

Assessing the superelectrophilic dimension through σ -complexation, S_NAr and Diels–Alder reactivity

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In the domain of organic chemistry, S_NAr substitutions represent a class of reactions of overwhelming importance, both in synthesis and in the understanding of structure–reactivity relationships, especially the role of σ -complex intermediates. The primary factor necessary for achievement of S_NAr reactions is the presence of a good leaving group, which allows facile rearomatization of the ring undergoing nucleophilic attack. Consistent is the finding that the superelectrophilic chloronitrobenzofuroxans—or furazans—exhibit a very high S_NAr reactivity, allowing a number of C–C, C–N, C–O couplings to be achieved that are not accessible with the classical series of nitro-substituted aromatics. Of particular interest is the synthesis of a number of indoles, indolizines, pyrroles and extended π -excessive aromatic structures like azulene substituted by superelectrophilic moieties. The remarkable driving force for the facile completion of these reactions is the 10 orders of magnitude greater reactivity of 10π -electron-deficient heteroaromatics such as 4,6-dinitrobenzofuroxan (DNBF) than of the most reactive trinitrobenzene derivatives in σ -adduct complexation. Among the factors that have been recognized as governing superelectrophilicity, there is the poor aromaticity of 6-membered 10π -electron structures investigated, with a common origin for σ -complexation and pericyclic processes. A remarkable capacity of these structures is actually to contribute to a variety of Diels–Alder reactions. As an example, the DNBF molecule formally behaves as a nitroalkene, being susceptible to act as a dienophile as well as a heterodiene. Another remarkable Diels–Alder pathway is the capacity of the 6-membered carbocyclic ring of DNBF to act as a carbodiene. Also noteworthy is the successful Diels–Alder trapping of the dinitroso intermediate associated with 1-oxide/3-oxide tautomerism of the furoxan moiety of 4-aza-6-nitrobenzofuroxan. A point of fundamental importance in taking advantage of the reactivity of superelectrophilic structures at hand has been a successful calibration of their reactivity within the electrophilicity E scale developed by Mayr to describe nucleophile–electrophile combinations in general. It has thus been established that the E parameters measuring the electrophilicity of neutral heteroaromatics lie in the same region of the E scale as a number of highly reactive cationic reagents. Besides a reactivity rather similar to that of the 4-nitrobenzenediazonium cation (*vide supra*), the most electrophilic neutral molecules (DNBF, DNTP, DNBZ) are as electrophilic as tropylium cations or a number of metal-coordinated carbenium ions. Furthermore, there is a remarkable link between the $pK_a^{H_2O}$ and E scales, as evidenced by the existence of a unique linear relationship spanning more than 20 orders of reactivity. This relationship appears as being a nice probe to predict the feasibility of S_NAr substitutions and related σ -complexation processes. Also revealing in terms of feasibility of the reactions is the existence of a close correlation between the electrochemical oxidation potential E° of σ -adducts and their positioning on the $pK_a^{H_2O}$ scale. Our data can also be used to evaluate the potential of a theoretical model recently derived from DFT calculations, namely the global electrophilicity index ω , for the description of nucleophile–electrophile combinations. While showing several significant deviations, a reasonably linear ω vs. $pK_a^{H_2O}$ relationship is obtained when restricting the correlation to structurally similar electrophilic moieties. On this basis, valuable information could be derived regarding the polar character of some DA reactions. Overall, the global electrophilicity (ω) approach may be a promising avenue in future work of electrophile–nucleophile combinations.

Introduction

Superelectrophilic dimension

Our understanding of factors governing electrophilicity and nucleophilicity has undergone enormous change since such parameters were introduced in the 1950s and 60s through the

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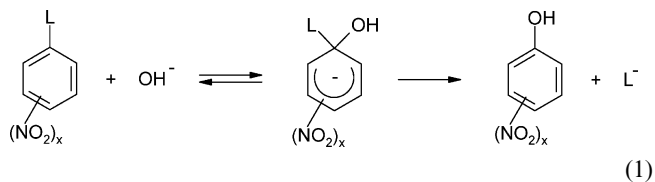
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Swain–Scott equation, Edward’s equation, as well as works by Hammett, Winstein, Bunnett, Ingold, Mayr and others (see recent Organic Chemistry texts). Herein we present a novel aspect of electrophilicity, as the **super-electrophilic dimension**. On the one hand we view some of the super-electrophilic structures prepared by Olah and others from the 1970s onward, which have become possible following the discovery of “Magic Acid” ($\text{HSO}_3\text{–SbF}_5$).^{1a} Typically these are multiply charged carbocations, persistent under the super acid conditions where they can be studied by NMR and other physical methods.^{1b} Contrastingly we have the second class of super-electrophiles, the heteroaromatic structures such as 4,6-dinitrobenzofuroxan (DNBF) and the related 2-*N*-picryl-4,6-dinitrobenzotriazole 1-oxide (Pi-DNBT) and 4,6-dinitrotetrazolo[1,5-*a*]pyridine (DNTP), which have been studied in our laboratories for over 2 decades, and can be prepared and studied under ambient conditions, and are the subject of the present perspective article. It will be seen that these super-electrophiles display a remarkable versatile range of reactivity, for example in σ -complexation where they are up to 10^{13} times more reactive than the benchmark 1,3,5-trinitrobenzene (TNB) and in pericyclic reactivity where, remarkably, DNBF exhibits 5 different modes of Diels–Alder reactivity.

The NO_2 group as benchmark of electrophilicity in aromatic substrates

Nucleophilic aromatic substitutions ($\text{S}_{\text{N}}\text{Ar}$ reactions) together with the formation of the related σ -anionic adducts represent reactions of overwhelming importance in organic synthesis.^{2–11} A model representative process is indicated in eqn (1) where OH^- is the nucleophilic partner reacting with an aromatic ring activated by electron-withdrawing NO_2 substituents and bearing a good leaving group L at the reactive center. The role of the NO_2 group in $\text{S}_{\text{N}}\text{Ar}$ reactions has featured extensively since the pioneering

work on the overall substitution processes by Bunnett in the early fifties.⁸



It will be shown in this article that current works of extending the field of applicability of eqn (1) through kinetic and thermodynamic investigations as well as other tools, including synthetic protocols, allow one to reconsider fundamental concepts of electrophilicity. In this context, focusing first on the nucleophilic addition step provides the opportunity to evaluate the factors governing formation of the intermediate σ -adducts.^{6,10} The most appropriate substrates for this purpose are those of eqn (1) with $\text{L} = \text{H}$, as reformulated and numbered in Scheme 1, in which H^- departure is virtually prohibited by the very poor nucleofugality of the hydride anion. Note, however, that a formal H^- displacement is possible through other methodologies such as the so-called vicarious nucleophilic aromatic substitution, as developed by Makosza,^{12,13} in which the leaving group is part of the nucleophile and not of the electrophilic partner.

The classical domain of σ -complex reactivity has been traditionally defined as covering the range of reactivity between the most electrophilic 1,3,5-trinitrobenzene (TNB) and the least electrophilic mononitrobenzene. Besides NO_2 , other electron-withdrawing groups (CN , CF_3 , SO_2R , COR , $\text{B}(\text{OR})_3$, etc.) have been employed to modulate the electrophilicity while structural modification has included extension to naphthalenes,¹⁴ and various heterocyclic series such as aza-aromatics,^{15,16} nitro-thiophenes,¹⁷ nitro-furans,¹⁸ nitro-2,1,3-benzoxadiazoles,¹⁹ -benzotriazoles,²⁰ -tetrazolopyridines,²¹ and related 10π -electron-deficient substrates. Altogether, the above forays coupled with



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environmental and materials chemistry, with 70 graduate students and PDFs, led to 350 research papers and book chapters, reviews and four books. Buncel was awarded the Syntex and R. U. Lemieux Awards. He has been editor of *Canadian Journal of Chemistry (CJC)* and the *Journal of Labeled Compounds and Radiopharmaceuticals*; he was honoured by *CJC* with a *Special Issue (Festschrift)*.

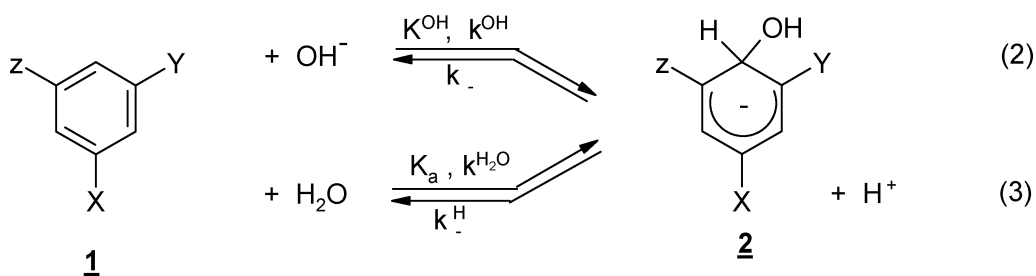
Erwin Buncel received his Ph.D. from University of London, (Prof. Alwyn Davies) in the School of Sir Christopher Ingold. After PDF work at the University of North Carolina (Bunnett), McMaster University (Bourns), and research chemist (American Cyanamid), he was appointed at Queen’s University reaching Full Professor (1970). Investigations in physical organic, bioorganic, bioinorganic chemistry, and now envi-



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σ -complexation and related nucleophilic aromatic substitutions, proton transfers at carbon, and exalted reactivity of α -nucleophiles. F. Terrier has published over than 220 research papers as well as review articles and book chapters. He is the author of “*Nucleophilic Aromatic Displacements. The Role of the Nitro Group*”, VCH, New York (1991).

François Terrier received his Ph.D. degree from the University of Paris (UPMC). After postdoctoring with Claude Bernasconi (UCSanta Cruz), he became Professor at the University of Rouen (1976). In 1991, he joined the University of Versailles as Head of the Chemistry Department and Head of the SIRCOB Laboratory (UMR CNRS 8086). Terrier’s research interests deal with various fields of organic reactivity. These include



- (a) X = Y = Z = NO₂ (TNB) ; (b) X = Y = NO₂, Z = H (DNB) ;
 (c) X = NO₂, Y = Z = H (NB with para-addition) ;
 (d) Y = NO₂, X = Z = H (NB with ortho-addition) ;
 (e) X = Y = NO₂, Z = aza ; (f) X = Y = NO₂, Z = CN ;
 (g) X = Y = NO₂, Z = CF₃ ; (h) X = Y = Z = CN ;
 (i) X = Y = Z = SO₂CF₃ (TTSB)

Scheme 1

methodologies such as microwave,²² ultrasonic,^{22c,23} high-pressure techniques,²⁴ use of room-temperature ionic liquids,²⁵ as well as organometallic activation,²⁶⁻²⁸ *etc.* have improved significantly the synthetic feasibility of C–O, C–N, C–S or C–C couplings through the S_NAr process and also led to wide-reaching analytical and biological applications, *e.g.* in trace analysis of toxic compounds.^{29,30} Recently, successful entries to asymmetric S_NAr reactions have been reported.³¹⁻³³

Quantitation of aromatic reactivity with superelectrophilic aromatics and heteroaromatics

As shown above, S_NAr reactivity is intimately related to σ-complexation. This makes it valuable to refer to the formation of the hydroxy adducts **2a–d** of TNB (**1a**), 1,3-dinitrobenzene (DNB, **1b**) and nitrobenzene (NB, **1c = 1d**) as a benchmark entry to the classical domain of nitroaromatic activation.

For self-consistency with the forthcoming discussion, this domain is presented in the left part of Fig. 1 with reference to water reactions, as formulated in eqn 3 (Scheme 1), and hence to pK_a^{H₂O} values. For the most part, these pK_a^{H₂O} values were readily obtained from direct measurements of the equilibrium constants K^{OH} for hydroxide ion addition (eqn 2), *via* the simple relationship pK_a^{H₂O} = pK_w – log K^{OH}. However, a few pK_a^{H₂O} values, namely those for formation of the adducts **2b**, **2f**, **2g** and **2i**, have been obtained from measurements in methanol and transposition of the related pK_a^{MeOH} values into the corresponding pK_a^{H₂O} values through the general relationship of eqn (4).³⁴ Lastly the inaccessible pK_a^{H₂O} values for hydroxide ion addition to the *para* and *ortho* positions of the nitro group of nitrobenzene to give the adducts **2c** and **2d**, respectively, have been estimated by correcting the pK_a^{H₂O} value of DNB for the loss of the stabilizing contribution of a *para* or an *ortho* NO₂ group, as proposed by Strauss and Fendler.^{10a,c,14,35} A similar approach was used to estimate the pK_a^{H₂O} value for formation of the tricyano adduct **2h** from the data pertaining to the TNB analogue **2a**.

$$pK_a^{\text{MeOH}} = pK_a^{\text{H}_2\text{O}} + 2.52 \quad (4)$$

As can be seen in Fig. 1, the pK_a^{H₂O} values pertaining to the various reactions depicted in Scheme 1 define a thermodynamic reactivity scale spanning about 15 orders of magnitude between the most and the least electrophilic nitroactivated benzenoid substrate. This classic domain also includes an aza-activated aromatic substrate, namely 3,5-dinitropyridine **1e**, which exhibits a slightly greater electrophilicity than TNB,^{36a,b} and three representative less electrophilic members, namely **1f**, **1g** and **1h**, of cyano and trifluoromethyl-substituted benzenes.^{36c,d}

A greater jump from the classical domain of electrophilic substrates is afforded with tris-1,3,5-(trifluoromethanesulfonyl) benzene **1i** (TTSB) having a pK_a^{H₂O} value of 6.6 for formation of the adduct **2i**, *i.e.* almost 7 pK units more electrophilic than TNB.^{34,37} In fact, TTSB represents a departure from the classical electrophilicity domain, and entry to the super electrophilic domain of reactivity in σ-complex formation and related reactivities of aromatic substrates.

A further quantum leap to super-electrophilic substrates follows on going to the heteroaromatic series, consisting of compounds identified in Scheme 2. These include a number of nitro-2,1,3-benzoxadiazoles and related 1-oxides **3a–j**, commonly referred to as nitrobenzofurazans and nitrobenzofuroxans, respectively, as well as nitro-substituted benzo-thiadiazole (**3k**), -selenadiazole (**3l**), -triazoles (**5a–d**) and two nitrotetrazolopyridines (**7a,b**).^{19-21,38,39} The most widely known is 4,6-dinitrobenzofuroxan (DNBF) whose formation of the adduct **4a** is associated with a pK_a^{H₂O} value of 3.75 in aqueous solution at 25 °C.¹⁹ However, an even lower pK_a^{H₂O} value of 0.4 has been measured for 4,6-dinitrotetrazolo[1,5-a]pyridine **7a** (DNTP).^{21a} Such an enormous fall in pK_a^{H₂O} has boosted the chemistry of S_NAr reactions in promoting couplings with weakly basic nucleophiles, notably a large set of carbon nucleophiles, *e.g.* anilines, enols, indoles, pyrroles, *etc.*, and other π-excessive substrates.³⁹⁻⁴⁵ This has resulted in further forays, especially on the synthetic front.

We can now express the subject of this perspective article as the story of the expansion of a superelectrophilicity dimension into different areas of S_NAr and related σ-complexation reactions.

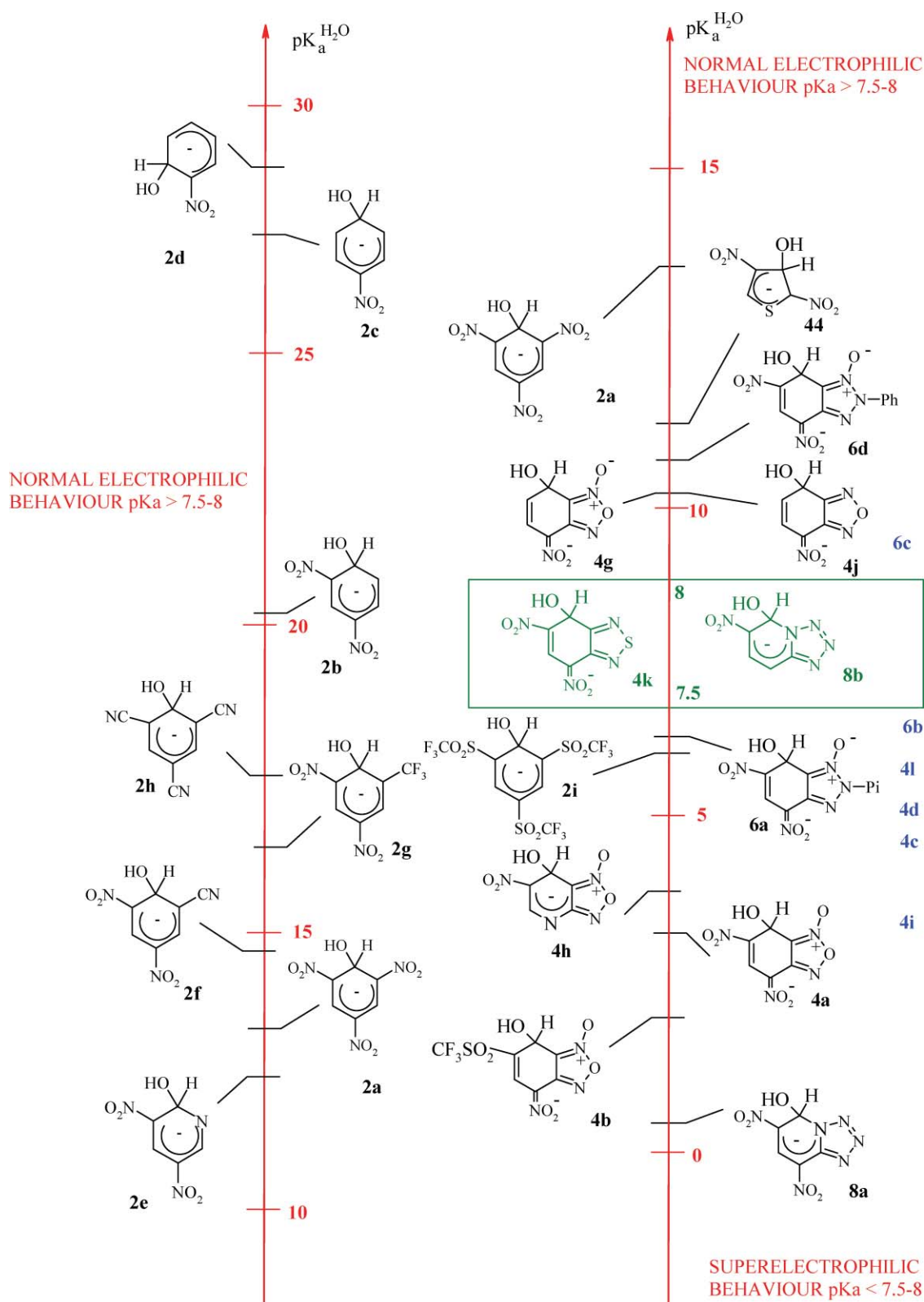
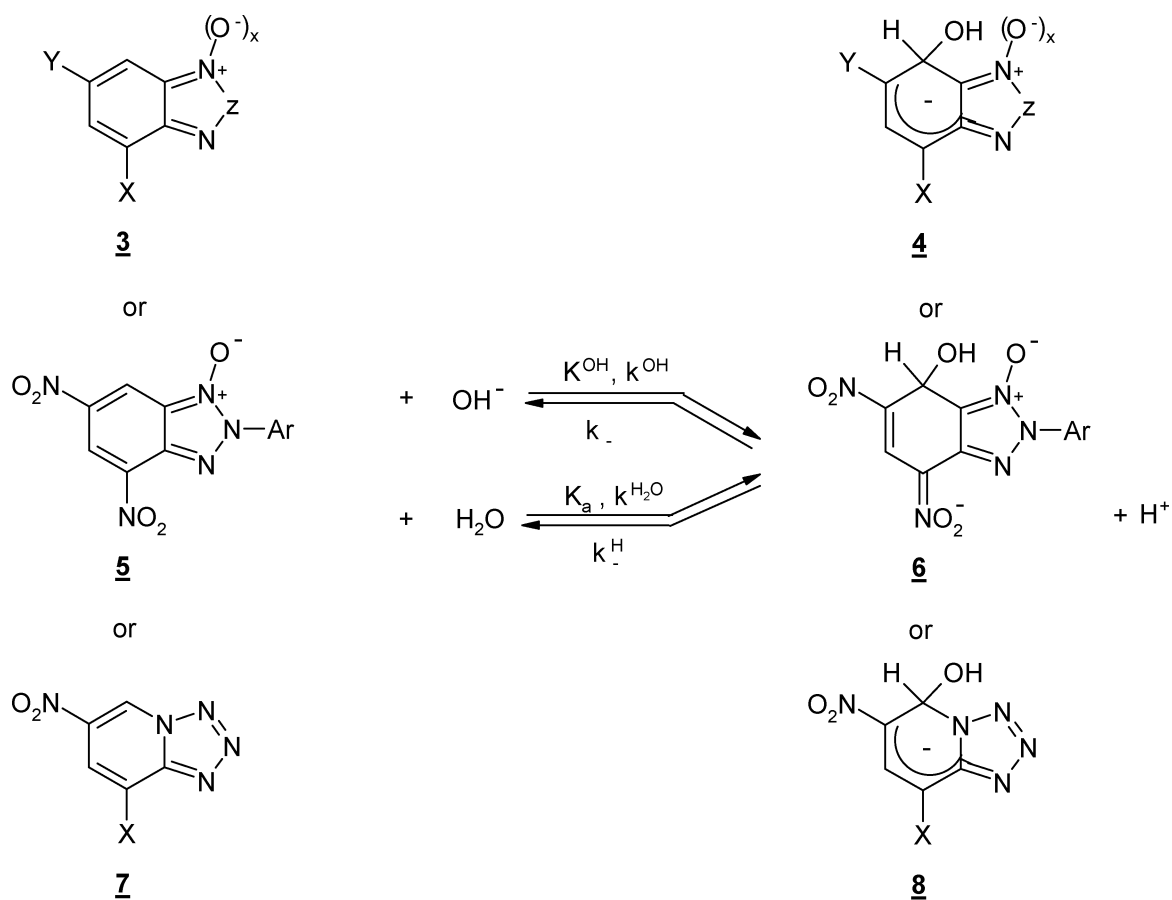


Fig. 1 The $pK_a^{H_2O}$ scale for σ -complexation of electrophilic aromatics and heteroaromatics, as derived from the ease of formation of hydroxy σ -adducts in aqueous solution. For clarity, a few adducts, namely **4c**, **4d**, **4i**, **6b** and **6c**, are only referred to by their identification numbering in blue (see structures in Schemes 1 and 2). The green insert defines the boundary between super- and normal-electrophiles.



Compounds **3** and Adducts **4** :

- $x = 1, z = O$ (a) $X = Y = \text{NO}_2$ (DNBF) ; (b) $X = \text{NO}_2, Y = \text{SO}_2\text{CF}_3$;
 (c) $X = \text{NO}_2, Y = \text{CN}$; (d) $X = \text{CN}, Y = \text{NO}_2$; (e) $X = \text{NO}_2,$
 $Y = \text{CF}_3$; (f) $X = \text{CF}_3, Y = \text{NO}_2$; (g) $X = \text{NO}_2, Y = \text{H}$ (NBF)
 (h) $X = \text{aza}, Y = \text{NO}_2$ (ANBF)
 $x = O$ (i) $X = Y = \text{NO}_2, Z = O$ (DNBZ) ; (j) $X = \text{NO}_2, Y = \text{H}, Z = O$
 (NBZ) ; (k) $X = Y = \text{NO}_2, Z = \text{S}$ (DNBS) ; (l) $X = Y = \text{NO}_2,$
 $Z = \text{Se}$ (DNBSe)

Compounds **5** and Adducts **6** :

- (a) Ar = 2,4,6-trinitrophenyl (Pi-DNBT) ; (b) Ar =
 2,4-dinitrophenyl (DNP-DNBT) ; (c) Ar = 4-nitrophenyl
 (NP-DNBT) ; (d) Ar = phenyl (P-DNBT)

Compounds **7** and Adducts **8** :

- (a) $X = \text{NO}_2$ (DNTP) ; (b) $X = \text{H}$ (NTP)

Scheme 2

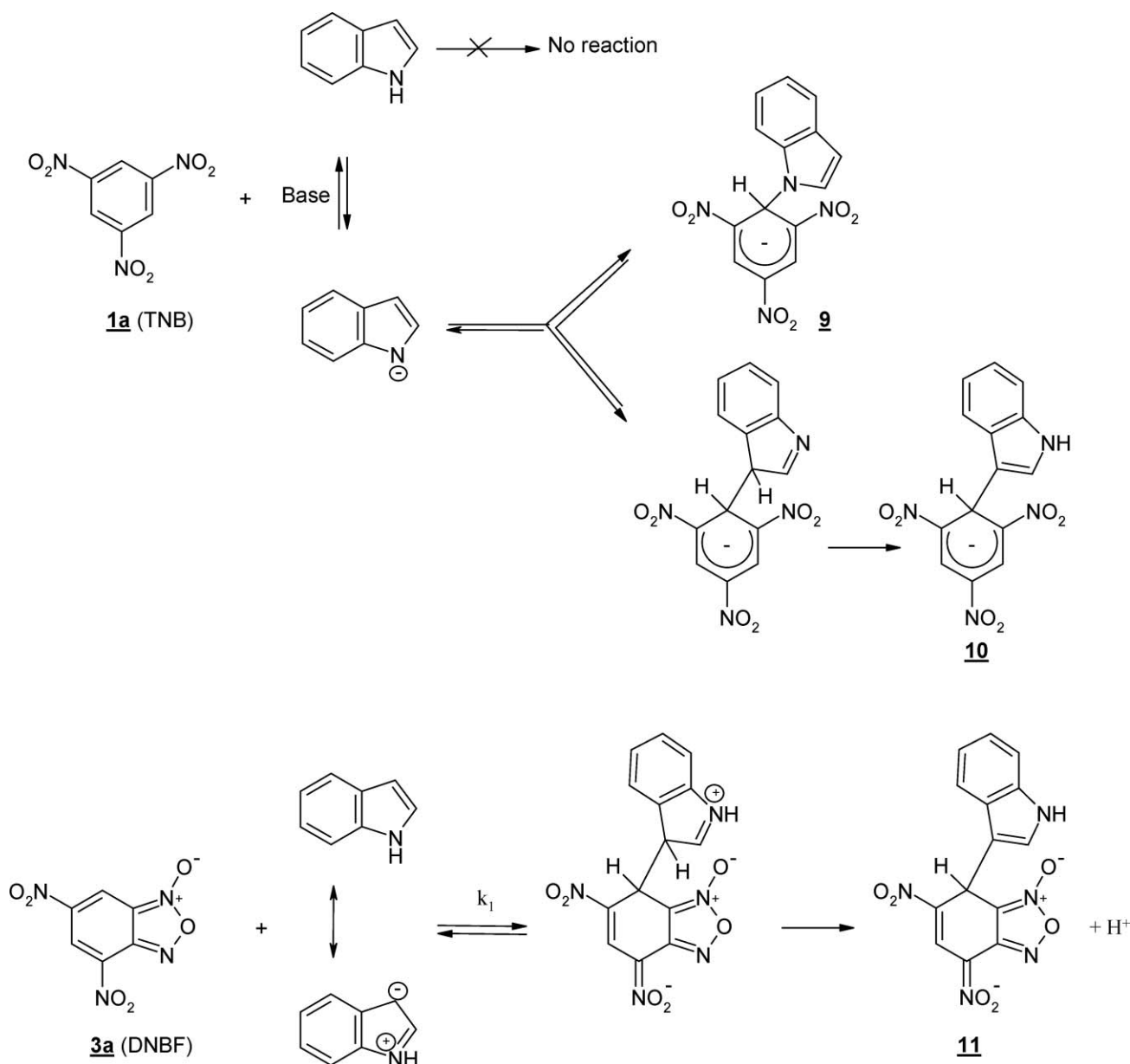
Demarcating between normal and superelectrophilic behaviour through σ -complexation

Documentation of exalted reactivity of superelectrophilic DNBF

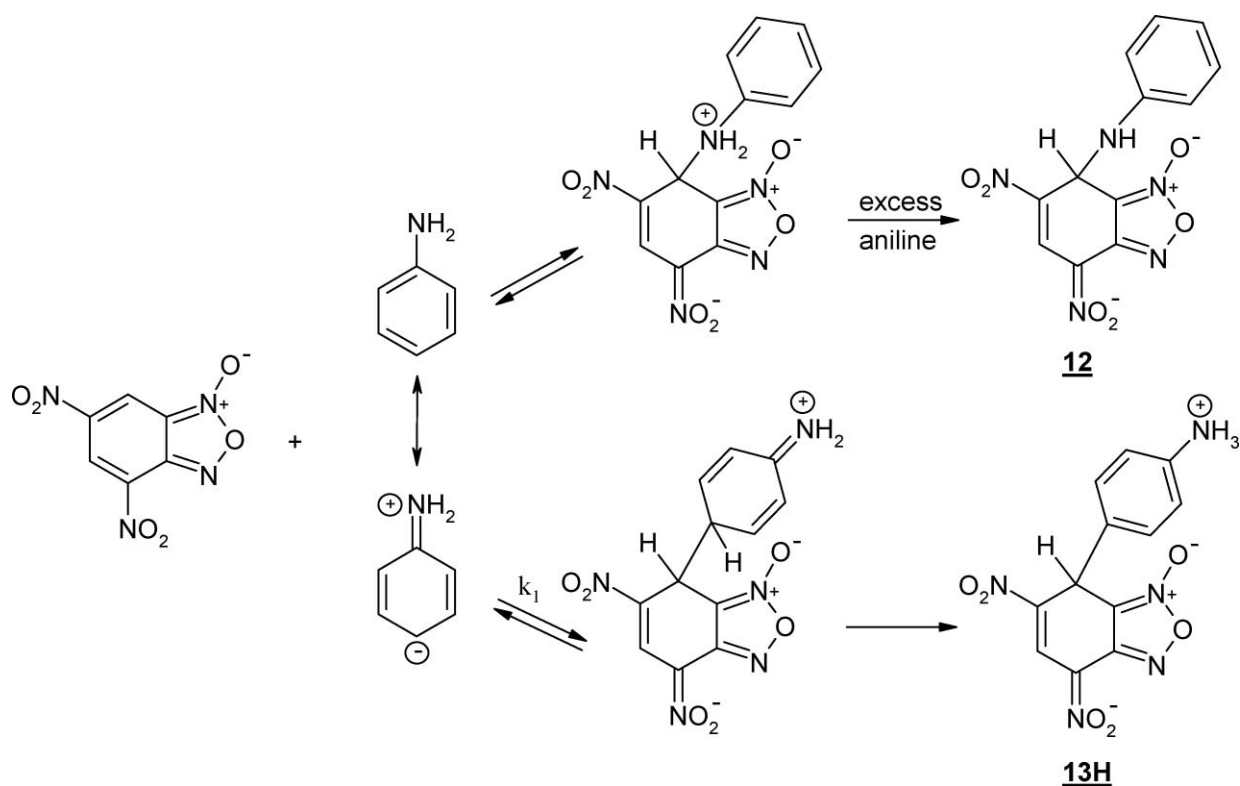
A common experience in synthetic organic chemistry based on classical nitroaromatics such as TNB is the lack of reactivity with weak neutral carbon nucleophiles whose C-protonation is generally associated with negative pK_a^{CH} values in water. An example is the inertness of TNB towards neutral indole itself ($pK_a^{CH} = -3.46$).⁴⁶ In this instance, it is only upon generation of the conjugate indolide anion with a strong base that the reaction takes place. First the N-adduct **9** is formed under kinetic control and eventually the thermodynamically stable C-adduct **10** is obtained, resulting from electrophilic addition of TNB at C-3 of the indole

ring. Contrasting is the facile and quantitative reactivity of neutral indole with DNBF to give the highly stable and isolable C-adduct **11**, as depicted in Scheme 3.^{19b,47} A similar contrasting situation prevails when comparing the reactivity of TNB and DNBF with enols, a strong base being required in order to achieve C–C couplings of TNB while with DNBF no added base is needed.^{42,48}

Interestingly, a number of weak carbon bases such as aniline ($pK_a^{CH} = -7$), 2-aminothiazole ($pK_a^{CH} = -5.46$) as well as polyhydroxy- or polyalkoxy-benzenes, ($pK_a^{CH} = -9$ for 1,3-dimethoxybenzene) undergo similarly facile C–C coupling with DNBF.^{40,44,49} The case of aniline where kinetic control gives rise to the N-adduct **12** in the absence of base catalyst, is illustrative (Scheme 4).⁴⁰ This contrasts with the situation for TNB where the strongly basic DABCO is required for N-adduct formation.⁵⁰ On the other hand, the C-bonded adduct **13,H** (or its conjugate base)



Scheme 3 Illustration of the different reactivity patterns of TNB and DNBF with indole, highlighting the extremely strong electrophilicity of DNBF.



Scheme 4 N versus C reactivity of aniline with DNBF.

is formed under thermodynamic control, reflecting the propensity of DNBF, but not TNB, to react with very weak carbon bases.

In keeping with weak carbon nucleophilicity revealed by the superelectrophilic character of DNBF, it is a striking feature that 1,8-bis(*N,N*-dimethylamino)naphthalene, the proton sponge, reacts quantitatively with DNBF to afford the zwitterionic C-adduct **14,H**, despite the well-known fact that the close proximity of the two *N,N*-dimethylamino groups precludes conjugation with the naphthalene system (eqn (5)).⁵¹

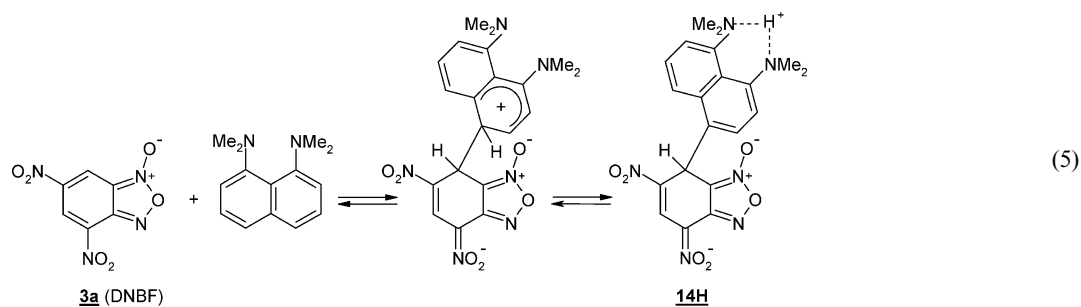
The water reaction as the baseline σ -complexation process

From the above qualitative trends, it emerges that going from TNB to DNBF is accompanied by a decisive leap forward in electrophilicity. Definitive assessment of this trend follows from a detailed kinetic and thermodynamic investigation of the reactions with water as the reference nucleophile.

It is of special relevance here to introduce the $k^{\text{H}_2\text{O}}$ parameter to assess the degree of participation of H_2O as a nucleophile in the

DNBF system (see Scheme 2). Following an approach developed by Bunting *et al.* for pseudobase formation from quinolinium and naphthyridinium cations,⁵² the $k^{\text{H}_2\text{O}}$ parameter could be readily derived from a dissection of the observed pH-rate profile for the combined formation and decomposition of the adduct **4a** (k_{obsd}) into its k_f and k_d components.^{19a} As seen in Fig. 2, the long plateau of the k_f component coincides nicely with the plateau characterizing the k_{obsd} profile. At the same time, the plateau seen in the k_d profile reflecting the decomposition of **4a** corresponds to a negligible contribution of the rate constant k_{d} to k_{obsd} . Hence, there is no doubt that the water reaction is the sole effective pathway for the formation of the adduct **4a** up to pH 8. At higher pH, the OH^- pathway (k^{OH}) becomes predominant, as expected.^{19a}

A similar strategy involving measurements of pH-rate profiles for the 10π -electron-deficient structures numbered in Scheme 2 has led to recognition of a contrasting situation which is illustrated in Fig. 3 for 4,6-dinitrobenzothiadiazole **3k** (DNBS).³⁹ In this instance, the upper plateau is now part of the k_d component of the pH-rate profile, implying a negligible contribution of $k^{\text{H}_2\text{O}}$ to the



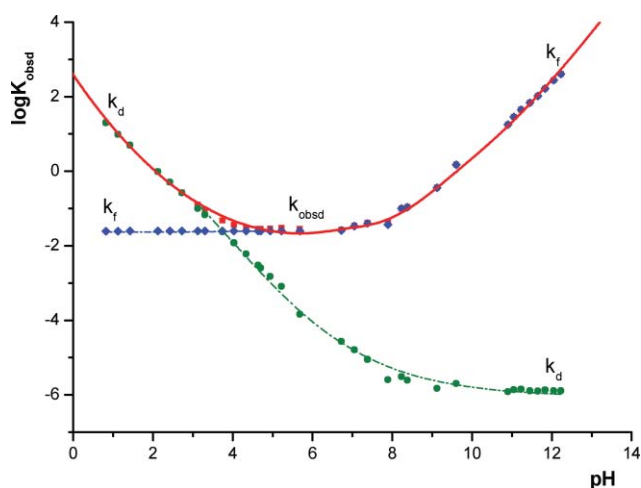


Fig. 2 pH-Rate profile for the formation and decomposition of the hydroxy adduct of DNBF (**4a**) at $T = 20\text{ }^{\circ}\text{C}$ in aqueous solution.^{16a}

observed rate. On this ground, the $k^{\text{H}_2\text{O}}/k_-$ ratio is the key factor determining the effective contribution of water in the formation of hydroxy σ -adducts. For a clear demonstration of the utility of this ratio, a few representative data are collected in Table 1.^{39,53,54} Obviously, large $k^{\text{H}_2\text{O}}/k_-$ values reflect a large contribution of the water pathway but this ratio decreases rapidly with increasing $\text{p}K_{\text{a}}$. This leads to the absence of any water contribution above $\text{p}K_{\text{a}}^{\text{H}_2\text{O}} > 8$.

Recently, we have proposed that the above defined $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ value is an appropriate benchmark to demarcate the boundary between super- and normal-electrophiles in σ -complex formation.^{39,53,54} Thus, the superelectrophilic dimension has been accorded not only to DNBF but also to a number of related heterocyclic structures. These include 4,6-dinitrotetrazolo[1-5a]pyridine **7a**

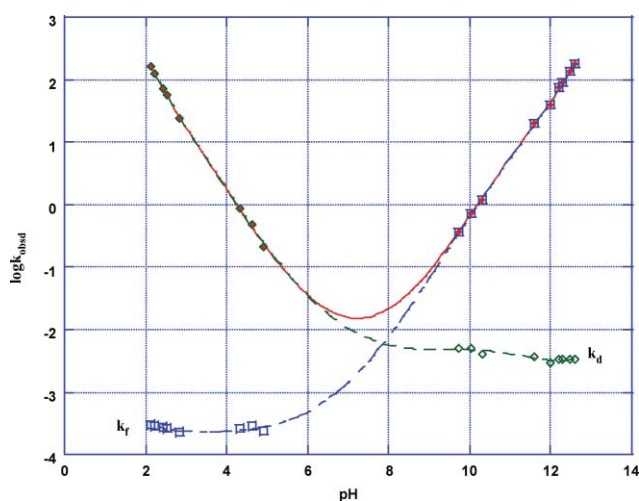


Fig. 3 pH-Rate profile for the formation and decomposition of the hydroxy adduct of DNBS (**4k**) at $T = 25\text{ }^{\circ}\text{C}$ in aqueous solution.^{16a}

(DNTP) (by three orders of magnitude the most electrophilic compound on the $\text{p}K_{\text{a}}$ scale),^{21a} 4-nitro-6-trifluoromethanesulfonyl benzofuroxan **3b**,⁵⁵ 4,6-dinitrobenzofurazan **3i** (DNBZ),^{39b} and 4-aza-6-nitrobenzofuroxan **3h** (ANBF).^{38,39,53} 2-*N*-picryl-4,6-dinitrobenzotriazole 1-oxide **5a** (Pi-DNBT) also belongs to the category of highly electrophilic substrates.^{20a,39b} On the other hand, apart from 6-nitrotetrazolo[1-5a]pyridine **7b** (6-NTP) for which the water contribution is weak but real,^{39b,53} all other compounds with $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ values $> 7.5\text{--}8$ undergo hydroxide addition exclusively.^{39,53} This situation can be substantiated by the break in the $\text{p}K_{\text{a}}$ scale shown in Fig. 1.

Importantly, the above approach leading to the definition of the $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ benchmark has been successfully extended to the

Table 1 Kinetic and thermodynamic parameters for covalent hydration of nitrobenzofuroxans and other superelectrophilic structures at $T = 25\text{ }^{\circ}\text{C}$ in aqueous solution.^a Related Mayr E parameters and global electrophilicity DFT-parameters (ω , ΔN_{max})

Electrophile	$\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$	$k^{\text{H}_2\text{O}}$	$k_{-}^{\text{H}^+}$	k^{OH}	k_{-}	$k^{\text{H}_2\text{O}}/k_{-}$	E value	ω	ΔN_{max}
7a , DNTP	0.4	1.93	3.87	—	—	—	-4.67^b	4.42	1.61
3b	2.95	0.15	100.3	7.2×10^4	10^{-6}	1.5×10^5	-4.91^b	5.33	1.80
3a , DNBF	3.75	3.5×10^{-2}	146	33500	2.5×10^{-6}	14000	-5.06^b	5.46	1.85
3i , DNBZ	3.92	2.0×10^{-2}	127	15300	1.7×10^{-6}	12000	-5.46^b	4.86	1.54
3h , ANBF	4.06	—	—	—	—	—	-5.86^b	4.80	1.70
3c	4.65	10^{-3}	31	1060	10^{-6}	1000	-7.01^b	5.25	1.81
3d	5.86	2.6×10^{-3}	3700	2740	3×10^{-5}	87	-6.41^b	5.15	1.78
3l , DNBS _e	6.34	5×10^{-3}	11350	305	5×10^{-6}	1000	-7.40^c	4.51	1.52
1i TTSB	6.60	3.02×10^{-3}	2.88×10^7	3.9×10^5	0.011	2.74	-7.57^c	—	—
5a , Pi-DNBT	6.70	1.1×10^{-3}	4215	392	2×10^{-5}	60	-7.63^c	5.98	2.06
5b , DNP-DNBT	7.15	6.7×10^{-4}	7050	1000	1.4×10^{-4}	4.8	-7.93^c	5.45	—
7b , 6-NTP	7.55	1.6×10^{-5}	630	285	9.5×10^{-5}	1.7×10^{-1}	-9.05^b	3.49	1.27
3k , DNBS	7.86	2.8×10^{-4}	17300	9400	5×10^{-3}	6×10^{-2}	-8.40^c	4.42	1.61
49 ,	8.48	—	—	—	—	—	-8.82	—	—
5c , NP-DNBT	9.00	1.8×10^{-5}	13300	680	3.5×10^{-3}	5×10^{-3}	-9.16^b	4.90	1.76
3j , 4-NBZ	10.07	—	—	59	1.1×10^{-2}	—	-9.85^a	3.79	1.35
3g , 4-NBF	10.37	—	—	30	1.1×10^{-2}	—	-10.04^a	4.21	1.47
5d , P-DNBT	10.73	8.3×10^{-7}	33000	680	3.5×10^{-3}	2.4×10^{-4}	-10.30^b	4.18	1.63
44	11.70	—	—	—	—	—	-12.33^a	—	—
2a , TNB	13.43	—	—	37	9.8	—	-13.19^a	—	—

^a Rate constants $k^{\text{H}_2\text{O}}$ and k_{-} in s^{-1} , k^{OH} and $k_{-}^{\text{H}^+}$ in $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$; rate constants and $\text{p}K_{\text{a}}$ values taken from ref. 19a, 21, 37, 38, 39c and 53. ^b E values experimentally determined in ref. 39 and 53. ^c E values calculated from known $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ values through the correlation of Fig. 6. ^d Rate constants for σ -complexation of TTBS in methanol; $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ value calculated from $\text{p}K_{\text{a}}^{\text{MeOH}}$ via eqn (4); see ref. 37. ^e See quotation and discussion of ω (in eV) and ΔN_{max} (in eV) parameters at the end of the paper.

formation of methoxy adducts in methanol.^{34,37,56} This has the practical consequence to allow a similar analysis of the electrophilicities of poorly soluble compounds in water. In this instance, the pK_a^{MeOH} benchmark can be defined on the basis of an effective contribution of methanol to the formation of the methoxy adducts and readily transposed in the water reactivity scale through the general relationship of eqn (4) (*vide supra*). This approach has proved to be especially useful for the case of aromatic triflones with a clear positioning of 1,3,5-tris-(trifluoromethanesulfonyl)benzene **1i** (TTSB) in the superelectrophilic domain, as evidenced by the estimate, through eqn (4), of a $pK_a^{\text{H}_2\text{O}}$ value of 6.6.^{34,37,56}

Reactivity in $S_N\text{Ar}$ substitution

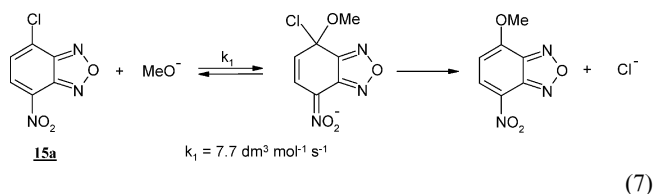
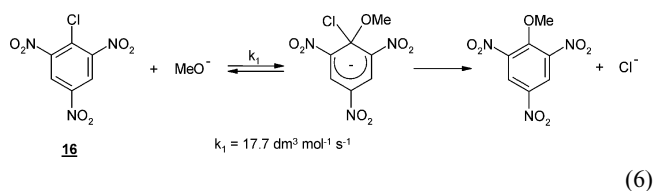
An important outcome of the above $pK_a^{\text{H}_2\text{O}}$ demarcation is that it fits nicely the experimental behaviour of the electrophiles at hand. In practice, all electrophiles ranked in the superelectrophilic region react readily with weak nucleophiles such as the aforementioned indoles, pyrroles, *etc.*^{39,53} This is illustrated in Table 2, which shows that the second order rate constants k_{11} for C–C coupling of most of these electrophiles with indoles are comparable or greater than those for related reactions with *para*-nitrobenzenediazonium or other diazonium cations.^{39,53,57a}

While it has been very useful to highlight the extremely strong electrophilicity of some of the substrates shown in Fig. 1 through covalent nucleophilic addition to an unsubstituted carbon, it remains that the synthetic potential becomes greatly enhanced when the nucleophilic addition step takes place at an activated position bearing a good leaving group with subsequent rearomatization and hence facile achievement of the overall $S_N\text{Ar}$ substitution.⁸

The $S_N\text{Ar}$ synthetic potential of chloronitrobenzodiazoles and related 10 π -heterocycles.

A first striking instance of the ease of $S_N\text{Ar}$ substitution is found with 4-chloro-7-nitrobenzofurazan **15a** (NBD-Cl) reacting with a variety of basic reagents, such as amines or hydroxide, alkoxide and thiolate ions.⁵⁸⁻⁶⁰ In fact, the reactivity of this mononitro activated substrate is comparable to that of picryl chloride **16** with rate constants of 7.7 and 17 $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ for reaction of

these compounds with methoxide ion in methanol (eqn (6) and eqn (7)).⁵⁹ It is because of its notable $S_N\text{Ar}$ reactivity that **15a** has long been used as a fluorescent reagent in protein labelling and for structure determination of enzymes.⁵⁸



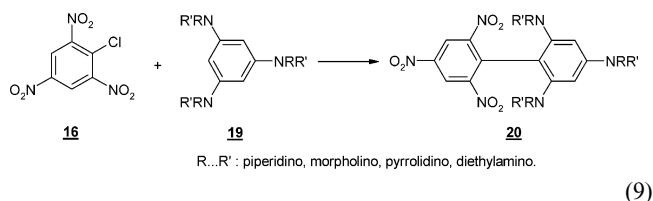
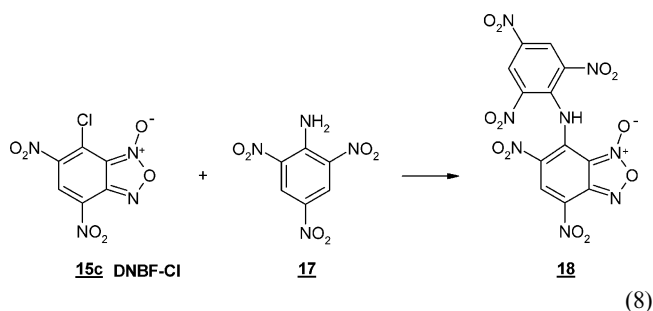
It could be anticipated that addition of a second nitro group to NBD-Cl will project the resulting substrate, namely 4,6-dinitro-7-chlorobenzofurazan **15b** (DNBZ-Cl; see structure in Scheme 5) into the realm of superelectrophilicity. This expectation is fully materialized when DNBZ-Cl and the related 4,6-dinitro-7-chlorobenzofuroxan **15c** (DNBF-Cl) are allowed to react with a variety of weak or very weak nucleophiles, including water, and electron-deficient anilines.⁶¹⁻⁶³ This is illustrated in eqn (8) for the reaction of DNBF-Cl with the poorly basic 2,4,6-trinitroaniline **17**, which takes place smoothly in methanol to give 7-(2,4,6-trinitrophenylamino)-4,6-dinitrobenzofuroxan **18**, a compound exhibiting interesting thermal and explosive properties.⁶³ π -Excessive structures of low carbon basicities such as azulene, polyalkoxybenzenes, indoles or pyrroles also readily react with DNBZ-Cl and DNBF-Cl.^{64,65} All reactions proceed at room temperature, leading instantaneously or in a few minutes to essentially complete formation of the expected substitution products, as shown in Scheme 5 for azulene.⁶⁵ The situation contrasts with that reported by Effenberger on the reactivity of picryl chloride with a series of 1,3,5-tris-(dialkylamino) benzenes **19** to give the biphenyls **20** as depicted in eqn (9).⁶⁶ Despite the much greater carbon nucleophilicity of these strongly electron-rich anilines

Table 2 Relative electrophilic reactivities of DNBF, DNBZ-Cl, DNBZ-Cl and related heteroaromatics towards indoles in acetonitrile. Comparison with a series of benzenediazonium cations

Electrophile	Nucleophile; k_1 in $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$		
	Indole ($pK_a^{\text{CH}} = -3.46$) ^a	<i>N</i> -Methylindole ($pK_a^{\text{CH}} = -2.32$) ^a	2-Methylindole ($pK_a^{\text{CH}} = 0.26$) ^a
4-MeO-Ar-N ₂ ^{+b}	2.49×10^{-4}	2.46×10^{-3}	0.25
Ar-N ₂ ^{+b}	2.24×10^{-3}	2.57×10^{-2}	1.92
4-NO ₂ -Ar-N ₂ ^{+b}	1.24	6.61	42.7
Fe(Co) ₃ (2-MeOC ₆ H ₆) ^c	1.6×10^{-2}	9.7×10^{-2}	0.12
DNTP ^d	15.7	48.5	—
3b ^d	5.2	21.5	—
DNBF ^d	2.29	13.40	108
DNBZ ^d	1.6	10.3	—
ANBF ^d	0.83	2.3	—
DNBF-Cl ^d	6.56×10^{-2}	1.02	1.60
DNBZ-Cl ^d	—	1.15	—

^a pK_a^{CH} values for C-protonation of indoles taken from ref. 57b. ^b data from ref. 57a at $T = 25$ °C. ^c data from ref. 57c at $T = 20$ °C. ^d data from ref. 39, 45 and 65 at $T = 20$ °C.

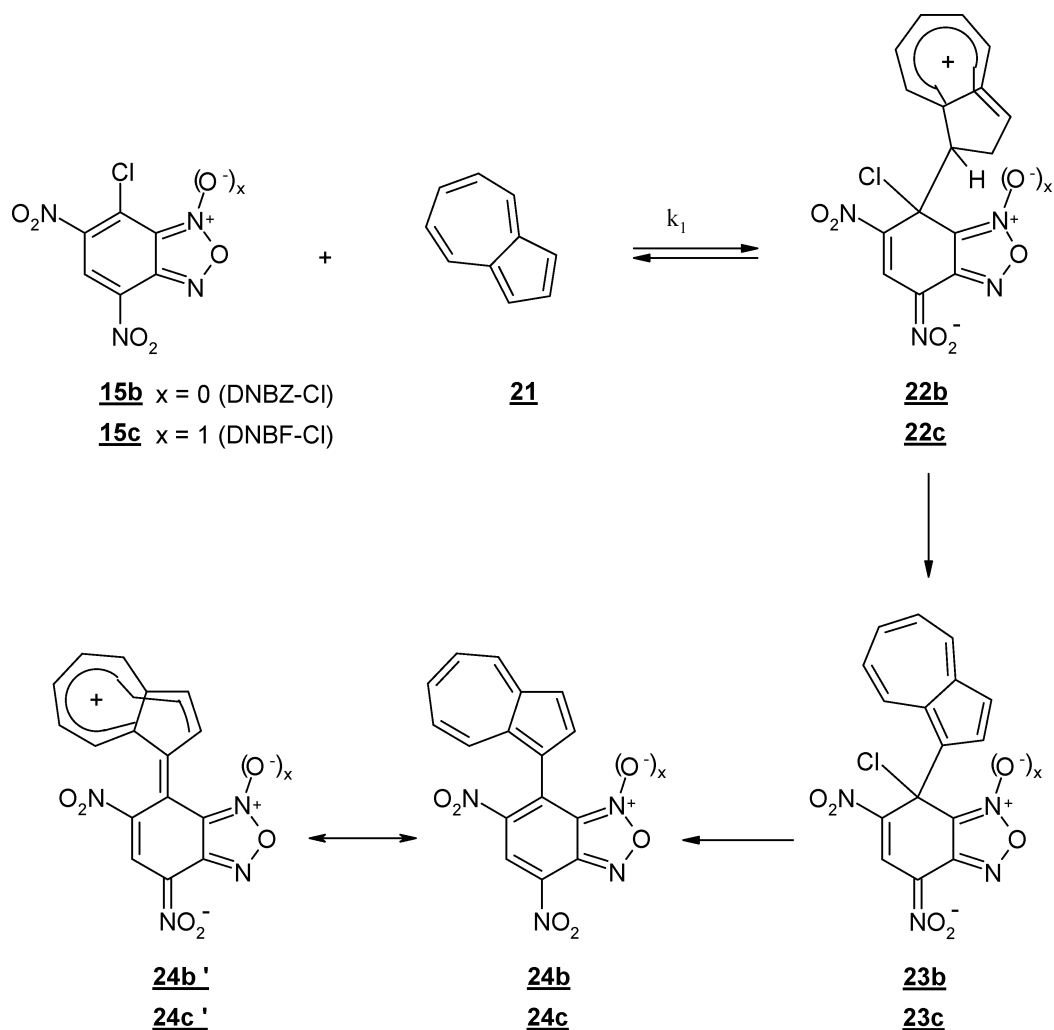
($pK_a^{CH} \geq 9$), the C–C coupling reactions of eqn (9) proceed only under considerable difficulty.



Furthermore, it is noteworthy that the overall S_NAr substitutions of DNBF-Cl and DNBF-Cl with aromatic or heteroaromatic

π -excessive structures are the result of a three-step rather than a two-step process. This is shown in Scheme 5 in which the initial addition of the nucleophile, here azulene **21**, affords a zwitterionic Wheland–Meisenheimer intermediate (**22b** or **22c**).^{64,65} In fact, it is only recently that such intermediates could be firmly characterized by NMR spectroscopy and kinetic experiments in the reactions of superelectrophilic DNBF with supernucleophilic tris-1,3,5-(dialkylamino) benzenes **19** as well as 2-aminothiazoles.^{49,67} Following its formation, the zwitterion undergoes facile rearomatization of its arenonium or hetarenium moiety, a process which is energetically assisted by the recovery of aromaticity in the nucleophilic partner, to afford the classical anionic Meisenheimer intermediate **23b** or **23c** in S_NAr substitutions. Finally the process becomes completed through facile departure of chloride ion from the Meisenheimer complex to afford the substitution products **24b** and **24c**.^{64,65}

A kinetic investigation of the C–C couplings, not only of azulene but of a large series of indoles and 1,2,5-trimethylpyrrole, could be made, including with the use of nucleophiles deuterated at the reaction site.⁶⁵ This study has revealed the absence of isotope effects, in accord with a rate-limiting nucleophilic addition step, allowing one to reject an alternative two-step mechanism in which



Scheme 5

the zwitterion, e.g. **22**, will directly eliminate HCl in a vicarious-type process.¹² Table 2 shows that the rate constants for reaction of DNBF-Cl and DNBZ-Cl are similar and lower by a factor of 20–90 than in coupling with DNBF. This decrease supports the S_NAr character of the substitutions, being simply the reflection of a general feature, namely that nucleophilic addition occurs always faster at an unsubstituted than at similarly activated substituted carbon.^{6,8,10,12,13}

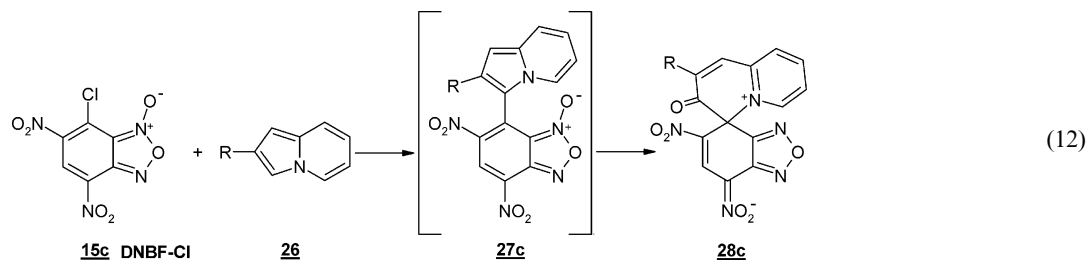
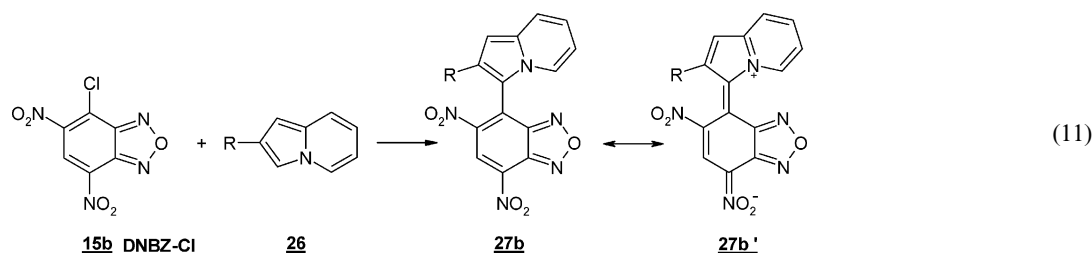
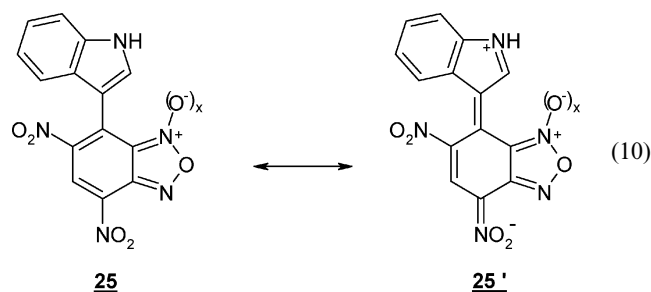
At this stage, a comment has to be made regarding the structure of the products obtained. In carrying out substitutions involving initial addition of such bulky nucleophiles as azulene or indoles, one could have anticipated that the so-called Boulton–Katritzky rearrangement might be operating, leading eventually to the formation of the products as a mixture of two isomers.⁶⁸ Importantly, no evidence for such a rearrangement has been found in reactions such as those described in Scheme 5, as it has also been the case with the reaction systems so far discussed.

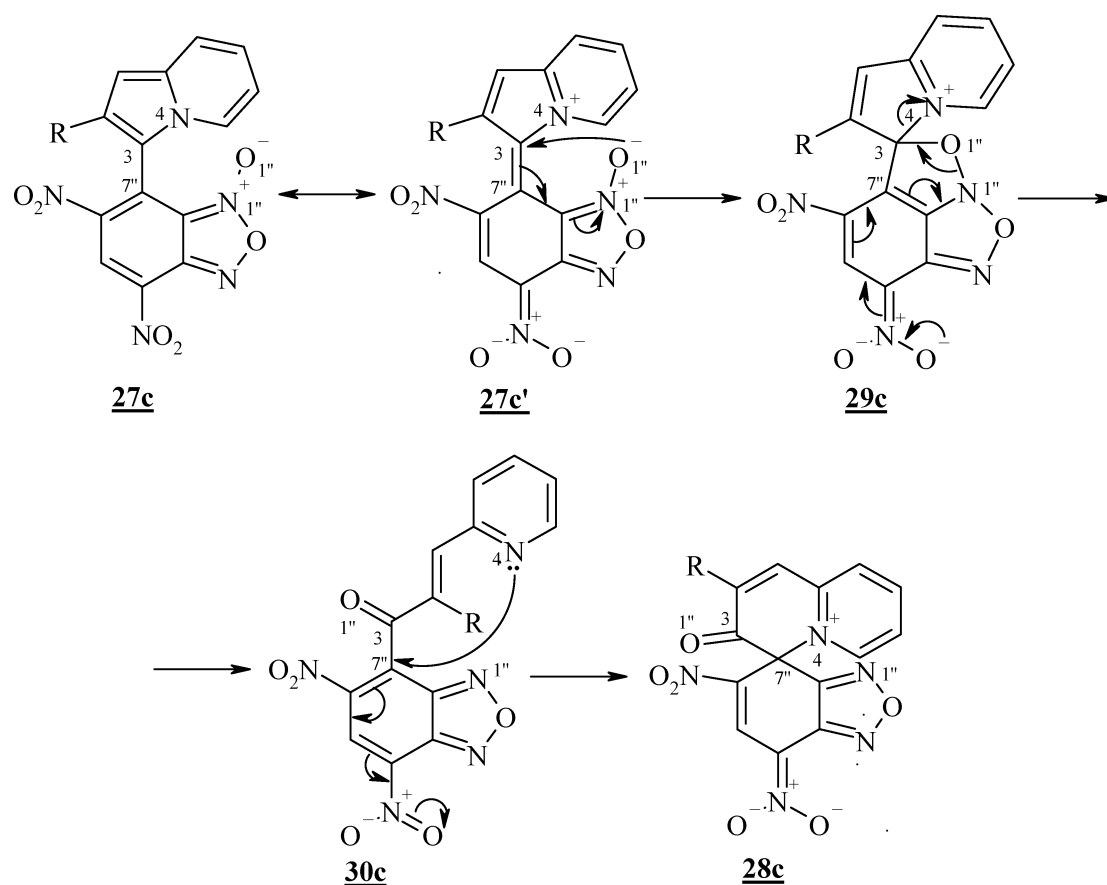
Inducing intramolecular charge transfer through superelectrophilic DNBF and DNBZ fragments

A significant finding illustrating the extreme electron-deficiency of the superelectrophilic structures is that the substitution products are all isolated as strongly colored crystals, showing intense absorption at long wavelengths ($\lambda_{\text{max}} = 500\text{--}600$ nm in acetonitrile).^{64,65} This reveals that a strong intramolecular charge transfer process takes place between the electron-rich donor moiety and the electron-deficient acceptor DNBF or DNBZ moiety, as depicted by the resonance structures **25** and **25'** in eqn (10) for indoles, and the resonance structures **24** and **24'** in Scheme 5 for azulene. Despite the fact that full coplanarity between the two rings is precluded by steric effects, the strong intramolecular charge transfer interaction is supported by both X-ray and spectroscopic data.^{64,65}

Overwhelming evidence for intense charge transfer in the S_NAr substitution products is the different behaviour of DNBZ-Cl and

DNBF-Cl upon reaction with indolizines **26**.⁶⁹ In this instance, DNBZ-Cl behaves as with other carbon nucleophiles to give the expected substitution products **27b** (eqn (11)). These are subject to the same intense intramolecular charge transfer as the indole, pyrrole or azulene analogues, with λ_{max} values up to 780 nm. In contrast, carrying out the reactions of DNBF-Cl with indolizines under the same experimental conditions leads to exclusive formation of the spiro adducts **28c** (eqn (12)). Based on a successful ¹H NMR characterization of the expected substitution products **27c** as transient species, a reasonable mechanism accounting for formation of the spiroadducts **28** is given in Scheme 6.⁶⁹ In this scheme, the intense charge transfer discussed above is the key factor determining the conversion of **27c** into adducts **28c**, reflecting the extreme capability of dinitro-benzofurazan and -benzofuroxan moieties to accommodate negative charge. This charge transfer has the effect of generating a positively charged indolizinium moiety, thereby promoting nucleophilic attack at the electron-deficient C-3 center of **27c'** by the negatively charged oxygen atom of the N-oxide functionality. The result is the formation of a five-membered isoxazole ring (**29c**), which becomes prone to undergo N1''–O1'' and C3–N4 bond breakings, to afford the 7-substituted-4,6-dinitrobenzofurazan **30c**, presumably through a concerted process. In a last step, intramolecular nucleophilic addition of the moderately basic pyridine nitrogen of **30c** takes place at C7''. This process is facilitated by the superelectrophilic character of the 4,6-dinitrobenzofurazan structure, leading to the spiro adducts **28c** whose stability is made possible by the delocalization of the positive charge over the pyridine ring.⁶⁹





Scheme 6

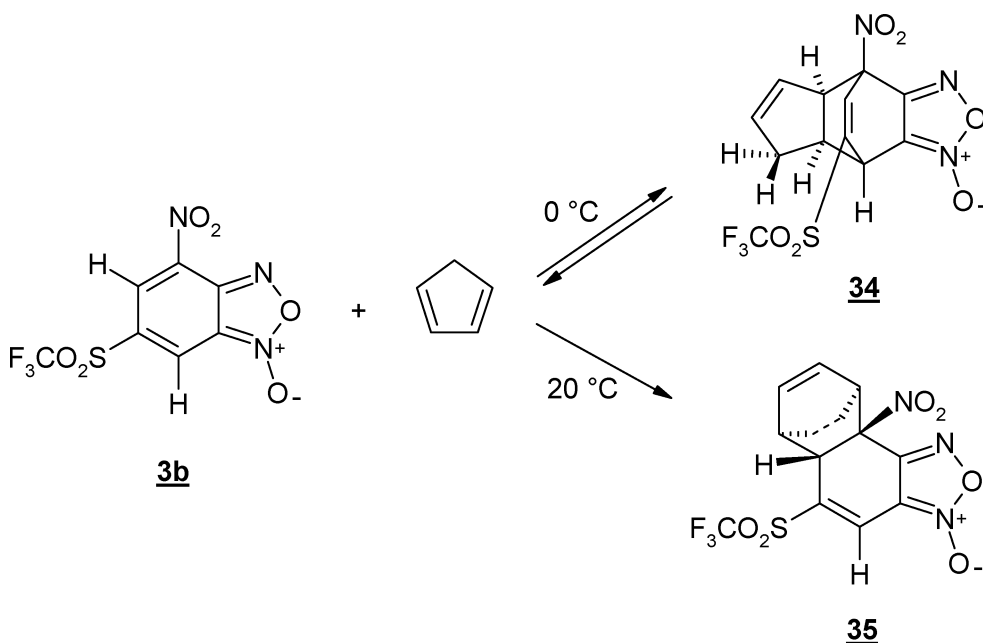
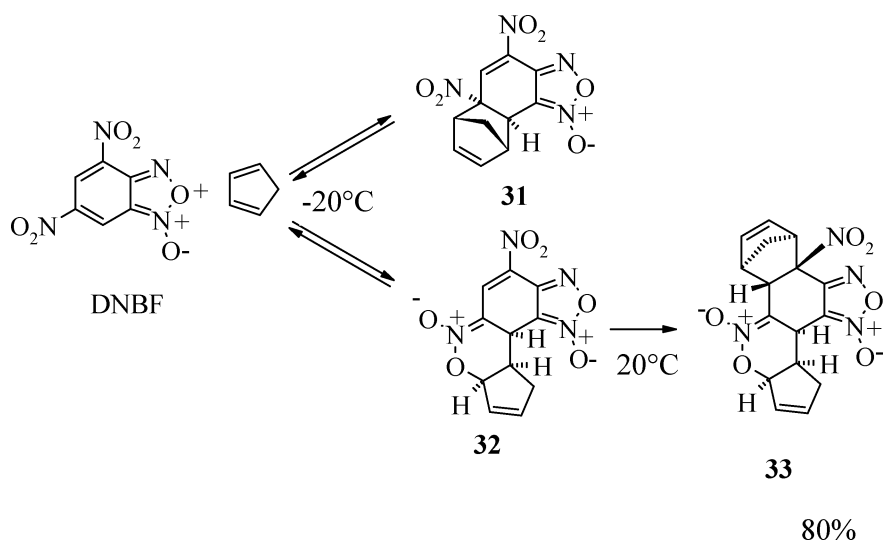
The dual Diels–Alder behaviour of superelectrophilic heteroaromatics

It has been recognized that two major factors contribute to the extremely high electrophilic reactivity of DNBF and related 10π -electron heterocycles. The first is the cumulation of the powerful electron-withdrawing effects of the two nitro groups and the annelated ring.^{8,19,40,41,70} This results in a significant electron-deficiency at C-7, thereby favoring nucleophilic attack at this position, while contributing to a strong stabilization of the resulting σ -adducts, as discussed so far. The second is the low aromaticity of the six-membered carbocyclic or pyridine ring.^{38,71} In this respect, the discovery of multifaceted Diels–Alder behaviour, first noted by Kresze and Bathelt,⁷² is of particular interest. As illustrated in Scheme 7, which refers to the DNBF/cyclopentadiene system,^{73a} DNBF can formally behave as nitroalkenes do,^{74,75} being susceptible to act as a dienophile in normal-electron demand processes as well as a heterodiene in inverse electron demand processes.^{38,73} In Scheme 7, the reaction initially affords a mixture of the two stereoselective NED and IED adducts **31** and **32**. Because the remaining nitroolefinic fragment of these monoadducts is also very reactive, diadduct formation subsequently occurs, proceeding here with high stereoselectivity to give the highly functionalized structure **33** as the thermodynamically stable product of reaction.^{73a}

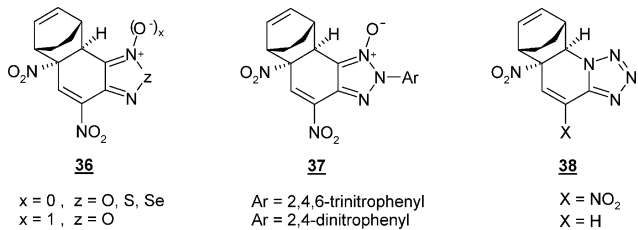
Another remarkable pathway is the reactivity of 4-nitro-6-trifluoromethanesulfonylbenzofuroxan **3b** whose six-membered

carbocyclic ring is found to act as a carbodiene, affording the adduct **34** at 0° C, which could be isolated and characterized by X-ray crystallography.⁷⁶ Keeping this adduct in solution and allowing the temperature to rise to room temperature leads to its conversion into the thermodynamically more stable NED adduct **35** (Scheme 8). Other reported Diels–Alder processes worth mentioning include a heterodienic contribution of the annelated furoxan ring of 4-nitro-6-trifluoromethyl- and 6-nitro-4-trifluoromethyl-benzofuroxans, **3e** and **3f**,⁷⁷ and a dienophilic reactivity of the NO groups of the dinitroso intermediate associated with the 1-oxide/3-oxide tautomerism which has been found to operate in the case of 4-aza-6-nitrobenzofuroxan **3h** (Scheme 9).³⁸

In the context of assessing the ease of Diels–Alder reactivity of the various electrophiles so far discussed, a major feature has been that the reactions with cyclohexadiene proceed exclusively *via* a NED process to afford the diastereomers **36**, **37** and **38**, respectively.^{54,73} This has allowed a thorough NMR investigation of these reactions leading to the results collected in Table 3. These reveal that the ease of pericyclic reactivity is closely related to the ease of σ -complexation of the electrophiles as measured by the $pK_a^{\text{H}_2\text{O}}$ values.³⁹ Thus, the most electrophilic heteroaromatics, *i.e.* DNTP, DNBF, DNBZ and the *N*-picrylbenzotriazole 1-oxide **5a** react quantitatively even though the time required to achieve cycloaddition increases with increasing $pK_a^{\text{H}_2\text{O}}$. Going to moderately activated electrophiles like DNBS (**3i**), the *N*-2,4-dinitrophenylbenzotriazole 1-oxide **5b**, 6-nitrotetrazolopyridine (**7b**) or DNBS (**3k**), the cycloaddition proceeds more slowly and



does not reach completion after 7 days. As for the electrophiles with $pK_a > 8-9$, they do not react at all with cyclohexadiene.



It follows from the above results that, in general, the $pK_a^{H_2O}$ values are valuable predictors of whether DA adducts would form and how rapidly. The order of pericyclic reactivity with common dienes is $DNTP > DNBF \approx DNBS > Pi\text{-DNBT} > DNBS_{Se} \gg NTP \approx DNBS$. DA adduct formation with $Pi\text{-DNBT}$ and NTP further

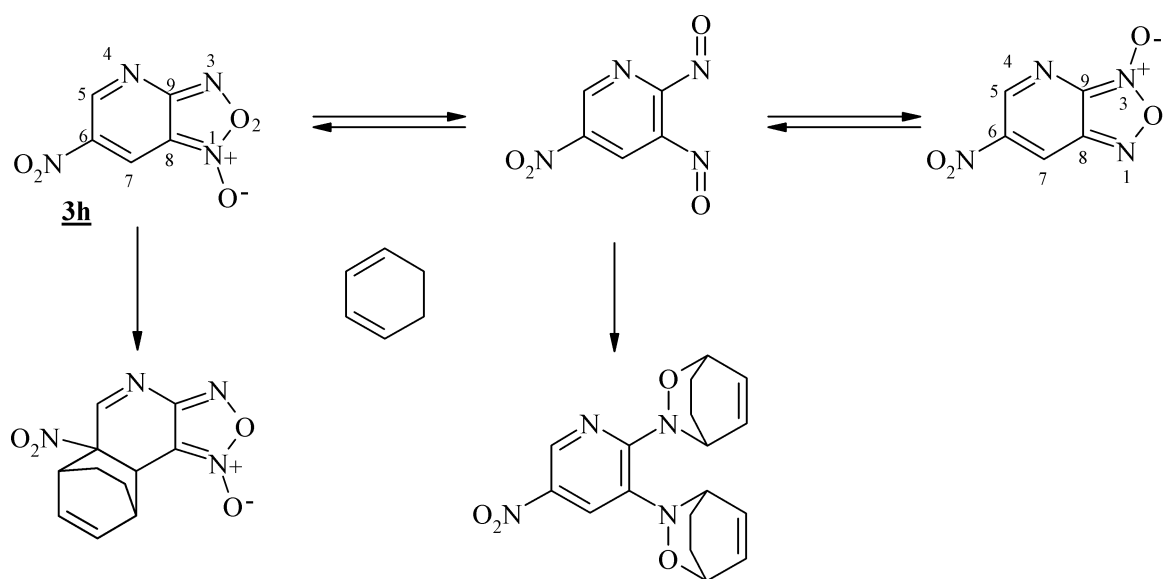
defines the demarcation line for σ -complexation and pericyclic reactivity with a $pK_a^{H_2O}$ value of 7.5–8 as the boundary between super- and normal-electrophiles and between reactive dienophiles and inert partners in Diels–Alder reactions.^{39c}

It is worth noting, however, that the above classification has to be modulated to take account of the greater or lesser reactivity of the dienes reacting with the heteroaromatics. In fact, use of highly electron-rich dienes such as the Danishefsky diene is still possible with the less electrophilic heterocycles. This is illustrated in Scheme 10, which shows that 7-chloro-4-nitrobenzofurazan **15a** reacts efficiently with this diene, allowing in three steps an easy access to a functionalized hydroxynaphthofurazan, **42**, which is obtained under mild conditions with an overall yield of 80%. All intermediates shown in Scheme 10, *i.e.* **39a,b**, **40a,b** and **41** have been characterized.⁷⁸

Table 3 Diels–Alder reactivity for selected nitro-substituted heteroaromatics

Parent electrophile		Electrophilic reactivity		Pericyclic reactivity adduct formation (%) ^a				
		<i>E</i> ^b	p <i>K</i> _a ^{H₂O}	2 h	8 h	24 h	48 h	7 days
7a	DNTP	−4.67 ^b	0.4	87	100	100	100	100
3a	DNBF	−5.06 ^b	3.75	70	100	100	100	100
3i	DNBZ	−5.46 ^b	3.92	65	100	100	100	100
5a	Pi-DNBT	−7.63	6.70	—	38 ^c	62	100	100
3l	DNBSe	−7.40	6.34	—	—	~10	30	60
5b	DNP-DNBT	−7.93	7.15	—	—	—	~10	~30
3k	DNBS	−8.40	7.86	—	—	—	~17	40
7b	6-NTP	−9.05 ^b	7.55	—	—	—	~5	~15
5c	NP-DNBT	−9.16	9.00	—	—	—	—	—
3j	4-NBZ	−9.85 ^b	10.07	—	—	—	—	—
3g	4-NBF	−10.04 ^b	10.37	—	—	—	—	—

^a As measured with reference to mixing of equimolar amounts of the electrophile and cyclohexadiene and NMR monitoring of the conversion into the DA monoadduct at room temperature in acetonitrile, see ref. 39c. ^b *E* values from ref. 39. ^c 4 h after mixing.

**Scheme 9**

It is further evident that the above results point to a common origin for the σ -complexation and pericyclic processes, suggesting in fact that the cycloadditions at hand have a strong polar character, going through either a strongly asynchronous concerted route involving a zwitterionic-like transition state (TS) or through an ionic two-step pathway involving the initial formation of a zwitterionic σ -complex intermediate of some stability. This important mechanistic outcome, especially in terms of stereochemistry, is part of our ongoing studies of the reactivity of these heteroaromatics. It is further discussed below on the basis of presently available results.

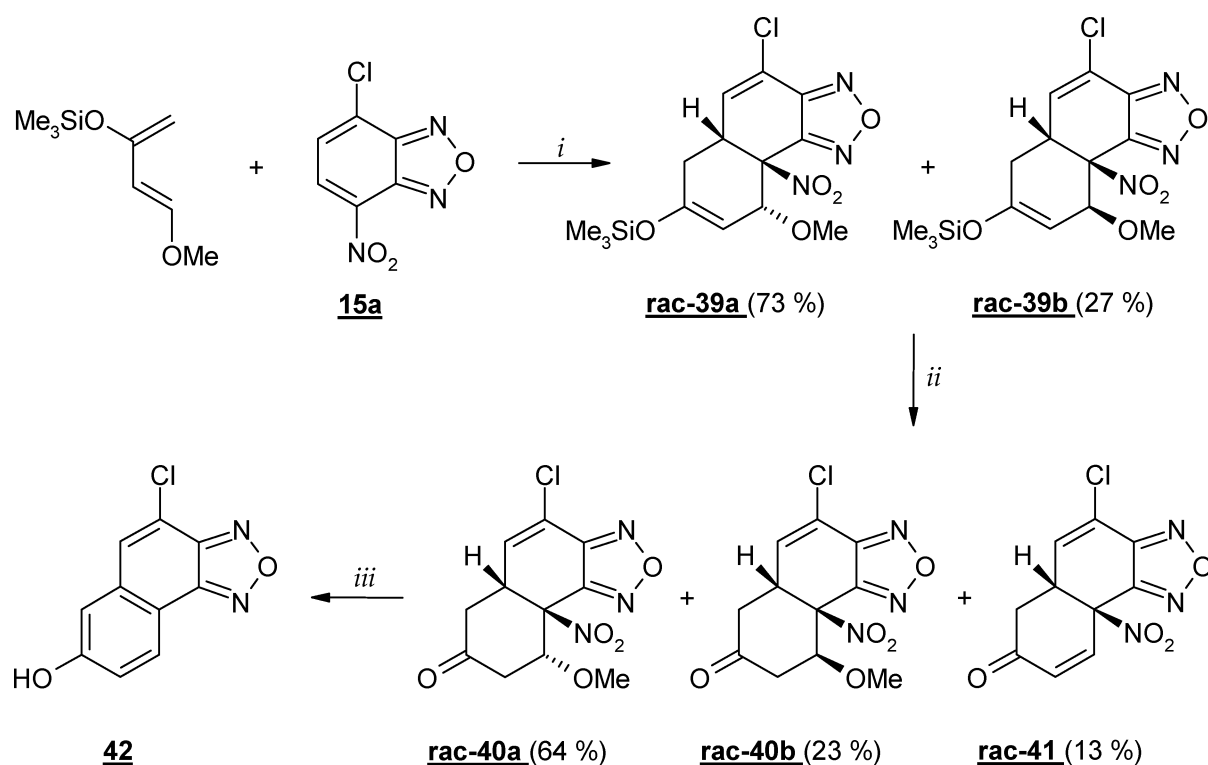
Electrophilicity indices. Experimental and theoretical

As discussed in an earlier section, the water addition σ -complexation process provides a suitable quantitative index of electrophilicity, covering both the domain of classical σ -complexes such as DNB and TNB and the superactive aromatic and heteroaromatic series spearheaded by the triflone TTSB and

also DNBF. Recently, there have been efforts to develop models which would be suitable for describing electrophile–nucleophile combinations in general. This work has followed largely along two fronts, namely the three-parameter eqn (13) put forward by Mayr,^{79,80} and the concept of global electrophilicity (ω) based on DFT theory.^{81–83} Also considered is current work based on electrochemical investigation of the rearomatization of σ -complexes and the construction of an E° scale.^{84–86} Herein, we examine the suitability of these models in the domain of S_NAr and σ -complexation reactions, and in particular as far as superelectrophilic reactivity is concerned.

Viewing the superelectrophilic dimension through the p*K*_a^{H₂O} scale and Mayr's *E* scale

In the last decade, a new and general approach to nucleophilicity and electrophilicity has been developed by Mayr and coworkers.^{79,80} Using a large series of diarylcarbenium ions and various π -excessive systems as reference sets for electrophiles and nucleophiles, respectively, these authors have shown that it is



Scheme 10 Illustrating the detailed reactivity patterns of the reaction of NBD-Cl (**15a**) with Danishefsky diene, affording in a one-pot reaction the naphthofurazan **42** in $\geq 80\%$ yield.

possible to describe the rates of a large variety of electrophile–nucleophile combinations by the three-parameter eqn (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. Based on eqn (13), general electrophilicity (E) and nucleophilicity (N) scales, each covering a reactivity range of about 40 orders of magnitude, have been defined and successfully used to assess the reactivity of many families of electrophile and nucleophile substrates as well as to predict the feasibility and rates of many interactions:^{79,80}

$$\log k (20^\circ\text{C}) = s(N + E) \quad (13)$$

This makes it worthwhile to address the question of whether S_NAr substitutions and related σ -complex reactions represent a group of nucleophile–electrophile combinations, which can be classified under the Mayr relationship. Obviously, a ranking of our series of electrophiles on the E scale will allow to assess their reactivity in a more general context than the one provided by the $pK_a^{H_2O}$ scale.

Selecting a set of reference nucleophiles consisting of calibrated indoles, pyrroles and enamines of known N and s parameters, the rate determining k_1 rate constants for the coupling of these reagents with most of the electrophilic structures considered in this work have been measured in acetonitrile; see Schemes 3, 4 and 6 for the significance of the second-order rate constant k_1 .^{39,45} Plots of $(\log k_1)/s$ vs. N for each of the electrophiles result in a series of parallel lines exhibiting slopes equal or very close to unity, as expected from eqn (13). This is illustrated in Fig. 4 for DNBF and DNBF-Cl, leading to a straightforward determination of the electrophilicity parameters for the various electrophiles (Tables 1

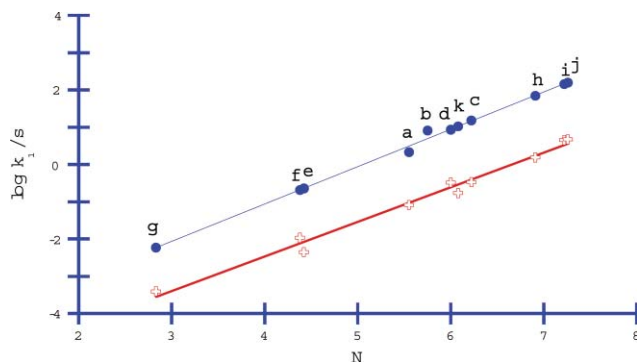


Fig. 4 Determination of the electrophilicity parameters E for DNBF (upper line) and DNBF-Cl (lower line), using the following set of indoles as reference nucleophiles:⁶⁵ (a) indole; (b) N-methylindole; (c) 5-methoxyindole; (d) 5-methylindole; (e) 5-methoxy-2-methylindole; (f) 5-bromoindole; (g) 5-cyanoindole; (h) 2-methylindole; (i) 2,5-dimethylindole; (j) 5-methoxy-2-methylindole; (k) 5-chloro-2-methylindole.

and 3). It is thus clear that the electrophilicity of these substrates, representing an extended series of neutral electron-deficient aromatics and heteroaromatics of widely different reactivity and structure, is appropriately described by eqn (13). This adds to the general significance of this relationship, which was originally mostly developed by modulating the strength of the electrophilic partner through structural variations of carbocationic structures.⁷⁹

The ranking of the calibrated electrophiles on the Mayr electrophilicity scale is shown in Fig. 5, which makes possible a comparison of their reactivity with that of representative structures previously classified by Mayr. On this basis, a comprehensive

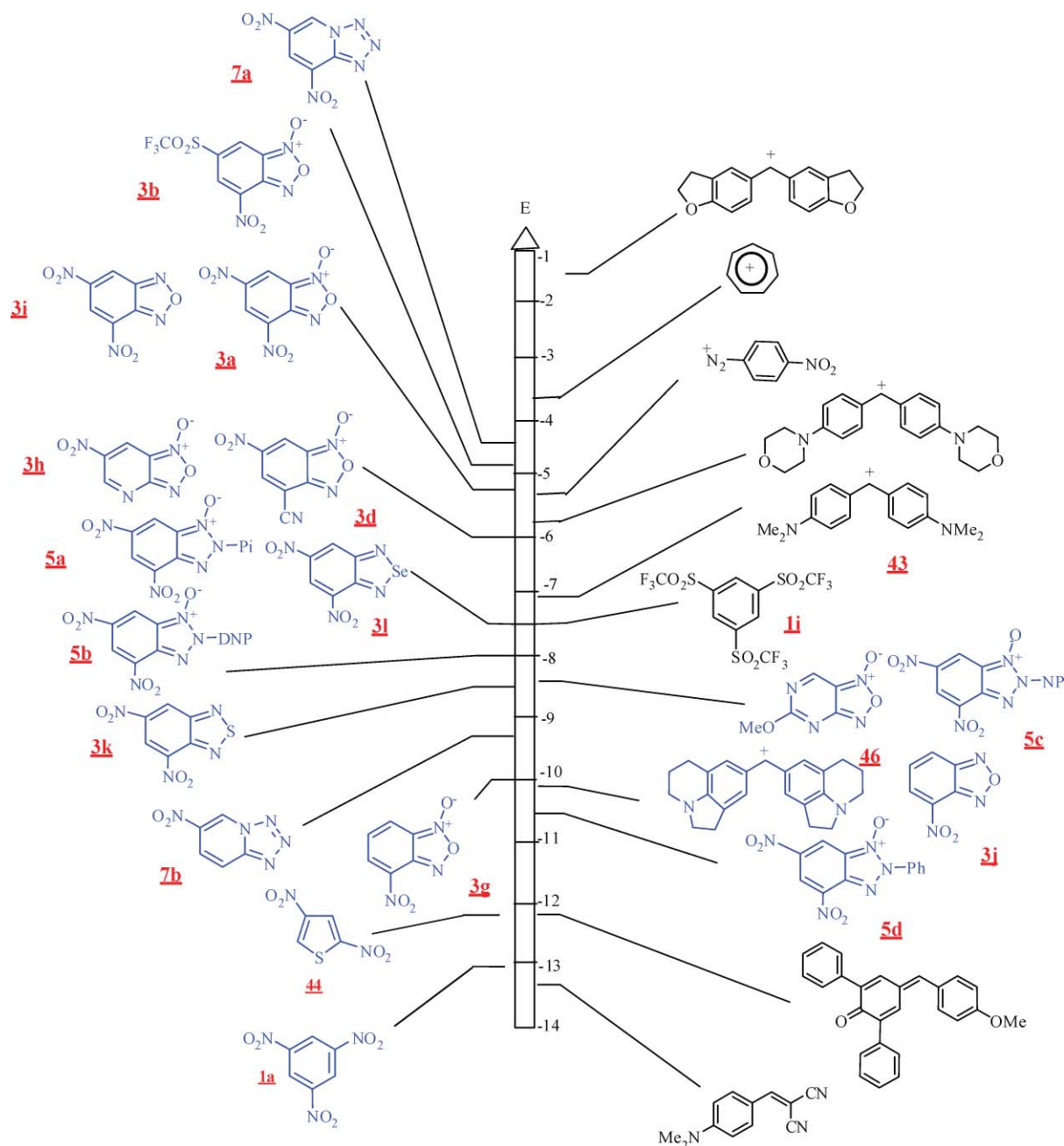


Fig. 5 Ranking of neutral electrophilic aromatics and heteroaromatics on the electrophilicity scale (E) defined for carbocationic structures and some uncharged electrophiles such as arylidene malonitriles and quinone methides.^{79,80}

understanding of the superelectrophilic dimension is possible in a general context. Within the E scale of Mayr, measured E values for the whole series of our electrophiles embraces a domain of reactivity of more than 8 orders of magnitude. This goes from $E \approx -5$ for the most electron-deficient compounds, DNTP, **3b**, DNBF and DNBFZ, to -13.19 for the less electron-deficient substrate, TNB, thus validating previous ordering of such electrophiles.^{39,45,87}

Referring to the set of cationic electrophiles used to construct the E scale, the finding of $E \approx -5$ for DNTP, triflone **3b**, DNBF and DNBFZ, indicates that these four heteroaromatic substrates are two orders of magnitude more electrophilic than Michler's hydrol blue ($E = -7.02$; structure in Fig. 5), *i.e.* the bis(4-

dimethylamino)phenyl carbenium ion **43**.^{79,80} More importantly, the four afore-quoted compounds exhibit an electrophilicity that compares well with that of the 4-nitrobenzenediazonium cation ($E = -5.1$), approaching in fact that of the most reactive members of the tropylium cation family ($E = -3$ to -6), as well as a number of metal-coordinated carbenium ions.⁷⁹ This ranking is in fact consistent with kinetic evidence that DNBF is as prone as the 4-nitrobenzenediazonium cation to undergo C–C couplings with π -excessive substrates such as indoles or pyrroles.^{196,47,57} As can be seen in Table 2, the rates of complexation of DNBF by indole, *N*-methylindole and 2-methylindole are twice higher than the rates of coupling of these weak carbon nucleophiles

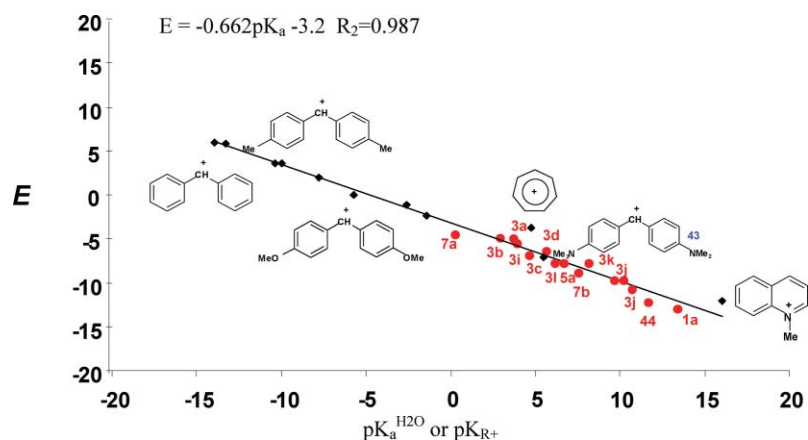


Fig. 6 Correlation of the electrophilicity parameters E of electrophilic aromatics and heteroaromatics and of some carbocations with the corresponding $pK_a^{H_2O}$ or pK_{R^+} values of these species in aqueous solution. To be noted is that the correlation applies to many other carbocationic structures (not shown for clarity of the figure).

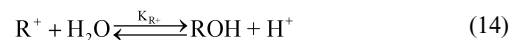
with the most reactive 4-nitrobenzenediazonium cation. All other benzenediazonium cations are much less reactive than DNBF, further emphasizing the exceptional electrophilic behaviour of this electron-deficient heteroaromatic. A similar high reactivity of DNTP, **3b**, DNBS as well as the azanitrobenzofuroxan **3h** ($E = -5.86$) towards weak carbon nucleophiles has been recently reported.^{39a}

Also classified as superelectrophiles on the $pK_a^{H_2O}$ scale for covalent hydration, the two cyanitrobenzofuroxans **3c** and **3d**, 4,6-dinitro-2,1,3-benzoselenadiazole **3l** and the picryl benzotriazole **5a** have E values varying from -6.41 to -7.63 . Thus, these electrophiles fall close to the Michler carbenium ion **43**, suggesting that this cationic structure may be an appropriate anchoring to define the superelectrophilic dimension on the E scale. On this ground, the ranking of **5b** (DNP-DNBT) and DNBS as borderline superelectrophiles is a reasonable proposal since these compounds have E values which are one order of magnitude more negative than that of **43**. Going to strongly negative E values, $E = -9$, clearly defines the region of normal electrophilicity. With E between -9 and -10 , the reactivity of the mononitrotetrazolopyridine **7b** (NTP), the two benzotriazoles **5c** and **5d** and the mononitrobenzofuroxan and -benzofurazan **3g** and **3j**, is comparable to that of neutral Michael acceptors, e.g. benzylidenemalonitrile ($E = -9.42$). Lastly, 2,4-dinitrothiophene **44** ($E = -12.33$) and TNB ($E = -13.19$) are by far the two weakest electrophiles of our series, falling in the domain of the less reactive arylidenemalonitriles and quinone methides.^{88,89}

$pK_a^{H_2O}$ vs. E relationship

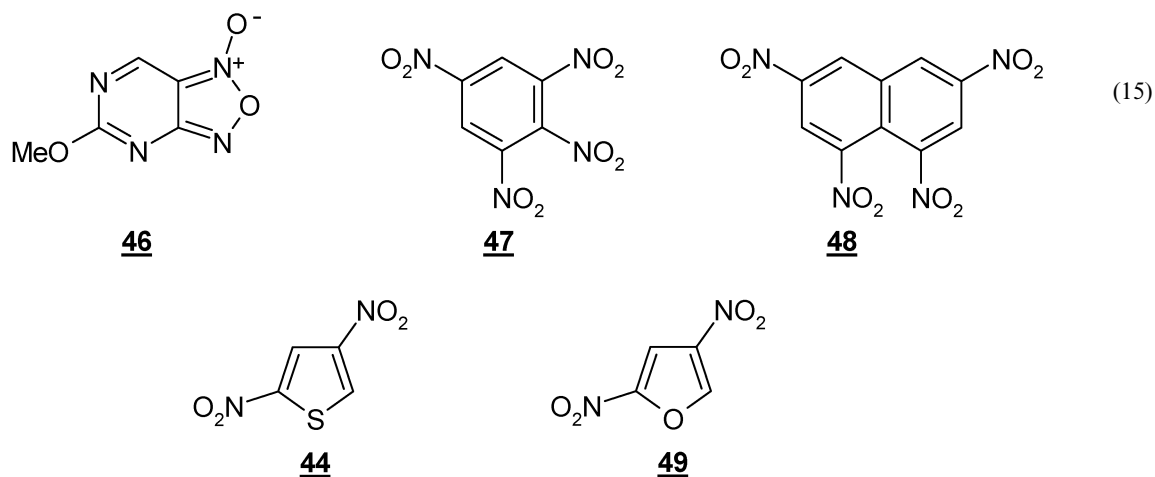
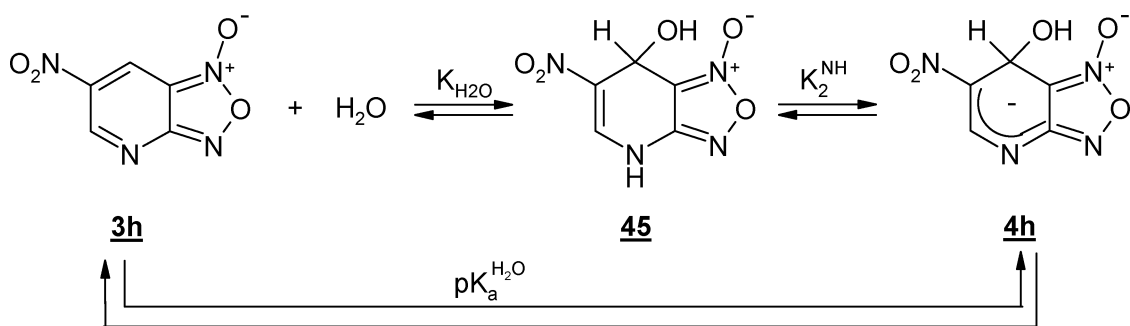
There is a remarkable link between the $pK_a^{H_2O}$ and E scales reflecting the reactivity of the present series of electrophiles. As shown in Fig. 6, E values determined in acetonitrile are linearly related to $pK_a^{H_2O}$ values for water addition to these neutral substrates in aqueous solution.^{39,53} This defines a correlation which is found to coincide nicely with the comparable correlation reported by Mayr by plotting E values of a large variety of carbocations *versus* the Lewis acidities of these species (pK_{R^+} ; eqn (14)) in aqueous solution.^{39,53,79,90}

This shows convincingly that the E scale defined by Mayr applies very well to our family of uncharged electron-deficient π -systems, further confirming the generality of eqn (13). Of particular interest is that the correlation of Fig. 6 enables a straightforward translation of the $pK_a^{H_2O}$ value 7.5–8 demarcating the boundary between super and normal electrophiles on the $pK_a^{H_2O}$ scale (a thermodynamic index in aqueous solution) into a value of $E \approx -8$ on the general electrophilicity E scale (a kinetic parameter in acetonitrile) of Mayr.^{39,53}



In as much as the above correlation is of general application to σ -complexation processes, it provides a tool to delineate the reactivity of systems for which only one of the two parameters, $pK_a^{H_2O}$ or E , is experimentally accessible. An illustrative example deals with the azanitrobenzofuroxan **3h** (ANBF), which shows a high tendency to form the stable covalent hydrate **45** in aqueous solution (eqn (15)).³⁸ In this instance, the $pK_a^{H_2O}$ value for formation of the anionic σ -complex **4h** could only be approximated from the sum of the hydration ($K_{H_2O} \approx 100$ – 1000) and NH ionization ($pK_a^{H_2O} = 5.79$) reactions, leading to a $pK_a^{H_2O}$ falling in the range 2.8–3.8.³⁸ Using in turn the E value determined accurately from a kinetic investigation of the C–C coupling of **3h** with various nucleophiles according to Mayr's methodology, a more accurate $pK_a^{H_2O}$ value of 4.06 could be derived.^{39a} Similarly, the unknown $pK_a^{H_2O}$ value for σ -complexation of 4,6-diaza-5-methoxybenzofuroxan **46** could also be estimated from measurement of its E parameter, $pK_a^{H_2O} = 7.8$.^{39a,91} Such a positioning goes along with a borderline electrophilic behaviour of **46**. Similarly, the E values of 1,2,3,5-tetranitrobenzene **47**, 1,3,6,8-tetranitronaphthalene **48** and 2,4-dinitrofurane **49** can in turn be predicted from $pK_a^{H_2O}$ values, $E = -9.57$ for **47**; $E = -9.79$ for **48**; $E = -8.81$ for **49**.⁵³ While the two former values fall in the domain of weak electrophiles, the value for 2,4-dinitrofurane approaches the boundary, reflecting a notable electrophilic character of this five-membered ring heterocycle.^{16c}

As discussed by Mayr, a given electrophilic reagent may be expected to react with a nucleophile at room temperature provided that the sum $E + N$ of the electrophilicity and



nucleophilicity parameters of the two partners be ≥ -5 .⁷⁹ On this basis, the successful positioning of aromatic and heteroaromatic electrophiles on the E scale makes it possible to anticipate whether each of these substrates can react readily or not with a given nucleophile on the N scale. Such an approach is important to define the individual domains of reactivity, a feature which will be of real benefit to broaden the range of synthetic and analytical applications of σ -complexation and S_NAr substitutions. As an example, the superelectrophilicity of DNBF or DNBF-Cl has been successfully used to detect and quantify trace amounts of weakly basic compounds of high toxicity in the environment.^{30,92}

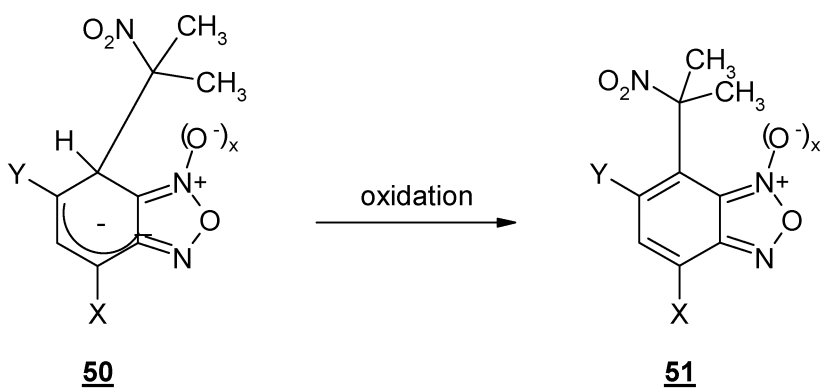
The E° scale

Regarding the $pK_a^{H_2O}$ scale, it could be reasonably anticipated that substitution of $pK_a^{H_2O}$ for another thermodynamic parameter would lead to a meaningful correlation. As a matter of fact, the chemical feasibility of oxidizing σ -adducts with rearomatization of the cyclohexadienyl moiety, and therefore completion of a substitution process through formal displacement of H^- has been considered.^{84-86,93} In particular, a detailed investigation of the electrochemical oxidation of the series of 2-nitropropenide adducts **50a-j** as well as of a few other DNBF adducts (see eqn (16) and structures **52-54**) has been made.^{84,94} The measured oxidation potentials E° are collected in Table 4 while Fig. 6 shows the correlation describing the changes in E° with varying $pK_a^{H_2O}$ values. Some available data pertaining to similar studies in the

benzene series are also given in Table 4. The results provide clear evidence that E° values mirror nicely the demarcating behaviour of normal- and super-electrophiles.

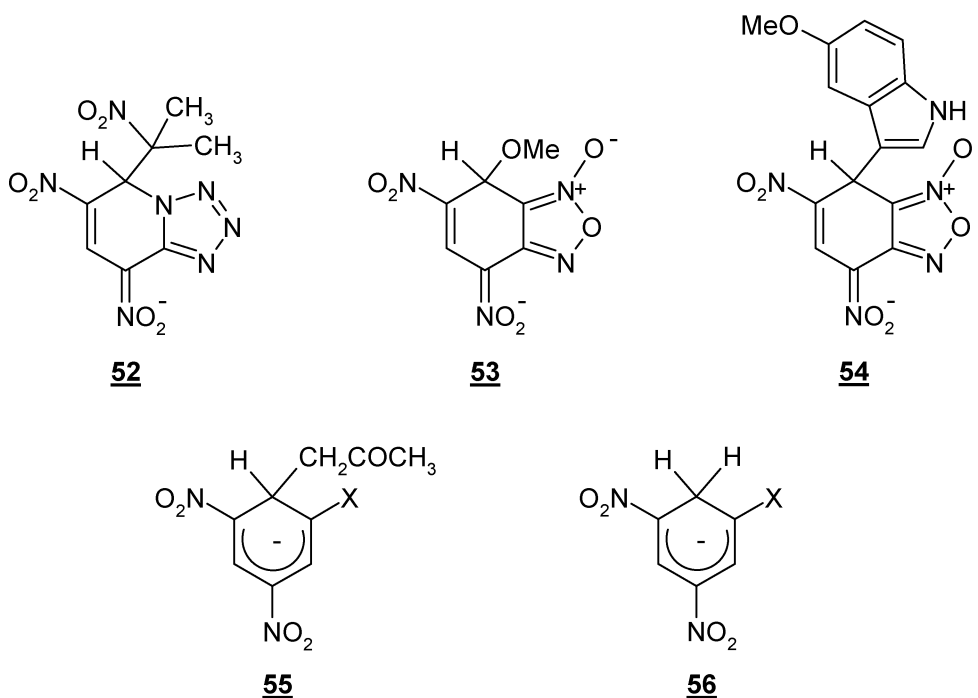
Fig. 7 shows that E° increases according to a satisfactory E° vs. $pK_a^{H_2O}$ linear relationship on going from the 4-nitro-benzofuroxan and -benzofurazan 2-nitropropenide adducts **50g** and **50j** to the 4,6-dinitro- or 4-nitro-6-trifluoromethanesulfonyl analogues **50a**, **50b** and **50i** to the 4,6-dinitro-tetrazolopyridine adduct **52**. This suggests that the propensity of charge delocalization in the cyclohexadienyl-type moiety of the adducts, and therefore the stability of these species, is a major factor governing the ease of the oxidation process. Consistent with this idea are two important findings: (1) the oxidation potential E° appears to depend very little on the moiety bonded at the sp^3 carbon, being similar for the three DNBF adducts **50a**, **53** and **54**. Although they refer to various experimental conditions, the data pertaining to benzene derivatives **55** and **56** show a similar trend.^{85,86} (2) The observed changes in E° within our series of 2-nitropropenide adducts parallel the changes in thermodynamic stability, as reflected by the linear relationship on plotting E° vs. $pK_a^{H_2O}$. Again, a similar situation emerges when comparing the E° values measured by Sosonkin *et al.* as well as Gallardo *et al.*, for the oxidation of adducts of TNB, DNB and related 3,5-dinitro-1-X-substituted benzenes **55** and **56**.^{85,86}

Going further in Table 4, it is noteworthy that the 4-nitro-benzofuroxan and -benzofurazan adducts are more stable by about 2 pK units but oxidize more readily than the TNB adducts ($\Delta E^\circ \approx 0.3$ V). In view of the accumulated evidence that the



- $n = 1$, (a) $X = Y = \text{NO}_2$; (b) $X = \text{NO}_2$, $Y = \text{SO}_2\text{CF}_3$;
 (c) $X = \text{NO}_2$, $Y = \text{CN}$; (e) $X = \text{NO}_2$, $Y = \text{CF}_3$;
 (f) $X = \text{CF}_3$, $Y = \text{NO}_2$; (g) $X = \text{NO}_2$, $Y = \text{H}$;
 $n = 0$ (i) $X = Y = \text{NO}_2$; (j) $X = \text{NO}_2$, $Y = \text{H}$

(16)



- (a) $X = \text{NO}_2$; (b) $X = \text{H}$;
 (g) $X = \text{CF}_3$; (j) $X = \text{COOEt}$;
 (k) $X = \text{CH}_3$; (l) $X = \text{OMe}$

- (a) $X = \text{NO}_2$; (b) $X = \text{H}$;
 (f) $X = \text{CN}$

aromatic character of a benzoxadiazole moiety is much lower than that of a benzene ring,^{8,38,71} the above trend is significant and can be readily understood. However, the important point of synthetic value is that the E° values fit well the experimental finding that the adducts **50g** and **50j** are readily rearomatized using the same mild oxidizing agents, *e.g.* Ag^+ or 2,3-dichloro-5,6-dicyanoquinone,

as those successfully employed for a number of TNB or DNB adducts.^{84,94}

Focusing on the other σ -adducts listed in Table 4, they are all notably more stable and therefore more reluctant to oxidation than **50g** and **50j**. In particular, there is a 10^6 – 10^7 increase in the equilibrium constant for adduct formation on going from

Table 4 The effect of complex stability on the oxidation potential E° of the σ -adducts^a

Parent Substrate	σ -adduct	E° / V (vs. SCE)	$pK_a^{H_2O}$
7a, DNTP	52	1.29	0.4
3b	50b	1.33	2.95
3a, DNBF	50a	1.15	3.75
	53	1.16	3.75
	54	1.06	3.75
3i, DNBZ	50i	1.12	3.92
3c	50c	0.96	4.65
3e	50e	0.94	6.50
3f	50f	0.91	8.19
3j, NBZ	50j	0.48	10.07
3g, NBF	50g	0.59	10.37
1a, TNB	55a	0.82	13.43
	56a	0.77	13.43
1f	56f	0.60	14.20
1g	55g	0.53	16.12
1j	55j	0.50	16.46
1b, DNB	55b	0.24	20.2
	56b	0.39	20.2
1k	55k	0.22	—
1l	55l	0.14	—

^a E° values for oxidation of adducts 50a–j and 52–54 taken from ref. 84 and 93. ^b E° values for oxidation of nitrobenzene adducts 55 and 56 taken from ref. 85 and 86. ^c Relevant $pK_a^{H_2O}$ values are for the most part taken from various sources quoted in ref. 10a; exceptions are the pK_a values for covalent hydration of the dinitrobenzenes 1j, 1k and 1l which have been estimated using the Strauss and Fendler approach.^{14,35}

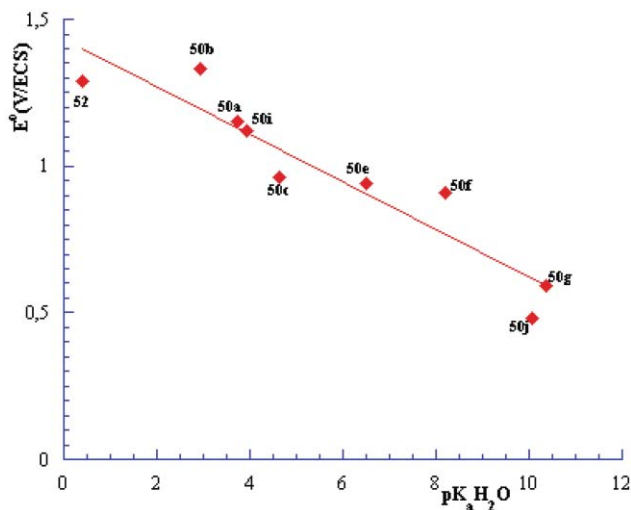


Fig. 7 Correlation of the oxidation potential of the nitropropenide adducts 50a–j and 52 with the $pK_a^{H_2O}$ values for formation of the related hydroxy σ -adducts.

4-nitrobenzofuroxan to superelectrophilic DNBF. As can be seen, this huge gain in adduct stability goes along with a 0.56 V increase in the oxidation potential, bringing E° to such a level that only strong oxidizing agents will be able to induce rearomatization of the carbocyclic ring.^{84,93} As a matter of fact, the experimental evidence is that chemical conversion of the DNBF adducts 50a, 53 and 54, as well as of the similarly stable DNBZ adduct 50i, can be achieved only with couples like Ce^{4+}/Ce^{3+} or MnO_4^-/Mn^{2+} (at pH 0).^{84,93} Also remarkable with respect to the definition of the superelectrophilic dimension in S_NAr and σ -complexation processes, is the especially powerful activating effect of the

SO_2CF_3 group which makes the 4-nitro-6- SO_2CF_3 -benzofuroxan adduct 50b the most stable complex studied in the benzofuroxan series.^{8,34,37,55} In this instance, the E° value is so high ($E^\circ = 1.33$ V vs. SCE) that the oxidation of 50b does not proceed satisfactorily with the two aforementioned couples, affording a so far unidentified high molecular weight product.^{84,93}

It follows from the above results that the difficulty in carrying out oxidative nucleophilic aromatic substitutions in the nitrobenzofuroxan and related series is primarily the reflection of the especially strong electron-deficiency of the six-membered ring of these heterocycles.

The global electrophilicity index

It has recently been pointed out that certain reactivity indices can be defined within the DFT that have proved very useful for predicting the feasibility as well as the mechanism of a number of electrophile–nucleophile reactions. These include the global electrophilicity index, ω , introduced by Parr and defined by eqn (17).⁸¹ In this equation, the electronic potential μ and the chemical hardness η of a substrate are two parameters which were evaluated in terms of the one-electron energies of the frontier molecular orbitals (FMOs), *i.e.* the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) at the ground state of the molecule: $\mu = \frac{1}{2}(\epsilon_H + \epsilon_L)$, $\eta = (\epsilon_L - \epsilon_H)$. Another informative index used by Domingo *et al.* is the so-called ΔN_{max} parameter, defined by eqn (18), which is a measure of the maximum amount of electronic charge that the electrophilic partner can accept.^{82,83}

$$\omega = \frac{\mu^2}{2\eta} \quad (17)$$

$$\Delta N_{max} = -\frac{\mu}{\eta} \quad (18)$$

Electrophile–nucleophile combinations which have been investigated through consideration of the ω values include a large variety of important polar reactions such as nucleophilic additions to activated C=C double bonds or coupling of nucleophiles with cationic electrophiles, *e.g.* benzhydryl and diazonium cations.^{82,83,95,96} Furthermore, recent work has been directed to understanding the polar nature of Diels–Alder reactions and other cycloadditions.^{82,96–98} Thus, it became of interest therefore to explore the potential which will be offered to S_NAr and σ -complexation reactions through application of the global electrophilicity approach.

Values of ω and ΔN_{max} calculated for our series of heteroaromatics are given in Table 1. In Fig. 8 is presented a graph plotting ω versus $pK_a^{H_2O}$. While showing several significant deviations, a reasonably linear relationship can be drawn. Clearly, a reasonable fit is obtained only when restricting the correlation to the behaviour of the 9 compounds having a carbocyclic six-membered ring and an annelated furazan, furoxan, thiadiazole or selenadiazole ring. On this basis, the points pertaining to 4,6-dinitro- and 6-nitro-tetrazolopyridines 7a and 7b, which have a six-membered pyridine ring, show a dramatic negative deviation reflecting a strongly underestimated reactivity. At the same time, the point for 4-aza-6-nitrobenzofuroxan 3h, which also has a six-membered pyridine ring, falls satisfactorily on the correlation line. In contrast, the points for 2-N-picryl-4,6-dinitrobenzotriazole

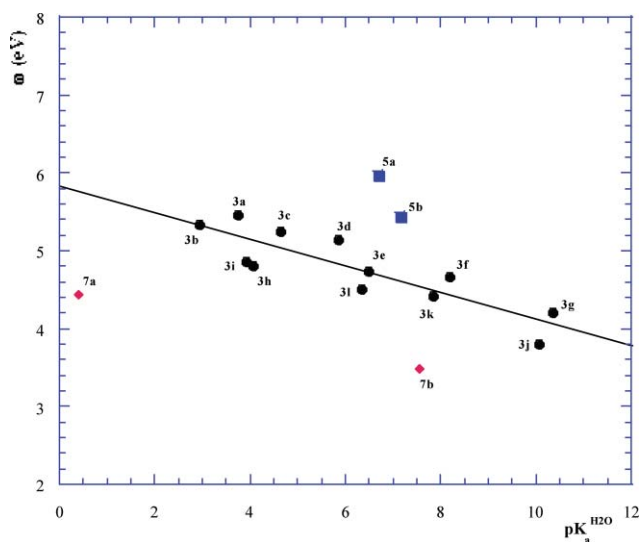


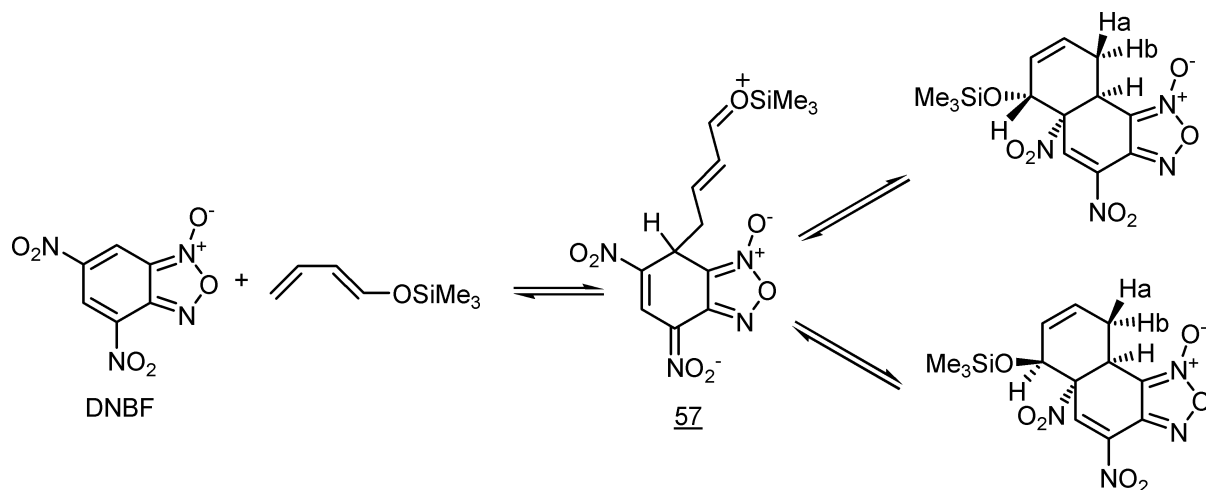
Fig. 8 The ω versus $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ correlation for nitrobenzofuroxans and related 10π -electron-deficient heteroaromatics.

1-oxide **5a** and the related 2-*N*-2',4'-dinitrophenyl compound **5b** show strongly enhanced ω values which correspond to a large overestimation of their reactivity. Overall, these results show that even within a similar class of reactions, the ω concept shows a marked sensitivity to structural variations, affecting the HOMO–LUMO properties.^{99,100}

Notwithstanding the above discussed deviations, an important message of Fig. 8 is that the ω values associated with all substrates referred to as in the ω vs. $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ correlation are very high, being in the range 3.80–5.46.^{82,96,101} This compares in particular with ω values for nitroalkenes such as nitroethylene ($\omega = 2.61$),⁸² *trans*- β -nitrostyrene ($\omega = 2.70$),⁹⁶ or 1,1-dinitro-2,2-diphenylethylene ($\omega = 3.16$),⁹⁶ as well as for a variety of carbonyl- and cyano-activated olefins, e.g. $\omega = 2.99$ for benzylidenemalonitrile.^{83d} The fact that the Diels–Alder behaviour of DNBF and other heterocycles can be viewed as reminiscent of the behaviour of nitroalkenes, supports the interest of this comparison.^{74,75} In fact, the two less reactive mononitro-benzofurazan and -benzofuroxan

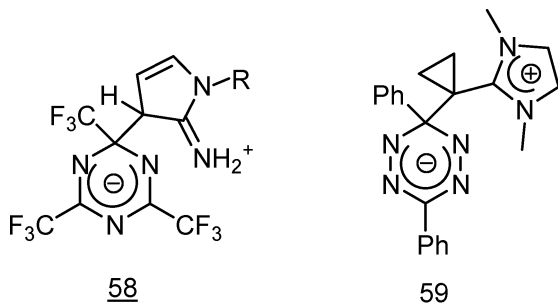
have ω values of 3.80 and 4.21, respectively, which are of the order of that describing the Diels–Alder reactivity of nitroethylene in the presence of a Lewis acid catalyst ($\omega = 4.33$ eV),^{82a} a system known to proceed *via* strongly polar pathways.^{74,75} It follows that the Diels–Alder reactivity of our heterocycles with typical dienes like cyclopentadiene ($\omega = 0.83$),^{82a} cyclohexadiene ($\omega = 0.90$),⁹⁹ 2,3-dimethylbutadiene ($\omega = 0.97$),⁹⁹ and more electron-rich dienes like 1-trimethylsilyloxybutadiene ($\omega = 0.73$)^{83a} or Danishefsky diene ($\omega = 0.65$)^{99b} is characterized by large $\Delta\omega$ and ΔN_{max} values. This criterion is recognized as associated with high polarity processes.^{82,83} Of particular interest is the case of DNBF whose ω value is ranked between that of tetracyanoethylene (TCNE; $\omega = 5.94$)^{83a} and 1-phenyl-2,4-triazoline-3,5-dione (PTAD; $\omega = 4.92$),^{99b} two strong electrophiles which have been shown to react with a number of dienes in two-step addition–cyclization processes involving the intermediacy of detectable zwitterionic intermediates.^{102–105}

Focusing especially on the behaviour of DNBF, the above results suggested the possibility that this heterocycle could be part of purely ionic processes, at least when opposed to electron-rich dienes such as 1-trimethylsilyloxybutadiene. Should this be the case, the reaction will occur as depicted in Scheme 11, through the intermediacy of a zwitterionic species **57** having the structure, and therefore the UV-visible absorption, of a DNBF σ -adduct ($\lambda_{\text{max}} = 460\text{--}480$ nm in acetonitrile).^{8,19,39–45} Such a σ -complex has in fact been recently observed and characterized not only by its typical maximum absorption at 480 nm, but also by ¹H and ¹³C NMR spectroscopy, and stopped-flow kinetics.^{99b} Confirming the electrophile–nucleophile character of the first step, the measured second-order rate constant k_1 for formation of the zwitterion **57** ($k_1 = 0.27$ M⁻¹ s⁻¹) obeys nicely Mayr's relationship, being in full agreement with the k_1 rate constant calculated from eqn (13) using the *E*, *N* and *s* parameters pertaining to the two reagents ($k_1 = 0.31$ M⁻¹ s⁻¹).^{99b} These results support the view that when a strong acceptor/electrophile such as DNBF is paired with a highly electron-rich donor/nucleophile diene, DA adduct formation likely proceeds in a step-wise manner *via* S_NAr-type intermediates. Conversely, with less electrophilic (electron deficient) acceptors and/or less electron-rich dienes any cycloaddition reaction tends towards an asynchronous concerted process.



Scheme 11

In addition to the zwitterionic intermediates characterized in systems involving TCNE, dimethyl dicyanofumarate or PTAD as electron-deficient dienophiles, it is noteworthy that such intermediates, e.g. **58**, have just been structurally identified in reactions of 2-aminopyrroles with 2,4,6-trifluoromethyl-1,3,5-triazines.¹⁰⁶ This extends previous identification of zwitterions such as **59**, in the reactions of substituted 1,2,4-triazines and 1,2,4,5-tetrazines with highly electron-rich dienes, namely 2-cyclopropylidene-1,3-dimethylimidazolidine.¹⁰⁷ A notable feature of these reactions, however, is that the ω values pertaining to the electrophilic heterocyclic structures are rather low ($\omega = 3\text{--}3.5$)^{99b,100} and do not really fit the criteria so far used to describe Diels–Alder reactivity.^{82,83}



Conclusion

Historically, measurements of $pK_a^{H_2O}$ values for water addition to electron-deficient aromatics and heteroaromatics led to the remarkable discovery that the classical domain covering the benzene series nitrobenzene, 1,3-dinitrobenzene, 1,3,5-trinitrobenzene ($pK_a^{H_2O} \approx 28, 20, 13$) could be strongly extended on going to 1,3,5-tris(SO_2CF_3)benzene ($pK_a^{H_2O} = 6.6$) and further still, to the series of annelated heteroaromatics with 4,6-dinitrobenzofuroxan ($pK_a^{H_2O} = 3.75$) upfront. Even lower $pK_a^{H_2O}$ values have since been measured for related substrates, namely 4,6-dinitrotetrazolopyridine (0.4) and 4-nitro-6- SO_2CF_3 -benzofuroxan (2.95). This led to recognition of the concept of superelectrophilicity in σ -complex formation and S_NAr substitutions. Subsequent investigations of reactivity followed with DNBF and related heteroaromatic structures toward weak nucleophiles such as aromatic amines, polyhydroxy- and alkoxy-benzenes, pyrroles, indoles, furans, enols, etc.

In this article we have highlighted some of the most significant areas where the superelectrophilic dimension has enabled one to reach a, so far, inaccessible domain of reactivity both in synthetic applications (Diels–Alder) and in classical structure-reactivity relationships. It has been shown that the S_NAr and σ -complexation reactions form an integral part of electrophile-nucleophile interactions recently developed by Mayr through the definition of general electrophilicity (E) and nucleophilicity (N) scales. Extension of the superelectrophilic dimension through application of DFT theory points to future directions that are on the horizon with these at first sight exotic molecules.

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