity of DNBF in Diels–Alder condensations is a feature of general significance, being a promising new approach to synthesis in heterocyclic chemistry. Also such behaviour is in itself evidence that DNBF has a low resonance energy, a feature which has been commonly accepted but has not yet been specifically addressed.[1]



**7**

Further experimental and theoretical work towards a better understanding of how one can modulate the dienophile or heterodiene behaviour of DNBF with respect to the structure of the opposed electron-rich substrate is currently underway.

## Notes and References

† E-mail: vichard@chimie.uvsq.fr

‡ E-mail: halle@chimie.uvsq.fr

§ E-mail: terrier@chimie.uvsq.fr

¶ *Synthetic procedure* for **4**: 2 ml of 1-trimethylsilyloxybuta-1,3-diene (11.4 mmol) were added to 48 mg of DNBF (0.212 mmol) charged in a tube. The mixture was maintained under stirring at room temperature for 30 mn. A pale yellow precipitate rapidly appeared. The precipitation was complete after addition of a large excess of pentane. The precipitate was isolated by centrifugation, washed with pentane and dried *in vacuo* (84%). For **6**: A similar procedure was applied, under 4 h stirring in the presence of vinyl ether ether (92%). A single crystal was obtained by slow diffusion of pentane into a THF solution of **6**.

‖ *Selected data* for **4**: $\delta_H$(300 MHz, $CDCl_3$) 0.13 [s, 9 H, $OSi(CH_3)_3$], 1.93 (ddt, 1 H, H-13b, $J_{11-13b}$ 2.3, $J_{12-13b}$ 3.2, $J_{13a-13b}$ 19.2, $J_{7-13b}$ 9.2), 3.03 (dddd, 1 H, H-13a, $J_{11-13a}$ 1.7, $J_{12-13a}$ 3.7, $J_{7-13a}$ 8.0), 4.40 (dt, 1 H, H-7, $J_{5-7}$ 1.0), 4.88 (d, 1 H, H-10, $J_{10-11}$ 5.4), 5.99 (ddt, 1 H, H-11, $J_{11-12}$ 9.9), 6.07 (dt, 1 H, H-12), 7.33 (d, 1 H, H-5); mp 148 °C (decomp.); *m*/*z* (electrospray) 391.1 $(M + Na)^+$. For **6**: (Found C, 46.58; H, 5.36; N, 12.73. $C_{17}H_{24}SiN_4O_8$ requires C, 46.36; H, 5.45; N, 12.73%) $\delta_H$(300 MHz, $CDCl_3$) 0.11 [s, 9 H, $OSi(CH_3)_3$], 1.28 (t, 3 H, $CH_3$, $J_{H17-H18}$ 7.2), 2.19 (m, 1 H, H-13b, $J_{13a-13b}$ 19.8, $J_{7-13b}$ 9.9), 2.41 (ddd, 1 H, H-16b, $J_{16a-16b}$ 13.4, $J_{5-16b}$ 7.5, $J_{15-16b}$ 3.0), 2.80 (ddd, 1 H, H-16a, $J_{5-16a}$ 10.3, $J_{15-16a}$ 7.4), 3.10 (ddd, 1 H, H-13a, $J_{12-13a}$ 2.3, $J_{13a-7}$ 8.1), 3.35 (dd, 1 H, H-5), 3.76 (dq, 1 H, H-17a-b, $J_{H17a,b}$ 9.5), 4.06 (dq, 1 H, H-17a-b), 4.18 (dd, 1 H, H-7), 4.71 (m, 1 H, H-10), 5.56 (dd, 1 H, H-15), 5.95 (m, 2 H, H-11 and -12); mp 187 °C (decomp.); *m*/*z* (electrospray) 441.3 $(M + H)^+$, 463.0 $(M + Na)^+$, 479.0 $(M + K)^+$.

** *Crystal data* for **6**: $C_{17}H_{24}SiN_4O_8$, $M$ = 440.5, monoclinic, space group $P2_1/c$ (no. 14), $a$ = 12.2186(3), $b$ = 7.1267(1), $c$ = 24.5675(2) Å, $\beta$ = 98.979(1)°, $U$ = 2113.08(6) Å$^3$, $Z$ = 4, $D_c$ = 1.385 g.cm$^{-3}$, $\mu$(Mo-K$\alpha$) = 1.63 cm$^{-1}$, $\lambda$ = 0.71073 Å, graphite monochromator, crystal dimensions: 0.3 × 0.12 × 0.04 mm. The data were collected up to $2\theta = 62°$ on a Siemens SMART three-circle diffractometer equipped with a bidimensional CCD detector. The exposure time was 60 s by frame. A total of 15 314 reflections corresponding to the whole reciprocal space were collected of which 6197 were unique ($R_{int}$ = 0.0546) with $I \geqslant 2\sigma(I)$. The data were corrected for absorption effects by the SADABS program (G. Sheldrick, unpublished) specific to the CCD detector. The structure was solved by direct methods using SHELX-TL and the hydrogen atoms were located using geometrical constraints. Refinement (276 parameters) was performed by full-matrix least-squares analysis of SHELX-TL up to $R_1(F_o)$ = 0.0554 and $wR_2(F_o^2)$ = 0.1334. CCDC 182/777.

1 F. Terrier, in *Nucleophilic Aromatic Displacement*, ed. H. Feuer, VCH, New York, 1991, p. 18 and 138; E. Buncel, M. R. Crampton, M. J. Strauss and F. Terrier, in *Electron-Deficient Aromatic and Heteroaromatic Base Interactions*, Elsevier, Amsterdam, 1984, p. 166 and 296.
2 F. Terrier, E. Kizilian, J. C. Hallé and E. Buncel, *J. Am. Chem. Soc.*, 1992, **114**, 1740; F. Terrier, M. J. Pouet, J. C. Hallé, S. Hunt, J. R. Jones and E. Buncel, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1665; F. Terrier, F. Millot and W. S. Norris, *J. Am. Chem. Soc.*, 1976, **98**, 5883.
3 M. J. Strauss, R. A. Renfrow and E. Buncel, *J. Am. Chem. Soc.*, 1983, **105**, 2473; E. Buncel, R. A. Renfrow and M. J. Strauss, *J. Org. Chem.*, 1987, **52**, 488; E. Buncel, R. A. Manderville and J. M. Dust, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1019; E. Buncel, J. M. Dust and R. A. Manderville, *J. Am. Chem. Soc.*, 1996, **118**, 6072.
4 R. J. Spear, W. P. Norris and R. W. Read, *Tetrahedron Lett.*, 1983, **23**, 1555; W. P. Norris, R. J. Spear and R. W. Read, *Aust. J. Chem.*, 1989, **36**, 297.
5 J. Kund and H. J. Niclas, *Synth. Commun.*, 1993, **23**, 1569; H. J. Niclas, B. Göhrmann and E. Gründemann, *ibid*, 1991, **333**, 909.
6 F. Terrier, E. Kizilian, J. C. Hallé, M. J. Pouet and E. Buncel, *J. Phys. Org. Chem.*, 1998, in the press.
7 F. Terrier, E. Kizilian, K. Gzouli, M. J. Pouet and J. C. Hallé, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2667.
8 F. Terrier, A. P. Chatrousse, Y. Soudais and M. Hlaibi, *J. Org. Chem.*, 1984, **49**, 4176.
9 M. J. Strauss, A. De Fusco and F. Terrier, *Tetrahedron Lett.*, 1981, **32**, 1945.
10 J. H. Atherton, M. R. Crampton, G. L. Duffield and J. A. Stevens, *J. Chem. Soc., Perkin Trans. 2*, 1995, 443.
11 G. Kresze and H. Bathelt, *Tetrahedron*, 1973, **29**, 1043.
12 P. Mac Cormack, J. C. Hallé, M. J. Pouet and F. Terrier, *J. Org. Chem.*, 1988, **53**, 4407.
13 J. C. Hallé, D. Vichard, M. J. Pouet and F. Terrier, *J. Org. Chem.*, 1997, **62**, 7178.
14 S. Pugnaud, D. Masure, J. C. Hallé and P. Chaquin, *J. Org. Chem.*, 1997, **62**, 8687.

*Received in Cambridge, UK, 13th January 1998; 8/00343B*