Ring opening and ring closure in an indolizine structure activated through S_NAr coupling with superelectrophilic 4,6-dinitrobenzofuroxan, an unusual intramolecular oxygen transfer from a N-oxide functionality

Sergey Kurbatov,[a] Artem Tatarov,[a] Vladimir Minkin,[a] Régis Goumont[b] and François Terrier*[b]

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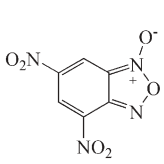
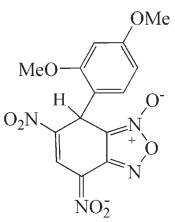
Coupling of superelectrophilic 4,6-dinitrobenzofuroxan with a π-excessive indolizine structure affords a strongly dipolar substitution product which undergoes a facile but unusual rearrangement induced by an intramolecular oxygen atom transfer from the N-oxide functionality of the DNBF moiety.

The last decade has witnessed a major new development in the field of electrophile–nucleophile combinations with the discovery of highly electron-deficient aromatic and heteroaromatic substrates such as nitrobenzoxadiazoles, nitrobenzotriazoles and related 10π-electron heterocycles.[1–4] Contrasting with 1,3,5-trinitrobenzene (TNB), the traditional aromatic electrophile reference, these new structures exemplified by 4,6-dinitrobenzofuroxan (DNBF) have been termed as superelectrophiles, being capable of reacting readily with weak nucleophiles.[5–9] As an illustration of this behaviour, DNBF undergoes facile carbon–carbon couplings with benzenoid aromatics *e.g.* anilines, polyhydroxy and alkoxybenzenes… or π-excessive heterocycles (pyrroles, indoles…) affording σ-adducts of type **1** or **2** exhibiting a high thermodynamic stability.[10–13]



DNBF



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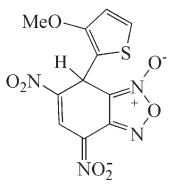

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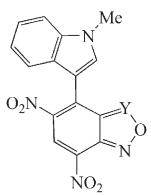
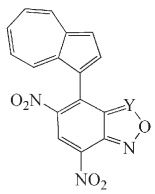
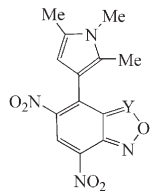
Recently, we have found that the remarkable propensity of nitrobenzofuroxans and related derivatives to react in σ-complexation processes extends to nucleophilic aromatic substitutions of the S_NAr type.[14] While only strong bases of $pK_a \geqslant 9$, *e.g.* 1,3,5-trispyrrolidinobenzene, react satisfactorily with picryl chloride,[15] the reactions of 7-chloro-4,6-dinitrobenzofurazan (DNBZ–Cl) and -benzofuroxan (DNBF–Cl) have been found to proceed smoothly at room temperature with such carbon bases as *N*-methylindole **3** ($pK_a = -2.32$), azulene **4** ($pK_a = -1.76$) and 1,3,5-trimethylpyrrole **5** ($pK_a = -0.49$) in ethanol, affording the related substituted products **S3–5a,b** in high yields.[14a] Importantly, these products exhibit an intense and solvent dependent UV-visible absorption at rather high wavelengths, *e.g.* λ_{max} = 664 nm for **S4b** in water, indicating that a strong intramolecular charge transfer is taking place between the π-system of the aromatic or heteroaromatic donor and the π-system of the benzofurazan or benzofuroxan acceptor, even though the full coplanarity of the two moities is precluded by steric effects.







Y= N **S3a** **S4a** **S5a**
Y= N^+-O^- **S3b** **S4b** **S5b**

In an attempt to maximize this charge transfer, we become interested in the couplings of DNBF–Cl and DNBZ–Cl with π-excessive structures of the indolizine-type whose carbon basicities, *e.g.* pK_a = 3.94 for unsubstituted indolizine,[16] lie in the range of that of the most basic pyrroles, *e.g.* pK_a = 3.75 for 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole).[17] While the reaction of DNBZ–Cl with 2-(4′-bromophenyl)indolizine **6** proceeded rapidly to give the expected substitution product **S6a**, we discovered rather unexpectedly that the analogous reactions with DNBF–Cl afforded the zwitterionic spiro adduct **8b** as the stable product. In this paper, we report on this unusual rearrangement which calls for an explanation based on an intramolecular oxygen transfer combined with ring opening and closure processes.

The ORTEP view in Fig. 1 shows that the reaction of DNBZ–Cl with 2-(4′-bromophenyl)indolizine **6** produced the substituted product **S6a**, presumably through a S_NAr–S_EAr coupling pathway involving the Wheland–Meisenheimer intermediate **7a**, as described for the reactions of this benzofurazan substrate with **3–5** (Scheme 1).

^1H and ^{13}C NMR data as well as the mass spectrometry and elemental analysis data are in full agreement with the structure of **S6a**.† This compound is a highly colored molecule with an absorption maximum λ_{max} = 780 nm in $CHCl_3$, pointing to an intense charge transfer from the donor indolizine moiety to the 4,6-dinitrobenzofurazanyl acceptor moiety (resonance structure **S′6a**).

As a matter of fact, the NO_2 group at $C_{6'}$ in **S6a** is twisted by only 26° from the plane of the benzofurazan skeleton and the length of the C_3–$C_{7'}$ bond is 1.427 Å, *i.e.* this bond is markedly

[a]*Department of Chemistry, Rostov State University, 7, Zorge St., 344090 Rostov-on-Don, Russia*
[b]*Institut Lavoisier, UMR 8180, University of Versailles, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France. E-mail: terrier@chimie.uvsq.fr*

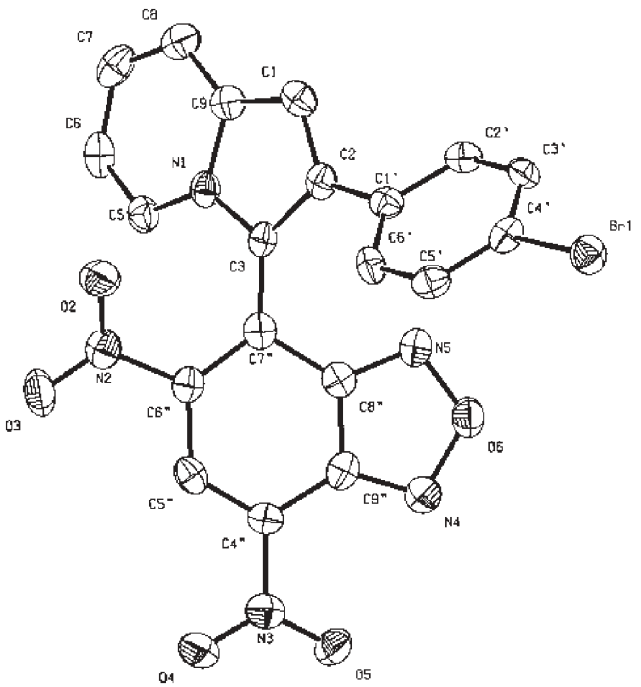
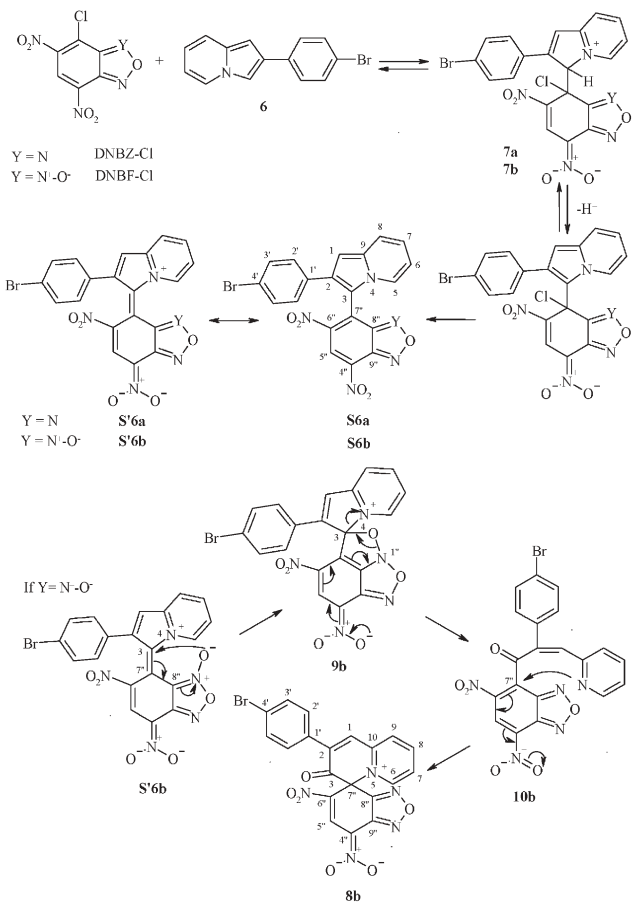


Fig. 1 ORTEP view of **S6a**.



Scheme 1

olefinic in nature. Accordingly, through conjugation between the two moieties is operating to a large extent. This is evidenced in particular by the strong shift to low-field of the ^{1}H resonance caused by the substitution of the indolizine partner (δ = 6.75 ppm in **6** and δ = 7.15 ppm in **S6a**). Atoms of the ORTEP representations are shown as thermal displacement ellipsoids at the 60% level.

A totally different pattern is observed for the DNBF–Cl–2-(4′-bromophenyl)indolizine system (Scheme 1). The ORTEP view in Fig. 2 shows that the dark purple solid obtained from the interaction is the zwitterionic adduct **8b**. As the first peculiarity of this structure, there is the loss of the N-oxide functionality and the overall conversion of the starting dinitrobenzofuroxan moiety into a negatively charged dinitrobenzofurazan one. A second noteworthy feature is that this conversion goes along with a skeleton rearrangement of the indolizine moiety, leading eventually to a C–N spiro σ-adduct.[2a]

A possible mechanism accounting for the overall formation of **8b** is outlined in Scheme 1. It is based on the reasonable assumption that DNBF–Cl reacts initially as its DNBZ analogue to afford the S_NAr–S_EAr substitution product **S6b**, *i.e.* the same behaviour as observed in the reactions of DNBF–Cl and DNBZ–Cl with **3–5**. Interestingly, a rapid recording of the spectra after mixing of the reagents has allowed the ^{1}H NMR characterization of this now short lived species. Then, a key point is the large intramolecular charge transfer occuring between the donor and acceptor moieties of **S6b**. This transfer has the effect of generating a positively charged indolizinium moiety (resonance structure **S′6b**), thereby favoring nucleophilic attack at the electron-deficient C_3 center by the negatively charged oxygen atom of the N-oxide

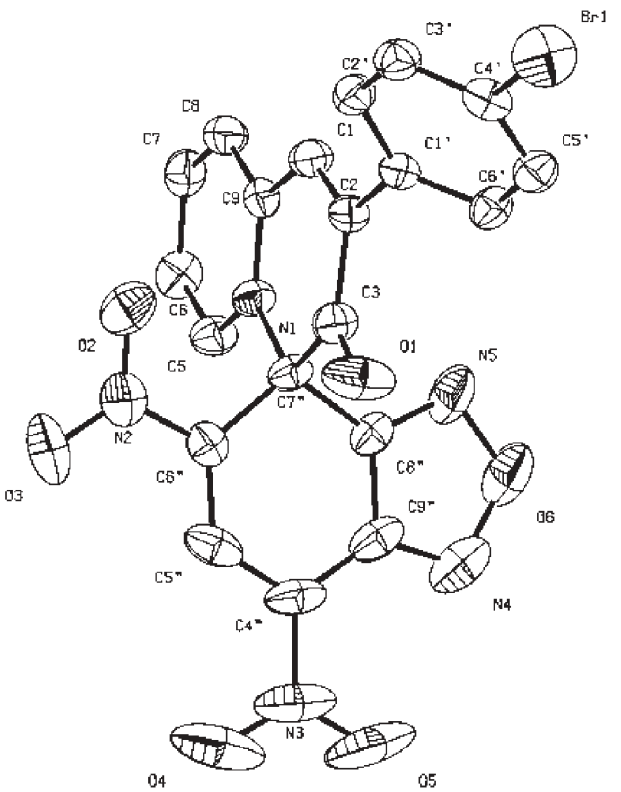


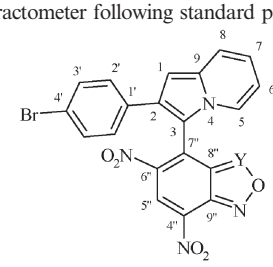
Fig. 2 ORTEP view of **8b**.

functionality. The result will be the formation of a five-membered ring (structure **9b**) which is prone to undergo $N_{1''}$–$O_{1''}$ and C_3–N_4 bond breakings, presumably through a concerted process, to afford the 7-substituted-4,6-dinitrobenzofurazan **10b**. Reflecting the superelectrophilic character of the 4,6-dinitrobenzofurazan structure, the weakly basic pyridine nitrogen atom readily adds covalently to $C_{7''}$, leading to the spiroadduct **8b**. In this regard, it has long been recognized that the formation of this type of σ-complexes is both thermodynamically and kinetically very much favored compared to that of analogous σ-complexes arising from intermolecular processes.[1,2,8,18,19]

Besides the novelty of the observed oxygen transfer from the N-oxide group, the reaction mechanism depicted in Scheme 1 includes two other remarkable features in terms of organic reactivity. The first is the major role played by the strong intramolecular charge transfer occuring in the S_NAr product **S6b** in promoting nucleophilic attack of the C_3 center by the N-oxide group and therefore, the overall rearrangement induced by the oxygen transfer. On the other hand, a large variety of Meisenheimer spiro adducts have been reported but no example is known to us of a spiro adduct derived from the combination of a C–C and a C–N coupling.

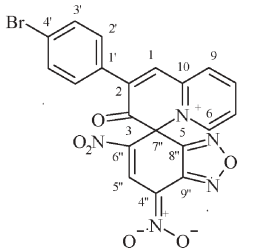
Notes and references

† *General procedure*: to a solution of 2-(4′-bromophenyl)indolizine[16b] (0.5 mmol, 136 mg) in chloroform (10 ml) at room temperature was added one equivalent of DNBF–Cl or DNBZ–Cl. The solution turned rapidly green and the reaction mixture was stirred at room temperature for one hour. The precipitate was collected by filtration and washed with chloroform. X-ray data were collected on a Bruker SMART CCD diffractometer following standard procedures.[20]



Y = N : **S6a**

Y = N^+-O^- : **S6b**



8b

S6a: dark blue solid; yield 87%; mp 278 °C; EI MS: *m*/*z* 339 $[M]^+$. Anal. Calc. for $C_{20}H_{10}BrN_5O_5$: C, 50.02; H, 2.10; N, 14.58. Found: C, 49.83; H, 2.02; N, 14.83%. ^{1}H NMR ($(CD_3)_2CO$, δ (ppm)): 9.25 (1H, $H_{5''}$, s), 8.14 (1H, H_5, d, $^3J_{5/6}$ 7.0 Hz), 7.79 (1H, H_8, d, $^3J_{8/7}$ 8.8 Hz), 7.38 (2H, $H_{2'}$, d, $^3J_{2',3'}$ 7.8 Hz), 7.28 (2H, $H_{3'}$, d, $J_{2',3'}$ 7.8 Hz), 7.24 (1H, H_7, dd, $^3J_{7/8}$ 8.8, $^3J_{7/6}$ 6.8 Hz), 7.06 (1H, H_1, s), 6.91 (1H, H_6, dd, $^3J_{6/7}$ 6.8, $^3J_{6/5}$ 7.0 Hz). ^{13}C NMR ($(CD_3)_2SO$, δ (ppm)): 151.4 ($C_{8''}$), 143.5 ($C_{9''}$), 137.8 (C_9), 134.0 ($C_{1'}$), 133.3 ($C_{7''}$). 133.0 ($C_{6''}$), 131.7 ($C_{2'}$), 130.6 ($C_{3'}$), 130.5 ($C_{4'}$), 129.1 ($C_{5''}$), 126.2 (C_5), 123.9 ($C_{4''}$), 122.8 (C_7), 119.4 (C_8), 113.4 (C_6), 112.2 (C_2), 104.7 (C_3, C_1). Crystal data for **S6a** $C_{20}H_{10}BrN_5O_5$, M = 480.24, T = 100(2) K, tetragonal, space group $I4_1/a$, a = 30.5756(10), b = 30.5756(10), c = 7.8321(4) Å, α = 90, β = 90, γ = 90°, V = 7322.0(5) Å^3, ρ_{calc} = 1.743 mg m^{-3}, μ = 2.294 mm^{-1}, Z = 16, reflections collected: 35505, independent reflections: 5019 (R_{int} = 0.0792), final R indices [for 4082 reflections with $I > 2\sigma(I)$]: $R1$ = 0.0329, w$R2$ = 0.0484, R indices (all data): $R1$ = 0.0439, w$R2$ = 0.0502. CCDC 607711.

S6b (transient species): ^{1}H NMR ($CDCl_3$, δ (ppm)): 9.07 (1H, $H_{5''}$, s), 7.68 (1H, H_5, d, $^3J_{5/6}$ 6.8 Hz), 7.46 (m, 3H: 1H, d, H_8, $^3J_{8/7}$ 8.6 Hz and 2H, $H_{2'}$, d, J 7.7 Hz), 7.32 (1H, H_7, dd, $^3J_{7/8}$ 8.6, $^3J_{7/6}$ 6.5 Hz), 7.10 (2H, $H_{3'}$, d, 7.7 Hz), 6.96 (1H, H_6, dd, $^3J_{6/7}$ 6.5, $^3J_{6/5}$ 6.8 Hz), 6.88 (1H, H_1, s).

8b: dark purple solid; yield 78%; mp 204 °C. Anal. Calc. for $C_{20}H_{10}BrN_5O_6$: C, 48.41; H, 2.03; N, 14.11. Found: C, 48.27; H, 1.96; N, 14.31%. ^{1}H NMR ($(CD_3)_2SO$, δ (ppm)): 9.17 (1H, H_5, d, $^3J_{5/6}$ 6.6 Hz), 9.13 (1H, $H_{5''}$, s), 8.76 (1H, H_7, dd, $^3J_{7/8}$ 8.8, $^3J_{7/6}$ 6.8 Hz), 8.69 (1H, H_1, s), 8.53 (1H, H_8, d, $^3J_{8/7}$ 8.8 Hz), 8.03 (1H, H_6, dd, $^3J_{6/7}$ 6.8, $^3J_{6/5}$ 6.6 Hz), 7.74 (2H, $H_{2'}$, d, $J_{2',3'}$ 7.8 Hz), 7.64 (2H, $H_{3'}$, d, $J_{2',3'}$ 7.8 Hz). ^{13}C NMR ($(CD_3)_2SO$, δ (ppm)): 185.2 (C_3), 149.5 ($C_{8''}$), 148.2 (C_7), 145.9 (C_5), 143.7 ($C_{9''}$), 142.6 (C_9), 136.2 ($C_{1'}$), 135.4 ($C_{5''}$), 134.4 (C_1), 131.8 ($C_{3'}$), 130.9 (C_8, $C_{2'}$), 130.2 (C_2), 129.1 (C_6), 124.6 ($C_{4'}$), 121.6 ($C_{6''}$), 111.7 ($C_{4''}$), 71.9 ($C_{7''}$). Crystal data for **8b** $C_{20}H_{10}BrN_5O_6$, M = 496.24, T = 293(2) K, monoclinic, space group $P2_1/n$, a = 7.1510(14), b = 19.421(4), c = 14.006(3) Å, α = 90, β = 102.22(3), γ = 90°, V = 1901.1(7) Å^3, ρ_{calc} = 1.734 mg m^{-3}, μ = 2.215 mm^{-1}, Z = 4, reflections collected: 4561, independent reflections: 4104 (R_{int} = 0.0342), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0480, w$R2$ = 0.1055, R indices (all data): $R1$ = 0.1274, w$R2$ = 0.1263. CCDC 607710. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608350a

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