Mayr electrophilicity predicts the dual Diels–Alder and σ-adduct formation behaviour of heteroaromatic super-electrophiles

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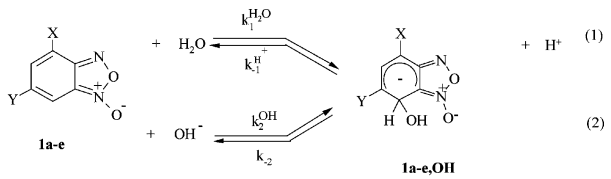
We report on the dual reactivity, *i.e.* anionic Meisenheimer sigma adduct formation and Diels–Alder adduct formation, of a series of heteroaromatic super-electrophiles, including 4,6-dinitro-benzofuroxan, -*N*-arylbenzotriazoles (4), -benzothiadiazole and -benzoselenadiazole. Measured $pK_a^{H_2O}$ values for sigma adduct formation provide a quantitative measure of super-electrophilic reactivity with a satisfactory correlation between the Mayr *E* electrophilicity parameter and $pK_a^{H_2O}$:

$$E = -0.662\ pK_a^{H_2O}\ (\text{or } pK_{R+})\ -3.20\ (r^2 = 0.987)$$

The most highly electrophilic, pre-eminent super-electrophile is 4,6-dinitrotetrazolopyridine ($E = -4.67$, $pK_a^{H_2O} = 0.4$), which supercedes the reference Meisenheimer super-electrophile, 4,6-dinitrobenzofuroxan ($E = -5.06$, $pK_a = 3.75$), having itself an *E* value superior by 8 orders of magnitude compared to 1,3,5-trinitrobenzene as the benchmark normal Meisenheimer electrophile ($E = -13.19$, $pK_a^{H_2O} = 13.43$). (For relevant kinetic parameters as well as *E* and pK_a values, see Table 1.) In a parallel study we have investigated Diels–Alder (normal and inverse electron demand) reactivity of this series of heteroaromatic electrophiles and have shown that Mayr *E* values are valid predictors of whether DA adducts will form and how rapidly. The observed order of pericyclic reactivity corresponds to $E = -8.5$ as the demarcation *E* value, in close agreement with sigma complexation; thus pointing to a common origin for the two processes, *i.e.* an inverse relationship between the degree of aromaticity of the carbocyclic ring and ease of sigma complexation, or DA reactivity, respectively.

Introduction

The field of electrophile–nucleophile combinations has, during the last two decades, received a boost in the discovery of a novel class of aromatic and heteroaromatic highly electrophilic species, termed herein as super-electrophiles. Moreover, it is shown that not only is this super-electrophilic reactivity exhibited in anionic σ-complexation but also extends to Diels–Alder reactivity. The propensity of the most electron-deficient substrates such as 4,6-dinitrobenzofuroxan (DNBF, **1a**) to form persistent anionic σ-adducts[1–12] (Meisenheimer complexes, *e.g.* **1a-OH**) with extremely weak carbon nucleophiles, such as polyhydroxybenzenes, anilines, or π-excessive heterocycles, including pyrroles, indoles and furans, delineates the super-electrophile class[4,5,7,13,14] from the latter traditional electrophilic aromatics exemplified by 1,3,5-trinitrobenzene (TNB), as the other class.[15,16] Evaluation of thermodynamic reactivity for these Meisenheimer electrophiles was afforded from a comparison of pK_a values for H_2O addition to yield the respective σ-complexes: $pK_a^{DNBF} = 3.75$[3a,15] *versus* $pK_a^{TNB} = 13.43$[16] (Scheme 1 for DNBF, **1a**) and supports the definition of DNBF and a set of structural analogues as super-electrophiles.[12–14,17–19] The reactivity



(a) X = Y = NO_2 (DNBF); (b) X = NO_2, Y = SO_2CF_3 ; (c) X = CN, Y = NO_2 ; (d) X = NO_2, Y = CN (e) X = NO_2, Y = H, (4-NBF)

Scheme 1

of these compounds has led to many synthetic, analytical and biological applications.[20–24]

Recently we applied the methodology of Mayr[25] to the assessment of the intrinsic electrophilicity (*E*) of a series of neutral Meisenheimer electrophiles, namely, **1a–d**, **1f–g**, **2a–b**, **4** (TNB) and **5**.[18] *Via* reaction with a series of reference nucleophiles (including *N*-methylpyrrole, *N*-methylindole and a group of enamines) these electrophiles were ranked on the comprehensive Mayr electrophilicity scale. Measured *E* values were found to cover a large domain of reactivity, varying from ~ −5 for the most electron-deficient substrates, *i.e.* **1a–b**, **1g**, **2a**, to −13.19 for the less electron-deficient substrate *i.e.* TNB **4**, thus validating previous qualitative ordering of such electrophiles.[1] Further, an apparent correlation emerged between the electrophilicity parameter *E* and the $pK_a^{H_2O}$ value for this set of Meisenheimer electrophiles,[18] which in fact coincides with the comparable correlation reported by the Mayr group for addition of H_2O to carbocations.[25b,26] Hence, if the correlation holds more generally for Meisenheimer electrophiles the quantification of the electrophilicity of these important

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reaction partners could be made solely on the basis of their tendency to form σ-adducts with water.[27] Herein we strengthen the general character of this correlation, showing that it describes nicely the electrophilic behaviour of a new series of six heteroaromatics consisting of 4,6-dinitro-2,1,3-benzoselenadiazole **1h** (DNBSe), 4,6-dinitro-2,1,3-benzothiadiazole **1i** (DNBS) and the four benzotriazoles **3a–d**. Also, we demonstrate its application to the prediction of Diels–Alder reactivity for these Meisenheimer electrophiles, with important synthetic consequences.

Results and discussion

Reaction of the weak nucleophile, H_2O, with an electron-deficient substrate to give an anionic σ-adduct is a sensitive measure of the electrophilicity of the substrate.[1,3,15,28] For most of the compounds identified in Scheme 1 and Chart 1, Table 1 lists this thermodynamic reactivity parameter as $pK_a^{H_2O}$ and related rate constants (as defined in Scheme 1 for **1a**; $k_1^{H_2O}$, $k_{-1}^{H^+}$, k_2^{OH}, k_{-2}) for σ-adduct formation and decomposition in aqueous solution.

Fig. 1 shows the unique correlation ($r^2 = 0.987$) line obtained from plotting E values against either $pK_a^{H_2O}$ for addition of water to **1a–d**, **1f–g**, **2a–b**,[3a,15,28] **4** (TNB)[1] and **5**[18b] or pK_{R+} for the Lewis acidities[25,26] of members of a set of resonance-delocalized carbocations such as diphenylmethyl, di-4-methoxyphenylmethyl and *N*-methylquinolinium carbocations. The equation of the linear regression fit is:

$$E = -0.662\ pK_a^{H_2O}\ (\text{or } pK_{R+}) - 3.20 \qquad (3)$$

Assuming that this correlation is suitable to describe the σ-complexation reactivity of Meisenheimer substrates generally, the E values for **1h–i** and **3a–d** can be readily estimated from eqn (1) by referring to the measured $pK_a^{H_2O}$ values for these compounds. Thus, a critical test for the significance of these E values can be made by checking whether they fit or not the three parameters eqn (4) introduced by Mayr *et al.* to describe the rate, *i.e.* $\log k$, of a large variety of nucleophilic–electrophilic combinations.[25,26] In this equation, the aforementioned E parameter measures the strength

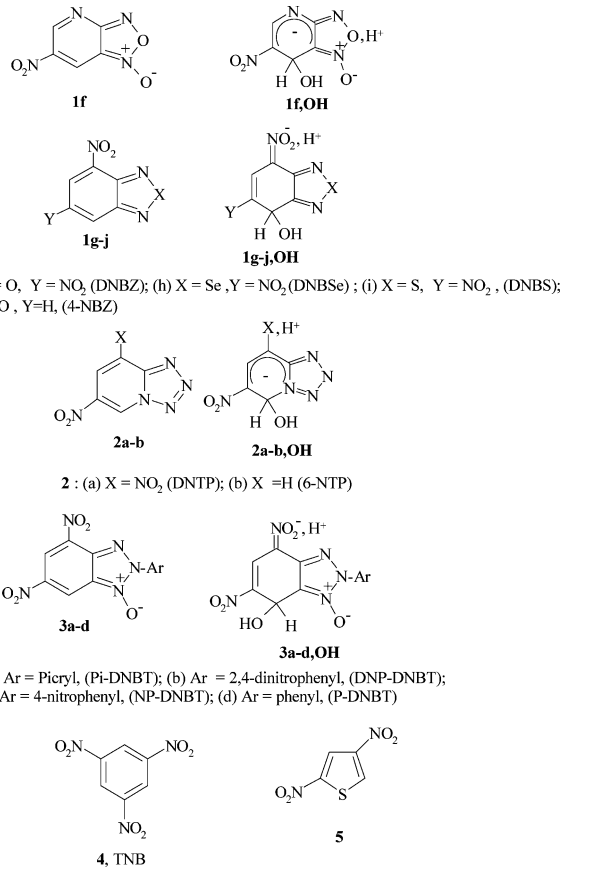


Chart 1 Structures and numbering of electrophiles and related hydroxy adducts.

of the electrophile while the N and s parameters characterise the reactivity of the nucleophilic partner.

$$\log k\ (20\ ^\circ\text{C}) = s\ (N + E) \qquad (4)$$

For this purpose, the σ-complexation reactions of **1h–i** and **3a–d** with at least two of the following reference nucleophiles, *i.e.*

Table 1 Kinetic and thermodynamic parameters for covalent hydration of nitrobenzofuroxans and related heteroaromatics at $T = 25\ ^\circ$C in aqueous solution[a]

Electrophile	$pK_a^{H_2O}$	$k_1^{H_2O}/s^{-1}$	$k_{-1}^{H^+}/s^{-1}$	k_2^{OH}/s^{-1}	k_{-2}/s^{-1}	$k_1^{H_2O}/k_{-2}$	E value
2a, DNTP	0.4	1.93	3.87	—	—		−4.67[b]
1b	2.95	0.15	100.3	7.2×10^4	10^{-6}	1.5×10^5	−4.91[b]
1a, DNBF	3.75	3.5×10^{-2}	146	33 500	2.5×10^{-6}	14 000	−5.06[b]
1g, DNBZ	3.92	2.0×10^{-2}	127	15 300	1.7×10^{-6}	12 000	−5.46[b]
1d	4.65	10^{-3}	31	1060	10^{-6}	1000	−7.01[b]
1c	5.86	2.6×10^{-3}	3700	2740	3×10^{-5}	87	−6.41[b]
1h, DNBSe	6.34	5×10^{-3}	11 350	305	5×10^{-6}	1000	−7.40[c]
3a, Pi-DNBT	6.70	1.1×10^{-3}	4215	392	2×10^{-5}	60	−7.63[c]
3b, DNP-DNBT	7.15	6.7×10^{-4}	7050	1000	1.4×10^{-4}	4.8	−7.93[c]
2b, 6-NTP	7.55	1.6×10^{-5}	630	285	9.5×10^{-5}	1.7×10^{-1}	−9.05[b]
1i, DNBS	7.86	2.8×10^{-4}	17 300	9400	5×10^{-3}	6×10^{-2}	−8.40[c]
3c, NP-DNBT	9.00	1.8×10^{-5}	13 300	680	3.5×10^{-3}	5×10^{-3}	−9.16[c]
1j, 4-NBZ	10.07	—	—	59	1.1×10^{-2}	—	−9.85[b]
1e, 4-NBF	10.37	—	—	30	1.1×10^{-2}	—	−10.04[b]
3d, P-DNBT	10.73	8.3×10^{-7}	33 000	680	3.5×10^{-3}	2.4×10^{-4}	−10.30[c]
4, TNB	13.43	—	—	37	9.8	—	−13.19[b]

[a] Rate constants ($k_{-1}^{H^+}$ and k_2^{OH} in $dm^3\ mol^{-1}\ s^{-1}$, $k_1^{H_2O}$ and k_{-2} in s^{-1}) and pK_a values taken from ref. 28*b* (**2a**,**2b**), 28*c* (**1b**); 3*a* (**1a**), 28*a* (**1g–i**), 28*e* (**1c**,**1d**), 15 (**3a–d**), 19 (**1e**,**1j**). [b] E values experimentally determined in ref. 18 and 24*a*. [c] E values calculated in this work from known $pK_a^{H_2O}$ values through the E *vs.* pK_a correlation of eqn (3).

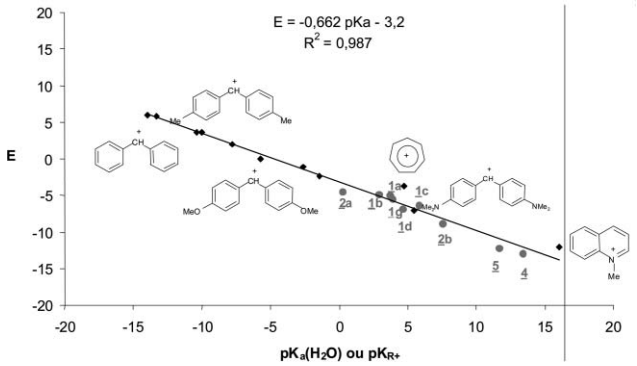
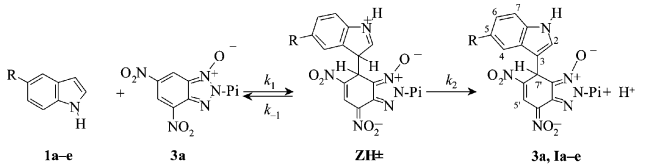
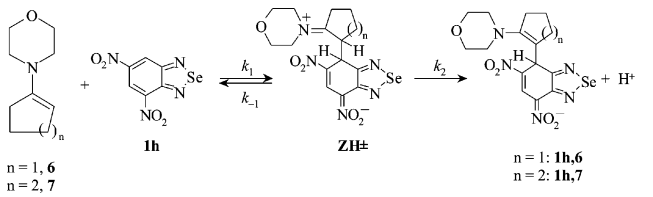


Fig. 1 Correlation of the electrophilicity parameter E of nitrobenzofuroxans and related neutral heterocycles (●) and some carbocations (◆) with the corresponding $pK_a^{H_2O}$ or pK_{R+} values of these species in aqueous solution (data taken from ref. 18 and ref. 25–26). Application to the determination of E values for **3a–d** and **1h–i**.

5-hydroxyindole (**Ia**), 5-methoxyindole (**Ib**), 5-methylindole (**Ic**), indole (**Id**), 5-chloroindole (**Ie**), 1-(*N*-morpholino)cyclohexene **6**, and 1-(*N*-morpholino)cyclopentene **7** have been kinetically studied under the same first-order conditions (excess nucleophile) as those previously used for the similar couplings of **1a–d**, **1f–g**, **2a–b**, **4** and **5** in acetonitrile.[18,27] Eqn (5) and (6) exemplify the processes studied by using the reaction of Pi-DNBT with indoles and the reactions of DNBSe with enamines as prototype systems.



(5)



(6)

The oscilloscope trace shown in Fig. 2 is illustrative of the unique first order process associated to the formation of the expected indole and enamine adducts through reactions (5) and (6). For all electrophile–nucleophile combinations studied, the general expression for the observed first-order rate constant, k_{obsd}, for the formation of the adducts, *e.g.* **3a**, **Ia–d**, **1h**, **6** and **1h**, **7**, as derived under the assumption that the zwitterion ZH ± are low concentration intermediates, is given by the following equation in which Nuc denotes the indole or enamine nucleophile used.

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2}[\mathrm{Nuc}] = k\,[\mathrm{Nuc}] \qquad (7)$$

In accordance with eqn (7), excellent straight lines with zero intercepts were obtained in all systems, when the k_{obsd} values were plotted *vs.* the indole (Fig. 3) or enamine (Fig. 4) concentration.

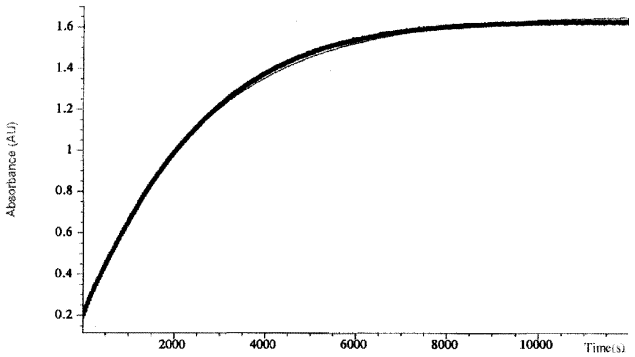


Fig. 2 Oscilloscope picture showing the unique relaxation process observed in the reaction of **3b** (6×10^{-5} M) with **Ic** (5×10^{-2} M) at $T = 20$ °C in acetonitrile.

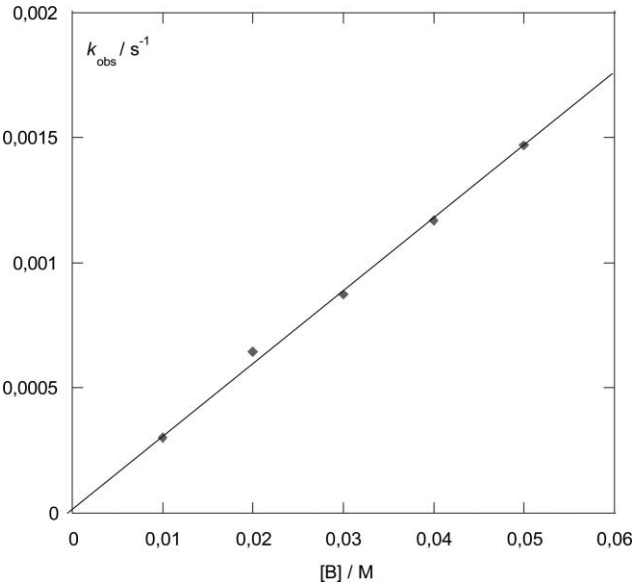


Fig. 3 Effect of the concentration of indole (**Id**) on the observed rate of formation of the adduct **3a**,**Id** of *N*-2-picryl-4,6-dinitrobenzotriazole-1-oxide **3a** at 20 °C in CH_3CN.

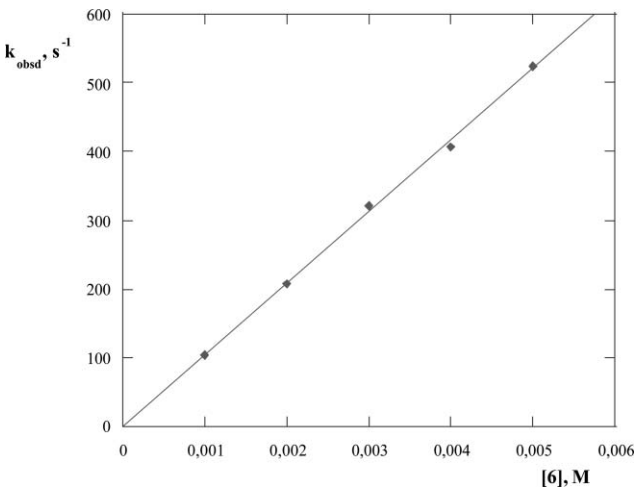


Fig. 4 Effect of the concentration of enamine (**6**) on the observed rate of formation of the adduct **1i**,**6** of 4,6-dinitrobenzothiadiazole **1i** at 20 °C in CH_3CN.

Determination of the second order rate constants k from the slopes of these lines was therefore straightforward. Importantly, a number of experiments were carried out with indole-1,3-*d2* and 5-methylindole-1,3-*d2* which did not reveal a significant influence of the nature of the isotopic substitution at C-3 of indoles on the rates of formation of the adducts **3a**,**Ia–d**. The experimental k_H/k_D ratios were all in the range of 1.1 ± 0.1. This leaves no doubt that the electrophilic addition step is largely rate-limiting in reactions (5), *i.e.* we have $k_2 \gg k_{-1}$. Thus, the second order rate constant k is identical to the second-order rate constant k_1 for the C–C coupling step, as found for all similar couplings involving previously studied electrophiles, *i.e.* **1a–d**, **1f–g** and **2a–b**. In as much as the required deuterated enamines were not available, firm evidence that reactions of type (6) also involved a rate limiting coupling step could not be obtained through isotope effects. However, this situation can be reasonably postulated since proton removal from the zwitterion is strongly favored by the adjacent iminium moiety.

As can be seen in Tables 2 and 3, the k_1 values thus obtained for **1h–i** and **3a–d** are in remarkable agreement with the rate constants k_1 calculated from eqn (4) using the afore estimated E values for these six substrates and the relevant N and s parameters previously determined by Mayr *et al.* for the nucleophilic partners at hand.[23,25,26] In the case of 2-*N*-picryl-4,6-dinitrobenzotriazole **3a**, eqn (4) predicts the rate constants k_1 within a factor 3–8, an accuracy which remains largely in the acceptable domain of prediction of eqn (4) (within a factor of 20).[23,25,26] In the other systems, the consistency of k_1^{calc} and k_1^{obsd} is very nice and in itself evidence that the correlation of Fig. 1 applies not only to carbocationic electrophiles but also to the whole family of uncharged electron-deficient π-systems (see Chart 1).

At this stage, the whole set of E values quoted in Table 1 is worthy of comments. With an E value of −4.67, the 4,6-dinitrotetrazolopyridine **2a** is the most reactive and also exhibits the smallest $pK_a^{H_2O}$ (0.4). In this regard, **2a** is also markedly more electrophilic than DNBF, **1a** ($E = -5.06$; $pK_a^{H_2O} = 3.75$). While **1a** has been taken to be the reference Meisenheimer super-electrophile[3–12] it is apparent that **2a** is the pre-eminent member of this class.[28c] At the other extreme, TNB which does not undergo measurable addition of water to give the corresponding hydroxy adduct, **5-MC**, is the least electrophilic polynitro substrate studied, in accord with its E value (−13.19); TNB serves as the benchmark normal Meisenheimer electrophile.[1,27] From Table 1, the order of electrophilicity in σ-adduct formation ($pK_a^{H_2O}$; E) for the heteroaromatics activated by two NO_2 groups in the six membered ring is: DNTP (0.4; −4.67) ≫ DNBF (3.75; −5.06) ~ DNBZ (3.92; −5.46) ≫ DNBSe (6.34; −7.40) ~ Pi-DNBT (6.70; −7.63) ≫ DNBS (7.86; −8.40) ≫ NP-DNBT (9.00; −9.16).

Comparison of individual pairs of electron-deficient substrates emphasizes the generality of this approach and reveals interesting structure–reactivity relationships. Replacement of X = O in **1g** by Se in **1h**, for example, results in a decrease in electrophilicity for **1h** of 2.3 E units, *i.e.* E(**1g**) − E(**1h**) = ΔE = 2.3. However, substitution of X = Se in **1h** by X = *N*-2,4,6-trinitrophenyl in **3a** yields a small change in electrophilicity (ΔE = 0.36).

Low $pK_a^{H_2O}$ values which reflect high Meisenheimer electrophilicity require an effective contribution of the water pathway ($k_1^{H_2O}$, Scheme 1 for example) to the formation of hydroxy σ-adducts in aqueous solution. As elaborated on in detail in previous

Table 2 Comparison of measured and calculated rate constants for the coupling of heterocycles **1h–i** and **3a–d** with reference indole nucleophiles **Ia–e** in acetonitrile (T = 20 °C)

			5-Hydroxyindole **Ia**			5-Methoxyindole **Ib**			5-Methylindole **Ic**			Indole **Id**			5-Chloroindole **Ie**		
			N^c	s^e		N^c	s^e		N^c	s^e		N^c	s^e		N^c	s^e	
			6.44	1.10		6.22	1.10		6.00	1.10		5.55	1.10		4.38	1.10	
Electrophile	$pK_a^{H_2O}$ [a]	E^b	k^{measd}	k^{calcd}		k^{measd}	k^{calcd}		k^{measd}	k^{calcd}		k^{measd}	k^{calcd}		k^{measd}	k^{calcd}	
3a	6.70	−7.63	0.138	0.05		0.218	0.028		0.066	0.016		0.03	5.1×10^{-3}		1.6×10^{-3}	2.7×10^{-4}	
3b	7.15	−7.93	0.02	0.023		0.013	0.013		9.1×10^{-3}	7.5×10^{-3}		8×10^{-3}	2.4×10^{-3}		1.1×10^{-4}	1.2×10^{-4}	
3c	9.00	−9.16	1.4×10^{-3}	10^{-3}		7.7×10^{-4}	5.8×10^{-4}		4.4×10^{-4}	3.3×10^{-4}		—	—		—	—	
3d	10.73	−10.30	7.3×10^{-5}	5.7×10^{-5}		—	—		—	—		—	—		—	—	
1h	6.34	−7.40	6.3×10^{-2}	8.8×10^{-2}		2.4×10^{-2}	5×10^{-2}		7.2×10^{-3}	2.9×10^{-2}		—	—		—	—	
1i	7.86	−8.40	8.5×10^{-3}	7×10^{-3}		3×10^{-3}	4×10^{-3}		1.9×10^{-3}	2.3×10^{-3}		—	—		—	—	

[a] $pK_a^{H_2O}$ values from ref. 15 and 28*a*; k^{measd} and k^{calcd} in $dm^3\ mol^{-1}\ s^{-1}$. [b] E values determined through the E *vs.* $pK_a^{H_2O}$ correlation of eqn 3. [c] N and s values taken from ref. 23.

Table 3 Comparison of measured and calculated rate constants for the coupling of heterocycles **1h** and **3a–d** with reference enamine nucleophiles **6** and **7** in acetonitrile ($T = 20$ °C)

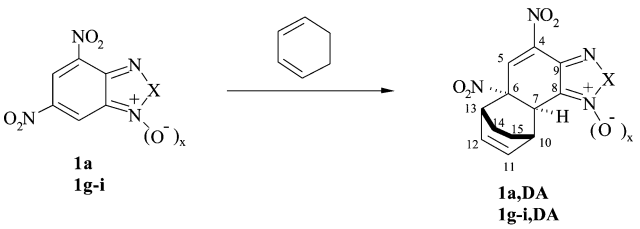
			7		**6**	
			N^c	s^c	N^c	s^c
			11.40	0.83	13.41	0.83
Electrophile	$pK_a^{H_2O}$ [a]	E^b	k^{measd}	k^{calcd}	k^{measd}	k^{calcd}
3a	6.70	−7.63	8950	1350	—	—
3b	7.15	−7.93	1300	760	—	—
3c	9.00	−9.16	116	72.3	—	—
3d	10.73	−10.30	—	—	85	380
1h	6.34	−7.40	6450	2090	10^5	9.7×10^4

[a] $pK_a^{H_2O}$ values from ref. 15 and 28*a*; k^{measd} and k^{calcd} in $dm^3\ mol^{-1}\ s^{-1}$. [b] E values determined through the E *vs.* $pK_a^{H_2O}$ correlation of eqn 3. [c] N and s values taken from ref. 25*a* and 26.

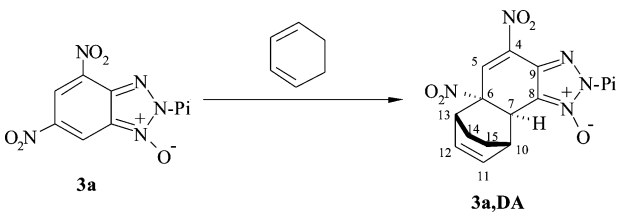
kinetic and thermodynamic investigations of σ-complexation in aqueous solution,[3a,15,28] a primary requirement for having H_2O compete effectively as a nucleophile with OH^- in the formation of a hydroxy σ-adduct is that the first-order rate constant $k_1^{H_2O}$ be appreciably greater than the first-order rate constant k_{-2} for spontaneous decomposition of this species, *i.e.* $k_1^{H_2O} \gg k_{-2}$. Table 1 lists the ratio of these constants ($k_1^{H_2O}/k_{-2}$) and from the table it is apparent that the ratio is large for all systems with E values less negative than about −8. This region, then, demarcates the boundary between super-electrophiles and normal electrophiles in σ-complexation. Thus, Pi-DNBT is situated on one side of the border and DNBS on the other side; these are borderline super-electrophiles, while TNB ($E = -13.19$) remains a classical albeit important Meisenheimer electrophile and DNTP ($E = -4.67$) and DNBF ($E = -5.06$) and DNBZ ($E = -5.46$) are benchmark super-electrophiles.

On the basis of the Diels–Alder reactivity of a series of Meisenheimer electrophiles—this includes **1a–b**, **1f–i**, **2a–b** and **3a** with cyclopentadiene, where normal electron-demand (NED) and inverse electron-demand (IED) Diels–Alder adducts may initially form and where diadduct formation may subsequently occur, we suggested that the reactivity of these electrophiles in σ-complexation and pericyclic reactivity were linked.[27,28a] Since the degree of aromaticity in heteroaromatic systems has been recognized to be inversely proportional to the Meisenheimer reactivity of a heterocycle such as **1a** as compared to **4**, for example, we speculated that pericyclic reactivity in these electrophiles was also governed by this aromaticity factor.

To further extend the generality of the Mayr electrophilicity scale to these super-electrophilic systems and further define the line of demarcation between super- and normal-electrophiles, we examined Diels–Alder adduct formation for **1a**, **1g–i**, **2a–b** and **3a** where cyclohexadiene was chosen as the reactive diene. Table 4 presents the results of these Diels–Alder (DA) reactions. The reactions were performed by combining equimolar amounts of the reagents at room temperature in acetonitrile; the reactions were monitored at 2 h, 8 h, 24 h, 48 h and 7 days from time of mixing by NMR by following the appearance of the DA adduct, **1a**,**DA**, **1g–i**,**DA**, **3a**,**DA** (shown in eqn (8) and (9)) and **2a–b**,**DA** (the DNTP and 6-NTP analogues of **1a**,**DA**). Where adducts formed, one equivalent of cyclohexadiene added *via* the NED process involving the nitroactivated C(6)–C(7) double bonds of the heteroaromatics as dienophilic centers to yield monoadducts in their racemic forms.



1 : (a) x = 1, X = O, (DNBF); (g) x= 0, X = O, (DNBZ); (h) x= 0, X = Se, (DNBSe); (i) x = 0, Y= NO_2, X= S (8)



(9)

Table 4 Diels–Alder reactivity for selected nitro-substituted heteroaromatics

		Electrophilic reactivity	Pericyclic reactivity adduct formation (%)[a]				
Parent electrophile		E^b	2 h	8 h	24 h	48 h	7 days
2a	DNTP	−4.67[b]	87	100	100	100	100
1a	DNBF	−5.06[b]	70	100	100	100	100
1g	DNBZ	−5.46[b]	65	100	100	100	100
3a	Pi-DNBT	−7.63	—	38[c]	62	100	100
1h	DNBSe	−7.40	—	—	~10	30	60
3b	DNP-DNBT	−7.93	—	—	—	~10	~30
1i	DNBS	−8.40	—	—	—	~17	40
2b	6-NTP	−9.05[b]	—	—	—	~5	~15
3c	NP-DNBT	−9.16	—	—	—	—	—
1j	4-NBZ	−9.85[b]	—	—	—	—	—
1e	4-NBF	−10.04[b]	—	—	—	—	—

[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 text. [b] E values from ref. 18. [c] Four hours after mixing.

As highlighted by Table 3, the Mayr E values for the 5 heterocyclic electrophiles studied are valid predictors of whether Diels–Alder adducts will form and how rapidly. The order of pericyclic reactivity is **2a** $\gg$ **1a** $\gg$ **3a** $\ggg$ **2b** $\sim$ **1i**. DA adduct formation with **3a** and **2b** further define the demarcation line for Meisenheimer and pericyclic reactivity; a value of $E \sim -8.5$ which corresponds to $pK_a^{H_2O}$ of 8–8.5 for Meisenheimer complexation with water demarcates the boundary between super- and normal-electrophiles and between reactive dienophiles and inert partners in DA adduct formation.

In conclusion, we have shown that the Mayr electrophilicity scale can be generalized to neutral electron-deficient heteroaromatic substrates and that the E scale correlates with $pK_a^{H_2O}$ for addition of water to the Meisenheimer electrophiles. The boundary between super- and normal-electrophilicity is defined at an E value of ~ -8.5 and the heteroaromatics having less negative E values form DA adducts with cyclohexadiene while those with more negative E values do not. Further, as shown by Mayr,[29] such a positioning of an electrophile on the E scale can be very useful in identifying whether Diels–Alder cycloadditions take place through a concerted pathway or proceed in two steps with an initial electrophile–nucleophile combination of the two partners. Beyond such mechanistic considerations the correlation also demonstrates the predictive power of the E scale in determining pericyclic reactivity and, so, will be of real benefit in synthetic organic chemical applications.

Experimental

Materials

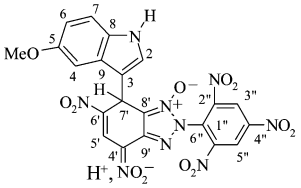
All electrophilic reagents referred to in this work, including the test series consisting of **1h**, **1i** and **3a–d**, were available from previous studies.[3,18,28,30] Reference nucleophiles, *i.e.* 5-hydroxyindole (**Ia**), 5-methoxyindole (**Ib**), 5-methylindole (**Ic**), indole (**Id**), 5-chloroindole (**Ie**), 1-(*N*-morpholino)cyclohexene **6**, and 1-(*N*-morpholino) cyclopentene **7**, were commercial products which were purified by recrystallization or distillation prior to use. Cyclohexadiene was used without purification. The synthesis and characterization of the Diels–Alder adducts whose formation could be kinetically investigated, *i.e.* **1a**,**DA**, **1g–i**,**DA**, **2a–b**,**DA** and **3a**,**DA** (see eqn (8) and (9) as well as Table 4) have been previously reported.[18,23,27]

All σ-adducts resulting from the reactions of various indoles and enamines with compounds **1a–g** and **2a–b** have been previously isolated and structurally characterized in their acid form as well as sodium salts.[13,18,23] This work has revealed that changes in the substitution pattern of the carbocyclic ring or in the nature of the annelated ring of the electrophile had no influence of the mode of σ-complexation. This synthetic work has therefore been extended to the adducts **3a–c**,**Ib** and **1h–i**,**Ib** as a model series corresponding to the σ-complexation of **1h–i** and **3a–c** reacting with 5-methoxyindole **Ib**. The general procedure is as follows: a solution of 1 mmol of the electrophile (**1h–i**, **3a–c**) in acetonitrile (2 ml) and a solution of 1 mmol of 5-methoxyindole in acetonitrile (2 ml) were mixed with stirring at room temperature. Subsequent addition of diethyl ether resulted in the formation of a precipitate which was collected by filtration, washed with copious amounts of diethyl ether and dried thoroughly under vacuum to give the expected σ-adducts in their acid form in good yields (60–90%). Representative NMR (^{1}H, ^{13}C), UV–visible and mass spectroscopy data are given below. As with all σ-adducts of nitrobenzofuroxans and nitrotetrazolopyridines so far obtained,[3–5,13,15,18,28] the red-orange solids obtained for **3a–c**,**Ib** and **1h–i**,**Ib** did not melt prior to decomposition (vigorous in most cases) and attempts to obtain satisfactory elemental analyses have been unsuccessful. However, dissolution of these solids in d_6-DMSO gave NMR spectra identical to those recorded in the *in situ* generation of these adducts in this solvent. Among other diagnostic features for the proposed structures, there is the fact that the H-7′ and C-7′ resonances of the electrophilic moieties are in the ranges of 5.64–5.83 and 30.4–32.4 ppm, respectively, which are typical for C-adduct formation.[1,4–8] Also noteworthy is that the σ-complexation process goes along with the loss of the resonance of the H-3 proton of the parent 5-methoxyindole. Concomitantly, there is a significant low-field shift of the C-3 resonance, in agreement with the fact that the negatively charged dinitrobenzoselenadiazole, dinitrobenzothiadiazole and dinitrobenzotriazole structures of the adducts still exert, as does a negatively charged DNBF structure, a strong –I effect. Definitive evidence that the adducts **3a–c**,**Ib** and **1h–i**,**Ib**[3,13,18,23,24,28] were actually isolated in their acid form comes from mass spectra experiments performed with the electrospray technique. Also, the UV–visible spectra of these adducts exhibit a strong absorption maximum at $\lambda = 470$–480 nm, a wavelength typical for the σ-complexation of **1h–i** and **3a–c** in acetonitrile.

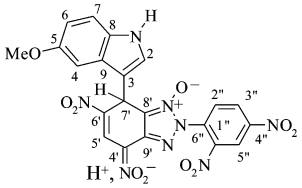
3a,Ib. Red solid; yield 90%; m/z (CI) : 582 $(M - H)^+$. ^{1}H NMR (200 MHz, Me_2SO-d_6): 3.63 (s, 3H, OMe), 5.73 (s, 1H, $H_{7'}$), 6.65 (dd, 1H, $J = 2.1$ Hz, $J = 8.8$ Hz, H_6), 6.80 (d, 1H, $J = 2.1$ Hz, H_4), 7.16 (d, 1H, $J = 8.8$ Hz, H_7), 7.21 (d, 1H, $J = 2.2$ Hz, H_2), 8.72 (s, 1H, $H_{5'}$), 9.18 (s, 2H, $H_{3''}$ and $H_{5''}$), 10.84 (bs, 1H, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 32.0 ($C_{7'}$), 55.2 (OMe), 100.8 (C_4), 110.7 (C_3), 111.2 ($C_{4'}$), 111.4 (C_6), 112.6 (C_7), 123.6 ($C_{1''}$), 123.8 ($C_{8'}$), 125.3 ($C_{3''}$, $C_{5''}$), 125.9 (C_2), 126.2 (C_9), 127.92 ($C_{6'}$), 129.9 ($C_{5'}$), 131.6 (C_8), 141.7 ($C_{9'}$), 145.3 ($C_{2''}$, $C_{6''}$), 147.8 ($C_{4''}$), 153.4 (C_5).

3b,Ib. Red solid; yield 92%; m/z (CI): 537 $(M - H)^+$. ^{1}H NMR (200 MHz, Me_2SO-d_6): 3.62 (s, 3H, OMe), 5.69 (s, 1H, $H_{7'}$), 6.66 (dd, 1H, $J = 2.1$ Hz, $J = 8.8$ Hz, H_6), 6.81 (d, 1H, $J = 2.1$ Hz, H_4), 7.18 (d, 1H, $J = 8.8$ Hz, H_7), 7.22 (d, 1H, $J = 2.2$ Hz, H_2), 8.04 (d, 1H, $J = 8.8$ Hz, $H_{2''}$), 8.63 (dd, 1H, $J = 1.9$ Hz, $J = 8.8$ Hz, $H_{3''}$), 8.76 (s, 1H, $H_{5'}$), 8.80 (d, 1H, $J = 1.9$ Hz, $H_{5''}$), 10.84 (bs, 1H, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 31.5 ($C_{7'}$), 54.9 (OMe), 100.6 (C_4), 110.6 (C_3), 111.4 (C_6), 111.6 ($C_{4'}$), 112.6 (C_7), 121.0 ($C_{5''}$), 123.4 ($C_{8'}$), 125.4 ($C_{1''}$), 125.4 (C_2), 125.8 (C_9), 127.4 ($C_{6'}$), 129.0 ($C_{2''}$, $C_{3''}$), 129.7 ($C_{5'}$), 131.2 (C_8), 140.2 ($C_{9'}$), 142.7 ($C_{6''}$), 146.7 ($C_{4''}$), 152.9 (C_5).

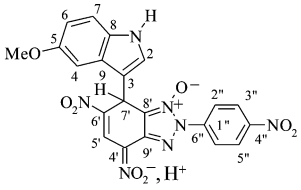
3c,Ib. Red solid; yield 85%; m/z (CI): 492 $(M - H)^+$. ^{1}H NMR (200 MHz, Me_2SO-d_6): 3.60 (s, 3H, OMe), 5.71 (s, 1H, $H_{7'}$), 6.65 (dd, 1H, $J = 2.1$ Hz, $J = 8.8$ Hz, H_6), 6.81 (d, 1H, $J = 2.1$ Hz, H_4), 7.18 (d, 1H, $J = 8.8$ Hz, H_7), 7.27 (d, 1H, $J = 2.2$ Hz, H_2), 8.37 (d, 2H, $J = 8.8$ Hz, $H_{3''}$ and $H_{5''}$), 8.20 (d, 2H, $J = 8.8$ Hz, $H_{2''}$ and $H_{6''}$), 8.75 (s, 1H, $H_{5'}$), 10.84 (bs, 1H, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 31.5 ($C_{7'}$), 54.9 (OMe), 100.5 (C_7), 110.3 (C_3), 111.1 ($C_{4'}$), 111.6 (C_6), 112.3 (C_4), 120.7 ($C_{2''}$, $C_{6''}$), 124.4 ($C_{8'}$), 124.5 ($C_{1''}$), 24.8 ($C_{3''}$, $C_{5''}$), 125.9 (C_2), 126.0 (C_9), 127.2 ($C_{6'}$), 129.8 ($C_{5'}$), 131.2 (C_8), 139.8 ($C_{9'}$), 145.8 ($C_{4''}$), 152.9 (C_5).



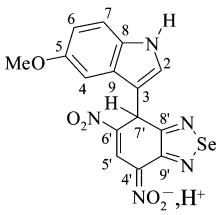
3a,Ib



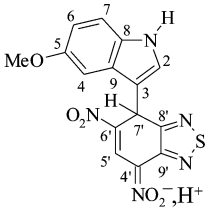
3b,Ib



3c,Ib



1h,Ib



1i,Ib

1h,Ib. Red solid; yield 75%; 418 $(M - H)^+$. ^{1}H NMR (300 MHz, Me_2SO-d_6): 3.52 (s, 3H, OMe), 5.92 (s, 1H, $H_{7'}$), 6.50 (d, 1H, $J = 2.31$ Hz, H_4), 6.53 (dd, 1H, $J = 2.3$ Hz, $J = 8.5$ Hz, H_6), 7.05 (d, 1H, $J = 8.5$ Hz, H_7), 7.31 (d, 1H, $J = 2.2$ Hz, H_2), 8.74 (s, 1H, $H_{5'}$), 10.67 (bs, 1H, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 37.3 ($C_{7'}$), 54.7 (OMe), 99.8 (C_4), 108.8 (C_6), 110.9 (C_7), 111.2 (C_3), 117.4 ($C_{4'}$), 125.5 (C_2), 126.2 (C_9), 126.6 ($C_{5'}$), 128.07 ($C_{6'}$), 129.9 (C_8), 150.3 ($C_{9'}$), 152.7 (C5), 160.3 ($C_{8'}$).

1i,Ib. Red solid; yield 88%; *m/z* (CI): 371 $(M - H)^+$. ^{1}H NMR (300 MHz, Me_2SO-d_6): 3.65 (s, 3H, OMe), 5.89 (s, 1H, $H_{7'}$), 6.67 (dd, 1H, $J = 2.3$ Hz, $J = 8.5$ Hz, H_6), 6.96 (d, 1H, $J = 2.31$ Hz, H_4), 7.11 (d, 1H, $J = 2.2$ Hz, H_2), 7.19 (d, 1H, $J = 8.5$ Hz, H_7), 8.49 (s, 1H, $H_{5'}$), 10.78 (bs, 1H, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 41.1 ($C_{7'}$), 55.5 (OMe), 101.0 (C_4), 111.3 (C_6), 112.3 (C_7), 114.6 (C_3), 119.7 ($C_{4'}$), 123.5 (C_2), 124.6 ($C_{5'}$), 125.9 (C_9), 131.4 ($C_{6'}$), 131.7 (C_8), 150.9 ($C_{9'}$), 153.5 (C_5), 163.5 ($C_{8'}$).

Rate measurements

Most of the couplings of **1h–i** and **3a–d** with the reference indole and enamine nucleophiles studied in this work (see Tables 2 and 3), were kinetically followed by the stopped flow technique. Measurements were performed on a stopped flow spectrophotometer, the cell compartment of which was maintained at 20 ± 0.1 °C. A conventional spectrophotometer was also used to follow the slowest processes. All kinetic runs were carried out in triplicate under pseudo first order conditions with an electrophile (**1h–i** and **3a–d**) concentration of *ca.* 3–5 × 10^{-5} mol dm^{-3} and a nucleophile (indoles, enamines) concentration in the range 10^{-3}– 0.1 mol dm^{-3}. In a given experiment, the rates were found to be reproducible to ±2–3% and to be similar whether the unique and clean process observed was followed by monitoring the increase in absorbance at λ_{max} of the resulting adducts or the decrease in absorbance at λ_{max} of the parent electrophile substrate as a function of time.

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