Nitrobenzoxadiazoles and related heterocycles: a relationship between aromaticity, superelectrophilicity and pericyclic reactivity†

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A study of the dual electrophilic and pericyclic reactivity of 4,6-dinitrobenzofurazan (DNBZ, **2**), 4,6-dinitro-2,1,3-benzothiadiazole (DNBS, **3**), 4,6-dinitro-2,1,3-benzoselenadiazole (DNBSe, **4**) is reported. Kinetic and thermodynamic measurements of the ease of covalent hydration of **2**–**4** to give the corresponding hydroxy σ-adducts **C-2**–**C-4** have been carried out over a large pH range in aqueous solution. Analysis of the data has allowed a determination of the rate constants $k_1^{H_2O}$ pertaining to the susceptibility of **2**–**4** to water attack as well as the pK_a values for the σ-complexation processes. With pK_a values ranging from 3.92 for DNBZ to 6.34 for DNBSe to 7.86 for DNBS, the electrophilic character of the three heteroaromatics is much closer to that of the superelectrophilic reference, *i.e.* 4,6-dinitrobenzofuroxan (DNBF, **1**; pK_a = 3.75), than that of the standard Meisenheimer electrophile 1,3,5-trinitrobenzene (TNB, pK_a = 13.43). Most importantly, water is found to be an efficient nucleophile which contributes strongly to the formation of the adducts **C-2** and **C-4**. This confirms a previous observation that a pK_a value of *ca.* 8 is a primary requirement for having H_2O competing effectively as a nucleophile with OH^- in the formation of hydroxy σ-adducts. On the other hand, **2**–**4** are found to exhibit dienophilic and/or heterodienic behaviour on treatment with isoprene, 2,3-dimethylbutadiene, cyclopentadiene or cyclohexadiene, affording Diels–Alder mono- or di-adducts which have all been structurally characterized. A major finding is that the order of Diels–Alder reactivity follows clearly the order of electrophilicity, pointing to a direct relationship between superelectrophilic and pericyclic reactivity. This relationship is discussed.

Introduction

The last decade has witnessed considerable interest in studies of nitrobenzofuroxans, a class of electron-deficient aromatic compounds that show increased reactivity with nucleophiles in the formation of σ-bonded anionic (Meisenheimer) complexes.[1–13] The high susceptibility of 4,6-dinitrobenzofuroxan[1] (DNBF, 4,6-dinitro-2,1,3-benzoxadiazole 1-oxide) to undergo σ-complexation in the absence of any added base in aqueous solution is a nice illustration of this behaviour.[4a] The pK_a for the formation of the hydroxy adduct **C-1** according to eqn. (1) in Scheme 1 is 3.75 at 25 °C, as compared with a pK_a value of 13.43 for formation of the analogous adduct **C-6** of 1,3,5-trinitrobenzene (TNB), the conventional reference aromatic electrophile in σ-complex chemistry.[14] Use of dilute alkali hydroxide solutions is in fact necessary to achieve the formation of **C-6** in aqueous solution [eqn. (3), Scheme 2]. Importantly, it has been found that DNBF also reacts very readily and quantitatively with such weak carbon nucleophiles as benzenoid aromatics (phenols, anilines…) or π-excessive heteroaromatics (indoles, pyrroles, thiophenes, furans…) whose carbon basicities are associated with large, negative pK_a values, *e.g.* 1,3-dimethoxybenzene (pK_a = −9), aniline (pK_a = −6) or 3-methoxythiophene (pK_a = −6.5).[4–6,15] In all of these reactions, covalent addition of the nucleophile takes place at C-7 of the carbocyclic ring of DNBF to give very stable carbon-bonded σ-adducts. Altogether, the results obtained have revealed that the neutral DNBF molecule is in fact more electrophilic than such strong electrophiles as benzenediazonium cations, including the *p*-nitrobenzenediazonium cation, a situation which has led to numerous synthetic, analytical and biological applications.[4c,d,16–18]

Recent findings have revealed that the exceptional electrophilic reactivity of DNBF is largely the reflection of a low aromatic character of the benzofuroxan structure. First, there is the discovery that DNBF behaves as a very versatile Diels–Alder reagent, contributing to Normal (NDA) and Inverse (IDA) electron-demand cycloadditions which generally proceed with high regioselectivity and high stereoselectivity.[13,19–23] An illustrative example is given in Scheme 3 which shows that the reaction of DNBF with cyclopentadiene affords initially a mixture of the two stereoselective NDA and IDA monoadducts **7** and **8** in their racemic forms. Then, NDA addition of a second molecule of cyclopentadiene is kinetically more favored at the remaining nitroalkene C4–C5 fragment of **8** than of **7**, to afford the highly functionalized diadduct **9** in its racemic form. In as much as **9** is

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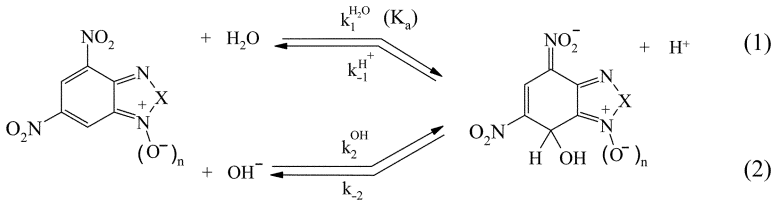
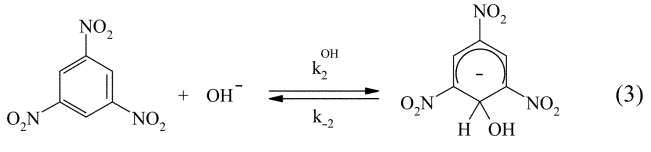
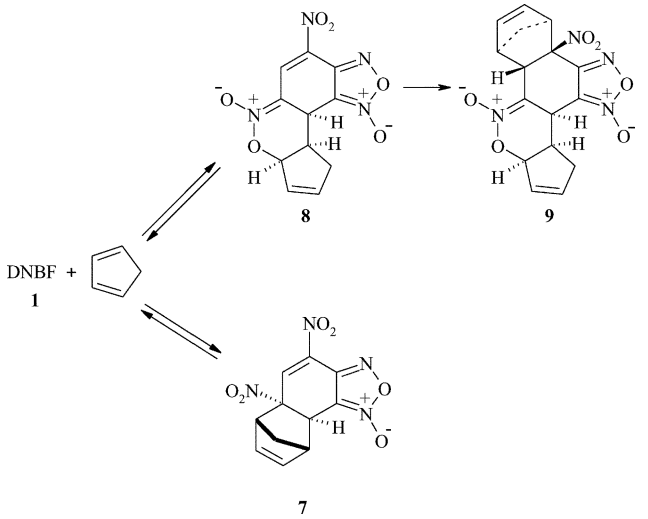


1 : DNBF	X = O, n = 1	**C-1**
2 : DNBZ	X = O, n = 0	**C-2**
3 : DNBS	X = S, n = 0	**C-3**
4 : DNBSe	X = Se, n = 0	**C-4**
5a : Pi-DNBt	X = N-(2,4,6-trinitrophenyl), n = 1	**C-5a**
5b : DNP-DNBT	X = N-(2,4-dinitrophenyl), n = 1	**C-5b**
5c : NP-DNBT	X = N-(4-nitrophenyl), n = 1	**C-5c**
5d : P-DNBT	X = N-(phenyl), n = 1	**C-5d**

Scheme 1

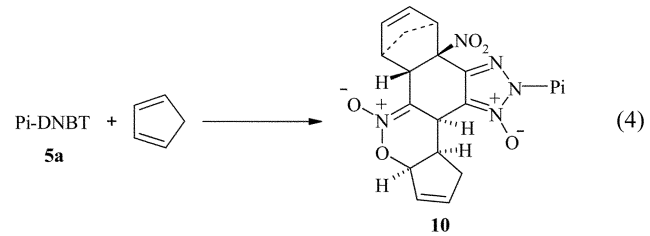


Scheme 2



Scheme 3

thermodynamically the most stable product, its formation at the expense of **7** has the effect to drive the complete equilibrium system of Scheme 3 towards completion of the second condensation.[21a] Second, there is the report that substitution of the oxygen atom of the related ring of DNBF for a less electronegative *N*-aryl group, including an *N*-(2,4,6-trinitrophenyl) group, has the effect of decreasing both the electrophilic reactivity – *e.g.* the pK_a value for formation of the 4,6-dinitrobenzotriazole 1-oxide adduct **C-5a** is equal to 6.70 in aqueous solution[13] – and the pericyclic reactivity – *e.g.* the formation of the diadduct **10** [eqn. (4), Scheme 4] occurs at



Scheme 4

a lower rate than that of **9**.[19c] The situation can only be understood in terms of the aromatic character of the parent molecules which increases in the order O < N–Ar and, correspondingly, of the electron-withdrawing effect of the annelated ring which decreases in the order O > N–Ar.[13]

Altogether, the above results suggest that the chemistry of nitrobenzofuroxans and related 10π-excessive heterocycles is governed by a close relationship between superelectrophilicity and pericyclic reactivity, each of these two facets being related to the aromaticity of the carbocyclic ring.[19c] To test this relationship further, this paper reports on a study of the reactivity of 4,6-dinitrobenzofurazan **2** (DNBZ, 4,6-dinitro-2,1,3-benzoxadiazole), 4,6-dinitro-2,1,3-benzothiadiazole **3** and 4,6-dinitro-2,1,3-benzoselenadiazole **4**. In this series, the aromaticity and activation of the carbocyclic ring are modulated through substitution of the oxygen atom of the oxadiazole ring of **2** for a sulfur or a selenium atom to give **3** and **4**, respectively. In addition to a thorough kinetic and thermodynamic investigation of the σ-complexation of **2**–**4** in aqueous solution according to Scheme 1, these compounds have been engaged in Diels–Alder condensations with isoprene, 2,3-dimethylbutadiene, cyclopentadiene and cyclohexadiene under the same experimental conditions as those used for DNBF and Pi-DNBT.[19c] Our results provide a clear demonstration that superelectrophilicity and pericyclic behaviour are closely interrelated in the reactivity patterns of these heterocycles. A communication dealing with the cyclohexadiene reactions has appeared.[23]

Results

Kinetic and thermodynamic studies

All rate and equilibrium measurements pertaining to Scheme 1 were made at 25 °C and constant ionic strength of 0.2 mol dm^{-3} maintained with KCl in aqueous solution. Dilute hydrochloric acid solutions, various buffer solutions and dilute potassium hydroxide solutions were used to cover a pH range of 0.8–13.0. To be noted is that all pH values have been measured relative to the standard state in pure water. Accordingly, the relation $[H^+] = 10^{-pH}/\gamma_\pm$ holds with $\gamma_\pm$ being the mean activity coefficient in 0.2 mol dm^{-3} KCl ($\gamma_\pm = 0.75$ at 25 °C).[4a,24]

pK_a Values of 2–4. Using appropriate buffer solutions (see the Experimental section), the pK_a values for the σ-complexation of **2**–**4** according to eqn. (1) were readily determined from the observed absorbance variations at $\lambda_{max} \approx 480$–490 nm of the resulting adducts **C-2**–**C-4** obtained at equilibrium as a function of pH. These actually describe clear acid–base-type equilibrations, as evidenced by the observation of good straight lines with unit slopes fitting eqn. (5). From these plots (see ESI†, Fig. S1), we readily obtained: p$K_a^2 = 3.92 \pm 0.05$; p$K_a^3 = 7.86 \pm 0.05$; p$K_a^4 = 6.34 \pm 0.05$.

$$\log\left[\frac{\text{Abs}\,(\mathbf{C}\text{-}n)}{\text{Abs}\,(n)}\right] = \text{pH} - \text{p}K_a \qquad (n = \mathbf{2} \rightarrow \mathbf{4}) \qquad (5)$$

pH Rate profiles for covalent hydration of 2–4. Using a stopped-flow spectrophotometer, the interconversions of **2**–**4** and the corresponding adducts **C-2**–**C-4** were kinetically investigated under first-order conditions with a substrate or adduct concentration of between 3×10^{-5} and 5×10^{-5} mol dm^{-3}. In agreement with the direct equilibrium approach depicted in Scheme 1, only one relaxation time corresponding to the formation (pH > pK_a) or decomposition (pH < pK_a) of the adducts was observed in all cases. The logarithmic values of the observed first-order rate constants k_{obsd} for the combined formation and decomposition of **C-2**–**C-4** at 25 °C are plotted in Fig. 1 and 2 as a function of pH. In

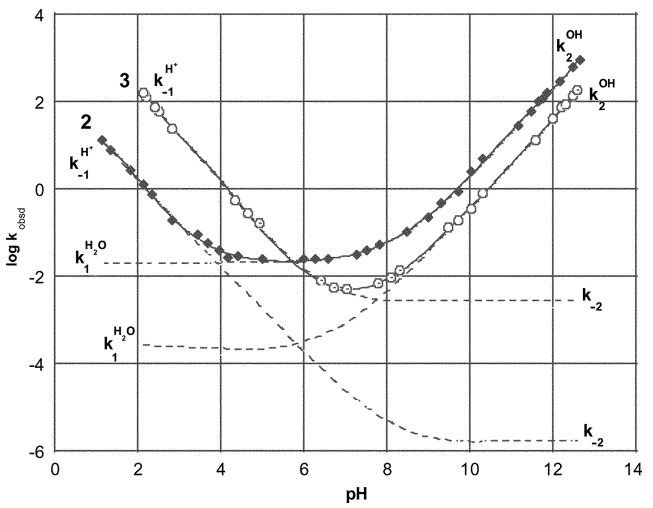


Fig. 1 pH Dependence of k_{obsd} (s^{-1}) for the formation and decomposition of the adducts **C-2** (◆) and **C-3** (○) in aqueous solution; $T = 25$ °C, $I = 0.2$ mol dm^{-3} KCl. The dashed lines refer to the calculated contributions of the k_f and k_d components according to eqns. (7) and (8); see text.

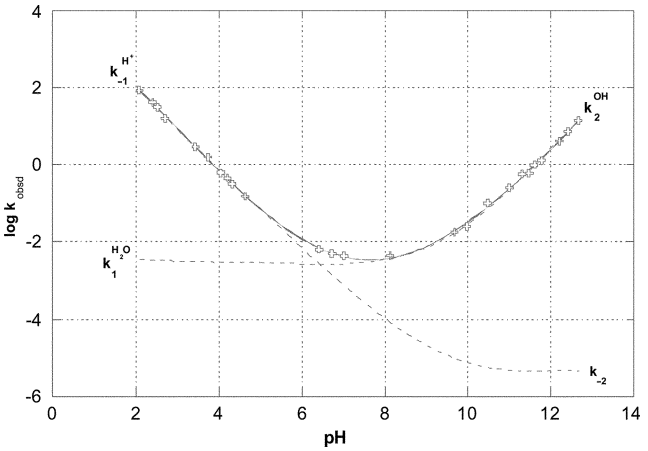


Fig. 2 pH Dependence of k_{obsd} (s^{-1}) for the formation and decomposition of the adduct **C-4** in aqueous solution; $T = 25$ °C, $I = 0.2$ mol dm^{-3} KCl. The dashed lines refer to the calculated contributions of the k_f and k_d components according to eqns. (7) and (8); see text.

the experiments where buffer catalysis was observed (*vide infra*), the k_{obsd} values used to draw the pH rate profiles where those extrapolated to zero buffer concentration (see also ESI: Tables S1–S3†)

The observed rate constants at a given pH are, of course, the sum of the individual first-order rate constants for formation (k_f) and decomposition (k_d) of the adducts [eqn. (6)]. As discussed in detail in previous studies of the covalent hydration of DNBF and Pi-DNBT as well as of various heterocyclic cations,[4a,13,25] values of k_f and k_d can be readily obtained from k_{obsd}, using eqns. (7) and (8).

$$k_{obsd} = k_f + k_d \qquad (6)$$

$$k_f = \frac{k_{obsd}}{1 + \frac{10^{-pH}}{10^{-pK_a}}} \qquad (7)$$

$$k_d = \frac{k_{obsd}}{1 + \frac{10^{-pK_a}}{10^{-pH}}} \qquad (8)$$

The corresponding pH–rate profiles are shown in Fig. 1 and 2. They are nicely consistent with eqns. (9) and (10) in which $k_1^{H_2O}$, k_2^{OH}, $k_{-1}^{H^+}$ and k_{-2} refer to the various reactions depicted in Scheme 1. Least-squares fitting of k_f and k_d to eqns. (9) and (10) gave the parameters which are collected in Table 1.

$$k_f = k_1^{H_2O} + \frac{k_2^{OH} K_w}{10^{-pH}\,\gamma_\pm} \qquad (9)$$

$$k_d = \frac{k_{-1}^{H^+} 10^{-pH}}{\gamma_\pm} + k_{-2} \qquad (10)$$

Buffer catalysis. Regarding measurements in buffer solutions, no significant catalysis of the interconversion of **2**–**4** to **C-2**–**C-4** has been observed in buffers of p$K_a < 7$, *i.e.* the formic acid, acetic acid, benzoic acid, cacodylic acid and dihydrogenophosphate buffers, at least at the relatively low total buffer concentrations used in our experiments (<2×10^{-2} mol dm^{-3}). This is exemplified for the formic acid/formate buffers in Fig. S2 (ESI†), which refers to the DNBSe compound **4**.

Table 1 Kinetic and thermodynamic parameters for formation and decomposition of hydroxy σ-adducts in aqueous solution[a]

	Parent electrophile	$pK^{H_2O}{}_a$	$k_1^{H_2O}/s^{-1}$	$k_{-1}^{H^+}/dm^3\ mol^{-1}\ s^{-1}$	k_2^{OH}/s^{-1}	$k_{-2}/dm^3\ mol^{-1}\ s^{-1}$
1	DNBF[b]	3.75	0.035	146	33 500	2.5×10^{-6}
2	DNBZ[c]	3.92	0.020	127	15 300	1.7×10^{-6}
4	DNBSe[c]	6.34	5.0×10^{-3}	11 350	305	5.0×10^{-6}
5a	Pi-DNBT[d]	6.70	1.1×10^{-3}	4215	392	2.0×10^{-5}
5b	DNP-DNBT[d]	7.15	6.7×10^{-4}	7050	1000	1.4×10^{-4}
3	DNBS[c]	7.86	2.8×10^{-4}	17 300	9400	5.0×10^{-3}
5c	NP-DNBT[d]	9.00	1.8×10^{-5}	13 300	680	3.5×10^{-3}
26	NBF[e]	10.27	—	—	30	0.011
27	NBZ[e]	10.57	—	—	59	0.011
5d	P-DNBT[d]	10.73	8.3×10^{-7}	33 000	317	0.17
6	TNB[f]	13.43	—	—	37.5	9.8

[a] $T = 25\ °C$, $I = 0.2$ mol dm^{-3} KCl. [b] Ref. 4*a*. [c] This work. [d] Ref. 13. [e] Ref. 6*d*; in these instances, the data refer to σ-complexation at carbon C-5. [f] Ref. 14.

As found for the 4,6-dinitrobenzofuroxan system,[4a] notable base catalysis was observed for the formation of the benzofurazan adduct **C-2** in bicarbonate and carbonate buffers.[4a] In these systems, the k_{obsd} data were found to obey eqn. (11) with B = HCO_3^- or CO_3^{2-}, as illustrated in Fig. 3 and Fig. S3 (ESI†). The fact that parallel lines were obtained in plotting k_{obsd} *vs.* $[CO_3^{2-}]$ at different pH values revealed that the catalytic contribution of the dianionic species CO_3^{2-} overcomes that of the monoanionic one (HCO_3^-) in the carbonate buffers. From the slopes of the linear plots of Fig. 3 and Fig. S3 (ESI†), the following catalytic rate constants were derived for **2**: $k^{HCO_3^-} = 180$ mol^{-1} dm^3 s^{-1}; $k^{CO_3^{2-}} = 2900$ mol^{-1} dm^3 s^{-1}. Interestingly, the intercepts of these plots agreed well, within experimental error, with the values of the $k_2^{OH}[OH^-] + k_1^{H_2O}$ term, as calculated at each pH using the k_2^{OH} value directly determined in dilute hydroxide solutions.

$$k_{obsd} = k_2^{OH}[OH^-] + k_B[B] + k_1^{H_2O} \quad (11)$$

No catalysis by HCO_3^- was detected for the sulfur and selenium systems in bicarbonate buffers (pH = 8.38) where the formation of the adducts **C-3** and **C-4** is, however, largely achieved. In carbonate buffers, base catalysis of the formation of **C-4** but not of **C-3** was observed (Fig. 4) with the k_{obsd} data obeying eqn. (11). From these data, one obtained: $k^{CO_3^{2-}} = 5.1$ mol^{-1} dm^3 s^{-1}.

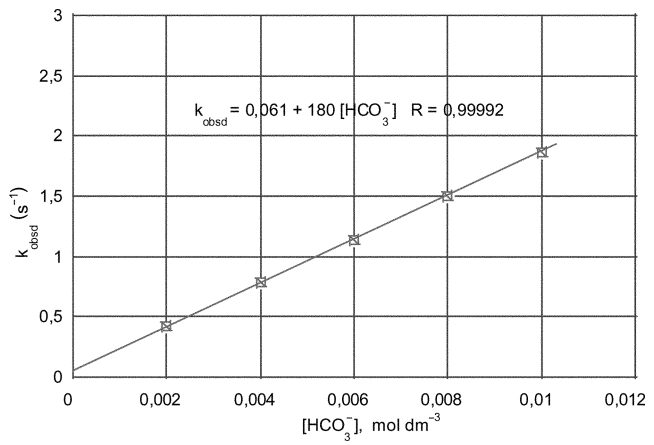


Fig. 3 Effect of bicarbonate concentration on the rate constant k_{obsd} for formation of the DNBZ adduct **C-2** at pH = 8.38 in aqueous solution; $T = 25\ °C$, $I = 0.2$ mol dm^{-3} KCl.

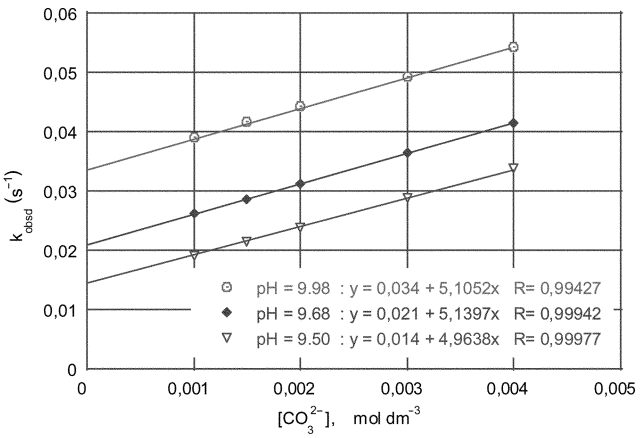


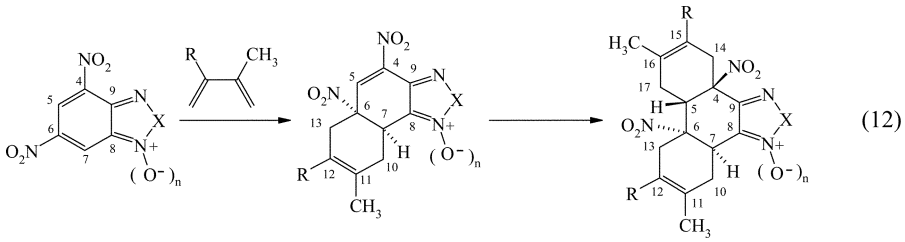
Fig. 4 Effect of carbonate concentration and pH on the rate constant k_{obsd} for formation of the DNBSe adduct **C-4** in aqueous solution; $T = 25\ °C$, $I = 0.2$ mol dm^{-3} KCl.

Diels–Alder reactivity

Compounds **2**–**4** have been opposed to the following dienes: isoprene, 2,3-dimethylbutadiene, cyclopentadiene and cyclohexadiene in dichloromethane or chloroform at room temperature.

Isoprene and 2,3-dimethylbutadiene systems. The reactions of **2** with excess isoprene or 2,3-dimethylbutadiene (10 equiv.) proceed similarly to those of DNBF,[22] affording in about two days the highly stereoselective diadducts **14a** and **14b** in their racemic forms [only one enantiomer is shown in eqn. (12), Scheme 5] in high yields. Under similar experimental conditions, the structurally related diadducts **16a**, **16b** and **18a**, **18b** are also obtained with **3** and **4** but much longer times (10 days to two weeks) are required to get these species in satisfactory yields.

The proposed stereochemistry for **14a**,**b**; **16a**,**b** and **18a**,**b** agrees well with the structural information provided by a detailed analysis of the ^1H and ^{13}C spectra recorded in $CDCl_3$ *via* COSY and HSQC as well as NOE and *J*-modulation experiments. The whole data are summarized in Tables S4 and S5 (ESI†); only the data for **16a**,**b** and **18a**,**b** are given in the Experimental section. Among other notable features, there is the observation that the disappearance of the low-field proton and carbon resonances associated with the $C_4C_5C_6C_7$ fragment of the carbocyclic ring goes along with

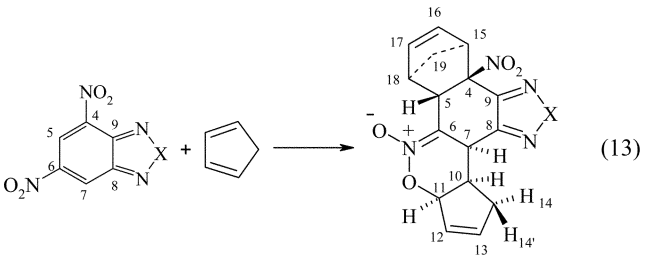


Scheme 5

a strong deshielding of the two sp^3 carbons C_4 and C_6. Both benefit from the strong electron-withdrawing effect exerted by a NO_2 group.[26] Apart from the resonance of the C_8 carbon, which is known to be very much shielded in a benzofuroxan structure ($\delta \approx 110 \pm 5$ ppm),[27,28] all resonances pertaining to the adducts **14a**,**b**; **16a**,**b** and **18a**,**b** are closely similar to those for the related DNBF adducts **12a** and **12b**. In as much as the structure of the diadduct **12a** could be firmly established by X-ray crystallography,[22] there is no doubt that the series of diadducts **14a**,**b**; **16a**,**b** and **18a**,**b** is the result of two successive *trans* cycloadditions at the C_6C_7 and C_4C_5 double bonds of the carbocyclic ring of **2**–**4** and DNBF.

In the reactions of DNBF with isoprene and 2,3-dimethylbutadiene it could be unambiguously demonstrated, using in particular ^{15}N labelling of the 4- and/or 6-NO_2 groups, that the formation of the diadducts **12a** and **12b** followed that of the monoadducts **11a** and **11b**, resulting from a first regioselective and stereoselective NDA process involving the C_6C_7 double bond of DNBF as the dienophilic contributor [eqn. (12)].[22] Recently, theoretical calculations have confirmed the greater Diels–Alder reactivity of this bond as compared with its C_4C_5 counterpart.[29,30] The overall conversion of the reagents into the stable diadducts being faster in the DNBZ than in the DNBF–isoprene or –2,3-dimethylbutadiene systems, it is only in working with an excess of DNBZ (1 equiv.) over the diene at hand (0.8 equiv.) that we have succeeded in characterizing the transient monoadducts **13a** and **13b** in the early stages of the reactions. Under these experimental conditions, ^1H and ^{13}C NMR spectra recorded immediately after mixing showed in fact the presence of signals typical for the formation of these monoadducts. As shown in Tables S4 and S5 (ESI†), these resonances are closely similar to those identified for the related DNBF adducts **11a** and **11b**.[22] Although similar attempts to detect the sulfur and selenium analogues **15a**,**b** and **17a**,**b** have failed, it seems on the grounds of analogy reasonable to view these monoadducts as the precursors of the diadducts **16a**,**b** and **18a**,**b**.

Cyclopentadiene systems. Each of the compounds **2** and **3** reacted with excess cyclopentadiene (10 equiv.) to give only one product which was much more rapidly formed in the case of the oxygen than in the case of the sulfur compound. ^1H and ^{13}C NMR spectra of the solids obtained (see Experimental) consisted of only one set of signals, indicating that the reactions have proceeded with high stereoselectivity to afford the diastereomers **19** and **20** in their racemic forms [only one enantiomer is shown in eqn. (13), Scheme 6]. Contrasting with **2** and **3**, the selenium compound **4** was not found to produce a stable product.



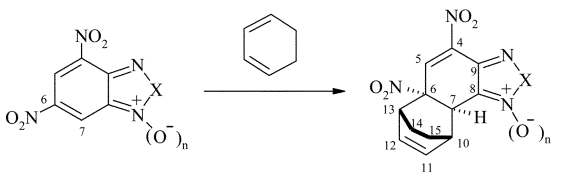
Scheme 6

The proposed stereochemistry for **19** and **20** in eqn. (13) could be derived from a detailed NMR analysis. In particular, NOESY experiments have revealed that the H_7, H_{10}, H_{11} and H_{14} protons (but not the $H_{14'}$ proton) are located on the same side of the dihydrooxazine *N*-oxide and cyclopentadiene rings of **19** and **20**. The values of the related ^3J coupling constants ($^3J_{H_7-H_{10}} = 5.6$ and $^3J_{H_{10}-H_{11}} = 8.9$ Hz for **19**; $^3J_{H_7-H_{10}} = 5.6$ and $^3J_{H_{10}-H_{11}} = 8.9$ Hz for **20**) agree with the *cis* arrangement of the H_7, H_{10} and H_{11} protons. On the other hand, the observation of a W-type ^4J coupling constant between the H_5 and H_7 protons ($^4J_{H_5-H_7} = 2.8$ Hz for **19** and **20**) implies a *trans* addition of the two Cp molecules.[31,32] In accord with the strong electron-withdrawing effect of the O–N^+–O^- fragment of the dihydrooxazine ring, both the sp^3 carbon C_{11} and the related H_{11} proton of **19** and **20** are strongly deshielded ($\delta_{C_{11}} = 91.84$ and $\delta_{H_{11}} = 5.79$ ppm for **19**; $\delta_{C_{11}} = 91.82$ and $\delta_{H_{11}} = 5.77$ ppm for **20**) with the C_{11} resonance comparing well with that of the nitro-substituted quaternary carbon C_4 ($\delta_{C_4} = 90.07$ and $\delta_{C_4} = 94.55$ for **19** and **20**, respectively).[26] Again the close analogy between the resonances of the protons and carbons of the carbocyclic rings of **19** and **20** with those of the related DNBF and Pi-DNBT adducts **9** and **10** [Tables S6 and S7 (ESI†)] further supported our stereochemical assignment.[19c,21a] To be noted is that the stereochemistry illustrated in structure **9** and in structures **19** and **20** was determined independently for the DNBF adduct by X-ray diffraction studies. In the DNBF system, experiments at low temperature have also shown that the interaction proceeds through the initial formation of a mixture of the NED and IED monoadducts **7** and **8**. However, the NED addition of the second molecule of Cp is kinetically more favored at the remaining nitroalkene moiety of **8** than of **7**. The diadduct **9** being thermodynamically the most stable product, its formation at the expense of **8** has therefore the effect of driving

the complete equilibrium system of Scheme 3 toward completion of the second condensation. Here, such a detailed study of the interactions has not been carried out, but it cannot be excluded that the formation of the diadduct **19** and **20** occurs along similar lines [eqn. (13)].

Cyclohexadiene systems. As previously found for the DNBF–cyclohexadiene reaction,[21a] treatment of **2**–**4** with excess cyclohexadiene resulted in the regioselective and stereoselective formation of the NED monoadducts **22**–**24** in their racemic form. No evidence for the subsequent addition of a second molecule of diene at the remaining nitro-activated C_4C_5 double bond of **22**–**24** could be found. As shown in Tables S6 and S7 (ESI†), the various ^1H and ^{13}C NMR parameters deduced from the analysis of the ^1H and ^{13}C NMR spectra of the three adducts compare well with those for the DNBF and Pi-DNBT analogues **21** and **25**.[21a] In this particular case, the *endo* configuration assigned to **21** was firmly confirmed by an X-ray structure, providing indirect support to the formulation of **22**–**24**.[21a]

Taking advantage that reactions [eqn. (14), Scheme 7] are restricted to a monoaddition process, the relative dienophilic reactivities of **2**–**4** could be assessed by mixing equimolar amounts of the two reagents and monitoring by NMR the appearance of the resulting adducts **22**–**24** as a function of time at room temperature in acetonitrile. This solvent was chosen for comparison with previous results obtained for DNBF and a number of related heteroaromatic electrophiles.[23] Table 2 summarizes the results which will be discussed below.



(14)

1	X = O, n = 1	**21**
2	X = O, n = 0	**22**
3	X = S, n = 0	**23**
4	X = Se, n = 0	**24**
5a	X = N-Picryl, n = 1	**25**

Scheme 7

Discussion

Relative stabilities of hydroxy adducts

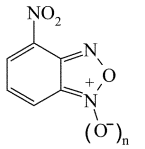
Table 1 reveals that the pK_a values for the conversion of **2**–**4** into the adducts **C-2**–**C-4** fall in the range 3.92–7.86. Interestingly the most activated compound (DNBZ, **2**) has a pK_a value (3.92) which is essentially the same as that of the related 1-oxide compound **1** (DNBF) (3.75).[4a] This is somewhat unexpected since it is well known that the presence of an electron-donating 1-oxide functionality has a major effect in governing the electron deficiency of the carbocyclic ring of a 2,1,3-benzoxadiazole structure, *e.g.* benzofuroxan is more prone to nitration than benzofurazan.[3,4b] On the other hand, DNBS (**3**) and DNBSe (**4**) have pK_a values of 7.86 and 6.34, respectively, which are more than six units lower than the pK_a value of TNB (13.43).[14] While this corresponds to a considerable increase in electrophilic character from that of the common reference electrophile in σ-complex chemistry, it is rather far from being comparable to that of DNBF or DNBZ. The hydroxy σ-adducts **C-3** and **C-4** are 10^4 and 250 times less stable than **C-1** and **C-2**, respectively. Substituting the oxygen atom of the oxadiazole ring of DNBZ for a sulfur or a selenium atom thus reduces markedly the adduct stability. This situation is reminiscent of the one observed upon σ-complexation of the corresponding mononitro derivatives, *i.e.* 4-nitrobenzofurazan, 4-nitrobenzothiadiazole and 4-nitrobenzoselenadiazole in methanol,[33] and it can be explained in terms of the aromatic character of the parent molecules which increases in the order O < Se < S and the electron-withdrawing effect of the annelated ring which increases in the order S < Se < O.[33] It is on the same grounds that the lesser stability of the series of *N*-arylbenzotriazole adducts **C-5a**–**d** relative to the DNBF adduct **C-1** was previously accounted for.[13] In this instance, however, nitro-substitution of the *N*-bonded phenyl ring has a major effect on the ease of σ-complexation. While the electrophilic character of the carbocyclic ring of the benzotriazole moiety of the *N*-picryl and *N*-2,4-dinitrophenyl derivatives (pK_a = 6.70; pK_a = 7.15) lies between that of the selenium and sulfur compounds, a strong reduction in reactivity is observed on going to the *N*-(4-nitrophenyl) and *N*-phenyl substrates.[13] These two latter derivatives have pK_a values of 9.0 and 10.73 respectively, falling in the same domain as the pK_a values

Table 2 Electrophilic *vs.* Diels–Alder reactivity of nitrobenzoxadiazoles and related substrates[a]

	Parent electrophile	Electrophilic reactivity $pK_a^{H_2O}$	Pericyclic reactivity adduct formation (%) 8 h	24 h	48 h	7 days
1	DNBF	3.75	100	100	100	100
2	DNBZ	3.92	100	100	100	100
4	DNBSe	6.34	—	*ca.* 10	30	60
5a	Pi-DNBT	6.70	38	62	100	100
3	DNBS	7.86	—	—	*ca.* 17	40
5c	NP-DNBT	9.00	—	—	—	—
26	NBF	10.27	—	—	—	—
27	NBZ	10.57	—	—	—	—
5d	P-DNTP	10.73	—	—	—	—

[a] As measured with reference to the mixing of equimolar amounts of the electrophile and cyclohexadiene and NMR monitoring of the conversion into the Diels–Alder adducts **21**–**25** [see eqn. (14)] at room temperature in acetonitrile.

of 4-nitrobenzofuroxan (NBF, **26**; 10.27) and 4-nitrobenzofurazan (NBZ, **27**; 10.57).[6d]



n = 0, NBZ **26**
n = 1, NBF **27**

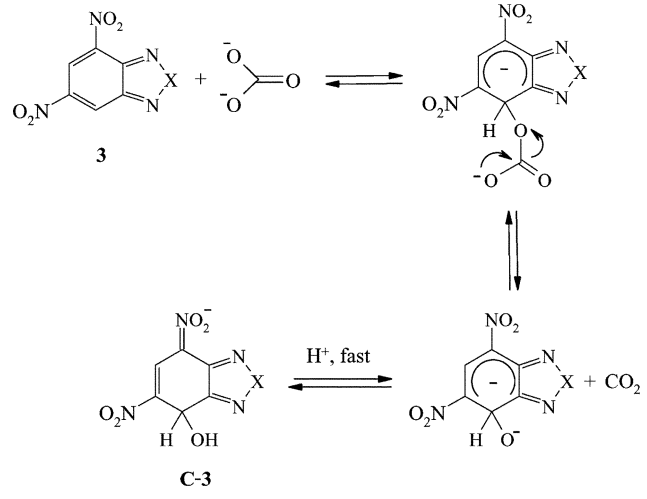
Reactivity of 2–4

The high susceptibility of DNBF to covalent hydration through water attack has been the major feature as a result of which this molecule has been accorded superelectrophilic properties.[2,4] As elaborated on in detail in previous kinetic and thermodynamic investigations of σ-complexation in aqueous solution,[4a,13] a primary requirement for having H_2O compete effectively as a nucleophile with OH^- in the formation of an hydroxy σ-adduct is in fact 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.* $k_1^{H_2O} > k_{-2}$. With a $k_1^{H_2O}/k_{-2}$ ratio of 1.2×10^4, this condition is clearly fulfilled for DNBZ, accounting for the identification of the k_{obsd} plateau of Fig. 1 to the upper plateau corresponding to $k_f = k_1^{H_2O}$ in the pH range of 4–7.5 in this figure. To be noted is that the similar $pK^{H_2O}{}_a$ values of DNBF and DNBZ go along with similar rate parameters for the formation ($k_1^{H_2O}$, k_2^{OH}) and decomposition ($k_{-1}^{H^+}$, k_{-2}) of the adducts **C-1** and **C-2**.

With a $k_1^{H_2O}/k_{-2}$ ratio of 1000, the contribution of the water pathway to the formation of the DNBSe adduct **C-4** is also very important but only in the reduced pH range of 6.5–8.5 (Fig. 2). Overall, the decreased stability of **C-4** relative to **C-1** and **C-2** is the result of a decrease in the rate constants for water and hydroxide ion additions and a concomitant increase in the susceptibility of **C-4** to decomposition. Contrasting with the situation for DNBF and DNBZ, the water pathway is negligible in the case of DNBS, as reflected by a $k_1^{H_2O}/k_{-2}$ ratio of 0.056 and the identification of the upper plateau to k_{-2} in Fig. 1. In this instance, the situation resembles that found previously for all compounds with $pK^{H_2O}{}_a \geqslant 8$, as it is the case for **5c**, **5d** as well as NBF and NBZ in Table 1.[13] The possible significance of this borderline pK_a value as a key index to demarcate the superelectrophilic reactivity from a normal electrophilic reactivity of electron-deficient aromatic or heteroaromatic substrates will be considered in the conclusion of this paper.

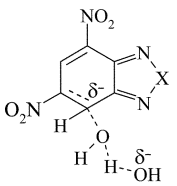
Buffer catalysis

Owing to the exalted contribution of the water pathway to the σ-complexation of **2**, the set of base catalysts involved in the formation of **C-2** is restricted to HCO_3^-, CO_3^{2-}, and OH^-. A most remarkable feature, however, is the finding that the carbonate ion is a remarkably efficient catalyst, being only five times less reactive than the more basic hydroxide ion. Even though it is well known that the reactivity of the strongly H-bonded solvated OH^- ion may be reduced relative to weaker oxyanionic bases,[34] the effect is here too important to be accounted for only in these terms. As previously discussed for the covalent hydration of DNBF, an interpretation in terms of CO_3^{2-} acting as a nucleophilic catalyst is more reasonable[4a] (Scheme 8), being in accord with the fact that DNBF is known to displace CO_2 from carbonate solutions.[4a]



Scheme 8

Instead, OH^- will act as a general base catalyst for the reaction of water with **2**, implying a transition state of type **28**. Interestingly, several authors have discussed the occurrence of such hydroxide-catalyzed water attacks in reactions of carbonyl compounds, and evidence for a similar catalytic behaviour of OH^- has been reported in various systems including S_NAr and related σ-complexation reactions.[35–44]



28

Support for the above mechanistic proposals is provided by the decrease in catalytic efficiency of CO_3^{2-} with decreasing electrophilic character of the substrate. The $k^{OH^-}/k^{CO_3^{2-}}$ ratio increases from 5 to 60 on going from DNBZ to DNBSe while no catalytic contribution of CO_3^{2-} to the formation of the less stable DNBS adduct **C-3** was detected under the experimental conditions employed. Such a trend seems to be consistent with a loss in the ability of CO_3^{2-} to act as a nucleophilic catalyst rather than with a systematic change in the transition state structure associated with the mechanism of nucleophilic catalysis. In other words, the nucleophilic pathway of Scheme 8 will only contribute importantly in the hydration of the strongest electrophiles while the general base mechanism is the predominant route in the case of electrophiles having $pK_a \geqslant 7$.

Diels–Alder reactivity

Structural and mechanistic features. Exhibiting a strong analogy with the related DNBF interactions, the reactions of **2**–**4** with isoprene, 2,3-dimethylbutadiene, cyclopentadiene and cyclohexadiene call only for a few structural and mechanistic comments. In the case of the reactions of **2** (DNBZ) with isoprene and 2,3-dimethylbutadiene, it is important that the NMR characterization of the transient monoadducts **13a** and **13b** (in their racemic forms)

could be made. This supports the view, previously formulated for the corresponding DNBF systems,[22] that the thermodynamically stable products of the reactions, *i.e.* the diadducts **14a** and **14b** are formed through the two-step sequence of eqn. (12). Following a first diastereoselective and regioselective normal electron-demand condensation leading to **13a** and **13b**, a second and also highly stereoselective NDA process takes place at the remaining nitroalkene-like C_4C_5 fragment of these monoadducts to afford the NDA–NDA diadducts **14a** and **14b**. These have a stereochemistry which is the same as that firmly established by an X-ray structure for the DNBF analogues **12a** and **12b**.[22] The reaction sequence of eqn. (12) is consistent with theoretical calculations which point to the activated C_6C_7 double bond of DNBF and DNBZ as being the preferred site for normal (as well as inverse) Diels–Alder reactivity.[29,30] Although we were not able to carry out a similar characterization of the precursor monoadducts **15a**,**b** and **17a**,**b**, the obtention of the diadducts **16a**,**b** and **18a**,**b** as the unique products of the interactions leaves no doubt that the two-step process of eqn. (12) is also operating in the DNBS and DNBSe systems.

As recalled in the Introduction, it has been shown that the interaction of DNBF with cyclopentadiene proceeds initially to afford a mixture of the two stereoselective NDA and IDA monoadducts **7** and **8** (Scheme 3).[21a] Then, addition of a second molecule of cyclopentadiene takes place preferentially at the remaining nitroalkene moiety of **8** to afford the diadduct **9**. In as much as **9** is the stable product of the reaction, its formation at the expense of **8** has the effect of driving the complete equilibrium system of Scheme 3 toward completion of the second condensation. An X-ray structure of **9** has confirmed that the two successive condensations proceed through *endo* processes with a *trans* addition of the cyclopentadiene molecules.[21a] Here, it is noteworthy that the reactions of DNBZ and DNBS afford diadducts, namely **19** and **20**, exhibiting the same stereochemistry as that of the DNBF and Pi-DNBT analogues **9** and **10**. This suggests that eqn. (13) must at least be viewed as consisting of an IDA–NDA sequence similar to that described in the upper part of Scheme 3. Why DNBSe failed to react similarly is not presently understood.

A most interesting result is the exclusive formation of the NDA monoadducts **22**–**24** upon treatment of **2**–**4** with cyclohexadiene, a situation which is presumably the reflection of steric hindrance to approach of the second molecule of cyclohexadiene. In as much as this behaviour is reminiscent of the one observed with DNBF and Pi-DNBT – only the monoadducts **21** and **25** were obtained in these systems[23] – the simple condensation process of eqn. (14) is appropriate to assess the relative dienophilic reactivities of our substrates. As revealed by Table 2, there is a clear correlation between the electrophilic behaviour, as measured by the $pK^{H_2O}_a$ values for water addition – and pericyclic behaviour, as measured by the time needed to achieve the condensation process of eqn. (14). As the most electrophilic substrates, DNBF ($pK^{H_2O}_a = 3.75$) and DNBZ ($pK^{H_2O}_a = 3.92$) undergo facile addition of cyclohexadiene, with the related adducts **21** and **22** being quantitatively formed in about 8 h at room temperature. Going to the 10^3 times less electrophilic 2-picryl-4,6-dinitrobenzotriazole 1-oxide (Pi-DNBT; $pK^{H_2O}_a = 6.70$), two days are required to carry out an essentially complete conversion into the NDA adduct **25**. Despite a rather similar electrophilicity, DNBSe ($pK^{H_2O}_a = 6.34$) is somewhat less reactive than Pi-DNBT with only 30% conversion into the adduct **24** after two days. On the other hand, DNBS ($pK^{H_2O}_a = 7.86$) is poorly reactive (40% conversion into **23** after a week) while all compounds with $pK^{H_2O}_a$ values $\geqslant 9$, such 2-(4-nitrophenyl)-4,6-dinitrobenzotriazole 1-oxide **5c** ($pK^{H_2O}_a = 9$), 4-nitrobenzofuroxan **27** (NBF, $pK^{H_2O}_a = 10.27$), 4-nitrobenzofurazan **26** (NBZ, $pK^{H_2O}_a = 10.57$), and 2-phenyl-4,6-dinitrobenzotriazole 1-oxide **5d** ($pK^{H_2O}_a = 10.73$), are totally inert to condensation with cyclohexadiene. Based on the above figures, it is clear that only the most activated heterocycles can be involved in pericyclic processes with cyclohexadiene and that a $pK^{H_2O}_a$ value of 8–8.5 seems to be a benchmark demarcating those electrophiles than can react according to eqn. (14) from those which do not. Importantly and even though most of the related interactions proceed through more complicated patterns – as exemplified in Scheme 3, they can involve diadduct formation and/or competition between NDA and IDA processes – the available experimental evidence is that the above benchmark also accounts well for the reactivity of the electrophiles **1**–**5** towards isoprene, 2,3-dimethylbutadiene or cyclopentadiene. As found for the cyclohexadiene systems, these three dienes do not react with the 4-mononitro compounds (NBF and NBZ) under similar conditions. It is only upon treatment with extremely reactive dienes like the Danishefsky diene that such mononitro-activated structures were found to exhibit some pericyclic reactivity.[45]

We have previously proposed that an effective contribution of the water pathway [$k_1^{H_2O}$ in eqn. (1), Scheme 1] to the formation of an hydroxy σ-adduct in aqueous solution is a major prerequisite for according superelectrophilic properties to an electron-deficient aromatic or heteroaromatic substrate.[4,13] In comparing the reactivity of **2**–**4** with that of the other electrophiles listed in Table 1, it is apparent that the σ-complexation process of eqn. (1) must be associated to $pK^{H_2O}_a$ values $\leqslant 8$ for having H_2O competing efficiently as a nucleophile with OH^- in the formation of a corresponding adduct. It follows that $pK^{H_2O}_a \approx$ 8–8.5 can be used as a key and readily accessible thermodynamic index, both to define the frontier between superelectrophilicity and electrophilicity in σ-complexation processes and to demarcate the boundary between those electrophiles than can exhibit dual pericyclic and electrophilic behaviour from those which do not.

Since the degree of aromaticity in heteroaromatic systems has been recognized to be inversely proportional to the Meisenheimer reactivity of heterocycles such as **1**–**5** as compared to **6** for example,[1–6] the above relationship between superelectrophilicity and pericyclic reactivity further highlights the role of the aromaticity factor in governing the behaviour of these substrates. It follows that a simple positioning of the electrophilic reactivity on the σ-complexation scale in aqueous solution is of great value for predicting the potential pericyclic reactivity of a given heterocycle, a feature which is of real benefit for synthetic organic chemical applications.

Experimental

Materials

Commercially available 2,3-dimethylbutadiene, isoprene and cyclohexadiene were used as received. Cyclopentadiene was obtained from the heating of bicyclopentadiene and used without

further purification. 4,6-Dinitrobenzofurazan (DNBZ), 4,6-dinitrobenzothiadiazole (DNBS), and 4,6-dinitrobenzoselenadiazole (DNBSe) were prepared according to procedures reported in the literature: DNBZ mp 130 °C (lit. 129–130 °C)[4b]; DNBS mp 145 °C (lit. 148 °C);[46] DNBSe mp 209 °C (lit. 211 °C).[47] The preparation and characterization of compounds **9** and **10**,[19c,21a] **11**–**14**[22,48] and **21**–**25**[23] were previously described.

Buffers

HCl and KOH solutions were prepared from Titrisol. Buffer solutions were made up from the best available commercial grades of reagents. Buffers used were formate (pH 3–4), benzoate (pH 3.6–4.3), acetate (pH 4.0–5.2), succinate (pH 4.0–5.8), cacodylate (pH 6.0–6.8), phosphate (6–7.5), *N*-[tris(hydroxymethyl)methyl]-2-aminoethanesulfonic acid (TES; pH 7.5–8), bicarbonate (pH 8.38) and carbonate (pH 9.5–10.5). Solutions were prepared and their pH measured as described previously.[4a,13]

Preparation of the Diels–Alder adducts. General procedure

To a solution of **2**–**4** (0.5 g) in CH_2Cl_2 (10 ml) at room temperature was added an excess (10 equiv.) of diene. The solution turned rapidly to an orange colour and the reaction mixture was stirred at room temperature for a few days. Addition of pentane resulted in the immediate formation of a precipitate which was collected by filtration and dried under vacuum and then purified by column chromatography, using pentane–ethyl acetate mixtures as eluents.

16a. Yellow solid; yield 57%; mp 100 °C; MS (CI): 363 $(M + H)^+$. Anal. calc. for $C_{16}H_{18}N_4O_4S$: C, 53.04; H, 4.97; N, 15.47; Found: C, 52.84; H, 4.85; N, 15.68%. ^{1}H NMR data (δ/ppm, J/Hz): 4.03 (H_5, dd, $^3J_{5/17a,b} = 8.5$, $^4J_{5/7} = 1.1$), 4.07 (H_7, dd, $^3J_{7/10} = 7.7$, $^4J_{7/5} = 1.1$), 2.52 (H_{10}, m, 2H), 5.27 (H_{12}, m), 2.52 (H_{13}, m, 2H), 2.94 (H_{14}, m, 1H), 3.31 (H_{14}, m, 1H), 5.43 (H_{15}, m), 2.20 (H_{17a}, m, 2H), 1.69 (CH_3, s), 1.66 (CH_3, s). ^{13}C NMR data (δ/ppm): 92.1 (C_4), 41.6 (C_5), 89.4 (C_6), 37.5 (C_7), 160.9 (C_8), 152.4 (C_9), 31.9 (C_{10}), 132.7 (C_{11}), 115.6 (C_{12}), 33.2 (C_{13}), 35.2 (C_{14}), 116.8 (C_{15}), 123.9 (C_{16}), 27.9 (C_{17}), 22.5, 22.2 (CH_3).

16b. Yellow solid; yield 45%; mp 93 °C; MS (EI): 390 $(M)^+$. Anal. calc. for $C_{16}H_{22}N_4O_4S$: C, 55.38; H, 5.64; N, 14.35; Found: C, 55.37; H, 5.18; N, 14.31%. ^{1}H NMR data (δ/ppm, J/Hz): 3.86 (H_5, dd, $^3J_{5/17a,b} = 8.6$, $^4J_{5/7} = 1.1$), 4.06 (H_7, dd, $^3J_{7/10} = 7.7$, $^4J_{7/5} = 1.1$), 2.75 (H_{10}, m, 2H), 2.80 (H_{13}, m, 1H), 2.39 (H_{13}, m, 1H), 2.87 (H_{14}, m, 1H), 3.22 (H_{14}, m, 1H), 2.10 (H_{17a}, m, 2H), 1.62 (CH_3, s), 1.60 (CH_3, s), 1.58 (CH_3, s), 1.56 (CH_3, s). ^{13}C NMR data (δ/ppm): 92.8 (C_4), 42.7 (C_5), 89.8 (C_6), 36.9 (C_7), 160.8 (C_8), 152.4 (C_9), 34.0 (C_{10}), 124.4 (C_{11}), 121.2 (C_{12}), 37.2 (C_{13}), 41.0 (C_{14}), 123.1 (C_{15}), 124.8 (C_{16}), 29.6 (C_{17}), 18.5, 18.3, 18.2, 18.0 (CH_3).

18a. Yellow solid; yield 62%; mp 107 °C; MS (CI): 363 $(M - HNO_2)^+$. Anal. calc. for $C_{16}H_{18}N_4O_4Se$: C, 49.65; H, 4.43; N, 13.69; Found: C, 50.05; H, 4.32; N, 13.28%. ^{1}H NMR data (δ/ppm, J/Hz): 3.99 (H_5, dd, $^3J_{5/17a,b} = 8.5$, $^4J_{5/7} = 1.1$), 4.12 (H_7, dd, $^3J_{7/10} = 7.5$, $^4J_{7/5} = 1.0$), 2.68 (H_{10}, m, 2H), 5.34 (H_{12}, m), 2.82 (H_{13}, m, 2H), 2.59 (H_{14}, m, 1H), 3.50 (H_{14}, m, 1H), 5.45 (H_{15}, m), 2.27 (H_{17a}, m, 2H), 1.72 (CH_3, s), 1.68 (CH_3, s). ^{13}C NMR data (δ/ppm): 91.7 (C_4), 39.7 (C_5), 92.7 (C_6), 41.7 (C_7), 163.7 (C_8), 157.0 (C_9), 34.6 (C_{10}), 132.3 (C_{11}), 115.9 (C_{12}), 32.5 (C_{13}), 34.3 (C_{14}), 117.2 (C_{15}), 133.5 (C_{16}), 27.3 (C_{17}), 22.7, 22.2 (CH_3).

18b. Colorless solid; yield 73%; mp 101 °C; MS (EI): 392 $(M - HNO_2)^{+\bullet}$. Anal. calc. for $C_{16}H_{22}N_4O_4Se$: C, 49.38; H, 5.03; N, 12.80; Found, C, 49.76; H, 5.01; N, 12.81%. ^{1}H NMR data (δ/ppm, J/Hz): 4.10 (H_5, dd, $^3J_{5/17a,b} = 8.5$, $^4J_{5/7} = 1.3$), 3.91 (H_7, dd, $^3J_{7/10} = 7.7$, $^4J_{7/5} = 1.1$), 2.68 (H_{10}, m, 2H), 2.72 (H_{13}, m, 1H), 2.62 (H_{13}, m, 1H), 2.65 (H_{14}, m, 1H), 3.40 (H_{14}, m, 1H), 2.22 (H_{17a}, m, 2H), 1.67 (CH_3, s), 1.65 (CH_3, s). ^{13}C NMR data (δ/ppm): 92.8 (C_4), 41.3 (C_5), 93.5 (C_6), 41.6 (C_7), 164.0 (C_8), 157.2 (C_9), 35.4 (C_{10}), 124.2 (C_{11}), 124.0 (C_{12}), 38.0 (C_{13}), 40.6 (C_{14}), 124.0 (C_{15}), 124.8 (C_{16}), 29.5 (C_{17}), 18.9, 18.5, 18.3, 18.0 (CH_3).

19. Pale yellow solid; yield 68%; mp 167 °C; MS (CI): 343 $(M + H)^+$, 297 $(M + H - NO_2)^+$. Anal. calc. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.09; N, 16.37; Found: C, 55.61; H, 3.94; N, 16.64%. ^{1}H NMR data (δ/ppm, J/Hz): 3.55 (H_5, d, $^4J_{5/7} = 2.8$), 4.35 (H_7, dd, $^3J_{7/10} = 5.6$, $^4J_{7/5} = 2.8$), 3.89 (H_{10}, m, 1H), 5.79 (H_{11}, m, 1H), 5.95 (H_{12}, m, 1H), 6.19 (H_{13}, m, 1H), 2.34 (H_{14}, dd, $^3J_{14/10} = 8.8$, $^2J = 18.3$), 2.00 (H_{14}, dd, $^3J_{14/10} = 2.6$, $^2J = 18.3$), 4.00 (H_{15}, m, 1H), 6.38 (H_{16}, dd, $^3J_{16/15} = 2.6$, $^3J_{16/17} = 5.5$), 6.69 (H_{17}, dd, $^3J_{17/18} = 3.3$, $^3J_{16/17} = 5.5$), 3.52 (H_{18}, m, 1H), 1.74 (H_{19}, m, 1H), 1.00 (H_{19}, m, 1H). ^{13}C NMR data (δ/ppm): 90.1 (C_4), 47.6 (C_5), 123.2 (C_6), 32.7 (C_7), 152.2 (C_8), 150.7 (C_9), 43.0 (C_{10}), 91.8 (C_{11}), 127.0 (C_{12}), 140.0 (C_{13}), 35.2 (C_{14}), 55.2 (C_{15}), 134.6 (C_{16}), 141.2 (C_{17}), 46.4 (C_{18}), 46.6 (C_{19}).

20. Pale yellow solid; yield 38%; mp 140 °C; MS (CI): 366 $(M + NH_4)^+$, 349 $(M + H)^+$. Anal. calc. for $C_{16}H_{14}N_4O_4$ S: C, 55.17; H, 4.02; N, 16.09; Found: C, 55.31; H, 4.21; N, 16.32%. ^{1}H NMR data (δ/ppm, J/Hz): 3.52 (H_5, d, $^4J_{5/7} = 2.8$), 4.31 (H_7, dd, $^3J_{7/10} = 5.6$, $^4J_{7/5} = 2.8$), 3.90 (H_{10}, m, 1H), 5.77 (H_{11}, m, 1H), 5.94 (H_{12}, m, 1H), 6.15 (H_{13}, m, 1H), 2.19 (H_{14}, dd, $^3J_{14/10} = 8.8$, $^2J = 18.3$), 1.98 (H_{14}, dd, $^3J_{14/10} = 2.6$, $^2J = 18.3$), 3.98 (H_{15}, m, 1H), 6.39 (H_{16}, dd, $^3J_{16/15} = 2.6$, $^3J_{16/17} = 5.5$), 6.64 (H_{17}, dd, $^3J_{17/18} = 3.3$, $^3J_{16/17} = 5.5$), 3.50 (H_{18}, m, 1H), 1.64 (H_{19}, m, 1H), 0.96 (H_{19}, m, 1H). ^{13}C NMR data (δ/ppm): 94.5 (C_4), 54.5 (C_5), 124.7 (C_6), 38.4 (C_7), 157.0 (C_8), 154.7 (C_9), 43.2 (C_{10}), 91.8 (C_{11}), 127.0 (C_{12}), 140.0 (C_{13}), 35.0 (C_{14}), 54.8 (C_{15}), 135.2 (C_{16}), 140.7 (C_{17}), 46.3 (C_{18}), 46.3 (C_{19}).

Rate and pK_a measurements

Stopped-flow determinations were performed on an Applied-Photophysics SX-18MV spectrophotometer, the cell compartment of which was maintained at 25 ± 0.1 °C. Other kinetic and pK_a determinations were made using a conventional HP8453 spectrophotometer. All kinetic runs were carried out in triplicate under pseudo first-order conditions with an electrophile (**2**–**4**) concentration of *ca.* (3–5) × 10^{-5} moldm^{-3}. The rates were found to be reproducible to ±2–3%.

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