

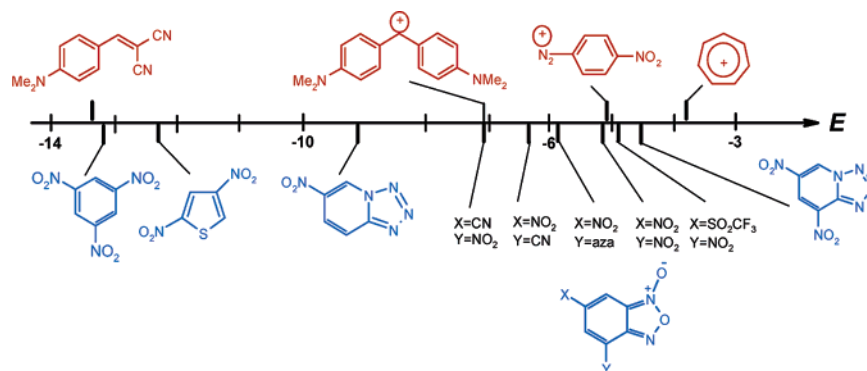
Ranking the Reactivity of Superelectrophilic Heteroaromatics on the Electrophilicity Scale

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The kinetics of the reactions of a series of reference carbon nucleophiles, consisting of *N*-methylpyrrole **A**, indole **B**, *N*-methylindole **C**, and enamines **D–G**, with 10 electron-deficient aromatic and heteroaromatic substrates (**1–10**), resulting in the formation of stable anionic σ -adducts, have been investigated in acetonitrile at 20 °C. It is shown that the second-order rate constants k_1 pertaining to the carbon–carbon coupling step of these processes fit nicely the three-parameter equation $\log k(20\text{ °C}) = s(N + E)$, allowing the determination of the electrophilicity parameters E of **1–10** and therefore the ranking of these neutral electron-deficient compounds on the comprehensive electrophilicity scale defined for cationic electrophiles by Mayr et al. (Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66). The E values of **1–10** are found to cover a range from -13 to -5 , going from 1,3,5-trinitrobenzene **1**, the least reactive molecule, to 4,6-dinitrotetrazolo[1,5-*a*]pyridine **8**, 4-nitro-6-(trifluoromethyl)sulfonylbenzofuroxan **3**, and 4,6-dinitrobenzofuroxan **2**, the three most reactive heterocycles. Of major interest is that the E value of **2** is essentially the same as that for 4-nitrobenzenediazonium cation ($E = -5.1$), approaching that of the tropylium cation family ($E \sim -3$ to -6) as well as a number of metal-coordinated carbenium ions. Such a ranking holds promise for expanding the range of coupling reactions which can be envisioned with such strongly electron-deficient neutral heteroaromatics as nitrobenzofuroxans and related compounds. Arguments are also given which exclude the possibility for the reactions studied to proceed via an electron-transfer mechanism.

How to relate nucleophilicity and electrophilicity through simple free energy relationships has been a challenge for organic chemists.^{1,2} Following various approaches, notably by Swain and Scott,^{3–5} a landmark in this quest for a widely applicable relationship has been the discovery by Ritchie that the rates of reactions of

stabilized carbocations and diazonium ions with a variety of nucleophiles (water, alcohols, amines, alkoxides, thiolates ...) can be appropriately described by eq 1.^{6,7} In this equation, N_+ is a nucleophile-dependent parameter

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while $\log k_0$ is a nucleophile-independent electrophilicity parameter that was initially defined as the rate constant for the reaction of an electrophile with water. Equation 1 implies that nucleophilicity is an intrinsic property of the reagent which can depend on the solvent but not on the electrophilicity of the reaction partner. Although this conclusion is in conflict with the reactivity-selectivity postulate,⁸ the so-called “constant selectivity” relationship of eq 1 has been successfully used in a number of mechanistic investigations of nucleophile–electrophile interactions.

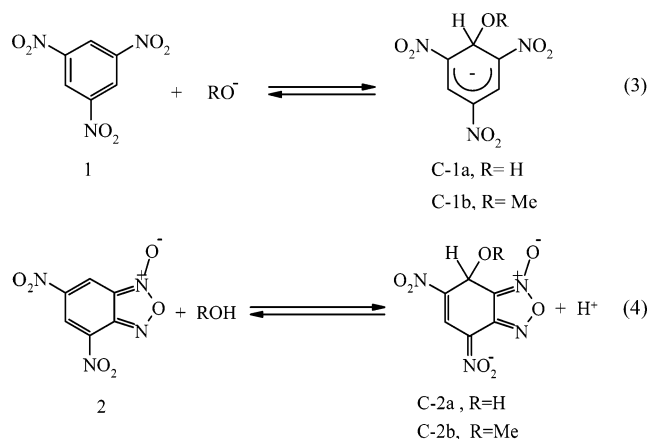
$$\log(k/k_0) = N_s \quad (1)$$

$$\log k(20^\circ\text{C}) = s(N + E) \quad (2)$$

Using a large series of diarylcarbenium ions and various π -excessive systems as reference sets for electrophiles and nucleophiles, respectively, Mayr and co-workers have shown in 1994 that it is possible to describe the rates of a large variety of electrophile–nucleophile combinations by the three-parameter equation, eq 2.^{9–11} In this equation, the E parameter measures the strength of the electrophile while the N and s parameters characterize the sensitivity of the nucleophile. Equation 2 differs from eq 1 by the introduction of the nucleophile-specific slope parameter which was set to 1 for 2-methyl-1-pentene and can be viewed as a correction term that improves considerably the fit of data compared to eq 1. Thus, the Ritchie equation becomes a special case of eq 2, holding only for reactions involving nucleophiles that have identical slope parameters.

Based on eq 2, general electrophilicity (E) and nucleophilicity (N) scales, each covering a reactivity range of about 25 orders of magnitude, have been defined and successfully used to predict the feasibility and rate of many interactions.^{9–12} In the exploration of the applicability of eq 2, Mayr has used a large variety of π -nucleophiles, including arenes, alkenes, allylsilanes,

enol ethers, ketene acetals, enamines ..., as well as carbanions and several σ - (e.g., hydride donors) and n - (e.g., amines, water, alcohols, OH^- , ...) nucleophiles.^{9–12} On the other hand, the strength of the electrophilic partner has been essentially modulated through structural variations of positively charged reagents, i.e., carbocations, diazonium ions, metal π -complexes So far, the description of the reactivity of uncharged electrophiles has been restricted to the behavior of a few Michael acceptors and quinone methides.^{9,10}



In recent years, we have paid particular attention to the reactivity of nitrobenzofuroxans, nitrobenzofurazans, and related heterocyclic compounds.^{13–16} These represent a class of neutral 10- π -electron-deficient heteroaromatic substrates which exhibit an extremely high electrophilic character in many covalent nucleophilic addition and substitution processes.^{13–18} While the common reference aromatic electrophile in anionic σ -complex chemistry, 1,3,5-trinitrobenzene **1** (also noted TNB),^{13,19} only reacts with the strong oxygen bases hydroxide and methoxide ions (eq 3), 4,6-dinitrobenzofuroxan **2** (DNBF) undergoes facile addition of water or methanol according to eq 4 to

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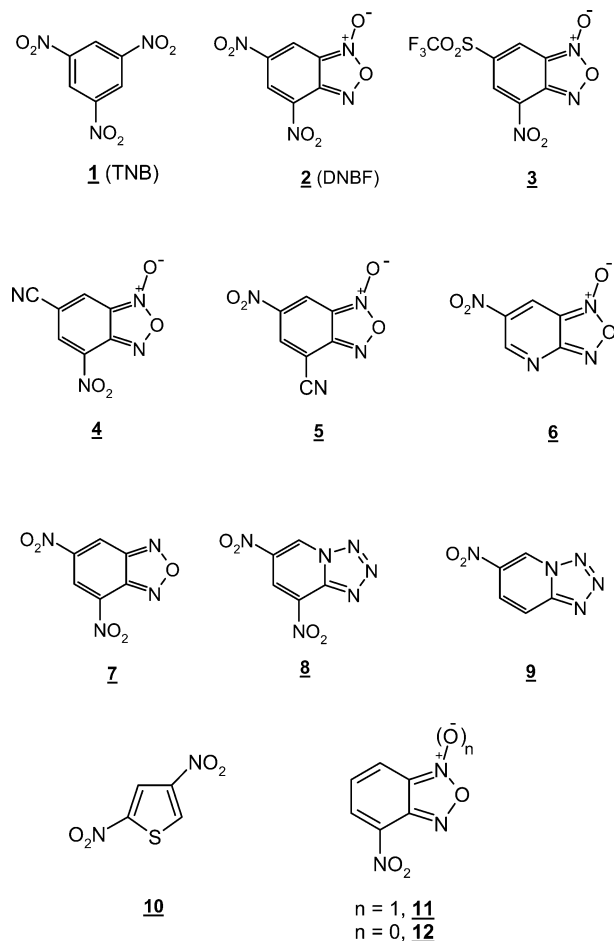


FIGURE 1. Structures and numbering of the aromatic and heteroaromatic electrophiles.

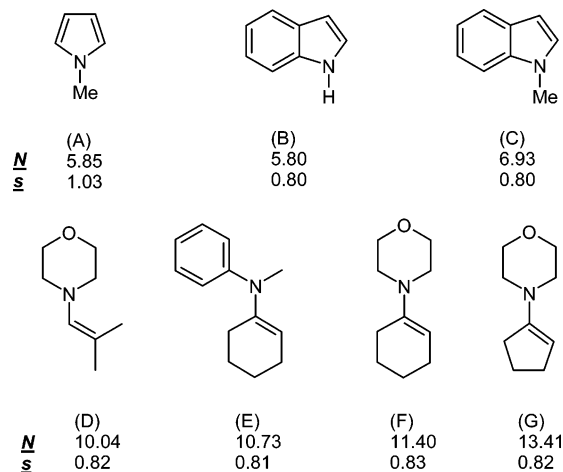


FIGURE 2. Structures, identification, nucleophilicity, and slope parameters for nucleophiles (N and s values taken from ref 9).

give the hydroxide or methoxide adducts **C-2a** and **C-2b**, which are 10^{10} times thermodynamically more stable than the analogous TNB adducts **C-1a** and **C-1b**.^{13,14} More importantly, **2** reacts quantitatively at room temperature with weak carbon π -nucleophiles such as benzenoid aromatics (phenols, anilines) or π -excessive het-

eroaromatics (indoles, pyrroles, thiophenes) whose conjugated acids (noted CH) are characterized by large pK_a^{CH} values, e.g., 1,3,5-trimethoxybenzene ($pK_a^{CH} = -5.7$),^{20a} indole ($pK_a^{CH} = -3.46$),^{15a,b} or 3-methoxythiophene ($pK_a^{CH} = -6.5$),^{20b} to afford stable anionic C-bonded σ -adducts which are formally the products of S_EAr substitution on the benzene or heteroarene ring. Coupling to weakly activated enolic double bonds is also a process that is much more readily achieved with **2** than with **1**.^{20c} On the basis of these findings, **2** has been accorded superelectrophilic properties and used as a convenient probe to assess the C-basidity of a number of very weak carbon nucleophiles, e.g., anilines, 1,8-bis(*N,N*-dimethylamino)naphthalene, 3-aminothiophenes, etc.^{13,17,18,21}

In view of the above results, the question arises of whether σ -complexation reactions of the type described in eqs 3 and 4, which involve two neutral electrophiles of widely different structure and reactivity, can be classified under the rubric of the Mayr relationship (eq 2). In this paper, we report on a successful calibration of the electrophilicity of **1** and **2**, as well as of the series of electron-deficient heteroaromatics **3–10** given in Figure 1 within the E scale. This finding holds promise for expanding the range of coupling reactions which can be envisioned with these neutral electrophiles. Moreover, the expansion of the applicability of eq 2 to σ -complexation processes further demonstrates the general utility of this relationship. A preliminary communication of this work has appeared.²²

Results

Product Characterization. A set of reference nucleophiles consisting of *N*-methylpyrrole (**A**), indole (**B**), *N*-methylindole (**C**), and the four enamines **D–G** (Figure 2) has been employed for characterizing the reactivity of electrophiles **1–10**.⁹ **A**, **B**, and **C** reacted appropriately with the strongest electrophiles, undergoing covalent addition at the most electron-deficient position, i.e., C-7, of the carbocyclic ring of **2**, **3**, and **5–8** to produce anionic σ -adducts which are formally the products of S_EAr substitution at C_α of the pyrrole and C_β of the indole rings. The process is exemplified for the DNBF systems

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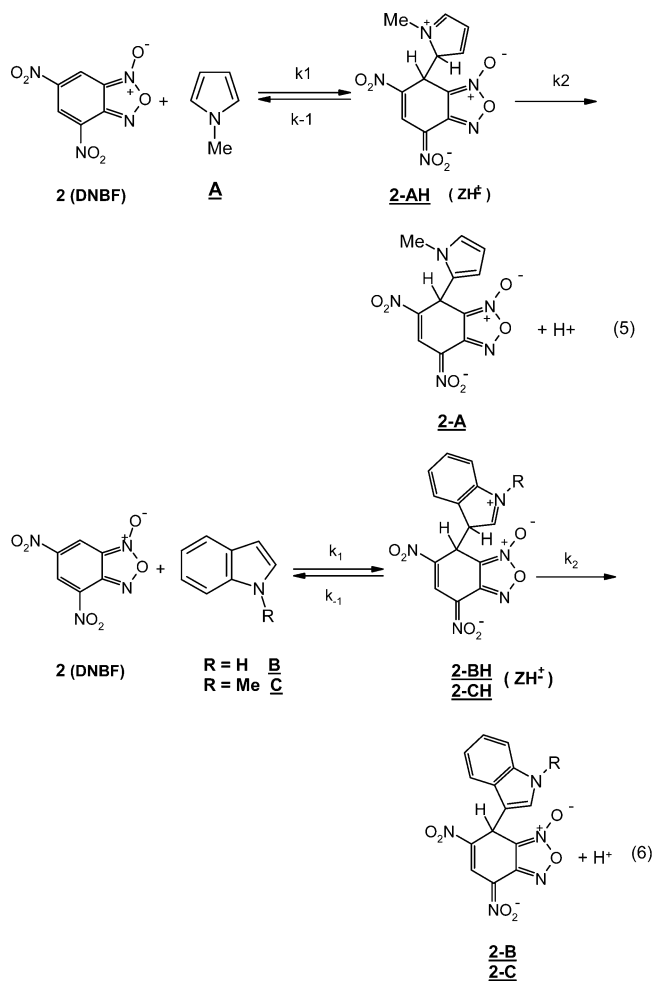
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in eqs 5 and 6. Many adducts of type **2-A**, **2-B**, or **2-C**

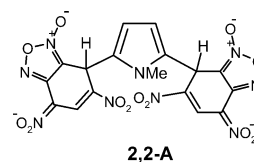


have been previously isolated and characterized as stable but somewhat explosive alkali salts after exchange of the H⁺ counterion with Na⁺ or K⁺.^{15a,b} Since changes in the substitution pattern of the carbocyclic ring or in the nature of the annelated ring of **2** to give **3**, **5,6**, or **7,8** had no influence on the mode of the σ -complexation process, product isolation has not been systematically performed but all resulting σ -adducts have been firmly characterized through analysis of the ¹H and ¹³C NMR spectra recorded after mixing of equimolar amounts of the parent reagents in Me₂SO solution (see the Experimental Section and Supporting Information Tables S₁–S₃ and Figures S₁–S₁₁). These in situ experiments confirmed the exclusive and quantitative formation of C _{β} -adducts of type **2-B** or **2-C** in all indole and *N*-methylindole systems. Under the same experimental conditions, the *N*-methylpyrrole reactions afforded predominantly the expected C _{α} -monoadducts, e.g., **2-A**, but in most cases the formation of a minor amount of the related C _{α} C _{α'} -diadducts, e.g., **2,2-A**, also occurred.^{23,24} Importantly, the formation of 1:2 products is very much reduced when the σ -complexation takes place in the presence of a large excess of the pyrrole reagent and it could not be detected

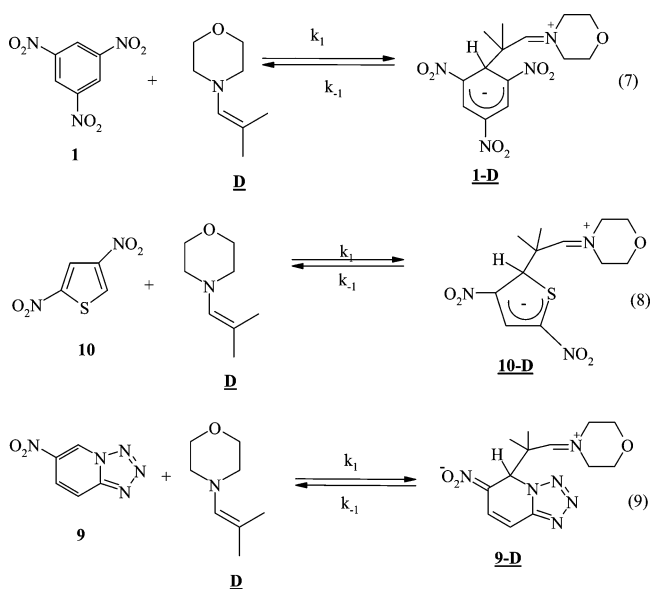
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(24) The NMR spectra reveal the formation of **2, 2-A** as a 1:1 mixture of two diastereomers.^{25a}

under the first order conditions employed for our kinetic investigation of reactions (5). In these instances, only one relaxation time corresponding to the formation of the expected monoadducts was observed (vide infra).



Each of the four enamines **D**–**G** reacted with the electrophiles **1**–**10** to produce the expected adducts, as shown in the model reactions represented for the enamine **D** in eqs 7–9. All of these adducts formed quantitatively upon mixing equimolar amounts of the two nucleophilic and electrophilic reagents in THF solution. Although they are not very stable in air,²⁵ a number of enamine adducts could be isolated and characterized in the solid state (see the Experimental Section). In all other cases, ¹H and ¹³C NMR spectra recorded in Me₂SO solution fully supported the proposed structures (see the Experimental Section and Supporting Information Tables S₄–S₈ and Figures S₁₂–S₃₂).



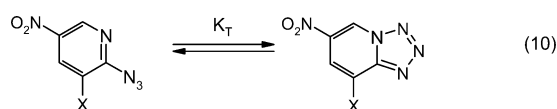
The tautomerisms of eqs 10 and 11 are structural transformations which are intimately related to the chemistry of nitrotetrazolopyridines and nitrobenzofuroxans, respectively.^{26–28} The question therefore arises of whether these equilibria could affect the σ -complexation of compounds **8** and **9** on one hand and **2**–**6** on the other hand. Regarding eq 10, the NMR evidence is that the conversion of **9** into **9-Az** is not detectable while that of

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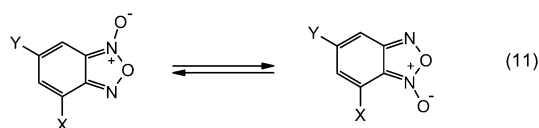
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8 into **8-Az** is of about 30% in acetonitrile and 10% in Me₂SO at room temperature.²⁶ However, the two compounds reacted similarly with the nucleophiles **A–G**, the corresponding σ -adducts being only obtained in their tetrazolo form i.e., **8A–G** and **9A–G**. A similar situation prevailed upon σ -complexation of **8** and **9** with water (or OH⁻) and methanol (or MeO⁻).^{16a,26d} Going to eq 11, it has been established that the equilibrium lies far to the 1-oxide side in the case of benzofuroxans bearing electron-withdrawing groups at both the 4- and 6- positions, including for the 4-aza-6-nitro derivative.^{26,27,28a,b,29,30} In addition, in all reactions of **2–6** with **A–G**, no evidence could be obtained for an appreciable 1-oxide/3-oxide exchange in the resulting σ -adducts. In accord with the absence of a substituent at the 5-position, neither the 4-nitrobenzofuroxans **2–4** nor the related σ -adducts were found to undergo a Boulton–Katritzky rearrangement.^{27,29,30}



X = NO₂, **8-Az**
X = H, **9-Az**

X = NO₂, **8**
X = H, **9**



X = Y = NO₂, **2**
X = NO₂, Y = SO₂CF₃, **3**
X = NO₂, Y = CN, **4**

Kinetic Studies. The rates of reactions, as depicted in eqs 5–9, were measured at 20 °C in acetonitrile, following the appearance of the resulting σ -adducts by conventional or stopped-flow spectrophotometry. These are all characterized by an intense visible absorption at wavelengths where neither the nucleophile nor the electrophile partner have a notable absorption, e.g., $\lambda_{\max} = 480$ nm, $\epsilon \sim 2.8 \times 10^4$ M⁻¹cm⁻¹ for DNBF adducts, $\lambda_{\max} = 530$ nm, $\epsilon \sim 16000$ M⁻¹ cm⁻¹ for 2,4-dinitrothiophene adducts, $\lambda_{\max} = 550$ nm, $\epsilon \sim 18000$ M⁻¹ cm⁻¹ for TNB adducts.^{13a} All experiments were carried out under first-order conditions with a 3×10^{-5} M concentration of the electrophile and a large excess (10^{-3} – 0.1 M) of the nucleophile. Figures S₃₃–S₄₇ (Supporting Information) show the oscilloscope traces illustrating the unique relaxation process corresponding to the formation of a

number of adducts representative of the various electrophile–nucleophile combinations studied.

For the *N*-methylpyrrole and indole reactions, the general expression for the observed first-order rate constant k_{obsd} , for the formation of the adducts, e.g., **2-A** or **2-B**, **2-C**, as derived under the assumption that the zwitterions ZH[±] are low-concentration intermediates, is given by

$$k_{\text{obsd}} = \frac{k_1 k_2}{k_{-1} + k_2} [\mathbf{A-C}] = k[\mathbf{A-C}] \quad (12)$$

In accordance with eq 12, excellent straight lines with zero intercepts were obtained in all systems when the k_{obsd} values were plotted vs the pyrrole or indole concentration (Figure 3). Determination of the second-order rate constants k from the slopes of these lines was therefore straightforward. Very importantly, a number of experiments were carried out with *N*-methylpyrrole-2,3,4,5-*d*₄, indole-1,3-*d*₂, and *N*-methylindole-3-*d* which did not reveal a significant influence of the nature of the isotopic substitution at the C_α or C_β positions on the rates of adduct formation (Figure 3). The experimental $k_{\text{H}}/k_{\text{D}}$ ratios were in the range 1.1 ± 0.1 , showing that proton removal from the zwitterions ZH[±] is rapid in acetonitrile, as previously observed in a kinetic study of the coupling of many indoles and pyrroles with DNBF in H₂O–Me₂SO and MeOH solutions.^{15a,b} Thus, electrophilic attack by **2**, **3**, and **5–8** at C_α or C_β of **A–C** is the rate-limiting step of reactions 5 and 6; i.e., the rate constant k is identical to the rate constant k_1 for the C–C coupling step. A similar situation prevailed in a large number of electrophilic substitutions, in particular the azo couplings of most indole and pyrrole derivatives by benzenediazonium cations.^{31,32}

For the enamine reactions, the observed first-order rate constant for the approach to equilibrium, as illustrated in eqs 7–9, is simply given by

$$k_{\text{obsd}} = k_1[\mathbf{D-G}] + k_{-1} \quad (13)$$

Figure 4 shows plots of k_{obsd} vs the enamine concentration for three representative examples. As called for by eq 13, they are linear with, however, negligible intercepts, indicating that the resulting σ -adducts have a high thermodynamic stability in acetonitrile solution.³³

Determination of the second-order rate constants k_1 from the slopes of the k_{obsd} vs [enamine] plots was straightforward in all reactions studied.

As discussed above, both tautomers **8** and **8-Az** are present in a 70/30 ratio at equilibrium in acetonitrile ($K_{\text{T}} = 2.33$, in eq 10). The kinetic evidence suggests, however, that in this solvent the formation of all 4,6-dinitrotetrahydropyridine adducts **8A–G** proceeds quantitatively through rate-limiting addition of the nucleophiles **A–G** to the major tautomer **8**, this species being part of a fast preequilibrium with the azido structure **8-Az**. On the

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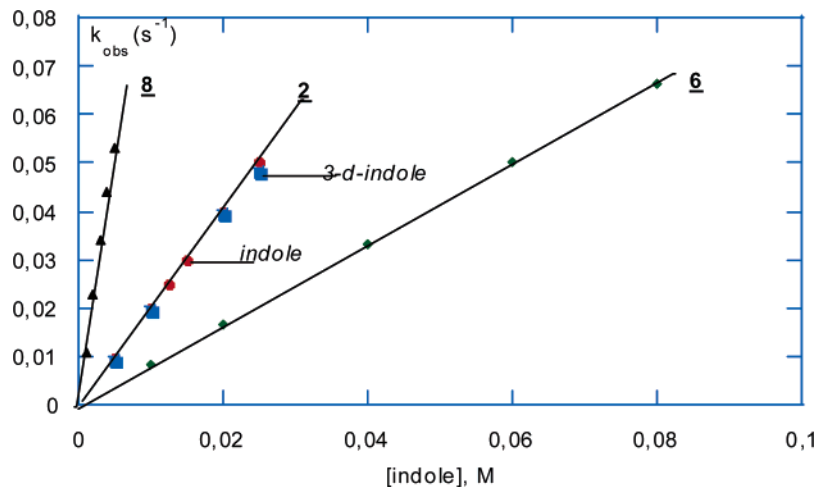


FIGURE 3. Influence of the concentration of indole (**B**) on the observed first-order rate constant for addition to 4-aza-6-nitrobenzofuroxan **6**, 4,6-dinitrobenzofuroxan **2**, and 4,6-dinitrotetrazolo[1,5-*a*]pyridine **8** in acetonitrile; $T = 20\text{ }^{\circ}\text{C}$. The data for the reaction of **2** with indole-1,3- d_2 illustrate the absence of notable isotope effects.

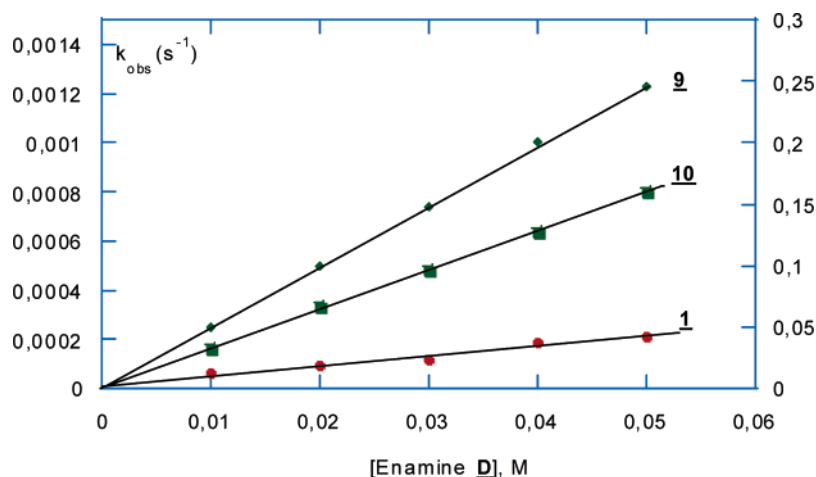


FIGURE 4. Influence of the concentration of the enamine **D** on the observed first-order rate constant for addition to 2,4-dinitrothiophene **10** and 1,3,5-trinitrobenzene **1** (left ordinate) as well as 6-nitrotetrazolo[1,5-*a*]pyridine **9** (right ordinate) in acetonitrile.

basis of this model, it follows that the slopes of the k_{obs} vs [nucleophile] plots of the type shown in Figures 3 and 4 are given by eq 14 from which the related rate constants k_1 were readily derived.

$$\text{slope} = k_1 \frac{K_T}{1 + K_T} \quad (14)$$

Discussion

Electrophilicity Parameters of 1–10. The k_1 rate constants describing the C–C couplings of **1–10** with the reference nucleophiles **A–G** at $20\text{ }^{\circ}\text{C}$ in acetonitrile are summarized in Table 1. Using the data, plots of $(\log k_1)/s$ vs N have been constructed for each of the electrophiles studied, resulting in a series of parallel lines exhibiting slopes equal to or close to unity (Figure 5), as expected from eq 2. From the intercepts of these lines with the ordinate axis, the electrophilicity parameters E of **1–10** could be readily derived. For maximum consistency with the electrophilicity scale established by Mayr et al.,^{9–12} the rate data of Table 1 have also been worked out according to the correlation analysis employed by these

TABLE 1. Second-Order Rate Constants (k_1 ($\text{M}^{-1}\text{ s}^{-1}$)) for Coupling of the Electrophiles **1–10** with the Reference Nucleophiles **A–G** in Acetonitrile at $T = 20\text{ }^{\circ}\text{C}$

	A	B	C	D	E	F	G
N	5.85	5.8	6.93	10.04	10.73	11.4	13.41
s	1.03	0.8	0.8	0.82	0.81	0.83	0.82
k_1 ($\text{M}^{-1}\text{ s}^{-1}$)							
8	5.06	15.7	48.5	3.9×10^4	9.5×10^4	6.3×10^5	
3	4.1	5.2	21.5	4.1×10^4	8.4×10^4	3×10^5	
2	1.81	2.3	13.4	1.6×10^4	5.8×10^4	2.6×10^5	
7	1.2	1.6	10.3	5850	3.1×10^4	1.4×10^5	
6	0.61	0.83	2.3	4600	1.3×10^4	9.7×10^4	
5	0.08	0.35	1.2	2020	5500	3.1×10^4	
4				260	1120	6950	1.2×10^5
9				5.0	19.24	99	5140
10				1.6×10^{-2}	5.2×10^{-2}	0.12	8.64
1				3.8×10^{-3}	6×10^{-3}	1.14×10^{-2}	5.0

authors in their investigation of many electrophile–nucleophile combinations.^{9,11}

It is the E values obtained from this analysis which are given, together with the derived standard deviations in Table 2. For purpose of discussion, the $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ values associated with the covalent hydration of **1–10**, e.g., see

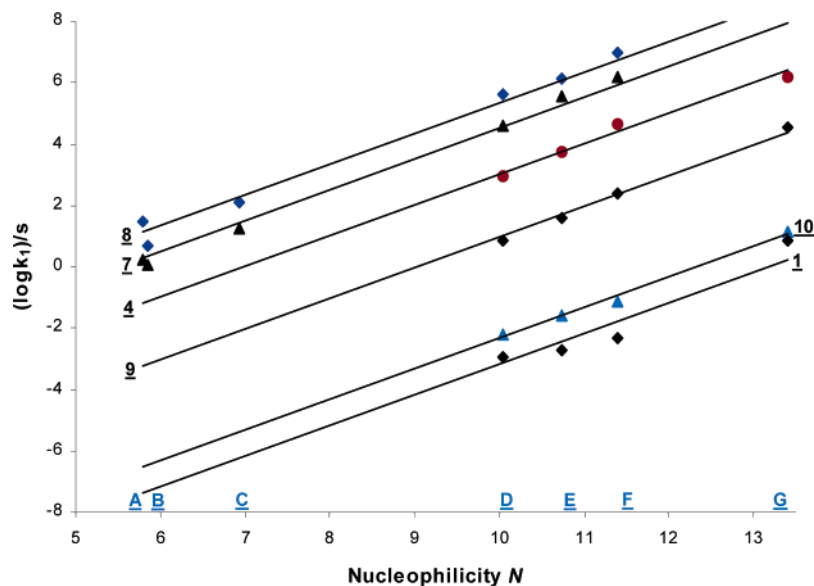


FIGURE 5. Plots of $(\log k_1)/s$ versus N for the reactions of representative electrophiles (**1**, **4**, **7–10**) with the reference π -nucleophiles **A–G** in acetonitrile solution. Data for compounds **2**, **3**, **5**, and **6** are omitted for clarity.

TABLE 2. Electrophilicity Parameters E and $pK_a^{H_2O}$ Values for Hydration of **1–10**

electrophile	1	2	3	4	5	6	7	8	9	10
E^a	-13.19 ± 0.45	-5.22 ± 0.32	-4.91 ± 0.31	-7.01 ± 0.16	-6.41 ± 0.38	-5.86 ± 0.36	-5.46 ± 0.23	-4.67 ± 0.30	-9.05 ± 0.12	-12.33 ± 0.11
$pK_a^{H_2O}{}^b$	13.43 ^c	3.75 ^d	2.95 ^e	4.65 ^f	5.86 ^f	4.06 ^g	3.92 ^f	0.3 ⁱ	7.55 ^h	11.7 ^j

^a The E parameters and the related standard deviations obtained by minimizing $\Delta^2 = \sum[\log k_1 - s(E + N)]^2$ as reported by Mayr.^{9d,11d}
^b All pK_a values refer to measurements at $T = 25$ °C. ^c Reference 19. ^d Reference 14a. ^e Reference 16c. ^f Reference 16d. ^g Value derived from the E - pK_a relationship shown in Figure 7 (see also the text). ^h Reference 16e. ⁱ Reference 16a. ^j Estimated from the pK_a value measured in methanol by correcting for the commonly observed solvent effect on the σ -complexation process.^{13b}

eq 4, are also included in Table 2. Figure 5 reveals that the electrophilicity of substrates **1–10**, representing an extended series of neutral electron-deficient aromatics and heteroaromatics of widely differing reactivity and structure, can be appropriately described by eq 2. This is a result of real significance since this relationship has been mostly developed by modulating the strength of the electrophilic partner through structural variations of carbocationic structures.^{9–12} So far, the description of uncharged electrophiles has been restricted to the behavior of a few Michael acceptors and quinone methides whose E values are all falling in the domain of rather weak electrophilicities.^{10a,b}

Within the E scale developed by Mayr, covering a range from +6 to -18 , our series embraces a domain of reactivity of more than 8 orders of magnitude, going from the four most electrophilic compounds with E values of ~ -5 , i.e., **2**, **3**, **7**, and **8**, to the least electrophilic TNB compound ($E = -13.19$). This ranking, shown in Figure 6, is a nice reflection of the accumulated evidence that strongly activated benzofuroxans and related compounds are considerably more electron-deficient structures than TNB, the common reference aromatic electrophile in nucleophilic addition or substitution processes.^{13–19,33,34} Referring to the set of electrophiles used to construct the E scale,⁹ the finding of $E \sim -5$ for 4,6-dinitrotetrazolopyridine **8**, 4-nitro-6-trifluoromethanesulfonylbenzofuroxan **3**, 4,6-dinitrobenzofuroxan **2**, and 4,6-dinitrobenzofurazan **7** indicates that these heteroaromatics are 2 orders of magnitude more electrophilic than Michler's hydrol blue ($E = -7.02$),⁹ i.e., the bis(4-dimethylami-

nophenyl)carbenium ion (Figure 6). Most importantly, the four aforementioned compounds exhibit an electrophilicity that compares well with that of 4-nitrobenzenediazonium cation ($E = -5.1$),^{9,35} approaching in fact that of the tropylium cation family ($E \sim -3$ to -6)^{12c} as well as a number of metal-coordinated carbenium ions.⁹ This ranking rationalizes a previous discovery that DNBF is as prone as 4-nitrobenzenediazonium and tropylium cations to undergo C–C coupling with many pyrrole and indole derivatives, including such weakly basic compounds as 5-cyanoindole ($pK_a^{H_2O} = -6$).^{15a,b,36} It also suggests that more of the rich chemistry established for the two above cations could find analogy with DNBF and similarly activated heteroaromatics.^{9b,c,36,37}

Being less than one unit lower than that for DNBF (**2**), the E value of -5.86 found for 4-aza-6-nitrobenzofuroxan **6** confirms that a 4-aza functionality is nearly as efficient as a p -NO₂ group in promoting covalent nucleophilic additions.³⁸ This is a feature of major relevance to the ease of S_NAr substitutions in the pyridine series.^{13,38} Substituting the remaining ortho-like 6-NO₂ group of **6**

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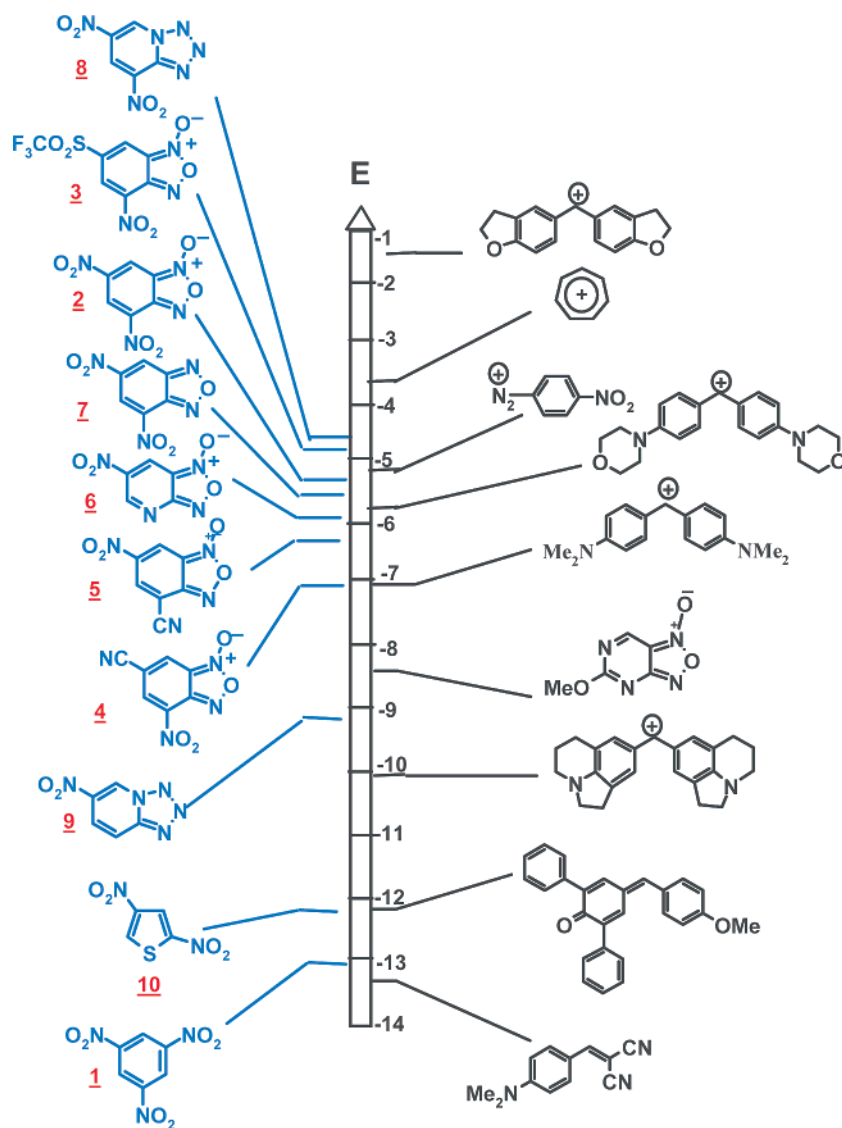
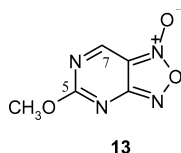


FIGURE 6. Comparison of the electrophilicity parameters of **1–10** with those of typical carbocationic structures and a few uncharged arylidene malonitriles (ref 10b) and quinone methides (ref 11a).

for a second intramolecular nitrogen atom is less favorable, however, since an E value of -8.37 has been reported for 4,6-diaza-5-methoxybenzofuroxan **13** during completion of this work.³⁹ Based on the reasonable assumption that the methoxy group does not deplete markedly the reactivity at C-7 of **13**, as it has been observed in pyridine and pyrimidine series,^{13a,b} this corresponds to a decrease of 3 orders of magnitude in electrophilic reactivity from that of **2** (DNBF). Such an E value remains considerably higher than that of TNB (by $\sim 5 E$ units), leaving no doubt that the 4,6-diazabenzofuroxan structure has to be classified as a strongly electron-deficient heteroaromatic.



Going to the other electrophiles considered in this work, it can be seen from Table 2 that there is only a

moderate decrease in electrophilicity of the carbocyclic ring upon substitution of the 4- or 6-NO₂ group of **2** by a cyano group. This finding agrees well with available data pertaining to the reactivity of nitro-substituted benzonitriles in anionic σ -complexation or S_NAr processes.¹³ In contrast, the effect of having only one activating substituent in the six-membered ring is more important, leading to a ranking of 6-nitrotetrazolopyridine **9** ($E = -9.05$) in the middle of the domain of electrophilicity covered by **1–10**. Last, 2,4-dinitrothiophene **10** ($E = -12.33$) and TNB **1** ($E = -13.19$) are by far the two weakest electrophiles of the series, being associated with E values falling in the domain defined by arylidene malonitriles and quinone methide compounds.^{10a,b}

As shown in Figure 7, the E values derived for **1–10** in acetonitrile are linearly related to the $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ values for water addition to these neutral aromatic and heteroaromatic electrophiles in aqueous solution (eq 4), defining a correlation which is identical to that obtained

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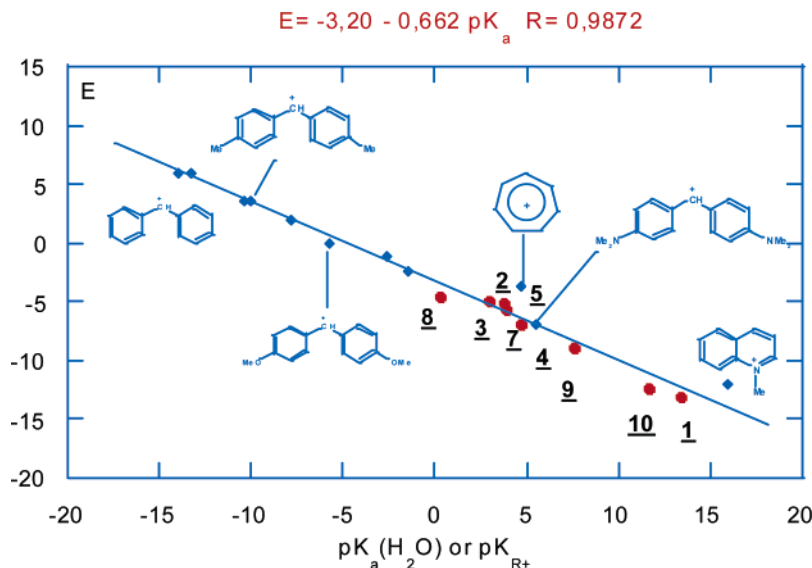
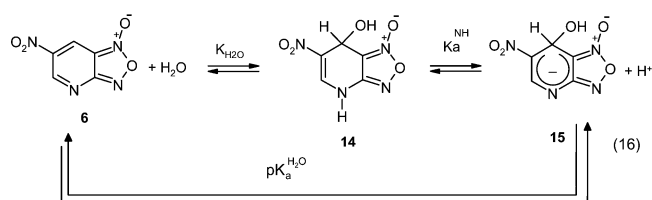


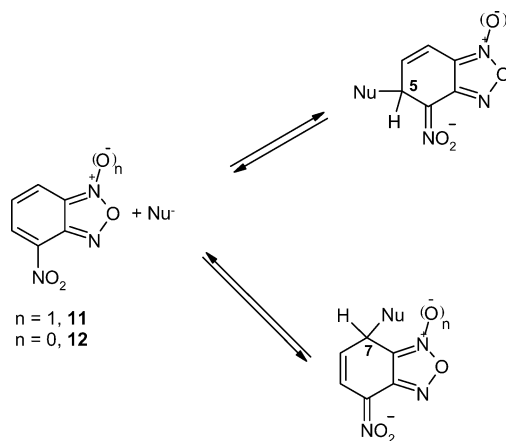
FIGURE 7. Correlation of the electrophilicity parameter E of electrophiles **1–10** (●) and of some carbocations (◆) with the corresponding $pK_{a}^{H_2O}$ or pK_{R^+} values of these species in aqueous solution. To be noted is that the correlation applies to many other carbocationic structures (not shown for clarity of the figure).^{9c,12a}

by Mayr by plotting the E values of a large variety of carbocations versus the Lewis acidities of these species (pK_{R^+}) in aqueous solution (eq 15)^{9b,12a} This convincingly shows that the E scale defined by Mayr applies very well to our family of uncharged electron-deficient π -systems, further confirming the generality of eq 2. Also, the correlation of Figure 7 implies that there is either no change or a similar change in the relative electrophilicities of **1–10** as well as the various carbocationic structures on going from the E scale (a kinetic parameter in acetonitrile) to the $pK_{a}^{H_2O}$ scale (a thermodynamic index in aqueous solution).



The correlation of Figure 7 is very useful to derive E or $pK_{a}^{H_2O}$ values which are not directly accessible. Because of the high tendency of 4-aza-6-nitrobenzofuroxan **6** to form the stable covalent hydrate **14** in aqueous solution, the $pK_{a}^{H_2O}$ value for formation of the anionic σ -complex **15** could only be approximated from the sum of the hydration ($K_{H_2O} \sim 100\text{--}1000$) and NH ionization ($pK_a^{H_2O} = 5.79$) reactions (eq 16), leading to a $pK_{a}^{H_2O}$ falling in the range 2.8–3.8.^{30b} Using the E value determined for **6** in acetonitrile, a more accurate $pK_{a}^{H_2O}$ value of 4.06 can be derived from Figure 7. This means that **6** is as electrophilic as DMBF (**2**), adding to the evidence discussed above that the activating effect of a para-like aza substituent is comparable to that of a NO_2 substituent. The unknown $pK_{a}^{H_2O}$ value for σ -complexation of 4,6-

SCHEME 1



diaza-5-methoxybenzofuroxan **13** can also be estimated from its E value through Figure 7: $pK_{a}^{H_2O} \approx 7.8$

A well-known feature of 4-nitrobenzofuroxan **11** and 4-nitrobenzofurazan **12** is their ability to behave as ambident electrophiles, being very prone to undergo competitive nucleophilic addition at both unsubstituted 5- and 7-positions.^{13,18} In some instances, comprehensive kinetic studies could be carried out which have allowed a determination of the rate and equilibrium parameters associated to each of the two σ -complexation processes (Scheme 1). Contrasting with this favorable situation, which is notably met in the case of the interactions of **11** and **12** with OH^- and MeO^- ions in aqueous and methanolic solutions, respectively,^{13,18c,40} we have failed to discriminate between the two competitive pathways on treatment of these compounds with the reference enamines **D–F** in acetonitrile. It was therefore interesting to use Figure 7 to estimate the E parameters describing the electrophilicities of **11** and **12** at C-7, the common site of reactivity in the series of heterocycles **2–9**. From the reported $pK_{a}^{H_2O}$ values for σ -complexation at this position,

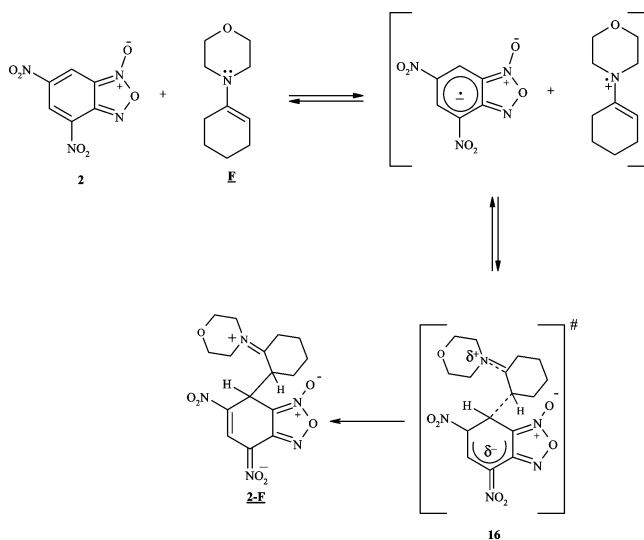
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i.e., 10.37 for **11** and 10.07 for **12**,⁴¹ E values of -10.04 and -9.85 are thus obtained, respectively. This makes **11** and **12** 1 order of magnitude less electrophilic than the 6-nitrotetrazolopyridine **9**, a picture which is consistent with the greater activating effect of an annelated tetrazolo moiety than a furoxan or furazan ring.^{16a}

Can single electron transfer be part of the σ -complexation reactions? A number of authors have emphasized that σ -complexation and S_NAr reactions involving strongly electron-deficient aromatic substrates may proceed via an electron-transfer mechanism.^{13a,42–47} As a matter of fact, E° values pertaining to the reduction of a number of nitrobenzofuroxans and related heterocycles have been recently measured and found to fall in the range $+0.10$ to -0.44 V (relative to SCE).^{14a,48} Such E° values are less negative than the corresponding E° values of -0.58 to -1 V (relative to SCE) which have been reported for radical anion formation from a large set of dinitro- and trinitro-benzene derivatives, e.g., $E^\circ = -0.68$ V for the reduction of trinitrotoluene.^{49,50} While attempts to characterize the postulated radical anions through EPR have failed due to the low lifetime of this type of species in the benzofuroxan and benzofurazan series,⁴³ it can reasonably be concluded from the available E° values that at least some of our reactions, namely those combining the strongest electrophiles and the strongest nucleophiles may have the affinity to take part in a SET rather than a polar S_NAr -type pathway. Should this be case for a system like the DNBF (**2**)–morpholinocyclohexene (**F**), the formation of the corresponding σ -adduct **2-F** will then proceed through initial (fast) electron transfer from the enamine to the nitrobenzofuroxan acceptor and subsequent (slow) coupling of the resulting cation and anion radicals within the solvent cage via the transition state **16** (Scheme 2).

We have recently reported that such a SET mechanism was actually prevailing in the reactions of 4-chloro-7-nitrobenzofurazane and 3-methyl-1-(4-nitrobenzofurazanyl)-imidazolium ion with a series of 4-X-substituted anilines in H_2O – Me_2SO mixtures.⁴³ In this instance, a key argument supporting the SET mechanism was a very abnormal answer of the rates of reactions to changes in nucleophile basicity; inconsistent β_{nuc} values up to 1.4 have thus been determined as compared with β_{nuc} values in the range 0.5–0.7 for polar σ -complexation and S_NAr

SCHEME 2



reactions.^{13a,51} More importantly, meaningful linear correlations between the rates of the reactions and the oxidation potentials of the respective anilines were obtained.⁴³

Referring to β_{nuc} as an indicator of the SET pathway is very informative with respect to Scheme 2. Assuming that going from water to acetonitrile does not markedly affect the relative basicities of these substrates, the known $pK_a^{H_2O}$ values for protonation of *N*-methylpyrrole (**A**; $pK_a^{H_2O} = -3.40$),⁵² indole (**B**; $pK_a^{H_2O} = -3.46$),⁵³ and *N*-methylindole (**C**; $pK_a^{H_2O} = -2.32$)⁵³ as well as of the two enamines (**D**; $pK_a^{H_2O} = 5.45$),^{54b} and **F**; $pK_a^{H_2O} = 7$),^{54a} can be used to build the Brønsted-nucleophilicity plots pertaining to our various electrophiles. As exemplified in Figure 8, satisfactorily linear and parallel plots are obtained with slopes, $\beta_{nuc} \sim 0.5$, falling in the domain recognized as typical of polar σ -complexation and S_NAr processes. On this ground, it seems reasonable to exclude the contribution of Scheme 2 to our reactions.

Additional, though qualitative evidence supporting the above conclusion is the finding that the behavior of all substrates **1–10**, embracing a domain of electrophilicity of more than 10 orders of magnitude in terms of pK_a values for water addition, is nicely described by Mayr's eq 2. Should a change from a polar (S_NAr -type) to a single electron transfer (SET) mechanism occur on going from the least electrophilic TNB compound to the most electrophilic DNTP compound, eq 2 should progressively fail to describe the reactivity. In a similar way, the occurrence of a mechanistic change will be difficult to reconcile with the finding that the electrophilic reactivity of **1–10** is found to obey the same E vs $pK_a^{H_2O}$ correlation as a large variety of carbocations (Figure 7).

Conclusion. The electrophilic reactivity of the series of electron-deficient heteroaromatic and aromatic structures **1–10** is found to follow nicely the linear-free energy relationship defined by Mayr et al. (eq 2). This finding is

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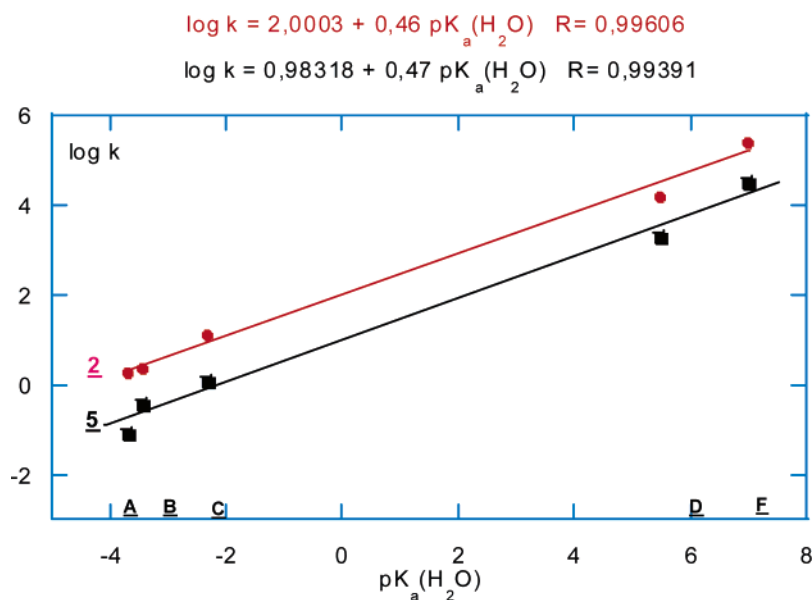


FIGURE 8. Brønsted-type nucleophilicity plots for the reactions of DNBF **2** and 4-cyano-6-nitrobenzofuroxan **5**. The $\text{pK}_a^{\text{H}_2\text{O}}$ value for *N*-methylpyrrole **A** (see text above) has been statistically corrected.

of major interest for two reasons: (1) it expands the applicability of eq 2 to σ -complexation processes involving neutral electrophiles, adding to the general significance of this relationship which has been essentially developed through studies of positively charged carbocationic electrophiles, and (2) it broadens considerably the range of coupling reactions which can be envisioned with nitrobenzofuroxans and related heterocyclic structures. As an example, a kinetic study of the reactions of the six most electrophilic substrates, i.e., **1–6**, with indoles of quite different basicities appears feasible. This should allow an additional and exhaustive comparison with the behavior of carbocationic electrophiles, resulting in an accurate ranking of the nucleophilicities of these π -excessive compounds.

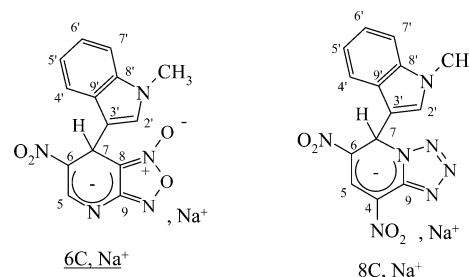
Experimental Section

Indole and Pyrrole Adducts. A large number of σ -adducts of type **2A–C** resulting from the reactions of DNBF (**2**) with pyrroles, including the reference *N*-methylpyrrole **A**, and indoles, including the two references indoles **B** and **C** as well as a number of 5-*X*-substituted indoles and 5-*X*-substituted-2-methylindoles, have been previously isolated and fully characterized as sodium salts.^{15a,b,25a} This synthetic work has been here extended to the salts **3-C,Na⁺** and **5–8-C,Na⁺** corresponding to the σ -complexation of the heteroaromatics **3** and **5–8** reacting with the reference *N*-methylindole under the same experimental conditions as used before.

The general procedure is as follows:

A solution of 1 mmol of the electrophile (**2**, **3**, **5–8**) in 2 mL of dioxane and a solution of 1 mmol of *N*-methylindole **C** in 2 mL of dioxane were mixed with stirring at room temperature. The solutions immediately turned orange or red and were allowed to stand for 5 min. Sodium bicarbonate (1 mmol) in 0.5 mL of water was then added to the mixture, which began to deposit crystals within a few minutes. After filtration, yellow to orange-red solids were obtained which were washed with cold methanol and then with copious amounts of diethyl ether and dried thoroughly under vacuum to give the expected sodium salts in 65–90% yield. Representative NMR (¹H, ¹³C), UV–vis, and mass spectroscopy data for the adducts **6-C,Na⁺** and **8-C,Na⁺** of 4-aza-6-nitrobenzofuroxan **6** and 4,6-dinitrotetrazolopyridine **8** are given below. Other analytical data are

available in Tables S1–S3 (Supporting Information). Figures S1–S11 (Supporting Information) show representative ¹H and ¹³C NMR spectra as well as two-dimensional correlations recorded for the adducts **2-C**, **5-C**, **6-C**, and **8-C**.



6-C,Na⁺: red solid; yield 80%; MS (ESI) m/z 312 $[\text{M} - \text{Na}^+]^-$; ¹H NMR (300 MHz, Me₂SO-*d*₆) δ 3.72 (s, 3H, N-CH₃), 5.71 (s, 1H, H₇), 7.02 (t, $J = 8.2$ Hz, 1H, H₆), 7.16 (t, $J = 8.2$ Hz, 1H, H₅), 7.35 (d, $J = 8.2$ Hz, 1H, H₄), 7.42 (d, $J = 8.2$ Hz, 1H, H₇), 7.45 (s, 1H, H₂), 8.41 (s, 1H, H₅); ¹³C NMR (75 MHz, Me₂SO-*d*₆) δ 29.4, C₇; 32.8, N-CH₃; 110.3, C₃; 107.4, C₈; 107.9, C₇; 113.9, C₈; 121.4, C₆; 119.4, C₄; 125.6, C₅ and C₉; 126.6, C₆; 132.9, C₂; 136.5, C₅; 136.5, C₈; 150.5, C₉; λ_{max} (CH₃CN) = 420 nm.

8-C,Na⁺: red solid; yield 85%; MS (ESI) m/z 340 $[\text{M} - \text{Na}^+]^-$; ¹H NMR (300 MHz, Me₂SO-*d*₆) δ 3.71 (s, 3H, N-CH₃), 7.02 (t, $J = 8.2$ Hz, 1H, H₆), 7.14 (t, $J = 8.2$ Hz, 1H, H₅), 7.35 (s, 1H, H₂), 7.43 (d, $J = 8.2$ Hz, 1H, H₄), 7.45 (d, $J = 8.2$ Hz, 1H, H₇), 7.46 (s, 1H, H₇), 8.79 (s, 1H, H₅); ¹³C NMR (75 MHz, Me₂SO-*d*₆) δ 32.4, N-CH₃; 53.4, C₇; 108.3, C₄; 110.1, C₇; 111.7, C₃; 118.6, C₄; 119.5, C₅; 121.2, C₆; 123.5, C₆; 125.2, C₉; 128.9, C₅; 129.0, C₂; 136.6, C₈; 146.1, C₉; λ_{max} (CH₃CN) = 470 nm.

As with the alkali salts of anionic DNBF adducts isolated so far, the crystals obtained for **3-C,Na⁺** and **5–8-C,Na⁺** were not found to melt prior to decomposition (explosion in most cases), and attempts to obtain satisfactory elemental analysis have failed. However, dissolution of these salts in Me₂SO-*d*₆ gave clean NMR spectra (¹H, ¹³C) which were identical to those recorded in the quantitative in situ generation of the acid form of the adduct in this solvent. In full accord with the proposed structures, the H₇ and C₇ resonances are typical of C-adduct formation, being in the ranges of 4.97–5.71 and 29.4–32.8, respectively, for **3-C** and **5–7-C** and of 7.46 and 53.4, respectively, for **8-C**. These latter figures reflect the greater electron-

withdrawing effect exerted by the annelated tetrazolo ring as compared with that of a furoxan or furazan ring (vide supra). Also noteworthy is that the σ -complexation process goes along with the loss of the resonance of the H₃ proton of the parent *N*-methylindole.

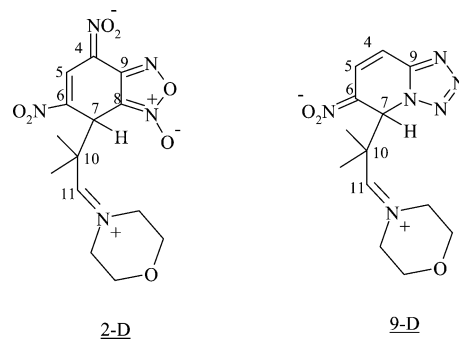
Enaminic Adducts. Our synthetic work has first focused on the series of adducts **1–10D** resulting from the reaction of the enamine **D** with each of the electrophiles **1–10**.

A 2 mmol solution of the electrophile (**1–10**) in 20 mL of dry THF was prepared in a small reactor equipped with a septum and cooled at 0 °C. To this stirred solution was added under argon atmosphere and by means of a syringe a slight excess of the enamine **D** (0.31 g, 2.2 mmol), which had previously been cooled at 0 °C. The solution turned immediately orange to red and was allowed to warm slowly at room temperature. After about 1 h, the colored crystals that formed were filtered, washed with copious amounts of dry diethyl ether, and then dried under vacuum to eliminate any associate solvent. Yields of 90% in the zwitterionic adducts **1–10D** were thus obtained. As above, attempts to obtain satisfactory elemental analysis have failed. To be noted is the high sensitivity of **1–10D** to air moisture, a situation which is typical of zwitterionic σ -adducts.²⁵ Dissolution of these salts in Me₂SO-*d*₆ gave clean NMR spectra (¹H, ¹³C) which were identical to those recorded in the quantitative *in situ* generation of these species upon mixing of equimolar amounts of the electrophile and nucleophile partners in Me₂SO-*d*₆. Representative NMR (¹H, ¹³C), UV–vis, and mass spectroscopy data for the DNBF adduct **2-D** and the 6-nitrotetrazolopyridine adduct **9-D** (eq 9) are given below which leave no doubt regarding the structures of these species. Among other features typical of the adducts **2-D** and **9-D** are the NMR observation of the two diastereotopic CH₃ groups in the enamine moiety as well as the strong deshielding of the sp² iminium carbon ($\delta \sim 200$ ppm) and the related proton ($\delta \sim 9.5$ ppm).⁵⁵ Analytical data for the other adducts are available in Tables S₄–S₆ (Supporting Information). Figures S₁₂–S₃₂ (Supporting Information) show ¹H and ¹³C NMR spectra as well as two-dimensional correlations recorded for the adducts **2–5-D** and **8-D**.

2-D: red solid; yield 90%; MS (EI) *m/z* 268 [M – C₅H₉NO]⁺; ¹H NMR (300 MHz, Me₂SO-*d*₆) δ 1.03 (s, 3H, CH₃), 1.04 (s, 3H, CH₃), 2.99 (m, 4H, N-CH₂), 3.69 (m, 4H, O-CH₂), 5.52 (s, 1H, H₇), 8.41 (s, 1H, H₅), 9.56 (s, 1H, H₁₁); ¹³C NMR (75 MHz, Me₂SO-*d*₆) δ 13.4, CH₃; 20.00, CH₃; 38.3, N-CH₂; 38.4, C₇; 54.2, C₁₀; 63.3, O-CH₂; 111.4, C₈; 114.4, C₄; 122.5, C₆; 133.1, C₅; 150.1, C₉; 201.0, C₁₁; λ_{\max} (CH₃CN) = 480 nm.

9-D: red solid; yield 90%; MS (EI) *m/z* 207 [M – C₅H₉NO]⁺; ¹H NMR (300 MHz, Me₂SO-*d*₆) δ 0.59 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 3.05 (m, 4H, N-CH₂), 3.73 (m, 4H, O-CH₂), 5.82 (s, 1H, H₄), 6.13 (s, 1H, H₇), 7.53 (s, 1H, H₅), 9.39 (s, 1H, H₁₁); ¹³C NMR (75 MHz, Me₂SO-*d*₆) δ 16.9, CH₃; 21.2, CH₃; 42.4, N-CH₂; 55.0, C₁₀; 55.6, C₇; 62.1, O-CH₂; 106.9, C₄; 126.0, C₆; 130.8, C₅; 150.8, C₉; 199.0, C₁₁; λ_{\max} (CH₃CN) = 380 nm.

A second series of anionic adducts resulting from the



addition of each of the three enamines **E–G** to DNBF **2** has been similarly isolated and characterized (Tables S₇, S₈, Supporting Information).

Kinetic Measurements. Most of the nucleophile–electrophile combinations studied in this work 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 (**1–10**) concentration of ca. 3×10^{-5} M and a nucleophile **A–G** concentration in the range 10^{-3} – 0.1 M. 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 (Figures S₃₃–S₄₇, Supporting Information) was followed by monitoring the increase in absorbance at λ_{\max} of the resulting adducts, e.g., 480–490 nm for the DNBF adducts **2A–G** or the decrease in the absorbance of the parent electrophile substrate, e.g., $\lambda_{\max} = 415$ nm for DNBF, as a function of time.

Acknowledgment. We are very grateful to Professor Herbert Mayr, Dr. Armin Ofial, and Dr. Bernhard Kempf (Universität München) for useful comments on this work as well as for treatment of our data with the correlation analysis employed in building the *E* scale.

Supporting Information Available: General experimental information (Materials). Spectral data (¹H NMR and ¹³C NMR, mass spectroscopy, and UV–vis data) for adduct formation (Tables S₁–S₈ and Figures S₁–S₃₂). Oscilloscope pictures showing the unique relaxation process in the various electrophile–nucleophile combinations studies (Figures S₃₃–S₄₇). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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