

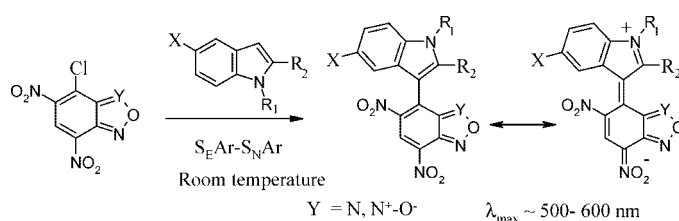
Carbon Nucleophilicities of Indoles in S_NAr Substitutions of Superelectrophilic 7-Chloro-4,6-dinitrobenzofuroxan and -benzofurazan

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Superelectrophilic 7-chloro-4,6-dinitrobenzofuroxan (DNBF-Cl) and 7-chloro-4,6-dinitrobenzofurazan (DNBFZ-Cl) are shown to undergo facile carbon–carbon couplings with a series of weak carbon nucleophiles consisting of a number of differently substituted indoles, 1,2,5-trimethylpyrrole and azulene, in acetonitrile. Despite the fact that steric effects preclude a coplanarity of the donor and acceptor moieties, the resulting substitution products are subject to an intense intramolecular charge transfer. A kinetic study of the various substitutions has been carried out. The absence of a significant dependence of the rates of coupling on the hydrogen or deuterium labeling at the reactive center of the nucleophiles indicates that the reactions take place through an S_EAr-S_NAr mechanism with the initial nucleophilic addition step being rate-limiting. A vicarious-type substitution is shown to be unreasonable. Referring to Mayr nucleophilicity parameters (N), which have become recently available for a large set of indoles, the electrophilicity of DNBF-Cl and DNBFZ-Cl, could be ranked on the general electrophilicity scale E developed by this author (*Acc. Chem. Res.* **2003**, *36*, 66). With essentially similar E values of -6.1 , these two compounds have an electrophilicity which approaches that of cationic structures such as 4-nitrobenzenediazonium cation or tropylium cations. Most important in the context of S_NAr substitutions, DNBF-Cl and DNBFZ-Cl are 7 orders of magnitude more electrophilic than picryl chloride, the conventional reference electrophile in this field. It is this so far unique behavior which allows the facile coupling of DNBF-Cl and DNBFZ-Cl with such weak carbon nucleophiles as indoles. Based on a nice Brønsted-type correlation for 5- X -substituted indoles, the unknown pK_a^{CH} values measuring the Brønsted C-basicity of several N -benzylindoles could be readily estimated. The influence of some steric effects in 2-methylindole systems is pointed out.

Introduction

The last two decades have witnessed a major development in the field of electrophile–nucleophile combinations with the discovery of highly electron-deficient heteroaromatic structures

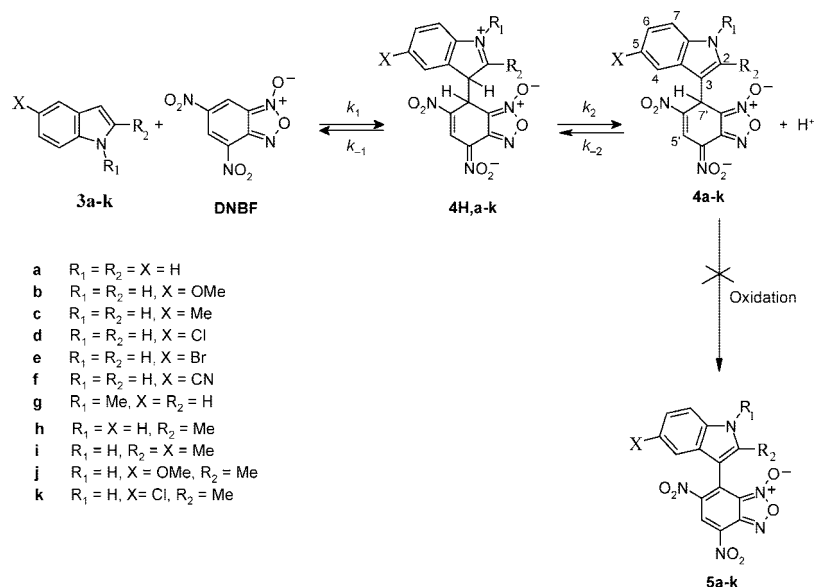
such as nitrobenzoxadiazoles, nitrobenzotriazoles, nitrotetrazolopyridines, and related $10-\pi$ electron heterocycles.^{1–10} In contrast to 1,3,5-trinitrobenzene (TNB), the traditional aromatic electrophile reference,¹¹ these new structures, exemplified by 4,6-dinitrobenzofuroxan (DNBF), are capable reacting readily with weak nucleophiles. As an illustration of this behavior, TNB only reacts with the strong oxygen base hydroxide ion (eq 1), while DNBF undergoes facile addition of water according to

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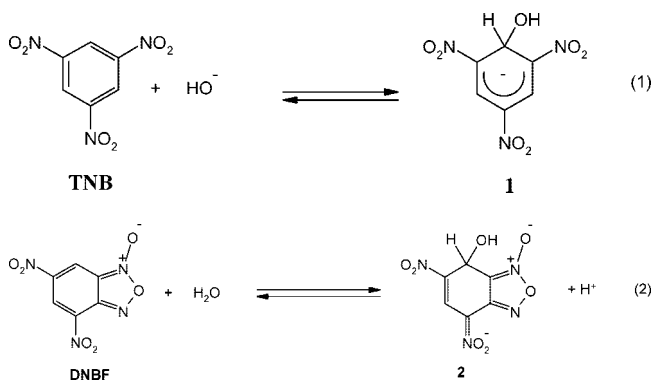
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SCHEME 1



eq 2 to give the hydroxyl adduct **2** which is 10^{10} times thermodynamically more stable than the analogous TNB adduct **1**.^{3a,11} More revealing evidence of DNBF reactivity is in terms of its propensity to undergo facile carbon–carbon couplings with benzenoid aromatics, e.g., anilines, polyhydroxy- and -alkoxybenzenes, etc.,^{4,5,12} or π -excessive heterocycles, e.g., pyrroles, indoles, etc.,^{13,14} to afford stable anionic σ -adducts which are formally the products of S_EAr substitution of the benzene or hetarene ring. Scheme 1 exemplifies these couplings for a number of indole systems (**3a–k**), giving rise to the

adducts **4a–k**. On the basis of these findings, DNBF and a number of related heterocycles have been accorded superelectrophilic properties.¹⁵



While the ease of σ -complexation of DNBF by weak nucleophiles has led to numerous biological and analytical applications,^{16–18} it has so far been of much less interest for synthetic purposes owing to the failure of converting efficiently most of the resulting σ -complexes into the corresponding substituted products, i.e., **5a–k**. As determined by electrochemical measurements, the high thermodynamic stability of DNBF σ -adducts is associated with particularly high oxidation potentials ($E^\circ = 1.4–1.5$ V),⁹ making it very difficult to achieve the rearomatization step through formal displacement of an hydride anion under smooth oxidation conditions. In view of these results, the question was posed whether C–C couplings of the type described in Scheme 1 could be more appropriately carried

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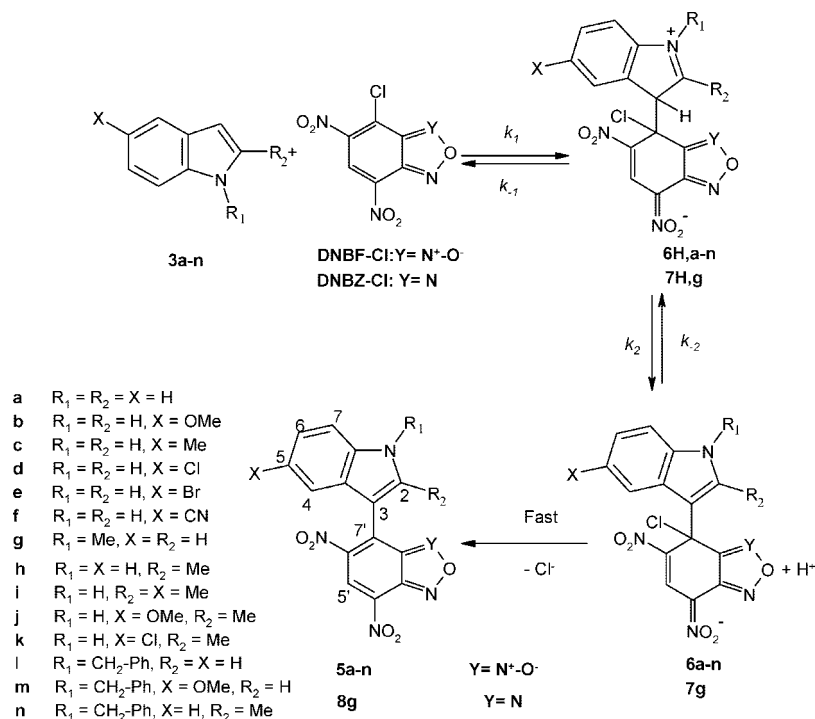
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SCHEME 2



out by using powerful electrophilic partners bearing a good leaving group at the reactive center, e.g., 7-chloro-4,6-dinitrobenzofuroxan (DNBF-Cl) and 7-chloro-4,6-dinitrobenzofuran (DNBZ-Cl).^{17,19}

In this paper, we report on a successful use of the strong electrophilicity of DNBF-Cl and DNBZ-Cl in promoting the achievement of remarkably facile S_EAr-S_NAr couplings with a number of differently substituted indoles **3a–n**, whose Brønsted carbon basicities range from $pK_a^{CH} = 0.26$ for the most basic derivative, i.e., 2,5-dimethylindole **3i**,^{20a} to $pK_a^{CH} = -6$ for the less basic compound, i.e., 5-cyanoindole **3f**,^{20b} (see Scheme 2).²¹ Couplings of DNBF-Cl and DNBZ-Cl with 1,2,5-trimethylpyrrole **9** ($pK_a^{CH} = -0.49$)²² and azulene **14** ($pK_a^{CH} = -1.76$)²³ have also been investigated. Besides the synthesis and characterization of the resulting products, a detailed kinetic investigation of the great majority of the C–C couplings studied has been carried out. The results obtained extend considerably the domain of reactivity of indoles as carbon nucleophiles,^{24,25} allowing a ranking of the electrophilicity of neutral DNBF-Cl and DNBZ-Cl substrates on the comprehensive electrophilicity scale E defined for cationic electrophiles by Mayr et al.²⁶ Although this result was perhaps to be expected, it is the first

time that the reactivity of S_NAr substrates is found to be suitably described by this general linear free energy relationship. A preliminary communication of this work dealing only with **3g**, **9**, and **14** has appeared.²⁷

Results

Product Characterization. Each of the indoles **3a–n** reacted with DNBF-Cl to produce the expected substitution products **5a–n**, for example, the 4-(1-methyl-1*H*-indol-3-yl)-5,7-dinitrobenzo[1,2,5]oxadiazole 3-oxide **5g** (see Scheme 2). Similarly, the reactions of DNBF-Cl with 1,2,5-trimethylpyrrole **9** and azulene **14** afforded compounds **11** and **16**, respectively. All isolated substitution products formed in high yields upon mixing equimolar amounts of the two nucleophilic and electrophilic reagents at room temperature (**5a–c,g–n**; **11**, **16**) or in boiling acetonitrile (**5d–f**).

These compounds have been fully characterized through ¹H and ¹³C NMR spectroscopy, mass spectrometry, UV–vis spectrophotometry, and elemental analysis (see the Experimental Section and Supporting Information). Some pertinent data referring to the indole reactions are collected in Table 1 for structural discussion.

Importantly, a X-ray structure of **5n**, the product of substitution of DNBF-Cl by 2-methyl-*N*-benzylindole **3n** could be obtained (Figure S58, Supporting Information). In the case of the hardly accessible DNBZ-Cl compound, our investigations were restricted to coupling with *N*-methylindole **3g**, 1,2,5-trimethylpyrrole **9**, and azulene **14**. The corresponding substitution products **8g**, **13**, and **18** have been obtained under the same experimental conditions as those used for the DNBF-Cl analogues.

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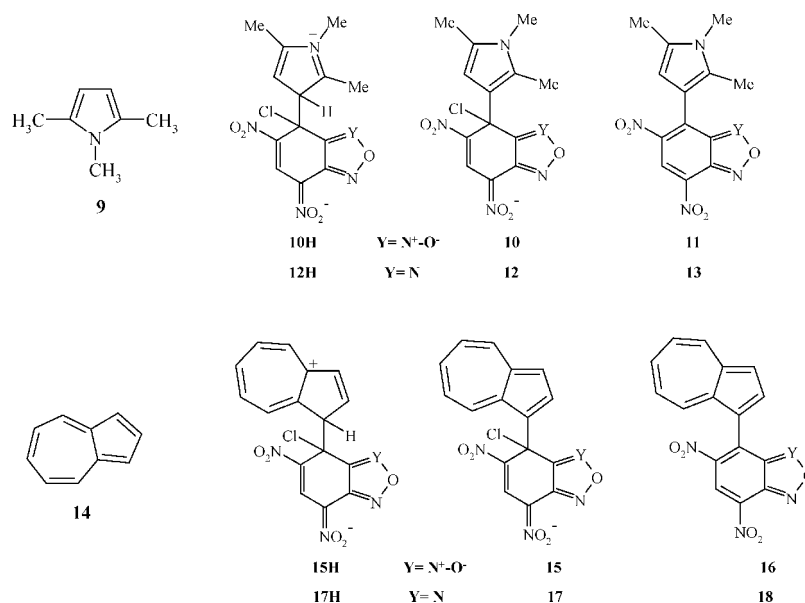
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CHART 1. Structures of Intermediate σ -Complexes and Substitution Products Involved in the Couplings of 1,3,5-Trimethylpyrrole **9 and Azulene **14** with DNBF-Cl and DNBZ-Cl****TABLE 1. Diagnostic ^1H and ^{13}C Chemical Shift Variations upon Substitution of DNBF-Cl by Indoles **3a–f** and 1,2,5-Trimethylpyrrole **9^a****

substrate	δ_{NH}	δ_{H_2}	δ_{C_2}	$\delta_{\text{C}_{8'}}$	$\delta_{\text{C}_{9'}}$
DNBF-Cl				116.5	150.5
5a	10.21	7.84	130.9	114.8	145.1
3a	8.00	7.20	125.2 ^b		
5b	10.13	7.78	131.5	112.8	145.2
3b	9.12	7.25	125.6 ^b		
5c	10.11	7.78	131.0	114.8	145.2
3c	7.83	7.05	125.2 ^b		
5d	10.25	7.79	133.9	116.3	145.0
3d	9.40	7.33	127.1 ^b		
5e	10.25	7.77	131.2	114.1	145.0
3e	9.45	7.31			
5f	10.46	7.75	131.5	116.5	144.9
3f	9.45	7.31	128.0 ^b		
11			131.1	114.3	142.4
9			127.9		

^a Solvent: CH_3CN ; δ in ppm, internal reference Me_4Si ; numbering of atoms as shown in Scheme 2. ^b Data taken from ref. ^{13b}

Kinetic Studies. As will be elaborated further in the Discussion, the most reasonable coupling pathway for the indole reactions is the one depicted in Scheme 2, which also applies to the 1,2,5-trimethylpyrrole and azulene reactions. In these latter instances, the formation of the substitution products (**11**, **13**, **16**, and **18**) goes through the intermediacy of the σ -complexes shown in Chart 1, e.g., **10H** and **10**. All couplings studied thus proceed through the successive formation of a zwitterionic Wheland–Meisenheimer adduct and an anionic Meisenheimer adduct. Finally, facile loss of chloride anion from this latter complex gives the $\text{S}_{\text{N}}\text{Ar}$ substitution product.

The rates of the overall coupling processes were measured at 20 °C in acetonitrile, following the appearance of the resulting strongly colored products, i.e., **5a–n**, **8g**, **11**, **13**, **16**, and **18**. These are characterized by an intense visible absorption at wavelengths (Table 2) where neither the nucleophilic nor electrophilic partners have a notable absorption. All experiments were carried out under pseudo-first-order conditions with respect to the nucleophile reagent as the excess component. Figures S1–S6 (Supporting Information) show oscilloscope traces

illustrating the unique relaxation process corresponding to the formation of a number of substitution products representative of the various electrophile–nucleophile combinations studied.

Based in Scheme 2, the general expression for the observed rate constant for formation of the products, k_{obsd} , as derived under the assumption that the zwitterions are low-concentration intermediates, is given by eq 3:

$$k_{\text{obsd}} = \frac{k_1 k_2}{k_{-1} + k_2} [\text{Nu}] = k [\text{Nu}] \quad (3)$$

In accordance with this equation, excellent straight lines with essentially zero intercepts were obtained in all systems on plotting k_{obsd} vs the nucleophile concentration ($\text{Nu} = \mathbf{3a–n}$, **9**, or **14**). From the slopes of these plots, exemplified in Figures S7–S29 (Supporting Information), the second-order rate constants k were readily derived. Importantly, a number of experiments were carried out with deuterated nucleophiles, namely indole-1,3- d_2 , *N*-methylindole-3- d , 5-methoxyindole-1,3- d_2 , 5-chloroindole-1,3- d_2 , 2,5-dimethylindole-1,3- d_2 , 1,2,5-trimethylpyrrole-3,4- d_2 , and azulene-1,3- d_2 . Despite the different C-basicities of the substrates, the $k^{\text{H}}/k^{\text{D}}$ ratios pertaining to the corresponding DNBF-Cl and DNBZ-Cl reactions are in the range 1.01–1.26 (see Table 2). This makes it very reasonable to consider that electrophilic attack at the reactive nucleophilic center is largely rate-limiting in the overall processes, as depicted in Scheme 2 for indole systems. In other words, proton removal from the zwitterion can be regarded as rapid in acetonitrile, allowing us to identify the composite rate constant k to the rate constant k_1 for the C–C coupling step.^{8a,13,24,28,29} The situation compares well with that described for the σ -complexation reactions of DNBF with indoles (Scheme 1)^{13,14,30} as well as of that prevailing in the majority of aromatic and heteroaromatic substitutions in which the formation of Wheland–Meisenheimer-

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TABLE 2. Second-Order Rate Constants, k_1 , for Coupling of DNBF-Cl and DNBZ-Cl with Indoles (3a–n), 1,2,5-Trimethylpyrrole (9), and Azulene (14) at 20 °C in Acetonitrile^{a,b}

nucleophile	$pK_a^{\text{CH}}(\text{H}_2\text{O})$	N	$k_1^{\text{DNBF-Cl}}, \text{M}^{-1} \text{s}^{-1}$	$\lambda_{\text{max}}, \text{nm}$	$k_1^{\text{DNBZ-Cl}}, \text{M}^{-1} \text{s}^{-1}$	$\lambda_{\text{max}}, \text{nm}$	$k_1^{\text{DNBF}}, \text{M}^{-1} \text{s}^{-1}$
3a	−3.46	5.55	6.56×10^{-2} (5.96×10^{-2})	550			2.29 ^d
3b	−2.90	6.22	0.29 (0.23)	565			20.84 ^d
3c	−3.30	6.00	0.29	560			10.71 ^d
3d	−4.53	4.42	2.60×10^{-3} (2.33×10^{-3})	530			0.20 ^d
3e	−4.30	4.38	6.78×10^{-3}	500			0.18 ^d
3f	−6.00	2.83	1.79×10^{-4}	510			3.5×10^{-3d}
3g	−2.32	5.75	1.02 (0.81) ^e	575	1.15	555	13.40 ^d
3h	−0.28	6.91	1.60	560			108 ^d
3i	+0.26	7.22	5.28	590			236 ^d
3j	+0.13	7.26	5.53 (5.33)	595			260 ^d
3k	−1.30	6.08	0.145	560			13.40 ^d
3l	−3.21 ^c		6.42×10^{-2}	560			
3m	−2.42 ^c		0.46	575			
3n	−0.41 ^c		0.56	560			
9	−0.49	8.79 (8.69) ^f	9.64 (8.92) ^e	590	3.45 (3.22) ^e	560	910 ^e
14	−1.76		0.50 (0.41) ^e	600	0.56 (0.51) ^e	600	5.88 ^e

^a The k_1 values given in parentheses refer to the reactions with deuterated nucleophiles. ^b $pK_a^{\text{CH}}(\text{H}_2\text{O})$ values are taken from refs 13, 20, 22, and 23. ^c pK_a^{CH} values estimated from the correlations of Figure 3 (see text). ^d k_1 values taken from ref 14. ^e from previous measurements at $T = 25$ °C, ref 27. The difference in temperature is too weak to affect the forthcoming discussion. ^f Ref 70.

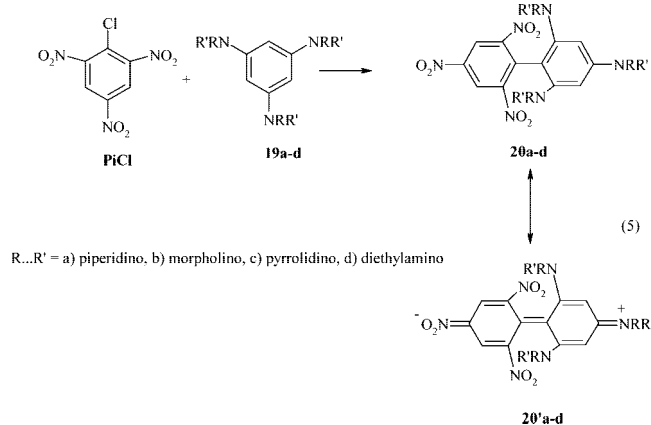
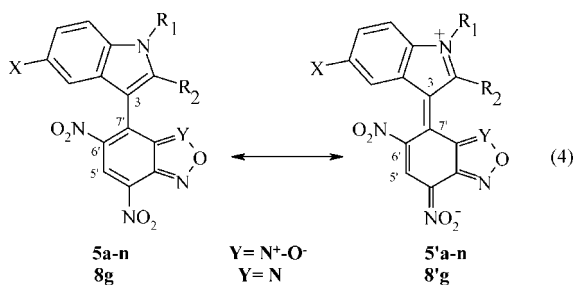
type intermediates is rate determining, e.g., the azo couplings of indole and pyrrole derivatives by benzenediazonium cations.^{24,28,31}

The k_1 rate constants describing the C–C couplings of DNBF-Cl and DNBZ-Cl with the various π -nucleophiles studied at 25 °C in acetonitrile are summarized in Table 2.

Discussion

In undertaking the present work, our main purpose was to delineate and assess the C-nucleophilicity of indoles and some other π -excessive structures in $S_N\text{Ar}$ reactions, using these compounds as reference nucleophiles to rank the reactivity of the superelectrophilic partners on the general electrophilicity scale of Mayr et al.²⁶ Before focusing in depth on this discussion, highlighting the mechanistic factors governing the course of the C–C couplings exemplified in Scheme 2, there is a need to comment on some remarkable structural features that characterize the products resulting from the various substitutions studied.

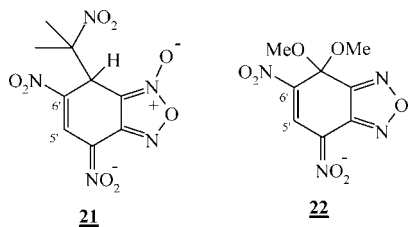
Structural Features. A significant feature of the substitution products, i.e., **5a–n**, **8g**, **11**, **13**, **16**, and **18**, is that they are all isolated as strongly colored crystals showing intense absorption maxima at high wavelengths (510–600 nm) in acetonitrile (Table 2). This suggests that a strong intramolecular charge-transfer process takes place between the electron-rich donor moiety and the electron-deficient acceptor DNBF or DNBZ moiety, as depicted in eq 4 for indoles.³² Effenberger et al. have reported a rather similar situation in a study of a series of donor–acceptor substituted biphenyls, eq 5.³³ For simplicity, only the *p*-quinonic mesomeric structures are drawn in eqs 4 and 5.



R...R' = a) piperidino, b) morpholino, c) pyrrolidino, d) diethylamino

Depending on the number of substituents in the *ortho*-positions of the two-ring linkage, it was reasonable to anticipate that the mesomeric interaction depicted in eq 4 be strongly affected by steric effects. In this regard, the X-ray structure of **5n**, the product resulting from the coupling of DNBF-Cl with 2-methyl-*N*-benzylindole **3n** is informative (Figure S58, Supporting Information). With three *ortho*-substituents (NO_2 and N-O in the DNBF moiety, CH_3 in the indole moiety), the dihedral angle between the two rings is found to be 49.2° , comparing well with that between the two rings of the biphenyls **20** (52.5° for **20c**).³³ As demonstrated by Effenberger in a thorough structural analysis of the latter compounds,³³ such far-from-orthogonal torsion angles about the two-rings linkage do not prevent the occurrence of a significant intramolecular charge transfer between the π -system of the indole donor and the π -system of the DNBF acceptor. As a matter of fact, the $\text{C}_3\text{--C}_7$ coupling bond has a notable olefinic character with a length of 1.432 Å. At the same time, the length of the $\text{C}_5\text{--C}_6$ bond of the negatively charged DNBF moiety is 1.398 Å, a value which is closer to the length of the same bond in the anionic σ -complexes **21** (1.372 Å) and **22** (1.368 Å) than in the parent DNBF molecule (1.44 Å).^{34,35} These data leave no doubt that the well-recognized *para*-quinonic structure of these adducts also prevails in the resonance stabilization of **5n**.

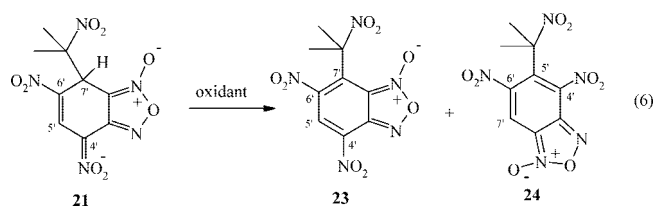
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Some NMR data, collected in Table 1, add to the evidence for the strong dipolar nature of the substitution products (structures **5'**). As a first diagnostic feature in the indole systems, there is the strong shift to higher frequency of the H₂ and C₂ resonances of the indole moiety on going from the parent substrate to the substitution product. For the unsubstituted indole/DNBF-Cl system, we thus have: $\delta_{\text{H}_2} = 7.20$ and $\delta_{\text{C}_2} = 125.24$ in **3a**; $\delta_{\text{H}_2} = 7.84$ and $\delta_{\text{C}_2} = 130.9$ in **5a** in acetonitrile. Similar variations are observed upon coupling of all 5-X-substituted indoles with DNBF-Cl and DNBZ-Cl (see Table 1 and Tables S1 and S2 Supporting Information). Obviously, the deshielding of the H₂ and C₂ resonances reflects the presence of a strong positive charge on the adjacent nitrogen atom in structures **5'**. Also consistent with this idea, there is a significant deshielding of the NH resonance upon substitution of the indoles **3a–f** and **3j–m**; $\Delta\delta \sim 0.8\text{--}2$ ppm. The formation of the 1,2,5-trimethylpyrrole and azulene products goes along with similar downfield shifts of some key resonances, e.g., δ_{C_2} moves from 127.9 ppm in **9** to 131.1 ppm in **11**.

Importantly, the X-ray structure of **5n** suggests that all DNBF-Cl substitutions proceed with no migration of the *N*-oxide group. In this regard, two sources of isomer formation in benzofuroxan derivatives have been identified, namely the 1-oxide/3-oxide tautomerism of the furoxan ring and the so-called Boulton–Katritzky (BK) rearrangement.^{36–40} In particular, this latter rearrangement is known to be typical of 4-nitrobenzofuroxans bearing a bulky substituent at the C-7' position.³⁹ This is illustrated in eq 6, which shows that the oxidative rearomatization of the DNBF/2-nitropropane σ -adduct **21** leads to an essentially 1:1 mixture of the two isomeric 7'- and 5'-[1-(1-methyl-1-nitroethyl)]-4',6'-dinitrobenzofuroxan molecules **23** and **24**.⁹ Similarly, the S_NAr substitutions of DNBF-Cl by anilines also involve the formation of two BK isomers.^{6b} Whether the NMR spectra were recorded in situ experiments, following the substitutions to completion in acetonitrile, or after dissolution of the isolated products in the same solvent, no evidence whatsoever could be found for the formation of two isomeric S_NAr products in the present DNBF-Cl/indole, pyrrole, or azulene couplings. In as much as the *N*-oxide fragment remains unchanged on going from the

parent DNBF-Cl substrate to **5n**, a molecule in which the 2-methyl group of the indole moiety is expected to induce a notable steric hindrance around the C–C linkage, it seems reasonable to assign the same structure **5** to all indole DNBF-Cl products and by analogy to assign structures **11** and **16** to the related pyrrole and azulene products.



In view of recent results obtained in investigating the substitutions of DNBF-Cl with indolizines in which the substitution products are not stable, undergoing a fast rearrangement with loss of the *N*-oxide group and formation of benzofurazan structures,⁴¹ it is a major feature that this functionality is present in the isolated products **5a–n**, **11**, and **16**. In addition to the above arguments, this fits the observation that all C_{8'} and C_{9'} resonances pertaining to the DNBF moiety in these products fall in quite different ranges, namely 116 ± 4 and 147.5 ± 3 ppm, respectively, comparing well with the situation in the DNBF-Cl molecule (see Table 1) or other nitrobenzofuroxans.^{6b,42–46} This is in accord with the fact that in a benzofuroxan structure the electron-donating +M effect of the *N*-oxide group increases especially the electron density on the adjacent quaternary carbon C_{8'}, while that on the remote C_{9'} carbon is only slightly affected.^{37,39,42,43} Accordingly, the C_{8'} resonance is always upfield by $\sim 30\text{--}35$ ppm relative to the C_{9'} resonance in DNBF products, but this pattern is no longer observed on going to the benzofurazan series where the C_{8'} and C_{9'} resonances become rather similar.^{42–46}

S_EAr–S_NAr couplings. A major result of the present work is certainly the finding that 7-chloro-4,6-dinitrobenzofuroxan and 7-chloro-4,6-dinitrobenzofurazan undergo remarkably facile S_NAr-type displacements of their chlorine atom by very weak carbon nucleophiles. In contrast with picryl chloride (PiCl), which hardly reacts with such strong carbon bases as 1,3,5-tris(*N,N*-dialkylamino)benzenes **19a–d** ($\text{p}K_{\text{a}}^{\text{CH}} \geq 9$; eq 5),^{33,47} DNBF-Cl and DNBZ-Cl react smoothly at room temperature with all carbon nucleophiles whose carbon basicities are associated with $\text{p}K_{\text{a}}^{\text{CH}}$ values ≥ -3.5 . These include the majority of indoles listed in Scheme 2 and Table 2 as well as 1,2,5-trimethylpyrrole and azulene. Couplings involving nucleophiles with more negative $\text{p}K_{\text{a}}^{\text{CH}}$ values such as 5-chloroindole ($\text{p}K_{\text{a}}^{\text{CH}} = -4.53$),^{20a} 5-bromoindole ($\text{p}K_{\text{a}}^{\text{CH}} = -4.30$),^{20b} and 5-cyanoindole ($\text{p}K_{\text{a}}^{\text{CH}} = -6.00$)^{20b} could be readily achieved upon heating of the reaction media in boiling acetonitrile. In all systems, the S_NAr substitution products are obtained in high yields, emphasizing qualitatively the high electrophilicity of

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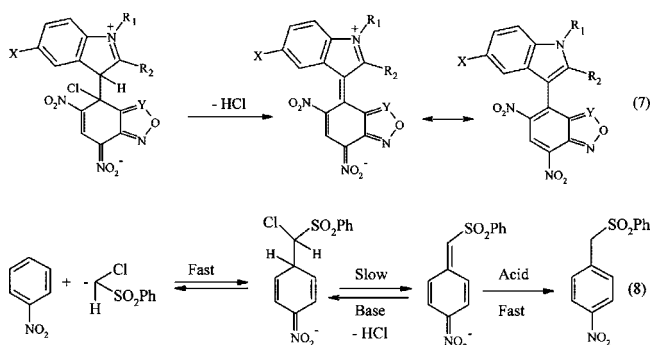
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DNBF-Cl and DNBZ-Cl. To be noted is that compounds **5a–n**, **8g**, **11**, **13**, **16**, and **18** can also be viewed as being formally the products of S_EAr substitution of the arene or heteroarene moiety of the nucleophiles by electrophilic DNBF-Cl and DNBZ-Cl, allowing the couplings to be classified as S_EAr-S_NAr processes.^{27,33}

At this stage, the question is posed of the mechanism of the observed substitutions, as proposed in Scheme 2. On the grounds of analogy with previous studies of the reaction of DNBF with a number of benzenoid and π -excessive heteroaromatic substrates, including indoles (Scheme 1),^{12,13} there is little doubt that the processes go through the initial formation of a zwitterionic Wheland–Meisenheimer intermediate, i.e., **6H** or **7H** in Scheme 2. Forlani et al. have successfully trapped such intermediates by ¹H and ¹³C NMR in reactions of DNBF with supernucleophilic carbon bases of type **19**.⁸ Then, two different routes can be envisioned for the conversion of the zwitterion into the substituted products.

The first that we have favored in drawing Scheme 2 involves the rearomatization of the hetarenium moiety of the zwitterion—a process which is energetically assisted by the recovery of the aromaticity of the indole or other nucleophilic structure—to give the related anionic σ -complex (i.e., **6** or **7**). Facile loss of chloride ion—a good leaving group ($pK_a = -7$) in S_NAr reactions⁴⁸ from the anionic adducts will then afford the substitution products. However, there is an alternative mechanism to the three-step sequence of Scheme 2. This is a direct conversion of the zwitterion into the substitution products through β -elimination of HCl, going along with a concomitant rearomatization of both the nucleophilic and electrophilic structures. Such a β -elimination step is depicted in eq 7, and it is reminiscent of the one involved in a number of vicarious nucleophilic aromatic substitutions of hydrogen, as exemplified in eq 8 with reference to the reaction of nitrobenzene with the anion of chloromethyl phenyl sulfone.^{1,49–55} The only difference is that in our systems the departing chlorine group is bonded to the electrophilic moiety while the L group (e.g., Cl) is part of the nucleophilic moiety in common vicarious substitutions.^{51–55}



That the rates of substitution do not depend significantly upon the nature of the isotopic labeling at the reactive carbon center of the nucleophile is key information to discriminate between the two mechanistic pathways. This rules out a rate-determining step involving C–H bond breaking and therefore the vicarious route of eq 8. Should this route be operative, significant isotope effects should be observed as found for a number of classical vicarious substitutions reactions.⁵² These proceed in general through a rate-limiting β -elimination step, at least at low concentrations of the base catalysts used to promote the

process.⁵⁶ In our systems, the absence of a base catalyst can explain why it is difficult to achieve the β -elimination step of eq 7, making it more favorable to complete the overall substitution process via the three-step sequence shown in Scheme 2, in which the initial carbon–carbon coupling is rate-limiting.

Consistent with a rate-limiting formation of a zwitterion in Scheme 2 is that the rate constants k_1 for DNBF addition of **3a–n**, **9**, and **14** to the chlorine-bearing C-7 carbon of DNBF-Cl are notably lower, i.e., by a factor 20–90, than those for addition of these nucleophiles to the unsubstituted C-7 carbon of DNBF (Table 2).¹⁴ Other structural things being equal, it is a general feature that nucleophilic addition occurs faster at an unsubstituted than a substituted carbon in nucleophilic aromatic substitutions and related σ -complexation processes.^{1,2,11,49,50,57} Also to be noted is that the rate constants k_1 for coupling of DNBZ-Cl with *N*-methylindole, 1,2,5-trimethylpyrrole, and azulene are very similar to those for the DNBF-Cl reactions. This confirms previous findings that the presence of an *N*-oxide group has very little influence on the electrophilic reactivity of mononitro- and dinitro-2,1,3-benzoxadiazoles in S_NAr and related σ -complexation processes.^{1,3b,5d,19}

Electrophilicity of DNBF-Cl and DNBZ-Cl. A quantitative assessment of the intrinsic electrophilicity of DNBF-Cl and DNBZ-Cl is possible by referring to the general approach to nucleophilicity and electrophilicity recently developed by Mayr and co-workers.^{26,58–60} Using a large series of diarylcarbenium ions and various π -excessive systems as reference sets for electrophiles and nucleophiles, respectively, these authors have shown that it is possible to describe the rates of a large variety of electrophile–nucleophile combinations by the three-parameter eq 9. In this equation, the *E* parameter measures the strength of the electrophile, while *N* measures the strength of the nucleophile and *s* is a nucleophile-specific parameter which describes the sensitivity of the rate constant upon variation of the electrophile.

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$$\log k(20\text{ }^{\circ}\text{C}) = s(N + E) \quad (9)$$

Based on eq 9, general electrophilicity (E) and nucleophilicity (N) scales, each covering a reactivity range of about 25 orders of magnitude, have been defined.²⁶ These scales have proven to be very useful in assessing the reactivity of many families of electrophilic and nucleophilic substrates.^{58–61}

Applying Mayr's methodology, the N and s parameters pertaining to most of the 5- X -substituted and 5- X -substituted-2-methylindoles engaged in the present study have recently become available.¹⁴ This makes it appropriate to use these compounds as a reference set for positioning DNBF-Cl on the electrophilicity scale.

As shown in Figure 1, a plot of $(\log k_1)/s$ vs N for the DNBF-Cl systems is nicely linear with only the point for N -methylindole showing some deviation from the correlation (N and s values for indoles are taken from ref 14). From the intercept of the obtained line with the ordinate axis, the electrophilicity parameter E of DNBF-Cl could be readily derived: $E = -6.11$. On the basis of the close similarity of the k_1 values for coupling of DNBF-Cl and DNBZ-Cl with a given nucleophile (see Table 2), the E value of DNBZ-Cl can be approximated to the same E value. The fact that these two chloro derivatives have E values lower by one unit than the E value of DNBF ($E = -5.06$)³⁰ is a direct reflection of the aforementioned feature that nucleophilic addition proceeds faster at an unsubstituted than a substituted carbon.^{1,57} Most importantly, the E values of DNBF-Cl and DNBZ-Cl are 7 units higher than the E value describing the reactivity of TNB ($E = -13.19$),³⁰ implying an even more negative E parameter for picryl chloride, the common S_NAr reference in the benzene series.^{1–5,11,57} Working out some literature data reveals that the difference in S_NAr reactivity of TNB and $PiCl$ toward common nucleophiles like OH^- and MeO^- is of the same order of magnitude as that found between DNBF and DNBF-Cl reacting in Scheme 2.^{11,62–64} For the reactions with OH^- in water, we thus have $k_1^{TNB} = 37.5\text{ M}^{-1}\text{ s}^{-1}$; $k_1^{PiCl} = 0.4\text{ M}^{-1}\text{ s}^{-1}$, $k_1^{TNB}/k_1^{PiCl} = 93$.^{11,62–64}

Notwithstanding the solvent change, these data agree qualitatively well with a more negative E value for $PiCl$ than for TNB. Obviously, the positioning of DNBF, DNBF-Cl, and DNBZ-Cl relative to that of TNB and $PiCl$ on the E scale fits well the experimental observation that the three former compounds are prone to C–C coupling with a large variety of carbon nucleophiles, including those exhibiting very weak carbon basicities, e.g., 5-cyanoindole ($pK_a^{CH} = -6$).^{20b} Contrasting with this behavior, TNB and $PiCl$ are totally inert to reaction with indoles and pyrroles unless a strong base be added to the reaction mixture to generate the conjugated bases, i.e., the indolide and pyrrolide anions.⁶⁵ So far, it is only with supernucleophilic carbon bases such as 1,3,5-tris(N,N -dialkylamino)benzenes **19a–d** (vide supra) that C–C couplings with both DNBF and TNB structures could be made.^{7b,33}

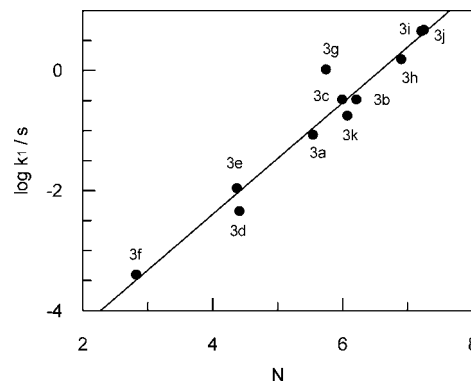


FIGURE 1. Determination of the electrophilicity of DNBF-Cl.

Within the E scale developed by Mayr, covering a range from +6 to -18 , the electrophilicity of DNBF, DNBF-Cl, and DNBZ-Cl appears to be higher than that of some amino-substituted benzhydrylium cations such as Michler's hydrol blue ($E = -7.02$), i.e., the bis (4-dimethylaminophenyl)carbenium ion, as well as of other positively charged species like triarylallyl cations (Figure 2).^{26,58–60} In fact, the electrophilicity of the three neutral structures is similar (DNBF) or approaches (DNBF-Cl and DNBZ-Cl) that of 4-nitrobenzenediazonium cation ($E = -5.1$) and tropylium cations ($E \sim -3$ to -6).^{26,30} In addition, the reactivity of DNBF-Cl and DNBZ-Cl is exactly the same as that of 4-nitrobenzodifuroxan (NBDF), a peculiar neutral nitroolefin which was recently found to readily couple with indoles, affording stable Michael adducts.^{66,67} On this basis, NBDF was classified with DNBF as a superelectrophilic reagent, making it reasonable to accord a similar qualification to DNBF-Cl and DNBZ-Cl.⁶⁶

Clearly, the exceptional electrophilic reactivity of the two latter heterocyclic structures provides an entry to the superelectrophilic dimension in S_NAr substitutions and related σ -complexation processes, thereby extending considerably the potentiality of these reactions in synthesis. On the other hand, the reactivity of TNB and $PiCl$, the usual references for these processes, is falling in the range of the weakest electrophiles so far classified on the E scale, being associated with E values of the order of those derived for arylidene malonitriles, arylidene indandiones, arylidene barbituric acids, and quinone methide compounds (Figure 2).^{58,61,68}

Steric Effects in the 2-Methylindole Series. For many years, the Brønsted carbon basicity of electron-rich aromatics and heteroaromatics, as measured by the $pK_a^{CH}(H_2O)$ values of their conjugated acids in aqueous solution, has been used as the main parameter to correlate the nucleophilic reactivity of these compounds in carbon–carbon couplings. In this regard, it is noteworthy that plotting the $\log k_1$ values determined for the indole reactions (Scheme 2) versus the known $pK_a^{CH}(H_2O)$ values of indoles **3a–k** results in two distinct linear and essentially parallel correlations corresponding to a different behavior of 5- X -substituted indoles and 5- X -substituted-2-methylindoles (Figure 3). This splitting is reminiscent of the one previously observed in describing the DNBF/indole reactions of Scheme

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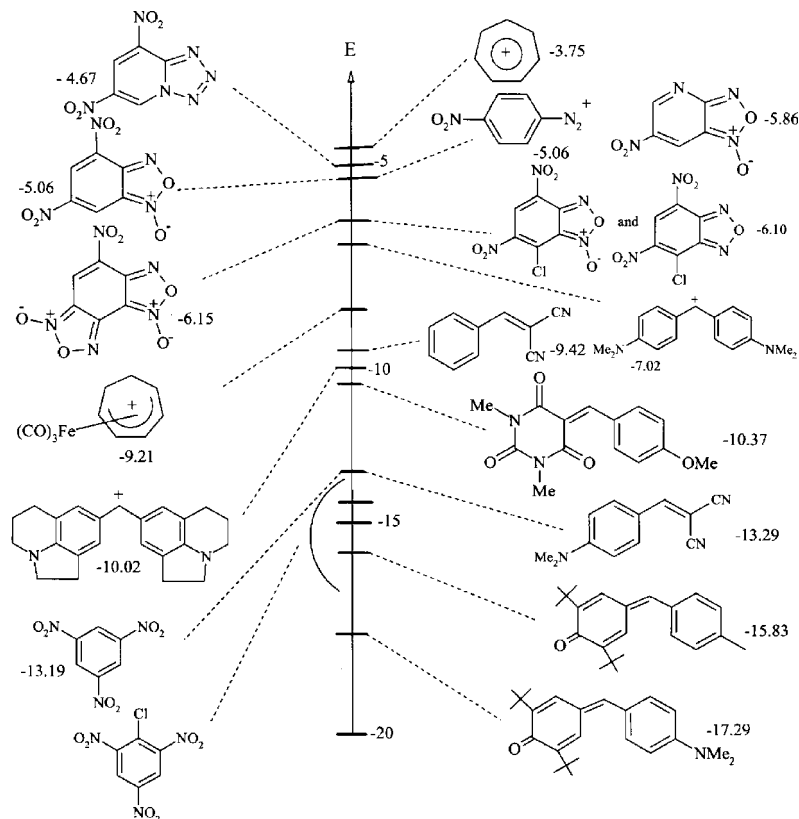


FIGURE 2. Ranking of Meisenheimer electrophiles (DNBZ, DNBF, TNB, ...) and related S_NAr substrates (DNBF-Cl, DNBZ-Cl, Pi-Cl) on the E scale, as defined by Mayr.²⁶

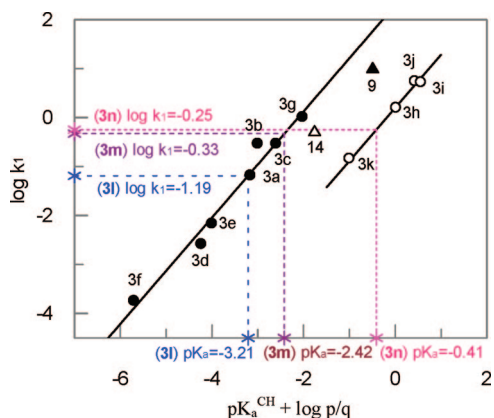


FIGURE 3. Effect of the presence of a 2-methyl group on the rate of coupling of DNBF-Cl with 5- X -substituted indoles in acetonitrile. Application to the estimation of unknown pK_a^{CH} values of indoles.

1 through similar Brønsted relationships.^{13b,30} It therefore appears that the 5- X substituent exerts a similar electronic influence in both indole series but that the presence of the methyl group in the position adjacent to the site of electrophilic attack reduces the efficiency of the DNBF and DNBF-Cl addition (ca. 1.2 $\log k$ unit). This decrease can be reasonably attributed to some steric hindrance of the approach of DNBF or DNBF-Cl from the C-3 position of 2-methylindoles.

Importantly, this conclusion implies that the N values for 2-methylindoles, which were previously determined from a kinetic study of their coupling with DNBF, used as the reference electrophile in eq 9, include some steric contribution from the electrophilic partner. Thus, in reactions with electrophiles having steric requirements different to DNBF, values of N might be

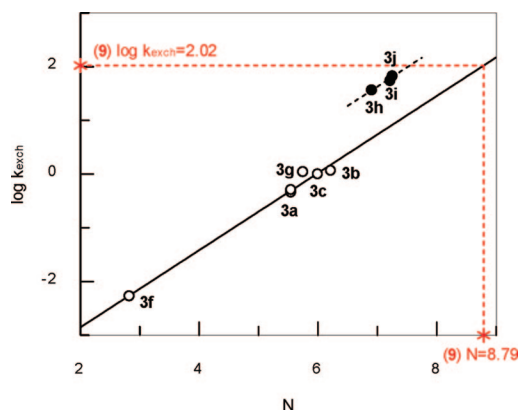


FIGURE 4. Correlation of the rates of protodetritiation (k_{exch}) of indoles-3- t in aqueous solution with the nucleophilicity parameters (N) previously derived from DNBF reactions.¹⁴

different. Support for this proposal is provided by looking at the behavior of a reaction system where steric effects are minimized, e.g., the protodetritiation at C-3 of indoles in aqueous solution.^{13b} In this instance, it has been shown that a unique Brønsted correlation describes the rates of exchange (k_{exch}) of the entire indole family.^{13b} This correlation is recalled in Figure S30 (Supporting Information).^{13b} In contrast, a plot of the $\log k_{exch}$ values versus the N values derived from the DNBF reactions gives rise to two separate lines for 5- X -indoles and 5- X -2-methylindoles (Figure 4). The fact that the 2-methyl line refers to only three compounds does not affect the message emerging from Figure 4, namely that the N values previously derived for 2-methylindoles from the DNBF reactions may have to be slightly incremented by about 1 N unit to approach the

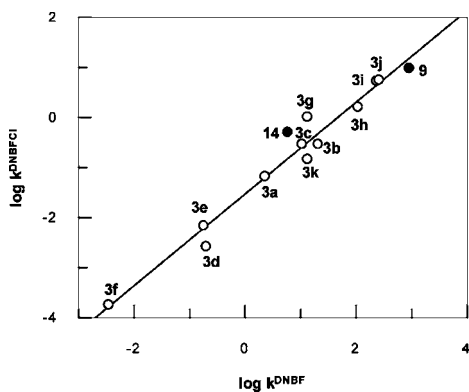


FIGURE 5. Linear free energy correlation linking the reactions of DNBF-Cl and DNBF with indoles in acetonitrile.

real intrinsic carbon nucleophilicity of these particular indoles. Interestingly, it has been shown that a suitable application of eq 1 tolerates deviations of 2 orders of magnitude in the rate constants.^{26a} On this ground, the above incrementation of 1 N unit is too weak to alter significantly our previous analysis of the reactivity of indoles, as quantified by the *N* parameters derived from the use of DNBF as the reference electrophile in eq 9. Thus, the set of *N* values quoted in Table 2 remains the appropriate tool for future discussion of the carbon nucleophilicity of indoles in other C–C coupling reactions. On the other hand, it is noteworthy that the reactivity of both indoles and 2-methylindoles toward DNBF-Cl is described by a unique linear $\log k_1 = f(N)$ correlation. This implies that similar steric effects are operating in DNBF and DNBF-Cl reactions, as demonstrated in Figure 5, which shows that plotting the $\log k_1^{\text{DNBF-Cl}}$ versus the $\log k_1^{\text{DNBF}}$ values for the indole reactions affords a good straight line.

Going to the azulene (**14**) and 1,2,5-trimethylpyrrole (**9**) reactions, Figure 3 shows that the two related $\log k_1^{\text{DNBF-Cl}}$ values reflect a reactivity which is intermediate between that of similarly basic 5-*X*-indoles and that of similarly basic 5-*X*-2-methylindoles. This situation can be attributed to some steric effects since the points pertaining to **9** and **14** fall nicely on the linear plot of Figure 5. Interestingly, the rate constants k_{exch} for protiodetritiation of azulene-*I-t* and 1,2,5-trimethylpyrrole-3,4-*t_2* have been measured in aqueous solution; $k_{\text{exch}} = 210 \text{ M}^{-1} \text{ s}^{-1}$ for **9**;⁶⁹ $k_{\text{exch}} = 0.181 \text{ M}^{-1} \text{ s}^{-1}$ for **14**.²³ As shown in Figure S30 (Supporting Information), the k_{exch} rate constant of 1,2,5-trimethylpyrrole, but not that of azulene, obeys satisfactorily the $\log k_{\text{exch}}$ vs $\text{p}K_{\text{a}}^{\text{H}_2\text{O}}$ correlation established for indoles, as it could be reasonably expected from the structural similarity linking the indole and pyrrole series. Inserting the k_{exch} value for **9** (after statistical correction) on the lower line of Figure 4 allows the evaluation of the *N* value for this pyrrole reacting at the unsubstituted β -position: $N = 8.79$. Interestingly, this value is nicely consistent with that recently measured by Mayr et al. from the reaction of **9** with a series of benzhydrylium ions ($N = 8.69$).⁷⁰

Returning to azulene, it is noteworthy that the nucleophilicity of this compound has just been determined by Mayr: $N = 6.66$, $s = 1.02$.⁷¹ Introduction of these parameters, together with the *E* value of the DNBF-Cl in eq 9 leads to the following estimate

of what should be the second order rate constant k_1 for the azulene/DNBF-Cl coupling: $k_1 = 3.72 \text{ M}^{-1} \text{ s}^{-1}$. This compares remarkably well with a measured k_1 value of $0.50 \text{ M}^{-1} \text{ s}^{-1}$. Such an agreement between experiment and predicted reactivity supports our finding that $\text{S}_{\text{N}}\text{Ar}$ substitutions are part of the nucleophile/electrophile combinations described by the Mayr relationship of eq 9.

As a last interesting result, Figure 3 can be used as a tool for estimating unknown $\text{p}K_{\text{a}}$ values associated to the C-protonation of *N*-benzylindole **3l**, 5-methoxy-*N*-benzylindole **3m**, and 2-methyl-*N*-benzylindole **3n**. Using the left line as the reference for **3l** and **3m** and the right line as a reference for **3n** and inserting the measured $\log k_1$ values on these lines leads to: $\text{p}K_{\text{a}}^{\text{CH}}(\text{H}_2\text{O}) \approx -3.21$ for **3l**, $\text{p}K_{\text{a}}^{\text{CH}}(\text{H}_2\text{O}) \approx -2.42$ for **3m**, and $\text{p}K_{\text{a}}^{\text{CH}}(\text{H}_2\text{O}) \approx -0.41$ for **3n**. This “kinetic” determination of the $\text{p}K_{\text{a}}$ values for C-protonation of these indoles is of interest since it avoids the drawback of acidity function studies in concentrated acid media.²⁰

Experimental Section

Materials. Apart the three *N*-benzylindoles **3l–n**, all nucleophilic reagents, i.e., the indoles **3a–k**, 1,2,5-trimethylpyrrole **9**, and azulene **14**, were commercially available products which were purified, as appropriate, by recrystallization, sublimation, or distillation prior to use. Compounds **3l–n** were prepared according to the procedure described by Heaney and Lay.⁷² All deuterated indoles used in this work, namely 1,3-indole-*d_2*, *N*-methylindole-3-*d*, 5-methoxyindole-1,3-*d_2*, 5-chloroindole-1,3-*d_2*, 2,5-dimethylindole-1,3-*d_2*, 1,2,5-trimethylpyrrole-3,4-*d_2*, and azulene-1,3-*d_2* were available from a recent study of the DNBF/indole and /pyrrole systems.³⁰ DNBF-Cl and DNBZ-Cl were prepared according to the procedures described by Sharnin et al. and Norris et al.^{36,73}

The synthesis and full structural characterization of the substitution products obtained upon treatment of DNBF-Cl and DNBZ-Cl with *N*-methylindole **3g**, 1,2,5-trimethylpyrrole **9**, and azulene **14**, i.e., **5g**, **8g**, **11**, **13**, **16**, and **18** have been reported.²⁷ All other substitution products have been obtained according to the following general procedure:

To a solution of the indole reagent (**3a–f** or **3h–n**, 0.2 g) in ethanol (20 mL) at room temperature was added 1 equiv of DNBF-Cl. In the case of the more basic indoles, i.e., **3a–c** and **3h–n**, the solution turned rapidly green and the reaction mixture was simply stirred at room temperature for 1 h. The precipitate was collected by filtration and then purified by column chromatography ($\text{SiO}_2/\text{CH}_2\text{Cl}_2$). For the less reactive indoles, i.e., **3d–f**, the reaction mixture was refluxed for 1 h. After evaporation of the solvent, the collected crystals were purified by column chromatography. Analytical and spectral data for each of the new indole substitution products are provided as Supporting Information.

Kinetic Measurements. Kinetic measurements pertaining to the indole reactions described in Scheme 2 and the related pyrrole and azulene reactions illustrated in Chart 1 were performed on a stopped-flow apparatus or a conventional spectrophotometer, the cell compartment of which was maintained at $20 \pm 0.1 \text{ }^\circ\text{C}$. All kinetic runs were carried out in triplicate under pseudo-first-order conditions with a DNBF-Cl or DNBZ-Cl concentration of approximately $5 \times 10^{-5} \text{ M}$ and a nucleophile (indole, pyrrole, or azulene) concentration in the range 10^{-3} – 0.5 M . In a given experiment, the rates were found to be reproducible to ± 2 – 3% . Figures S1–S6 (Supporting Information) show representative

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oscilloscope traces illustrating the unique relaxation process associated to the formation of the substitution products. The measured first-order rate constants pertaining to the various substitutions studied are given, together with the corresponding plots of k_1 versus the nucleophile concentration, in Figures S7–S29 (Supporting Information).

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Supporting Information Available: Oscilloscope picture and UV/vis spectra reflecting the reaction of DNBF-Cl with various

indoles at 20 °C in acetonitrile (Figures S1–S6). Rate constant determinations for the reactions of indoles, 1,2,5-trimethylpyrrole, and azulene with DNBF-Cl and DNBZ-Cl (Figures S7–S29). The Brønsted correlation for the protodetritiation of indoles in aqueous solution (Figure S30). Spectral data (^1H NMR and ^{13}C NMR spectra) for substitution products **5a–n** (Tables S1 and S2 and Figures S31–S57). Crystallographic data for **5n** (Tables S3–S7). X-ray crystal structure (ORTEP projection) of the product of substitution **5n** (Figure S58). Analytical data for **5a–f** and **5h–n**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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