Nucleophilic Reactivities of Indoles

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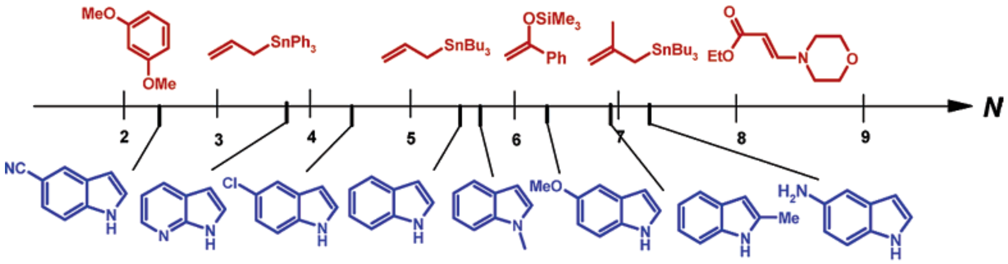

The N ranking extends to other indoles in the text.

The kinetics of the coupling of indole (**1a**), *N*-methylindole (**1b**), 5-methoxyindole (**1c**), and 5-cyanoindole (**1d**) with a set of reference benzhydryl cations have been investigated in acetonitrile and/or dichloromethane. The second-order rate constants for the reactions correlate linearly with the electrophilicity parameter *E* of the benzhydryl cations. This allows the determination of the reactivity parameters, *N* and *s*, characterizing the nucleophilicity of **1a**−**d** according to the linear free enthalpy relationship log k(20 °C) = $s(N + E)$ (*Acc. Chem. Res.* **2003**, *36*, 66). The nucleophilicity parameters thus defined describe nicely the reactions of **1a**−**d** with 4,6-dinitrobenzofuroxan (**2**), a neutral superelectrophilic heteroaromatic whose electrophilicity (*E*) has been recently determined. On this ground, the kinetics of the coupling of **2** with a large variety of indole structures have been studied in acetonitrile, leading to a ranking of this family of π-excessive carbon nucleophiles over a large domain of the nucleophilicity scale *N*. Importantly, two linear and parallel correlations are obtained on plotting the measured *N* values versus the pK_a(H_2O) values for protonation at C-3 of 5-X-substituted indoles and 5-X-substituted 2-methylindoles, respectively. This splitting reveals that the presence of the 2-methyl group causes steric hindrance to the approach of **2** from the adjacent C-3 position of an indole structure. The *N* vs pK_a(H_2O) correlation for 5-X-substituted indoles is used for a rapid determination of the C-3 basicity of indoles whose acidity constants cannot be measured through equilibrium studies in strongly acidic aqueous media.

Introduction

The indole unit is present in a wide variety of natural compounds, many of which have important physiological activities. Like pyrroles, indoles are π-excessive heteroarenes which react much faster with electrophiles than most benzene derivatives.[1,2] The Versailles group has previously investigated the mechanism of the reactions of indoles **1** with electron deficient arenes and reported second-order rate constants for the C−C coupling of 4,6-dinitrobenzofuroxan (**2**)—a strongly electron-deficient heteroarene—with a number of differently

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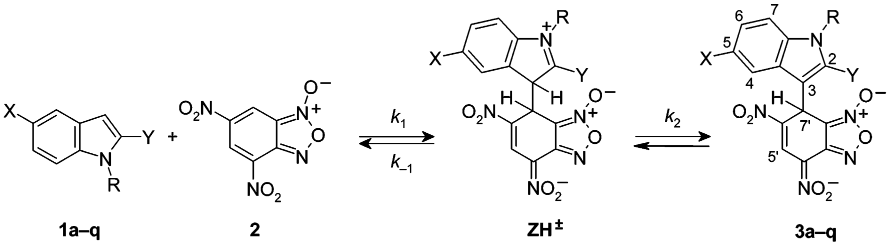
SCHEME 1



a R = Y = X = H
b R = Me, X = Y = H
c R = Y = H, X = OMe
d R = Y = H, X = CN
e R = Y = H, X = Br
f R = Y = H, X = Cl
g R = Y = H, X = Me
h R = H, Y = Me, X = Cl
i R = X = H, Y = Me
j R = H, X = Y = Me
k R = H, Y = Me, X = OMe
l R = Y = Me, X = H
m R = Y = H, X = NH_2
n R = Y = H, X = OH
o R = Y = H, X = COOH
p 4-methoxyindole
q 7-azaindole

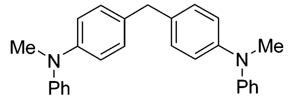
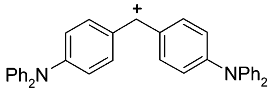
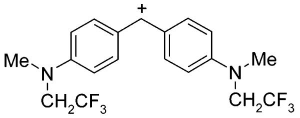
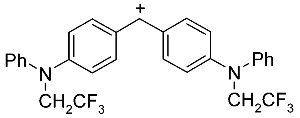
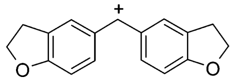
substituted indoles, namely **1a**−**k**, to give the corresponding anionic σ-adducts **3a**−**k** in different solvents (Scheme 1).[3] We have now extended this work and combined it with kinetic data on the reactions of indoles with benzhydrylium ions in order to include indoles into the comprehensive nucleophilicity scale based on benzhydrylium electrophiles,[4,5] which is useful for designing the use of indoles as nucleophiles in organocatalytic reactions.[6]

Reactions of carbocations and of electron deficient π_{CC} bonds with π-, n-, and σ-nucleophiles have been reported to follow eq 1

$$\log k(20\ °\mathrm{C}) = s(N + E) \qquad (1)$$

where electrophiles are characterized by one parameter (electrophilicity E) and nucleophiles are characterized by the nucleophilicity parameter N and the slope parameter s. Benzhydrylium ions **4** (see structures in Table 1) and structurally related quinone methides have been recommended as reference electrophiles for determining the N and s parameters of almost any nucleophile.[4,7]

TABLE 1. Benzhydrylium Ions 4 Used as Reference Electrophiles

benzhydrylium ions		E^a
	**4a**	–5.89
	**4b**	–4.72
	**4c**	–3.85
	**4d**	–3.14
	**4e**	–1.36

[a] Electrophilicity parameters from ref 7a.

Recently, it has been demonstrated that the N and s parameters defined by eq 1 can also be employed for S_N2 type reactions, if an additional, electrophile-specific sensitivity parameter s_E is considered.[7b]

Approximate N parameters of indole (**1a**), N-methylindole (**1b**), and 1,2-dimethylindole (**1l**) have previously been derived from the rate constants of the reactions of these compounds with the bis(4-phenyl(2,2,2-trifluoroethyl)amino)phenylmethylium ion (**4d**) assuming the same slope parameter ($s = 0.8$) as for enamines.[8] We have now directly determined the N and s

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parameters of the indoles **1a**−**c** from the kinetics of their reactions with a series of benzhydrylium ions **4** and found that these parameters fit also very well the electrophilic behavior of 4,6-dinitrobenzofuroxan.[3] Therefore, it was possible to link the two sets of data to derive the *N* parameters of an extended set of indoles.

Results

Reactions of Indoles with 4,6-Dinitrobenzofuroxan (2). A previous study has shown that 4,6-dinitrobenzofuroxan (**2**) reacts readily with the indoles **1a**−**k** to give stable anionic C-adducts **3a**−**k** quantitatively which were structurally characterized either in their acid form **3a**−**k**,**H** or as the corresponding potassium or sodium salts by exchanging the H^+ counterion for a K^+ or Na^+ cation. No evidence for even a minor addition of **2** to C-2 of the indole moiety was found for indoles **1a**−**g** devoid of a 2-methyl group.[3] Because of solubility problems in dichloromethane, we have now investigated the kinetics of the overall σ-complexation process of Scheme 1 at 20 °C in acetonitrile, extending the series of reactions studied to 5-aminoindole (**1m**), 5-hydroxyindole (**1n**), 5-carboxyindole (**1o**), 4-methoxyindole (**1p**), and 7-azaindole (**1q**). In general, the appearance of the resulting σ-adducts **3a**−**q** was followed by conventional or stopped-flow spectrophotometry at their absorption maxima (470−480 nm), where neither **2** nor the indoles **1a**−**q** have a notable absorption. All experiments were carried out under first-order conditions with a 3×10^{-5} mol L^{-1} concentration of **2** and a large excess of the indoles (1×10^{-3} to 2×10^{-2} mol L^{-1}). Figures S1 and S2 (Supporting Information) show oscilloscope traces illustrating the unique relaxation process corresponding to the formation of **3a-q**. For the reactions of Scheme 1, the general expression (2) of the observed first-order rate constant, k_{obs}, for the formation of the adducts **3a-q** can be derived under the assumption that the zwitterions $\mathbf{ZH}^{\pm}$ are low concentration intermediates.

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2}[\mathbf{1}] = k[\mathbf{1}] \tag{2}$$

In accordance with eq 2, excellent straight lines with zero intercepts were obtained in all systems when the k_{obs} values were plotted versus the indole concentrations [**1a**−**q**]. Determination of the second-order rate constants *k* from the slopes of these lines was therefore straightforward (Figures S3 and S4, Supporting Information). All measured k_H/k_D ratios were in the range 1.1−1.6, making it reasonable to consider that electrophilic attack of **2** at C-3 of **1a**−**q** is largely rate limiting in the overall process in Scheme 1.[9,10] Accordingly, the rate constant *k* could be identified to the rate constant k_1 for the C−C coupling step. This situation is reminiscent of that observed for the same reactions in aqueous or methanolic solution as well as of that prevailing in the majority of aromatic or heteroaromatic electrophilic substitution reactions in which the formation of the Wheland-Meisenheimer type intermediate (here $\mathbf{ZH}^{\pm}$) is rate determining.[3,11a] In line with this interpretation, Jackson and Lynch have reported that the initial attack of the electrophile is rate-limiting in the coupling of indole (**1a**), *N*-methylindole (**1b**), and 2-methylindole (**1i**) with the *p*-nitrobenzenediazonium cation.[3,11b]

TABLE 2. Second-Order Rate Constants k_1 for the Addition of DNBF (2) to Indoles 1a−q (MeCN, 20 °C)

indole	$\mathrm{p}K_a(H_2O)$[a]	k_1 (M^{-1} s^{-1})	*N*[b]	*s*[b]
1a	−3.46	2.29 (1.45)[c]	5.55	1.09
1b	−2.32	13.40	5.75	1.23
1c	−2.90	20.84 (13.2)[c]	6.22	1.12
1d	−6.00	3.5×10^{-3} (2.38×10^{-3})[c]	2.83	(1.10)[d]
1e	−4.30	0.18	4.38	(1.10)[d]
1f	−4.53	0.20	4.42	(1.10)[d]
1g	−3.30	10.71	6.00	(1.10)[d]
1h	−1.30	13.40	6.08	(1.10)[d]
1i	−0.28	108 (90)[c]	6.91	(1.10)[d]
1j	+0.26	236	7.22	(1.10)[d]
1k	+0.13	260 (245)[c]	7.26	(1.10)[d]
1l	+0.30		6.54[e]	(1.10)[d]
1m	−1.76[f] (∼ −1.75)[g]	235	7.22	(1.10)[d]
1n	−2.19	33.1 (28.2)[c]	6.44	(1.10)[d]
1o	−4.93[f] (∼ −4.91)[g]	0.064 (0.058)[c]	3.97	(1.10)[d]
1p	−3.53[f] (∼ −3.51)[g]	2.45	5.41	(1.10)[d]
1q	−5.03[f] (∼ −5.02)[g]	0.049	3.87	(1.10)[d]

[a] $\mathrm{p}K_a$ values for C-protonation at 25 °C from refs 12 and 13; the slight temperature dependence can only have a minor effect on the derived *N* values. [b] For the determination of the *N* values see below. [c] Second-order rate constants k_1 for 3-deuteriated indoles. [d] Estimated slope parameter *s*. [e] Recalculated from the rate constant for the reaction of **1l** + **4d** given in ref 8 assuming *s* =1.10. [f] $\mathrm{p}K_a$ values estimated from the *N* vs $\mathrm{p}K_a(H_2O)$ correlation established for indoles lacking a 2-methyl group. [g] $\mathrm{p}K_a$ values estimated through the Brönsted correlation of log k_1 vs $\mathrm{p}K_a(H_2O)$ drawn for 5-X substituted indoles **1a**,**c**−**g**,**n**; i.e., log $k_1 = 1.125\mathrm{p}K_a + 4.334$.

Table 2 summarizes the k_1 values measured for the various DNBF/indole couplings carried out at 20 °C in acetonitrile.

Reactions of Indoles with Benzhydrylium Ions. The benzhydrylium ions **4a**−**e**,[7] which were used as reference electrophiles, were either employed as tetrafluoroborates (**4a**−**d**)−BF_4 or generated in situ from the corresponding chloride **4e**-Cl and trimethylsilyl triflate[5b,14] (Table 1). The carbocations **4** reacted with the indoles **1** in dichloromethane to yield the 3-substituted indoles **5**, as demonstrated for the combinations listed in Scheme 2.

The kinetics of the reactions of the benzhydrylium ions **4** with the indoles **1a**−**d** in dichloromethane were monitored by UV/vis spectroscopy at 20 °C with the instruments described previously.[4,5b,7,14,15] In some cases, one equivalent of the weakly nucleophilic base 2,6-di-*tert*-butylpyridine was added to the solutions of the benzhydrylium ions **4** in order to neutralize the liberated HBF_4. As described above for the reactions with DNBF

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(9) As previously discussed for similar S_EAr processes, it is possible, using the observed KIE values and making different assumptions, to derive the actual rate constant k_1 from the measured composite rate constant *k*.[10] For the highest k_H/k_D ratio of 1.6 observed here, the correction is rather modest ($k_1 = 2.46$ instead of 2.29 M^{-1} s^{-1}) so that a direct identification of *k* to k_1 can be made without affecting the overall picture that emerges from our results.

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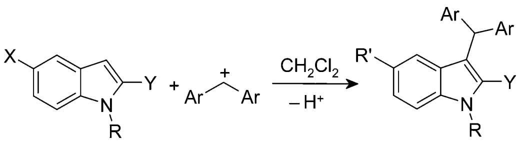
SCHEME 2



1		4	5
1a	R = X = Y = H	**4d**	**5a** (70 %)[a]
1b	R = Me, X = Y = H	**4d**	**5b** (22 %)[a]
1c	R = Y = H, X = OMe	**4e**	**5c** (58 %)
1l	R = Y = Me, X = H	**4d**	**5d** (34 %)[a]

[a] Taken from ref 8.

(**2**), the indoles **1a**−**d** were used in high excess (>10 equiv) to keep their concentration almost constant throughout the reactions. Exponential decays of the absorbances of the benzhydrylium ions were observed over more than 2 half-lives for all reactions with 5-methoxyindole (**1c**) and for most of the reactions with 1-methylindole (**1b**) in CH_2Cl_2 solution. When the latter nucleophile was combined with **4a**, the weakest electrophile of this series, exponential decay of **4a** was only observed when a high excess of **1b** (70−80 equiv) was employed. In this case, the second-order rate constant was obtained by dividing the first-order rate constant k_{obs} by the concentration of **1b**. In all other cases, the second-order rate constants k_2 were derived as the slopes of plots of k_{obs} versus the concentrations of the nucleophiles.

The reactions of the benzhydrylium ions **4a**−**e** with the parent indole **1a** (>10 equiv) in CH_2Cl_2 followed first-order kinetics only during the first 50−80% of conversion. Plots of k_{obs} for the first half-life versus the concentrations of **1a** gave the second-order rate constants listed in Table 3. When the reactions of **1a** with **4a**, **4b**, and **4d** were investigated in acetonitrile solution, however, first-order kinetics with exponential decay of the benzhydrylium absorbances were observed over more than 3 half-lives. The increase in reactivity from dichloromethane to acetonitrile solution (factor 3−5) is in the same order of magnitude as for additions of benzhydrylium ions to olefins.[4,15] Because variation of the base (2,6-lutidine instead of 2,6-di-*tert*-butylpyridine) affects the reactivity of the least electrophilic benzhydrylium ion **4a** toward **1a** and **1c** by less than a factor of 2, rate-determining C−C bond formation is assumed as in the reactions of the indoles **1** with 4,6-dinitrobenzofuroxan **2** (see above).

Complex kinetics were observed for the reactions of the benzhydrylium tetrafluoroborates **4c** and **4d** and the benzhydrylium triflate **4e** with 5-cyanoindole (**1d**) in CH_2Cl_2. Second-order rate laws were observed in acetonitrile solution, however, and the resulting rate constants are listed in Table 3.

Discussion

Nucleophilicities of Indoles. When the second-order rate constants obtained for the reactions of **1a**−**c** with a series of benzhydrylium ions **4** were plotted against the electrophilicity parameters *E* of the benzhydrylium ions, linear correlations were obtained (Figure 1 and S3), which yield the nucleophilicity parameters *N* and *s*, as defined by eq 1. Because only two rate constants were available for 5-cyanoindole (**1d**), which refer to different solvents, *N* and *s* parameters have not been calculated for this compound. Since the slopes of these correlations ($s \approx 1.10$) are larger than those of typical enamines, the previously published *N* values for indoles,[8] which were based on an estimated value of $s = 0.80$, have to be revised.

Reactions of Indoles with 4,6-Dinitrobenzofuroxan. When the revised *N* and *s* values of the indoles **1a**−**c** are used for the evaluation of the electrophilicity of 4,6-dinitrobenzofuroxan (**2**)[16] by minimizing $\Delta^2 = \Sigma[\log k_i - s_i(N_i + E)]^2$ the electrophilicity parameter $E(\mathbf{2}) = -5.06$ is obtained (Figure 2).

With the assumption of $s = 1.10$ for *N*-unsubstituted indoles, we can now employ eq 1 to calculate the *N* parameters for the indoles **1d**−**q** from the rate constants of their reactions with 4,6-dinitrobenzofuroxan (**2**) (Table 2). From these data, significant information emerges on the ranking of this family of π-excessive heteroarenes on the nucleophilicity scale.

As can be seen in Table 2, the *N* parameters of indoles cover a domain of nucleophilic reactivity of 5 orders of magnitude from the weakest nucleophile, 5-cyanoindole (**1d**), to the strongest ones, i.e., 5-aminoindole (**1m**), 2,5-dimethylindole (**1j**) and 2-methyl-5-methoxyindole (**1k**). With *N* values of ~7.2, these three latter compounds have in fact an enaminic reactivity which lies midway between the domains of stongly enaminic structures, e.g., $N = 10.04$ for morpholinoisobutylene, and weakly enaminic structures, e.g., $N = 3.84$ for 4-(bis(trimethylsiloxy)amino)pent-4-enoic acid methyl ester.[8] So far, it is the C-3 basicity of indoles, as measured by the $pK_a(H_2O)$ values of their conjugated acids in aqueous solution, which was the parameter employed to correlate the nucleophilic reactivity of these compounds in carbon−carbon coupling processes.[3,11,17] In this regard, it is interesting that plotting the *N* values determined above versus the known $pK_a(H_2O)$ values of indoles **1a**,**c**−**g**,**n** and **1h**−**k** gives rise to two separate linear correlations corresponding to a different behavior of 5-X-substituted indoles and 5-X-substituted-2-methylindoles (Figure 3). This splitting corresponds to that previously observed in describing the reactivity of these indoles through Brønsted relationships.[3]

It thus appears that the 5-X substituent exerts a similar electronic effect in the two series but that the presence of the methyl group in the position adjacent to the site of electrophilic attack reduces the rate of the 4,6-dinitrobenzofuroxan (**2**) addition to a notable extent (ca. 2 *N* units). This decrease can be reasonably attributed to steric hindrance of the approach of 4,6-dinitrobenzofuroxan (**2**) from the C-3 position of 2-methylindoles. Hence, the *N* values derived for these particular indoles include a steric contribution so that in reactions with electrophiles having steric requirements different to DNBF, values of *N* might be different. Support for this idea is provided by the finding that a unique linear Brönsted relationship describes the entire indole family in a reaction system where steric effects are minimized, for example, in the protiodetritiation at C-3 of indoles in aqueous solution.[3]

Figure 3 can be employed as a tool for estimating the basicities of the 3-positions of indoles for which the $pK_a(H_2O)$ values cannot be derived from equilibrium studies in strongly acidic media. 7-Azaindole (**1q**) is such an example because in aqueous solution the nitrogen in position 7 is much more basic

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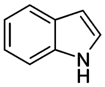
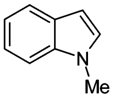
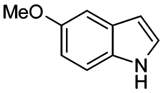
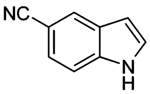
[16] The *E* parameter for 4,6-dinitrobenzofuroxan (**2**) determined in this work substitutes the previously reported $E(\mathbf{2}) = -5.22$ that was based on a smaller number of rate constants and on estimated *s* parameters for indoles: (a) Terrier, F.; Lakhdar, S.; Boubaker, T.; Goumont, R. *J. Org. Chem.* **2005**, *70*, 6242−6253. (b) Terrier, F.; Lakhdar, S.; Goumont, R.; Boubaker, T.; Buncel, E. *Chem. Commun.* **2004**, 2586−2587.

[17] Terrier, F.; Kizilian, E.; Hallé, J. C.; Buncel, E. *J. Am. Chem. Soc.* **1992**, *114*, 1740−1742.

TABLE 3. Second-Order Rate Constants (20 °C) for the Reactions of the Benzhydrylium Ions 4 with the Indoles 1a−d in the Presence of 2,6-Di-*tert*-butylpyridine (DTBP) or 2,6-Lutidine and Resulting Nucleophilicity (N) and Slope (s) Parameters for 1a−c

indole		N[a]	s[a]	Ar_2CH^+	solvent	base	k (M^{-1} s^{-1})
	**1a**	5.55	1.09	**4a**	CH_2Cl_2	DTBP	4.17×10^{-1}
				4a	CH_2Cl_2	lutidine	9.96×10^{-1} [b]
				4b	CH_2Cl_2	DTBP	1.63×10^{1}
				4c	CH_2Cl_2	DTBP	6.14×10^{1}
				4d	CH_2Cl_2		1.34×10^{2} [c]
				4e	CH_2Cl_2		(6.23×10^{4}) [d]
				4a	CH_3CN		2.08
				4b	CH_3CN		1.53×10^{2}
				4d	CH_3CN		3.19×10^{2}
				4e	TFE[e]		2.31×10^{5}
	**1b**	5.75	1.23	**4a**	CH_2Cl_2	DTBP	5.30×10^{-1}
				4b	CH_2Cl_2	DTBP	4.82×10^{1}
				4c	CH_2Cl_2	DTBP	1.32×10^{2}
				4d	CH_2Cl_2		1.09×10^{3} [c]
				4e	CH_2Cl_2		3.31×10^{5} [d]
	**1c**	6.22	1.12	**4a**	CH_2Cl_2	DTBP	1.81
				4a	CH_2Cl_2	lutidine	1.51 [b]
				4b	CH_2Cl_2	DTBP	7.67×10^{1}
				4c	CH_2Cl_2	DTBP	4.00×10^{2}
				4e	CH_2Cl_2		2.65×10^{5} [d]
	**1d**			**4d**	CH_3CN		2.54
				4e	CH_3CN		5.06×10^{2}

[a] N and s values refer to rate constants in CH_2Cl_2. [b] Not used for the calculation of N and s. [c] From ref 8. [d] Because a large part of the reaction occurred during mixing in the stopped-flow instrument, only the final part of the exponential decay was evaluated. [e] TFE = 2,2,2-trifluoroethanol, here with 9% CH_3CN.

[pK_a = 4.48] than C-3.[18] Coupling of **1q** with 4,6-dinitrobenzofuroxan (**2**) occurs, however, at a very convenient rate in acetonitrile (see Table 2), allowing a straightforward derivation of the N parameter through eq 1. Therefore, the desired pK_a(H$_2$O) of the 3-position of **1q** can be derived from the upper line in Figure 3 [N = 3.87; pK_a(H$_2$O) = −5.03]. This large negative pK_a value reflects the strong decrease of C-3 proton basicity caused by the electron-withdrawing effect of the 7-aza group in **1q**. Another interesting system is 5-aminoindole **1m**. Despite a rather high basicity in aqueous solution [pK_a = 5.99],[19] the aniline-like 5-NH$_2$ group of this indole is less susceptible to 4,6-dinitrobenzofuroxan (**2**) addition than the 3-position so that, in contrast to the behavior of aniline,[20,21] only the formation of the stable C-adduct **3m** is observed in acetonitrile. From the measured rate constant k for this reaction (see Table 2), N =

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(19) Salekh, M. A.; Kurkovskaya, L. N.; Krasavina, L. S.; Persianova, I. V.; Wigdorclik, M. M.; Suvorov, N. N. *Khim. Geterosikl. Soedin.* **1988**, 766−770.

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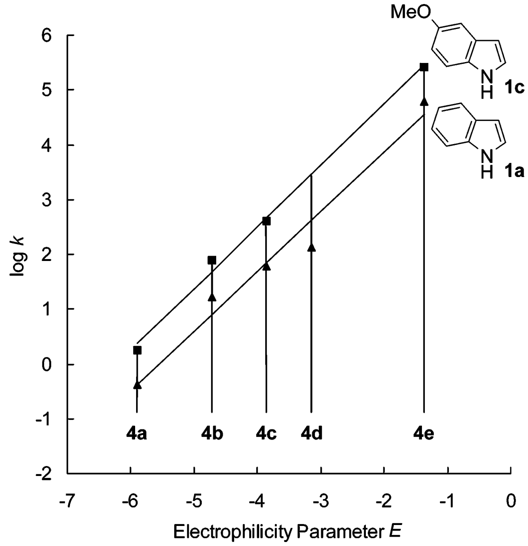

FIGURE 1. Correlation of the rate constants log *k* (20 °C, CH_2Cl_2) for the reactions of **1a** and **1c** with the benzhydrylium ions **4a**−**e** with the electrophilicity parameters *E*.

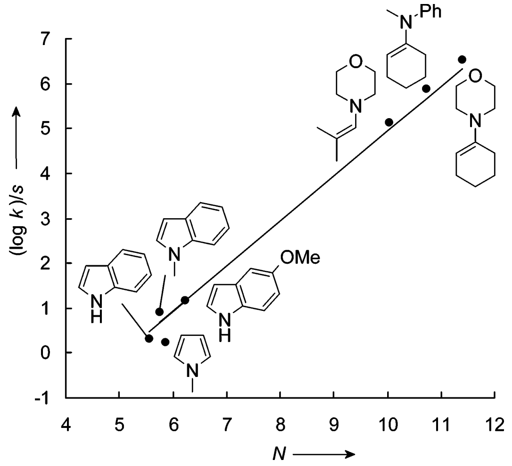

FIGURE 2. Determination of the electrophilicity of 4,6-dinitrobenzofuroxan (**2**).

7.22 and $pK_a(H_2O) = -1.76$ can be obtained. Analogously, the previously unknown basicities at the 3-position of indole-5-carboxylic acid (**1o**) [$pK_a(H_2O) = -4.93$] and of 4-methoxyindole (**1p**) [$pK_a(H_2O) = -3.53$] could be derived from Figure 3. To be noted is that the afore derived pK_a values agree well with those estimated through reference to the Brönsted correlation obtained on plotting logk_1 vs pK_a for 5-X substituted indoles **1a**,**c**−**g**,**n** (see Table 2).

The *N* parameters for 5-X-substituted indoles also correlate well with the oxidation peak potentials E_p^{ox} (Figure 4), as measured by electrochemical oxidation in acetonitrile by Mount and co-workers,[22] but it is found that the slope of this correlation is only one-third of that observed for a large variety of different C-nucleophiles.[23] The reason for this discrepancy is not clear at this stage.

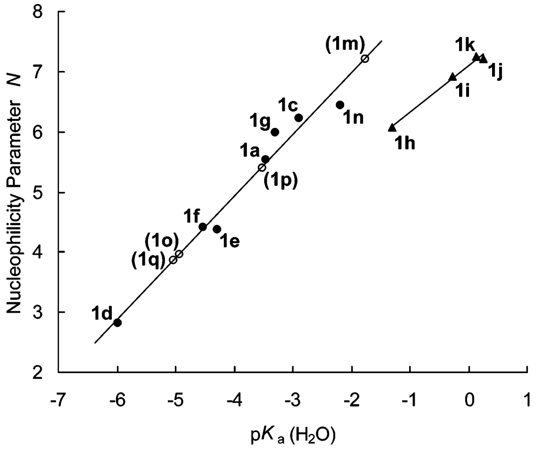

FIGURE 3. Correlation of the nucleophilicity parameters *N* of indoles **1a**,**c**−**g**,**n** (filled dots: $N = 1.025pK_a(H_2O) + 9.025$, $r^2 = 0.9669$, $n = 7$) and of 2-methylindoles **1h**−**k** (triangles: $N = 0.770pK_a(H_2O) + 7.097$, $r^2 = 0.9878$, $n = 4$) with the corresponding $pK_a(H_2O)$ values for C-3 protonation of these species in aqueous solution. Open dots: $pK_a(H_2O)$ values of indoles calculated from *N* on the basis of these correlations.

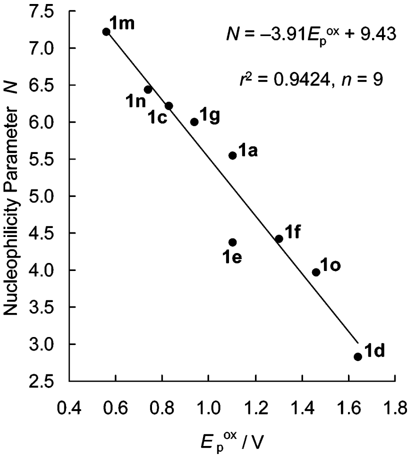

FIGURE 4. Correlation of the nucleophilicity parameters *N* of 5-X-substituted indoles **1** with the oxidation peak potentials E_p^{ox} of these species (from ref 22; the reported E_p^{ox} refer to a reference electrode (Ag/Ag^+ in MeCN) with a potential of +0.437 V vs SCE).

Comparison of the rate data pertaining to the couplings of 5-X-substituted indoles with 4,6-dinitrobenzofuroxan in acetonitrile with those obtained (at 25 °C) for these reactions in methanol, 50−50 (v/v) H_2O-Me_2SO and 70−30 (v/v) H_2O-Me_2SO reveals that the solvent has an appreciable effect on the rates of the reactions of Scheme 1. In accord with the rate-limiting formation of the zwitterionic Wheland-Meisenheimer intermediate **ZH**$^{\pm}$ through a strongly dipolar transition state of type **6**, the rates of the reactions decrease significantly with decreasing solvent polarity in the order 70−30 (v/v) H_2O-Me_2SO > 50−50 (v/v) H_2O-Me_2SO > methanol > acetonitrile.[3] Figure 5 shows the correlations obtained on plotting the logarithms of the rate constants k_1 measured in the four solvents versus the *N* values of the indoles **1a**,**c**−**g** in acetonitrile.

The four parallel correlation lines in Figure 5 indicate that the relative reactivities of the different indoles do not appreciably depend on the solvent. Because of the dipolar nature of the transition state it is difficult at this stage to dissect the observed solvent effects in terms of individual contributions of the

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(21) (a) Terrier, F.; Pouet, M. J.; Kizilian, E.; Hallé, J. C.; Outurquin, F.; Paulmier, C. *J. Org. Chem.* **1993**, *58*, 4696−4702. (b) Norris, W. P.; Spear, R. J.; Read, R. W. *Aust. J. Chem.* **1983**, *36*, 297−309.

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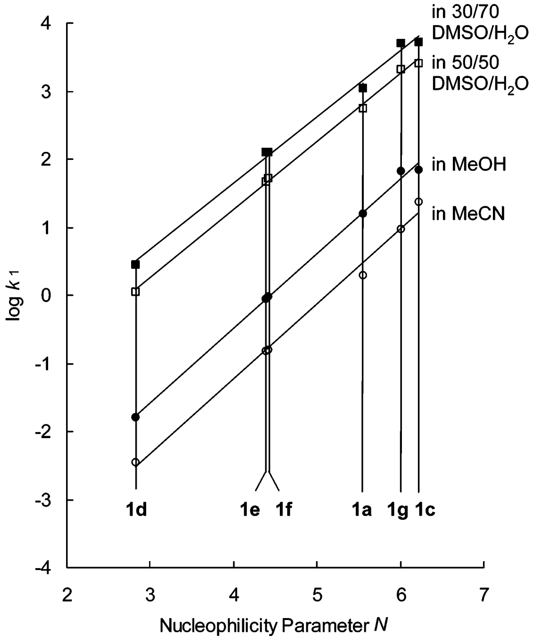
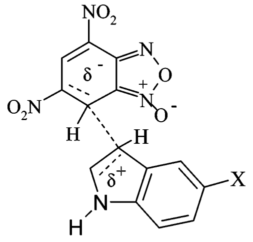


FIGURE 5. Effect of the solvent on the rates of the formation of σ-complexes of 4,6-dinitrobenzofuroxan (**2**) and the indoles **1a**,**c**−**g** (in MeCN at 20 °C from this work, for all other solvents at 25 °C from ref 3; the slight temperature difference between acetonitrile and the other solvents does not affect the comparison).



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electrophilic and nucleophilic partners. Kinetic investigations of other C−C couplings involving two neutral reagents are needed for this purpose.

Reactions of Indoles with Other Electrophiles. As reported by Jackson and Lynch, the initial attack of the electrophile is rate-limiting in the coupling of indole (**1a**), *N*-methylindole (**1b**), and 2-methylindole (**1i**) with the *p*-nitrobenzenediazonium cation.[11] The kinetics of the azo couplings between indoles **1a**, **1b**, and **1i** and a variety of aryl diazonium ions have extensively been studied by Shawali and co-workers.[24] Because the electrophilicity parameters of several diazonium ions have been determined previously,[25] we can use eq 1 to calculate rate constants for the azo couplings of indoles. The comparison of experimental and calculated rate constants for azo couplings provides a test of the reliability of our approach, and Table 4 shows that eq 1 predicts the rate constants of azo couplings within a factor of <20.[26]

With similar precision, the rate constants of the electrophilic alkylations of indoles **1a**, **1b**, and **1i** with the (2-methoxycyclohexadienylium)iron(tricarbonyl) ion which were reported earlier by Kane-Maguire and Mansfield[4a,27] can be reproduced within a factor of <40 by eq 1.

Such deviations are typical for the predictive power of eq 1, which covers a reactivity range of almost 30 orders of magnitude and usually predicts rate constants of polar organic reactions within a factor of 10−100.[4]

Experimental Section

The benzhydrylium cations **4** used in this work were prepared according to literature procedures.[7a] The various indoles **1a**−**q**, 2,6-di-*tert*-butylpyridine (DTBP), and trimethylsilyl triflate were commercially available products which were purified, as appropriate, by recrystallization, sublimation, or distillation prior to use. Deuteriation of **1a**,**c**,**d**,**i**,**k**,**n**,**o** was effected by acid-catalyzed exchange, according to a procedure which was previously reported in detail.[11−13,17,28,29] Deuteriation at C-3 was in all cases found to be ≥98% on the basis of ^{1}H NMR spectra recorded in Me$_2$SO-d_6. 4,6-Dinitrobenzofuroxan (**2**) was prepared according to the procedure by Drost[30] with mp 172 °C (lit.[17,21,31−34] mp 172−174 °C).

Adducts **3a**−**l** have previously been isolated and fully characterized either in their acid form or as sodium salts.[3] Following the same methodology, the synthetic work has been here extended to the adducts **3m**−**q**, which correspond to the σ-complexation of **2** by 5-aminoindole (**1m**), 5-hydroxyindole (**1n**), 5-indolecarboxylic acid (**1o**), 4-methoxyindole (**1p**), and 7-azaindole (**1q**), respectively. These have been prepared in their acid form upon mixing of acetonitrile solutions of **2** (1 equiv) and of the relevant indole (1 equiv) at room temperature. Subsequent addition of diethyl ether resulted in the precipitation of **3m**−**q** as red-orange solids in 60−90% yields. As all σ-adducts of 4,6-dinitrobenzofuroxan so far obtained, these solids did not melt prior to decomposition (explosion) and attempts to obtained satisfactory elemental analysis have been unsuccessful. However, dissolution of **3m**−**q** in DMSO-d_6 gave NMR spectra identical to those recorded in the in situ generation of these adducts in this solvent. In accord with the proposed structures, the H-7′ and C-7′ resonances are typical for C-adducts of **2**, being in the ranges of 5.64−5.83 and 30.4−32.4 ppm, respectively.[3,16,17,31−35] Also noteworthy is that the σ-complexation process goes along with the loss of the resonance of the H-3 proton of the parent indoles **1m**−**q**. Concomitantly, there is a significant low-field shift of the C-3 resonance, in agreement with the fact that a negatively charged dinitrobenzofuroxanyl moiety exerts a strong −I effect.[31,34] Also the NMR data leave no doubt that the adducts **3m** and **3q** are characterized by the positioning of the proton at the 5-amino group or at the 7-aza nitrogen, respectively; i.e., **3m** and **3q** can be regarded as real zwitterions. Among other evidence for structure **3m** are the especially low-field resonances of H-4 ($\delta_{\mathrm{H-4}} = 6.69$ for **1m**; $\delta_{\mathrm{H-4}} = 7.48$ for **3m**)

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[25] Mayr, H.; Hartnagel, M.; Grimm, K. *Liebigs Ann.* **1997**, 55−69.

[26] For an analogous comparison of calculated and experimental rate constants which was based on *N* parameters for indoles that were derived from $\sigma^+_{\mathrm{arene}}$ parameters, see ref 5b.

[27] (a) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525−543. (b) Kane-Maguire, L. A. P.; Mansfield, C. A. *J. Chem. Soc., Dalton Trans.* **1976**, 2192−2196.

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[31] (a) Crampton, M. R.; Rabbitt, L. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1669−1674. b) Crampton, M. R.; Lunn, R. A.; Lucas, D. *Org. Biomol. Chem.* **2003**, *1*, 3438−3443.

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[33] Boga, C.; Forlani, L. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1408−1413.

[34] (a) Terrier, F. In *Nucleophilic Aromatic Displacement*; Feuer, H., Ed.; VCH: New York, 1991; Chapter 2. (b) Terrier, F.; Millot, F.; Norris, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5883−5890. (c) Terrier, F. *Chem. Rev.* **1982**, *82*, 77−152.

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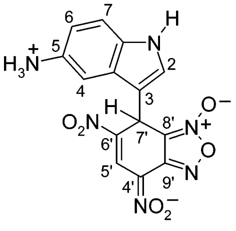
TABLE 4. Comparison between Calculated (20 °C, eq 1) and Experimentally Determined Second-Order Rate Constants for the Reactions of Indole (1a), *N*-Methylindole (1b), and 2-Methylindole (1i) with Different Electrophiles

	nucleophile (*N*/*s*)	electrophile	*E*	k_{calcd} (M^{-1} s^{-1})	k_{exp} (M^{-1} s^{-1})
1a	indole (5.55/1.09)	4-OMe-C_6H_4-N_2^+	−8.4 [a]	2.4×10^{-3}	2.49×10^{-4} [b]
		4-Me-C_6H_4-N_2^+	−7.7 [a]	1.1×10^{-2}	5.62×10^{-4} [b]
		C_6H_5-N_2^+	−7.2 [a]	3.1×10^{-2}	2.24×10^{-3} [b]
		4-Cl-C_6H_4-N_2^+	−6.7 [a]	8.8×10^{-2}	1.44×10^{-2} [b]
		4-CN-C_6H_4-N_2^+	−5.5 [a]	1.11	4.69×10^{-1} [b]
		4-NO_2-C_6H_4-N_2^+	−5.1 [a]	2.6	1.24 [b]
		(2-$MeOC_6H_6$)$Fe(CO)_3^+$	−8.94 [c]	7.8×10^{-4}	1.60×10^{-2} [d]
1b	*N*-methylindole (5.75/1.23)	4-OMe-C_6H_4-N_2^+	−8.4 [a]	7.0×10^{-3}	2.46×10^{-3} [b]
		4-Me-C_6H_4-N_2^+	−7.7 [a]	2.6×10^{-2}	5.80×10^{-3} [b]
		C_6H_5-N_2^+	−7.2 [a]	6.6×10^{-2}	2.57×10^{-2} [b]
		4-Cl-C_6H_4-N_2^+	−6.7 [a]	1.7×10^{-1}	1.18×10^{-1} [b]
		4-CN-C_6H_4-N_2^+	−5.5 [a]	1.6	3.72 [b]
		4-NO_2-C_6H_4-N_2^+	−5.1 [a]	3.4	6.61 [b]
		(2-$MeOC_6H_6$)$Fe(CO)_3^+$	−8.94 [c]	2.5×10^{-3}	9.70×10^{-2} [d]
1i	2-methylindole (6.91/1.10)	4-OMe-C_6H_4-N_2^+	−8.4 [a]	4.4×10^{-2}	2.50×10^{-1} [b]
		4-Me-C_6H_4-N_2^+	−7.7 [a]	1.9×10^{-1}	6.20×10^{-1} [b]
		C_6H_5-N_2^+	−7.2 [a]	5.4×10^{-1}	1.92 [b]
		4-Cl-C_6H_4-N_2^+	−6.7 [a]	1.6	1.51×10^{1} [b]
		4-CN-C_6H_4-N_2^+	−5.5 [a]	1.9×10^{1}	1.78×10^{2} [b]
		4-NO_2-C_6H_4-N_2^+	−5.1 [a]	4.4×10^{1}	4.27×10^{2} [b]
		(2-$MeOC_6H_6$)$Fe(CO)_3^+$	−8.94 [c]	1.4×10^{-2}	1.20×10^{-1} [d]

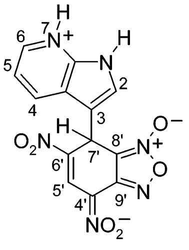
[a] From ref 25. [b] In acetonitrile at 25 °C, from ref 24. [c] From ref 4a. [d] In nitromethane at 20 °C, from ref 27.

and H-6 ($\delta_{H-6} = 6.49$ for **1m**; $\delta_{H-6} = 7.42$ for **3m**) as well as of the related carbons C-4 ($\delta_{C-4} = 103.2$ for **1m**; $\delta_{C-4} = 111.9$ for **3m**) and C-6 ($\delta_{C-6} = 111.8$ for **1m**; $\delta_{C-6} = 115.9$ for **3m**). Similarly, the H-4 ($\delta_{H-4} = 7.92$ for **1q**; $\delta_{H-4} = 8.39$ for **3q**) and C-4 ($\delta_{C-4} = 128.0$ for **1q**; $\delta_{C-4} = 133.7$ for **3q**) resonances of **3q** are typical for a protonated aza functionality. Definitive evidence that the adducts **3m**−**q** were isolated in their acid form comes from mass spectra experiments performed with the electrospray technique. Also, the UV−visible spectra of the adducts exhibit the strong absorption at $\lambda = 470-480$ nm typical of all σ-complexes of 4,6-dinitrobenzofuroxan (**2**) in acetonitrile.[3,16,17,31−35]

Representative NMR (^1H, ^{13}C) and mass spectroscopy data for the DNBF adducts **3m** and **3q** are given below which leave no doubt regarding the structures of these species. Analytical data for the other adducts are available in Table S_{37}−S_{39} (Supporting Information). Figures S_4−S_{28} (Supporting Information) show ^1H and ^{13}C NMR spectra as well as two-dimensional correlations and mass spectra recorded for the adducts **3m**−**q**.



3m



3q

3m: red solid; yield 90%; MS *m*/*z* (FAB) 357 (M − H)$^+$; ^1H NMR (300 MHz, Me_2SO-d_6) 5.64 (s, 1H, $H_{7'}$), 6.97 (d, 1H, J = 8.8 Hz, H_7), 7.21 (s, 1H, H_2), 7.42 (d, 1H, J = 8.8 Hz, H_6), 7.48 (bs, 1H, H_4), 8.73 (s, 1H, $H_{5'}$), 9.58 (bs, 3H, NH_3^+), 11.34 (s, 1H, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 31.3 ($C_{7'}$), 109.4 ($C_{4'}$), 109.5 (C_3), 111.9 (C_4), 113.0 (C_7), 113.3 ($C_{8'}$), 115.9 (C_6), 123.3 (C_5), 125.3 (C_9), 126.6 ($C_{6'}$), 127.8 (C_2), 130.4 ($C_{5'}$), 135.1 (C_8), 148.4 ($C_{9'}$).

3q: red solid; yield 85%; MS *m*/*z* (FAB) 344 M$^+$; ^1H NMR (300 MHz, Me_2SO-d_6) 5.83 (s, 1H, $H_{7'}$), 6.51 (bs, 1H, NH$^+$), 7.48 (dd, 1H, J = 5.6 Hz, 7.9 Hz, H_5), 7.76 (s, 1H, H_2), 8.39 (d, 1H, J = 7.9 Hz, H_4), 8.45 (d, 1H, J = 5.6 Hz, H_6), 8.75 (s, 1H, $H_{5'}$), 12.69 (bs, 1H, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6) 30.4 ($C_{7'}$), 109.6 ($C_{4'}$), 111.4 (C_3), 113.2 ($C_{8'}$), 115.7 (C_5), 122.6 (C_9), 123.3 (C_5), 125.8 (C_2), 128.0 ($C_{6'}$), 130.7 ($C_{5'}$), 133.7 (C_4), 136.0 (C_6), 140.2 (C_8), 148.2 ($C_{9'}$).

Compounds **5a**, **5b**, and **5d** have previously been prepared and characterized.[8] Compound **5c** was prepared by dropping a solution of **4e**-Cl and trimethylsilyl triflate in CH_2Cl_2 to a stirred solution of 5-methoxyindole (**1c**) (for details see the Supporting Information).

Kinetic Measurements. The kinetic investigations of the reactions of benzhydrylium ions **4** with the indoles **1a**−**d** in dichloromethane or acetonitrile were carried out, as previously described in detail for similar interactions.[4,5b,6,14,15] Kinetic measurements pertaining to the DNBF/indole couplings were performed on a stopped flow apparatus, 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 a concentration of **2** of ca. 3×10^{-5} M and a nucleophile (**1**) 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 S_2 and S_3, 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 **3m**−**q** or the decrease in absorbance at λ_{max} of DNBF (415 nm) as a function of time.

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Supporting Information Available: Oscilloscope pictures showing the unique relaxation process in the various DNBF-indole combinations studied (Figures S_1−S_2). Rate constant determinations for the reactions of indoles **1a**−**d** with benzhydrylium ions **4** (Tables S_1−S_{20}). Rate constant determinations for the reactions of indoles **1a**−**q** with DNBF (Figure S_3 and Tables S_{21}−S_{36}). Synthetic procedure for the preparation of the product **5c** resulting from the coupling of **1c** with benzhydrylium cation **4e**. Spectral data (^1H and ^{13}C NMR, mass spectroscopy) for adduct formation (**3m**−**q**) (Tables S_{37}−S_{39} and Figures S_4−S_{28}). This material is available free of charge via the Internet at http://pubs.acs.org.

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