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Superelectrophilicity of the Nitroolefinic Fragment of 4-Nitrobenzodifuroxan in Michael-Type Reactions with Indoles: A Kinetic Study in Acetonitrile

Sami Lakhdar,[b] Régis Goumont,[a] Guillaume Berionni,[a] Taoufik Boubaker,[b] Sergey Kurbatov,[c] and François Terrier*[a]

Abstract: The kinetics of the coupling of 4-nitrobenzodifuroxan (NBDF) with a series of indoles **8a–e** to give the expected Michael-type adducts **9a–e** have been investigated in acetonitrile solution. No significant influence of the nature of the isotopic substitution at C-3 of the indole ring has been found, indicating that the NBDF addition step is the rate limiting step of the S_EAr substitution of the indole moiety. This implies that the measured second-order rate constants (k) for the reactions are identical to the second order rate constants (k_1^{NBDF}) associated to the C–C coupling step. By using the known N and s parameters characterizing the nucleophilicity of indoles, the k_1^{NBDF} rate constants are found to fit nicely to the three parameters equation $\log k_1 = s(N+E)$ introduced by Mayr to describe the feasibility of nucleophilic–electrophilic combinations. Based on this, the electrophilicity parameter E of NBDF could be determined as $E = -6.15$. This corresponds to a positioning of the reactivity of the nitroactivated double bond of NBDF in the domain of superelectrophilicity previously defined for nitrobenzofuroxans, in accord with the finding that the rates of coupling of **8a–e** with NBDF are only one order of magnitude lower than those for the coupling of these indoles with 4,6-dinitrobenzofuroxan (DNBF). The theoretical scale of electrophilicity introduced by Domingo et al. on the basis of the global electrophilicity index ω defined by Parr is also a very useful tool to discuss the relative reactivities of NBDF, DNBF, and a number of differently activated C=C double bonds.

Keywords: indoles · Michael addition · nitrobenzofuroxans · structure–activity relationships · superelectrophilicity

Introduction

A major new development in the area of electron-deficient aromatics in the last two decades is the discovery of very powerful electrophilic heteroaromatic structures, such as 4,6-dinitrobenzofuroxan (DNBF).[1–3] The latter prototype compound undergoes σ-complex formation with extremely weak carbon nucleophiles such as benzenoid aromatics (aniline, phenols) or π-excessive heterocycles, for example, pyrroles, indoles, thiophenes, furans, aminothiazoles etc.[4–11] Quantitative evaluation of thermodynamic reactivity is nicely provided by a comparison of the pK_a values for water addition. The pK_a value for formation of the hydroxy adduct **1** is 3.75 at 25 °C in aqueous solution, as compared with a pK_a value of 13.43 for formation of the analogous adduct **2** of 1,3,5-trinitrobenzene (TNB),[3a] the conventional aromatic electrophile in σ-complex chemistry.[1,12] Recently, we applied the methodology of Mayr to the assessment of the intrinsic reactivity E of DNBF.[11] By reaction with a series of reference nucleophiles, the reactivity of this neutral compound was found to fit nicely to the three parameters [Eq. (1)] successfully developed by Mayr to describe the rates of a large variety of nucleophile–electrophile combinations.[11,13] In this equation, the E parameter measures the strength of the electrophile while the N and s parameters characterize the sensitivity of the nucleophile.[11,13] With an E value of -5.06, DNBF exhibits a reactivity that compares well with that of the 4-nitrobenzenediazonium cation ($E = -5.10$), approaching in fact that of the tropylium cation

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[a] Prof. R. Goumont, G. Berionni, Prof. F. Terrier
Institut Lavoisier de Versailles, UMR 8180
Université de Versailles, 45 Avenue des Etats-Unis
78035 Versailles Cedex (France)
Fax: (+33) 139-254-452
E-mail: terrier@chimie.uvsq.fr

[b] Dr. S. Lakhdar, Dr. T. Boubaker
Unité de Recherche de Physico-Chimie Moléculaire
Faculté des Sciences de Monastir
Avenue de l'Environnement
5019 Monastir (Tunisie)

[c] Dr. S. Kurbatov
Department of Chemistry, Rostov State University
7 Zorge St., 344090 Rostov-on-Don (Russia)

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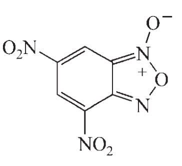
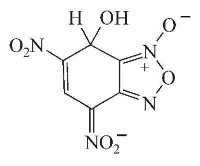


DNBF



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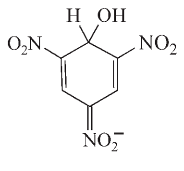

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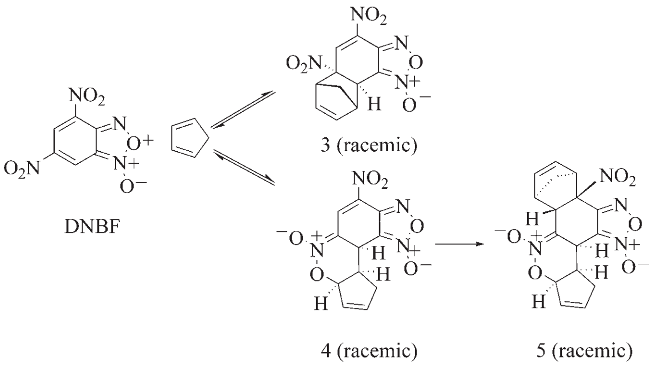
family ($E \approx -3$ to -6) as well as a number of metal coordinated carbenium ions.[13]

$$\log k(20\,^\circ\mathrm{C}) = s(N + E) \qquad (1)$$

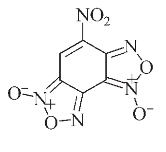
Of equal interest, however, is that DNBF has also been found to undergo a variety of Diels–Alder reactions, a behavior which is in itself evidence that the carbocyclic ring of this superelectrophilic heterocycle has a poor aromatic character relative to TNB.[14–16] As illustrated in Scheme 1,



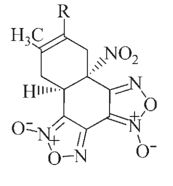
Scheme 1. Reactivity of DNBF with cyclopentadiene.

DNBF can formally behave as do nitroalkenes,[17,18] being susceptible to act as a dienophile in normal electron-demand (NED) Diels–Alder processes as well as a heterodiene in inverse electron-demand (IED) Diels–Alder processes. In Scheme 1, the reaction initially affords a mixture of the two stereoselective NED and IED adducts **3** and **4**.[15a] Because the remaining nitroolefinic fragment of the monoadducts is also very reactive, diadduct formation subsequently occurs, proceeding with high stereoselectivity to give the highly functionalized structure **5** as the thermodynamically stable product of the reaction.[15a]

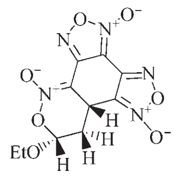
Evidence that the pericyclic behavior of DNBF is reminiscent of that of nitroolefins prompted us to look at the potential reactivity of the single nitro-activated double bond of the related 4-nitrobenzodifuroxan (NBDF) molecule. As anticipated, we recently reported that this peculiar nitroolefin behaves as a versatile Diels–Alder reagent, reacting for example with isoprene and 2,3-dimethylbutadiene to give exclusively the NED monoadducts **6a** and **6b** (in their racemic forms) and with ethyl vinyl ether to afford a 95:5 mixture of the *endo* and *exo* IED adducts **7a** and **7b**.[19] Of further interest, we also discovered that NBDF is capable of reacting with very weak carbon nucleophiles in Michael-type processes, undergoing, in particular, a facile addition of indoles **8a–e** to give **9a–e** according to Equation (2).[19a] The *trans* stereochemistry of **9a–e** was established by means of the X-ray structure of the 5-methoxyindole compound **9b**.[19a]



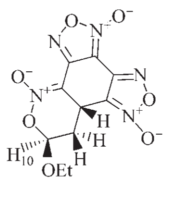
NBDF



R = H, **6a** (racemic)
R = CH_3, **6b** (racemic)

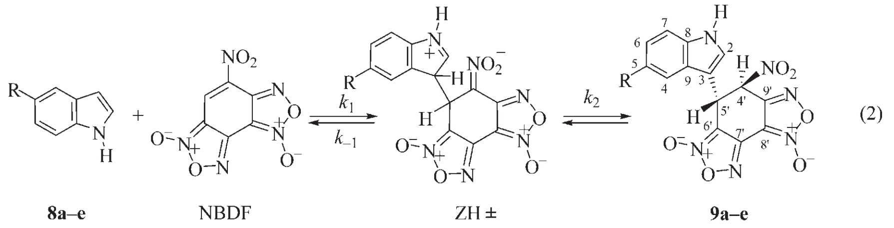


7a (racemic, *endo*)



7b (racemic, *exo*)

In this paper, we report a detailed kinetic investigation of the coupling reactions shown by Equation (2) in acetonitrile. As will be seen, the results obtained revealed that NBDF is several orders of magnitude more reactive than all previously studied activated olefins, including common nitroalkenes, making it reasonable to view this compound as a superelectrophilic olefin.



a: R = NH_2
b: R = OMe
c: R = Me
d: R = H
e: R = Cl

Results and Discussion

The rates of reactions, as depicted in Equation (2), were measured at 20 °C in acetonitrile, following the disappearance of NBDF at $\lambda_{max} = 355$ nm, for which neither the parent indoles **8a–e** nor the resulting Michael adducts **9a–e** have a notable absorption, by conventional or stopped-flow spectrophotometry. All experiments were carried out under first-order conditions with a $3–5 \times 10^{-5}$ M concentration of the electrophile and a large excess ($10^{-3}–5 \times 10^{-2}$ M) of the indole nucleophile.

Figure 1 refers to the NBDF/**8d** system to show that the absorption changes associated with the formation of the adducts **9a–e** are characterized by the presence of two clean isobestic points (at $\lambda = 305$ and $\lambda_{max} = 295$ nm for **9d**). As illustrated in Figure 2, these absorption changes go along with oscilloscope traces consisting of a unique first order relaxation process corresponding to the formation of **9a–e**.

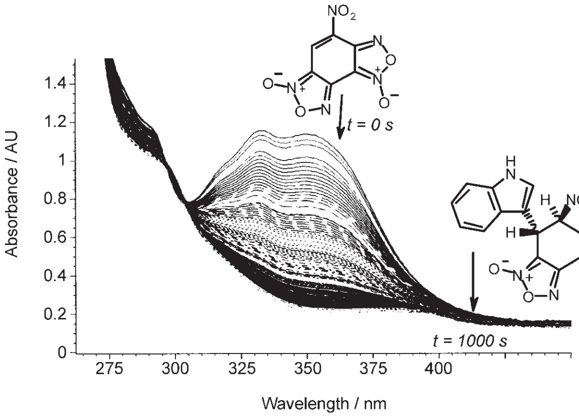


Figure 1. UV/visible spectra showing the formation of the adduct **9d**, resulting from the reaction of NBDF (3×10^{-5} M) with indole **8d** (2×10^{-3} M) at $T = 20$ °C in acetonitrile.

In Equation (2), the formulation of the formation of **9a–e** in terms of a two-step addition–rearomatization sequence is based on the fact that these Michael adducts are formally the products of S_EAr substitution at C-3 of the indole moiety. That S_EAr substitutions of indoles take place preferentially at C-3 rather than C-2 of the five-membered ring is a well-documented regioselectivity behavior.[20–22] On these grounds, the general expression for the observed first-order rate constant, k_{obsd}, for the formation of **9a–e** as described under the assumption that the zwitterions $ZH^{\pm}$ are low-concentration intermediates is given by:

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2}[\mathbf{8a-e}] = k[\mathbf{8a-e}] \quad (3)$$

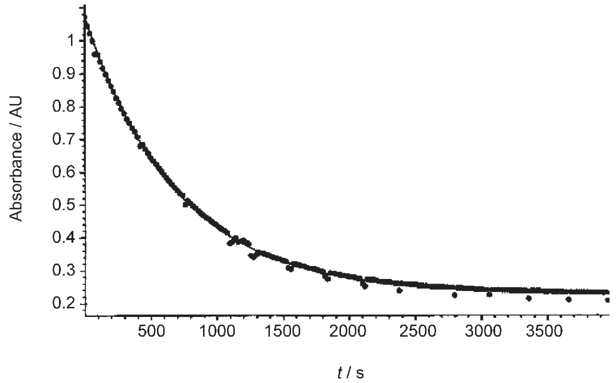


Figure 2. Oscilloscope picture showing the unique relaxation process observed in the reaction of NBDF (3×10^{-5} M) with **8c** (2×10^{-3} M) at $T = 20$ °C in acetonitrile at $\lambda = 360$ nm.

In accordance with Equation (3), excellent straight lines with zero intercept were obtained for all systems when the k_{obsd} values (Tables S1–S5 in the Supporting Information) were plotted versus the indole concentration (Figure 3). Determination of the second-order rate constant k from the slopes of these lines was therefore straightforward. These rate constants are summarized in Table 1.

Importantly, the reactions could also be kinetically investigated with 3-deuterated indoles, namely, $[D_3]$-5-methoxyin-

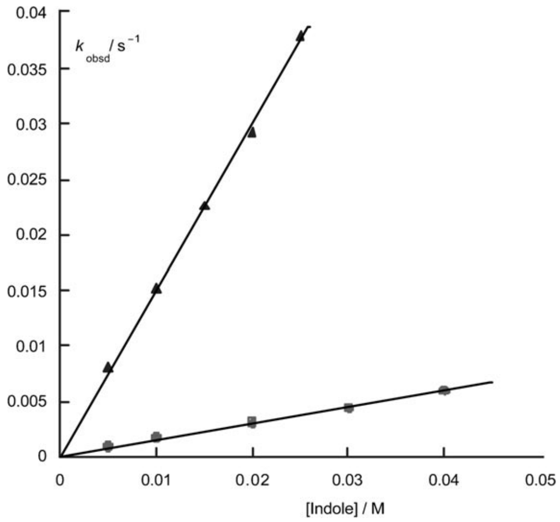


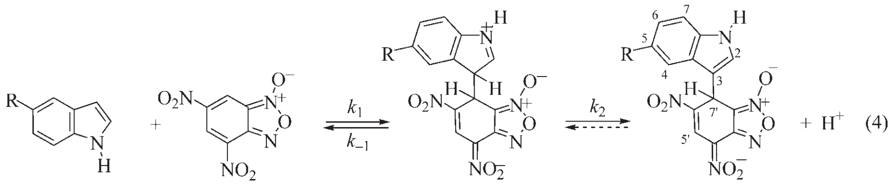
Figure 3. Effect of the concentration of indoles **8b** (▲) and **8d** (●) on the observed rate of formation of the NBDF adducts **9b** and **9d** at $T = 20$ °C in acetonitrile.

Table 1. Second order rate constants k_1 for the addition of indoles **8a–e** to NBDF and DNBF in acetonitrile solution.[a]

Indole	pK_a^{H2O}[b]	N[c]	k_1^{NBDF} [$M^{-1}s^{-1}$]		k_1^{DNBF} [$M^{-1}s^{-1}$][e]	$\frac{k_1^{DNBF}}{k_1^{NBDF}}$
8a	−1.76	7.22	13.80	–	235	17.02
8b	−2.90	6.22	1.47	1.42[d]	20.84	14.17
8c	−3.30	6.00	0.78	0.69[d]	10.71	13.73
8d	−3.46	5.55	0.142	0.138[d]	2.29	16.12
8e	−4.53	4.42	0.011	0.010[d]	0.20	18.18

[a] $T = 20$ °C. [b] pK_a values for C-3 protonation of indoles taken from references [10], [21], and [25]. [c] N values taken from reference [10]. [d] Second-order rate constants k_1 for 3-deuteriated indoles. [e] Data from reference [10].

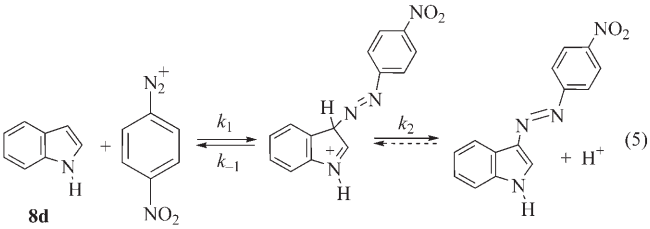
dole ([D$_3$]**8b**), [D$_3$]-5-methylindole ([D$_3$]**8c**), [D$_3$]indole ([D$_3$]**8d**), and [D$_3$]-5-chloroindole ([D$_3$]**8e**).[23] While exhibiting similar general features, the experiments did not reveal a significant influence of the nature of the isotopic substitution at C-3 on the rates of adduct formation. With experimental k_H/k_D ratios being in the range of 1.03–1.13 (see Table 1), there is little doubt that electrophilic addition of NBDF to the indole reagent is the rate-limiting step in Equation (2) in acetonitrile, that is, we have $k_2 \gg k_{-1}$, so that the second-order rate constant k is identical to the second-order rate constant k_1 for the C−C coupling step. As a matter of fact, the situation is similar to that observed for the σ-complexation reactions of DNBF with indoles in various solvents [Eq. (4)], including acetonitrile.[3c,d,10] It is also reminiscent of that which prevails in the majority of aromatic or heteroaromatic electrophilic substitution reactions in which the formation of the Wheland–Meisenheimer-type intermediates (here ZH$^{\pm}$) is rate determining.[20,21,25] In line with this behavior, Jackson and Lynch have reported that the initial attack of the electrophile is rate limiting in the coupling of a number of indoles with the *p*-nitrobenzenediazonium cation.[21b]



8a–e **DNBF** ZH ± **10a–e**

Prior to a discussion of the rate data in Table 1, it must be emphasized regarding the 5-aminoindole system that no kinetic and structural evidence (see the Experimental Section) could be obtained for even a minor competitive attack of NBDF onto the amino group of **8a**. Such a situation is not unprecedented, however, as exclusive preferences for a C−C rather than a C−N coupling has been recently found in different systems. These include not only the reaction of DNBF with **8a**,[3d,10] but also the reactions of this electrophile with 3-aminothiophenes and 2-aminothiazoles.[3f,7c]

Available data allow a comparison to be made of the electrophilic reactivity of NBDF with that of DNBF for which reactions with a large set of indoles, including **8a–e**, to give the σ-adducts **10a–e** have been kinetically studied in acetonitrile [Eq. (4)].[10,11] As can be seen in Table 1, the k_1^{DNBF} rate constants for DNBF σ-complexation are about 15 times greater than the related k_1^{NBDF}rate constants for NBDF addition to the indole ring. Interestingly, the $k_1^{\mathrm{ArN2+}}$ value for the diazo coupling of the unsubstituted indole **8d** with the *p*-nitrobenzenediazonium cation [Eq. (5)] has also been measured by Jackson and Lynch: $k_1^{\mathrm{ArN2+}} = 1.37\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ in acetonitrile.[21b] This value reveals that this positively charged species is slightly less reactive than neutral DNBF and only 10-fold more reactive than neutral NBDF. Altogether, the above figures demonstrate that NBDF is really one of the most powerful neutral electrophiles known to date.[13]



8d

A more precise assessment of the electrophilicity of NBDF can be obtained through the positioning of this substrate on the Mayr electrophilicity scale.[13] Equation (1) has been shown to describe nicely the reactivity of DNBF and other structurally related electron-deficient heteroaromatic substrates in σ-complexation processes.[10,11] On the other hand, the *N* and *s* parameters characterizing the nucleophilicity of a series of indoles, including **8a–e**, have become recently available.[10] By using these five indoles as reference nucleophiles, a nice linear correlation of a slope close to unity is in fact obtained when plotting the values of the (logk_1^{NBDF}/*s*) ratios against the nucleophilicity parameters, as expected from Equation (1) (Figure 4). From the intercept of the line with the ordinate axis, the electrophilicity parameter *E* of NBDF could be readily derived: $E = -6.15$. This leads to the positioning on the *E* scale shown in Figure 5.

The electrophilicity of a number of noncharged activated olefins consisting of the three arylidenemalonitriles **11a–c** and of various quinone methides (see Figure 5) have been determined.[13f,26,27] As revealed by Figure 5, the reactivity of

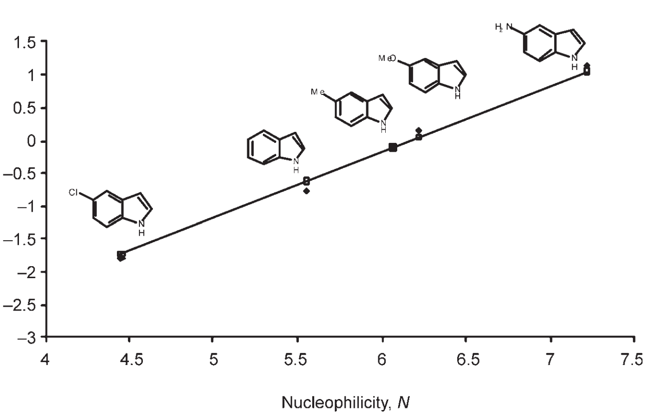


Figure 4. Plots of (logk_1)/*s* versus *N* for the reaction of NBDF with the indoles **8a–e** in acetonitrile solution.

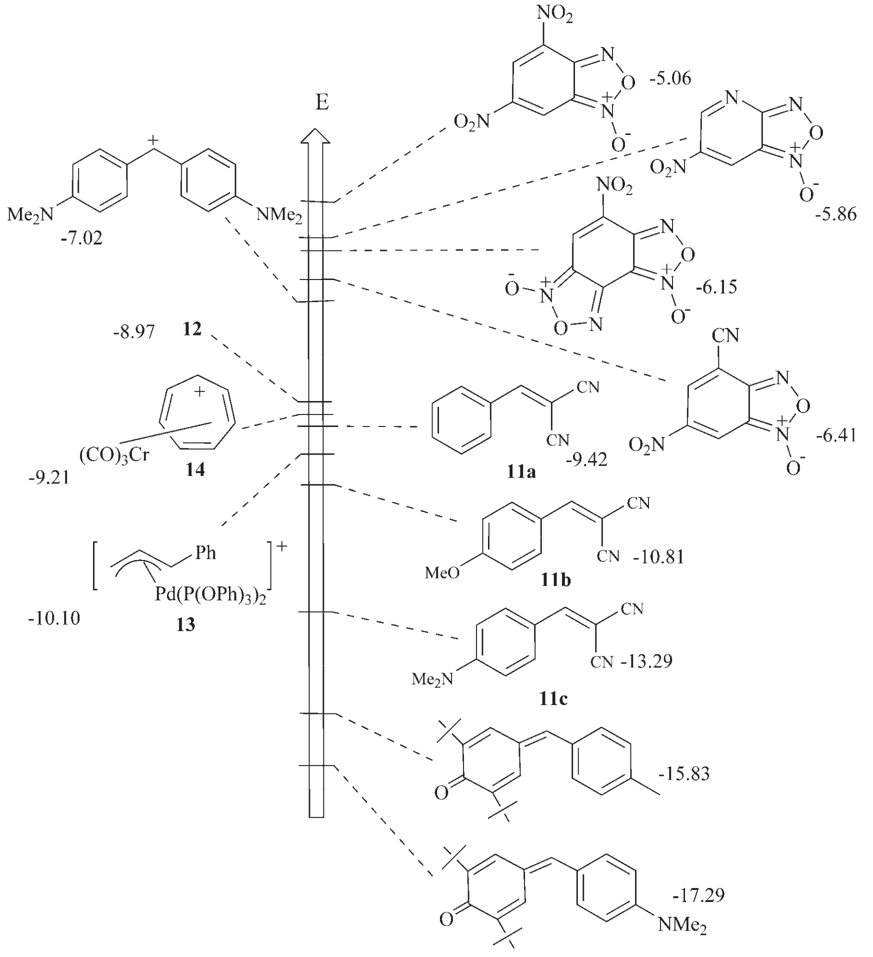
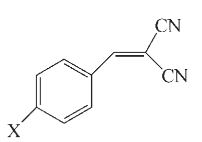
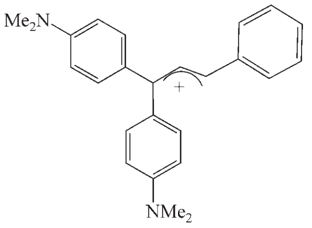


Figure 5. The ranking of NBDF and DNBF on the E scale, as defined by Mayr et al.[13]



11a: X = H
11b: X = OMe
11c: X=NMe$_2$



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all these compounds is considerably lower than that of NBDF. With an E value of -9.42, the most reactive arylidenemalonitrile studied, namely **11a**, is by more than three orders of magnitude less electrophilic than NBDF. In fact, the E value of NBDF falls only one E unit below that of DNBF, confirming the conclusion derived above from a direct comparison of the rates of reactions of Equations (2) and (4) which shows that the two compounds have relatively close electrophilicities.

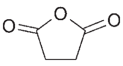
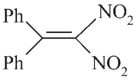
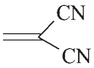
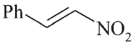
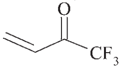
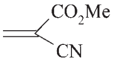
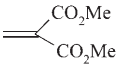
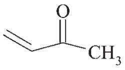
Returning to Figure 5, it is to be noted that the electrophilicity of NBDF appears to be intermediate between those of 4-aza-6-nitrobenzofuroxan ($E=-5.86$) and 4-cyano-6-nitrobenzofuroxan ($E=-6.41$),[11] two derivatives the general behavior of which are representative of a superelectrophilic ranking.[28] It follows that NBDF is more electrophilic than some amino-substituted benhydrylium cations, such as Michler's hydrol blue ($E=-7.02$),[13] that is, the bis(4-dimethylaminophenyl)carbenium ion, as well as of other positively charged species such as triarylallylcations, for example, **12** ($E=-8.97$),[29] arylallylpalladium complexes, for example, **13** ($E=-10.10$, Figure 5),[30] or even the tricarbonylcycloheptadienylium cation **14** ($E=-9.21$, Figure 5).[31]

Because it is often a key C–C bond-forming process on route to many biologically active compounds, the addition of indoles to C=C double bonds activated by the presence of adjacent electron-withdrawing groups, notably a nitro or carbonyl group has received considerable synthetic attention. In most cases, however, such Friedel–Crafts-type alkylations of the indole moiety require the use of Lewis acid or organocatalysis to be achieved.[32–38] As a matter of fact, nitroalkenes, such as nitroethylene or *trans*-β-nitro-styrene do not react with indoles in the absence of a catalyst.[32–36] The same is true for carbonyl- or cyano-activated olefins.[37,38] So far, a calibration of the reactivity of most of these olefins on the Mayr electrophilicity scale has not been made. This prevents us from referring to E values for a quantitative comparison of their reactivity with that of NBDF.

Recently, Domingo et al. have successfully developed a theoretical scale of electrophilicity on the basis of the global electrophilicity index, ω, introduced by Parr and defined in Equation (6).[39–44] In this equation, the electronic chemical potential, μ, and the chemical hardness, η, of a substrate are two parameters which were calculated in terms of the one-electron energies of the frontier molecular orbitals (FMO) HOMO and LUMO at the ground state of the molecules.[42–44] Table 2 compares the ω values characterizing the feasibility of nucleophilic addition to differently activated C=C double bonds, as calculated by Domingo,[39–41] with the ω values calculated in our laboratory for DNBF, NBDF, *trans*-β-nitrostyrene, and 1,1-dinitro-2,2-diphenylethylene.

$$\omega = \frac{\mu^2}{2\eta} \tag{6}$$

Table 2. Electronic chemical potential μ, chemical hardness η, and global electrophilicity ω of DNBF and NBDF, as compared to those of some commonly activated C=C double bonds.[a]

Olefin-type compound	μ	η	ω
DNBF	−0.2177	0.1180	5.46[b]
NBDF	−0.2144	0.1300	4.80[c]
nitroethylene, BH_3	−0.2046	0.1316	4.33[b]
	−0.2083	0.1821	3.24[d]
	−0.1835	0.1439	3.16[c]
acrolein, BH_3	−0.1837	0.1516	3.20[d]
11a	−0.1832	0.1529	2.99[d]
	−0.2074	0.2075	2.82[d]
	−0.1759	0.1582	2.63[c]
11b	−0.1672	0.1419	2.68[b]
nitroethylene	−0.1958	0.2001	2.61[b]
	−0.1865	0.1930	2.45[d]
	−0.1907	0.2119	2.33[d]
11c	−0.1489	0.1279	2.32[d]
acrolein	−0.1610	0.1922	1.84[d]
	−0.1683	0.2135	1.80[d]
	−0.1509	0.1929	1.60[d]

[a] Electronic chemical potential μ and chemical hardness η in atomic units; global electrophilicities ω (in eV), as defined by Equation (6).[42–44] [b] See reference [39]. [c] This work. [d] See reference [41b].

A first point highlighted by Table 2 is that the ranking sequence of electrophilicity of DNBF and NBDF and the three benzylidene malonitriles **11a–e** is the same within the *E* and ω scales. In accord with the conclusion drawn above from the *E* values, the ω value of NBDF (4.80 eV) is approaching that of DNBF (5.46 eV) whilst being much higher than those of the benzylidenemalonitriles **11a** (2.99 eV), **11b** (2.68 eV), and **11c** (2.36 eV). Also, Table 2 reveals that nitroethylene ($\omega = 2.61$ eV) and other nitroactivated olefins, such as *trans*-β-nitrostyrene ($\omega = 2.70$ eV) and 1,1-dinitro-2,2-diphenylethylene ($\omega = 3.16$ eV), have ω values comparable to those of **11a–e**. This accounts for the experimental finding that appropriate catalysts have often to be employed to enhance the electrophilicity of the compounds. As a matter of fact, the ω value of nitroethylene is strongly increased, that is, from to 2.61 to 4.33 eV, in the presence of a Lewis acid catalyst, such as BH_3.[39] Thus, the reactivity of this olefin becomes comparable to that of NBDF, making it possible to engage this attractive electrophile in many C−C coupling reactions, including strongly polar Diels–Alder reactions.[17,18,33–36,39,40] With $\omega \leqq 3$, carbonyl- or cyano-activated olefins similarly need catalytic assistance to become electrophilic enough in Friedel–Crafts-type reactions or Michael-type additions.[26,37,38,45–49] Obviously, the above comparison provides a last but very convincing demonstration of the especially strong electrophilic character of the NBDF olefin.

Conclusion

The superelectrophilic character of the single C=C double bond of 4-nitrobenzofuroxan (NBDF) has been demonstrated through its ease of reaction with a set of 5-X-substituted indoles. The ranking of NBDF on the electrophilicity scale of Mayr as well as on the theoretical electrophilicity scale of Domingo has been made, showing that the reactivity of this peculiar olefin surpasses that of commonly activated C=C double bonds by several orders of magnitude. It follows that no Lewis acid or organocatalytic assistance is required for the coupling of NBDF with such weak carbon nucleophiles as indoles, a feature which is promising for a facile access to new highly functionalized heterocyclic structures.

Experimental Section

General: The synthesis and characterization of the methoxy adduct **9b** has been previously described.[19] The same procedure has been used to prepare the Michael adducts **9a** and **9c–e**. Contrasting with **9b**, the resulting solids were not stable and they decomposed rapidly, so that satisfactory elemental analyses could not be obtained, a situation which is reminiscent of the one observed for a number of indole adducts of DNBF (in their neutral acid form).[3c,d,10] ^1H and ^{13}C NMR spectra recorded for **9a** and **9c–e** in CD_3CN solution leave no doubt, however, regarding the structures of the adducts. The data are summarized, together with those for **9b**, in Tables S1 and S2 given in the Supporting Information. A major diagnostic feature for **9a–e** is the C-4′ resonance which appears at $\delta \approx 80$ ppm and is typical for an sp^3 carbon bonded to a NO_2 group.[50] Also to be noted is that this resonance is markedly shifted to low field, as compared to the situation in nitroalkanes, for example, $\delta = 61.40$ ppm for CH_3NO_2.[51] This is a clear reflection of the strong $-I$ effect exerted by the NBDF moiety.[19] Mass spectra data fully agree with the proposed structures, for example, MS (EI): m/z: 208 $[M-NO-(Me-indole)]^+$ for **9c**.

All other reagents referred to in this work were available from previous studies.[3d,10,11,19]

Kinetic measurements pertaining to the reactions in Equation (2) were performed on a stopped flow apparatus or a conventional spectrophotometer, the cell compartments of which were maintained at 20 ± 0.1 °C. All kinetic runs were carried out in triplicate under pseudo-first-order conditions with a NBDF concentration of approximately 5×10^{-5} M and a nucleophile (indole) concentration in the range of 10^{-3}–5×10^{-2} M. In a given experiment, the rates were found to be reproducible to ±2–3%.

As quoted in the introduction, the *trans* stereochemistry of the NBDF-5-methoxyindole adduct **9b** could be established by a X-ray structure,[19a] and it has been assumed that it extends to other Michael adducts **9a** and **9c–d**. Should this reasonable assumption not be true, this will not affect the significance of our kinetic results as the NBDF addition step is in all cases the rate-limiting step of the coupling reactions described in Equation (2). All observed first-order rate constants k_{obsd} [Eq. (5)] are given in Tables S3-S7, which can be found in the Supporting Information.

Computational information: Full geometry optimizations for the dienes and dienophiles not yet studied (DNBF, NBDF, *trans*-β-nitrostyrene and 1,1-dinitro-2,2-diphenylethylene) have been performed at the B3LY8/6-31G* level of theory,[52,53] which is implemented in the Gaussian 03 package of programs.[54] The global electrophilicity power (ω) was evaluated by means of Equation (6). The electronic chemical potential (μ) and chemical hardness (η) values were approximated in terms of the one-electron energies of the frontier molecular orbitals (FMO), ε_H and ε_L, respectively, by using $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = \varepsilon_H - \varepsilon_L$,[43] respectively, at the ground state (GS) of the molecules.

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