Kinetics of the Friedel−Crafts Alkylations of Heterocyclic Arenes: Comparison of the Nucleophilic Reactivities of Aromatic and Nonaromatic π-Systems

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The kinetics of the reactions of benzhydryl cations with heteroarenes (*N*-methylpyrrole, furan, 2-methylfuran, and 2-methylthiophene) have been determined photometrically in dichloromethane, and the reaction products have been completely characterized by ^{1}H and ^{13}C NMR spectroscopy. The reactions follow second-order kinetics with rate-limiting formation of the σ-adducts. The second-order rate constants correlate linearly with the electrophilicity parameter *E* of the benzhydryl cations. This allows the determination of the reactivity parameters *N* and *s* for the heteroarenes according to the linear free enthalpy relationship log $k = s(E + N)$ (Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957). The nucleophilicity parameters *N* thus defined allow a direct comparison of the nucleophilic reactivities of aromatic and nonaromatic π-systems. Since *N* correlates linearly with σ^+_{arene}, it becomes possible to derive *N* parameters for arenes and heteroarenes with known σ^+ parameters and to calculate absolute rate constants for their reactions with carbenium ions and diazonium ions. Applications of the reactivity parameters thus determined for the quantitative and qualitative prediction of the rates of electrophilic aromatic substitutions are discussed.

Introduction

Electrophilic substitutions of arenes belong to the best investigated organic reactions.[1] The first mechanistic studies had already been performed by the late twenties by Ingold, who rationalized orientations and relative rates in terms of inductive and mesomeric substituent effects.[2] Since then most efforts to quantify the reactivities of arenes have concentrated on competition experiments, where an electrophile was allowed to select between a pair of arenes. It has been found that the reactivities follow the Hammett−Brown relationship (eq 1), where σ^+_{arene} (equivalent to σ^+_p or σ^+_m in the case of

$$\log k/k_0 = \rho\sigma^+_{arene} \tag{1}$$

monosubstituted benzenes) is a measure for the relative reactivities of one position of an arene in relation to one position of benzene.[3,4]

Only recently, the first absolute rate constants for the attack of carbocations at arenes have been reported,[5] and

it has been shown that these reactions follow the linear free enthalpy relationship (eq 2), where *E* represents the

$$\log k(20\ °C) = s(E + N) \tag{2}$$

strength of the electrophiles, while *N* and *s* characterize the nucleophiles' reactivity.[6] Since *N* and *s* parameters have also been determined for nonaromatic π-systems, a direct comparison of the nucleophilic reactivities of substituted benzenes, alkenes, and other π-nucleophiles became possible.

We now have extended this work on the kinetics of the reactions of stabilized carbocations with heterocyclic arenes in order to search for a correlation between the Hammett-Brown σ^+_{arene} parameters and the nucleophilicity parameters *N*. Such a correlation might allow one to employ eq 2 and the manifold of relative arene reactivities available in the literature for deriving absolute rate constants of electrophilic aromatic substitutions.

Results and Discussion

Preparative Investigations. The Lewis acid induced reactions of the diarylmethyl derivatives (**2a**−**d**)-X with

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
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Table 1. Lewis Acid Catalyzed Reactions of Diarylmethyl Derivatives with Heteroarenes in CH_2Cl_2[a]

arene	1	2	Lewis acid	[1]/[2]	3	4	yield, %	[3]:[4]
	1a	**2a**+BF_4^-		3	**3a**	**4a**	58	1.1
		2a+OTf^-		7			70	2.0
				15			66	2.9
		2b-OAc	$ZnCl_2 \cdot OEt_2$[b]	3	**3b**	**4b**	71	9.0
	1b	**2b**-OAc	$ZnCl_2 \cdot OEt_2$	3	**3c**	**4c**	67	0.1
			$ZnCl_2 \cdot OEt_2$	7			79	1.2
		2c-OMe	$ZnCl_2 \cdot OEt_2$	5	**3d**	**4d**	74	0.5
			TMSOTf	10			73	1.5
		2d-Cl	$ZnCl_2 \cdot OEt_2$	3	**3e**	**4e**	68	0.1
			$ZnCl_2 \cdot OEt_2$	10			70	0.5
			$ZnCl_2 \cdot OEt_2$	15			80	2.1
	1c	**2b**-OAc	$ZnCl_2 \cdot OEt_2$	3	**3f**		72	
		2c-OMe	$ZnCl_2 \cdot OEt_2$	3	**3g**		61	
		2d-Cl	$ZnCl_2 \cdot OEt_2$	3	**3h**		54	
	1d	**2b**-OAc	$ZnCl_2 \cdot OEt_2$	3	**3i**		68	
		2c-OMe	TMSOTf	3	**3k**		70	
		2d-Cl	$ZnCl_2 \cdot OEt_2$	3	**3l**		81	

[a] For a complete characterization of the substitution products **3** and **4**, see Supporting Information. [b] [$ZnCl_2$]:[OEt_2] = 3.9; see ref 7c.

Scheme 1
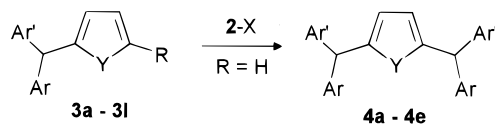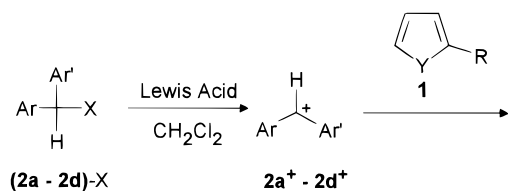
Scheme 2
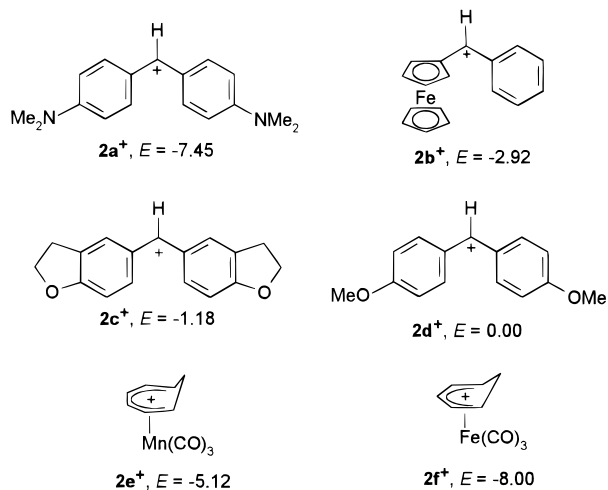
2-methylfuran (**1c**) and 2-methylthiophene (**1d**) yielded the products **3f**−**l** quantitatively according to NMR analysis of the crude products (Schemes 1 and 2). Purification of the products by chromatography or recrystallization gave the yields listed in Table 1. In the case of *N*-methylpyrrole (**1a**) and furan (**1b**), the mono-substituted compounds **3a**−**e** (R = H) were accompanied by the 2:1 products **4a**−**e**. The yield of **4** could be reduced by using the arenes **1** in excess.

Scheme 3
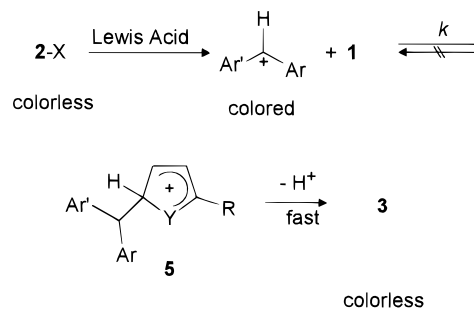
All substitution products **3** and **4** (with the exception of those containing the ferrocenyl group) are colorless crystals or oils, which become colored when exposed to air and/or light.

Kinetics. Since compounds **3** and **4** possess absorption maxima at considerably shorter wavelengths than the carbenium ions $2a^+$−d^+, the kinetics could be followed by determining the decay of the lowest energy absorption band of $2a^+$−d^+ using the work station described previously (Scheme 3).[7a]

Bis(*p*-dimethylamino)benzhydryl triflate (**2a**+OTf^-) is a stable salt. Its solutions can be used directly for the kinetic experiments. For the ionization of the covalent carbenium precursors (**2b**−**d**)-X we chose the weak Lewis acids Me_3SiOTf and $ZnCl_2 \cdot OEt_2$[7b,c] because of their low tendencies to coordinate with the heteroarenes **1**. As a consequence, the observed reaction rates were independent of the excess of the Lewis acid used for ionization. All reactions have been found to follow second-order kinetics, first order with respect to carbocations and first order with respect to the arenes (Table 2). In some cases (slight) deviations from the second-order rate law after two half-lifes were observed. If the attack of 2^+ at **1** were reversible, the reactions should proceed faster at higher concentrations of the counterions which behave as bases.[5b]

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Table 2. Rate Constants and Activation Parameters for the Reactions of the Heteroarenes 1 with the Carbenium Ions 2$^+$ in Dichloromethane^a

1	2$^+$	k(20 °C), L mol^{-1} s^{-1}	$\Delta H^{\ddagger}$, kJ mol^{-1}	$\Delta S^{\ddagger}$, J mol^{-1} K^{-1}
1a	2a$^+$	$(6.03 \pm 0.85) \times 10^{-2}$		
	2b$^+$	$(2.00 \pm 0.15) \times 10^3$	26.2 ± 1.3	-92.2 ± 5.8
	2e$^+$	9.14^b		
1b	2b$^+$	$(1.83 \pm 0.31) \times 10^{-2}$	40.5 ± 3.4	-139.9 ± 12.6
	2c$^+$	1.32 ± 0.18		
	2d$^+$	$(5.43 \pm 0.61) \times 10^1$	33.5 ± 2.6	-97.3 ± 11.4
	2f$^+$	4.78×10^{-7} ^{c}		
1c	2b$^+$	$(1.35 \pm 0.18) \times 10^1$	34.9 ± 1.6	-104.1 ± 6.8
	2c$^+$	$(2.53 \pm 0.14) \times 10^2$	21.3 ± 0.9	-126.1 ± 4.4
	2d$^+$	$(1.15 \pm 0.42) \times 10^4$ ^{d}		
	2f$^+$	4.14×10^{-5} ^{c}		
1d	2b$^+$	$(6.51 \pm 0.17) \times 10^{-2}$		
	2c$^+$	0.46 ± 0.08	42.7 ± 1.3	-105.6 ± 4.8
	2d$^+$	$(2.13 \pm 0.19) \times 10^1$	33.9 ± 0.9	-103.7 ± 3.9
	2f$^+$	7.09×10^{-7} ^{c}		

^{a} Counterion variable; for details see Supporting Information. ^{b} Taken from ref 10. Kinetics studied in nitromethane at 25 °C. Extrapolation to 20 °C was made with the assumption $\Delta S^{\ddagger} = -100$ J mol^{-1} K^{-1}. ^{c} Taken from ref 10. Kinetics studied in nitromethane at 45 °C. Extrapolation to 20 °C was made with the assumption $\Delta S^{\ddagger} = -100$ J mol^{-1} K^{-1}. ^{d} Mayr, H.; Grimm, K. Unpublished results.

Rate-determining formation of the σ-complex **5** was, therefore, derived from the fact that the observed rates were not affected by the addition of tetrabutylammonium salts with common anions.[8] Since all kinetics were performed in the presence of a high excess of arene, the formation of the 2:1 products **4** could be neglected under the conditions of the kinetic experiments. Evidence for an initial attack of the benzhydryl cations at the heteroatoms of **1a**–**d** has not been obtained. However, we cannot exclude the initial reversible formation of small concentrations of onium ions.[9]

Discussion

When the rate constants (log k) obtained with the different electrophiles **2**$^+$ are plotted against their electrophilicity parameters E,[6] linear correlations are found (Figure 1). It is thus shown that the linear free enthalpy relationship (2) previously derived for the reactions of carbocations with other noncharged nucleophiles[6,11] also holds for the reactions studied in this work.

Comparison with the corresponding correlations for 1-(trimethylsiloxy)cyclohexene and methylenecyclopentane reported earlier[6] shows that the slopes of these lines are closely similar for all nucleophiles studied. As a consequence, 1-(trimethylsiloxy)cyclohexene is generally somewhat less reactive than N-methylpyrrole and by a factor of about 100 more reactive than 2-methylfuran,

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(10) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525–543.

(11) (a) Mayr, H.; Schneider, R.; Irrgang, B.; Schade, C. *J. Am. Chem. Soc.* **1990**, *112*, 4454–4459. (b) Mayr, H.; Schneider, R.; Grabis, U. *J. Am. Chem. Soc.* **1990**, *112*, 4460–4467. (c) Mayr, H.; Basso, N. *Angew. Chem.* **1992**, *104*, 1103–1105; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1046–1048. (d) Mayr, H. In *Cationic Polymerizations*; Matyjaszewski, K., Ed.; M. Dekker: New York, 1996; pp 51–136.
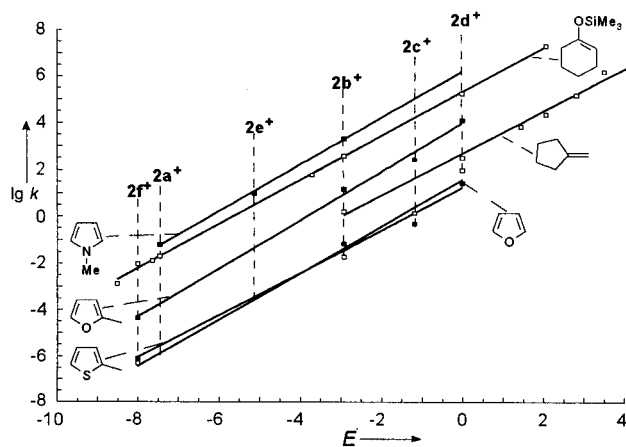

Figure 1. Linear free enthalpy relationships for the reactions of aromatic and aliphatic π-systems with stabilized carbocations. The rate constants (20 °C) for **2a**$^+$–**2d**$^+$ refer to CH$_2$Cl$_2$; those for **2e**$^+$ and **2f**$^+$, to CH$_3$NO$_2$ (see Table 2). Since previous studies showed a negligible effect of solvents on such rate constants, corrections for solvent were not made.

independent of the electrophilicity of the carbocationic reaction partner. Similarly, the reactivity of methylenecyclopentane is generally between that of 2-methylfuran and furan. It should be noted that the constant reactivity ratio of two arenes (independent of the electrophile) corresponds to a constant value of ρ for all of these reactions (eq 1). Only when two arenes of closely similar reactivity are compared, may intersections of the correlation lines be observed: Depending on the nature of the reference electrophile, furan or 2-methylthiophene is found to be slightly more reactive than the other.

The kinetic data presented in Table 2 and graphically displayed in Figure 1 can be used to determine the nucleophilicity parameters N and s of the heterocyclic compounds according to eq 2. The parameter s is given by the slope of the correlation lines, and N is obtained by dividing the intercept at $E = 0$ by s. Because of the similar slopes of these correlation lines ($0.91 \leq s \leq 1.03$), the relative reactivities of the arenes can be approximated by their nucleophilicity parameters N as shown in Figure 2, where nucleophiles are ordered according to increasing N values from top to bottom. Since $s \approx 1$, the distance between two nucleophiles in Figure 2 (ΔN) is directly proportional to their difference in reactivity, and the 18 units of N covered by Figure 2 correspond to a reactivity ratio of 10^{18}. Figure 2 also includes nonaromatic nucleophiles and thus provides a direct comparison of the reactivities of aromatic and aliphatic π-systems toward nonbridging electrophiles.

It can thus be seen that furan, allyltrimethylsilane, and isobutylene, representatives of three different classes of compounds, exhibit similar nuleophilic reactivities. N-Methylpyrrole, which has long been known to possess a similar reactivity as N,N-dimethylaniline in electrophilic aromatic substitutions (similar σ^+ values), is now shown also to possess a comparable nucleophilicity as allyltributylstannane and 2-(trimethylsiloxy)propene.

As mentioned above, relative reactivities of arenes, mostly determined by competition experiments, have previously been expressed by σ^+ or σ^+_{arene} parameters.[12–14]

(12) Reference 1a, Chapter 11, and references cited there.
(13) Katritzky, A. R.; Taylor, R. *Adv. Heterocycl. Chem.* **1990**, *47*, 1–467 and references cited there.
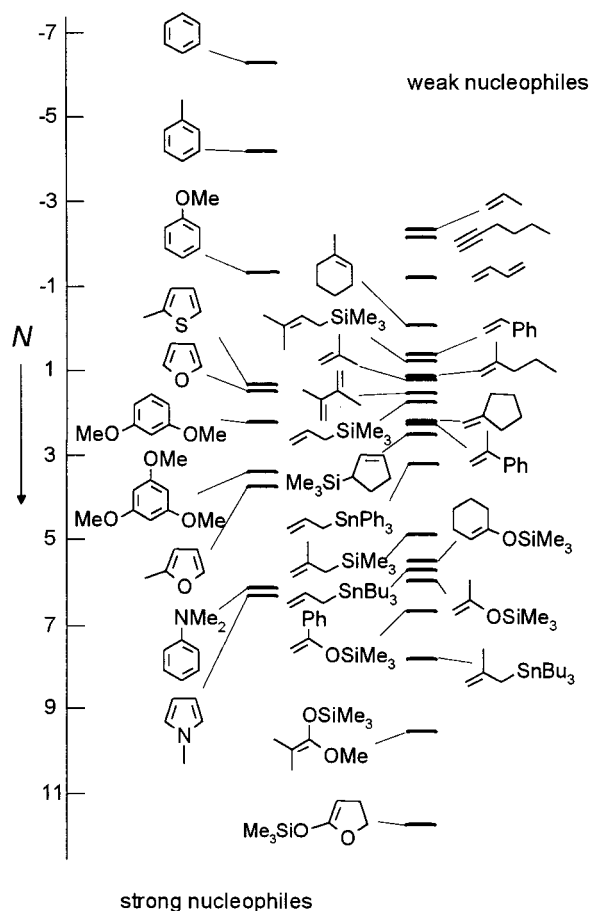
Figure 2. Nucleophilicity scale of aromatic and aliphatic π-systems. Nucleophiles are ordered according to their *N*-parameters with increasing reactivity from top to bottom.

Table 3. σ^+ and *N* Parameters of the Arenes Considered in Correlation (Eq 3)

arene	$\sigma^{+\ a}$	*N*	*s*
1a	−1.90	6.18 ± 0.42	1.02 ± 0.02
1b	−0.95	1.45 ± 0.20	0.98 ± 0.05
1c	−1.34	3.80 ± 0.20	1.03 ± 0.05
1d	−1.17	1.28 ± 0.29	0.91 ± 0.06
benzene	0.00	−6.29[b]	
toluene	−0.31	−4.22[b]	
anisole	−0.78	−1.56[b]	

[a] Heterocyclic compounds, refs 4 and 13; benzenoid compounds, ref 12. [b] Reference 6.

Since these quantities represent the nucleophilicities of arenes in the Hammett–Brown equation (eq 1), it is not surprising that there is also a correlation between *N* and σ^+ (Table 3, Figure 3).[15]

$$N = -6.8\sigma^+ - 6.2 \qquad n = 7, r = 0.986 \qquad (3)$$

Equation 3, which covers a reactivity range of more than 12 orders of magnitude (Figure 3), now allows the calculation of *N* parameters for all arenes, which have

(14) The definition of σ^+ for substituted arenes is not free of ambiguity and depends on the reference reaction chosen for its determination. For detailed discussion see refs 4, 12, and 13.

(15) A difference in the definition of *N* and σ^+_{arene} is the treatment of the statistical factor. While σ^+ refers to the reactivity of *one* nucleophilic position with respect to *one* position in benzene, *N* refers to the overall reactivity of a nucleophile. Since *N* has also been defined for alkenes which may react via more or less symmetrical transition states, the introduction of a statistical correction would sometimes be ambiguous and is, therefore, generally avoided.
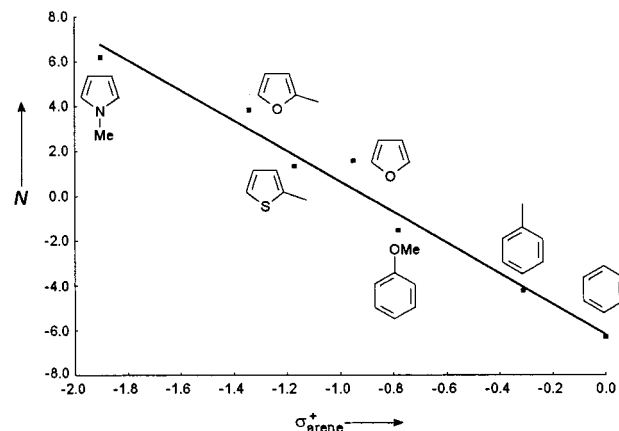

Figure 3. Correlation between the nucleophilicity parameters *N* and σ^+_{arene}.

Table 4. Nucleophilicity Parameters *N* for Various Iso- and Heterocyclic Arenes Calculated by Eq 3

arene	$\sigma^+_{arene}{}^a$	posn	*N*
aniline	−1.47	4	3.8
N,N-dimethylaniline	−1.74	4	5.6
fluorobenzene	−0.08	4	−5.6
chlorobenzene	0.12	4	−7.0
bromobenzene	0.15	4	−7.2
iodobenzene	0.14	4	−7.2
ethyl benzoate	0.32	3	−8.4
isopropylbenzene	−0.33	4	−3.9
thiophene	−0.85	2	−0.4
selenophene	−0.88	2	−0.2
tellurophene	−0.90	2	−0.1
2-bromothiophene	−0.72	5	−1.3
benzo[*b*]thiophene	−0.54	3	−2.5
benzo[*b*]furan	−0.49	2	−2.9
benzo[*b*]selenophene	−0.48	2	−2.9
benzo[*b*]tellurophene	−0.58	2	−2.3
dibenzofuran	−0.40	4	−3.5
dibenzothiophene	−0.37	4	−3.7
N-methylindole	−1.93	3	6.9
o-xylene	−0.37	4	−3.7
benzcyclopentane	−0.41	5	−3.4
tetralin	−0.41	6	−3.4
benzcycloheptane	−0.40	7	−3.5
biphenylene	−0.47	2	−3.0
anthracene	−0.81	9	−0.7
fluorene	−0.48	2	−2.9
2-methylfluorene	−0.55	7	−2.5
phenanthrene	−0.39	3	−3.5
1-methylphenanthrene	−0.44	9	−3.2
2-methylphenanthrene	−0.42	9	−3.3
naphthalene	−0.35	1	−3.8
1-methylnaphthalene	−0.57	4	−2.3
2-methylnaphthalene	−0.64	1	−1.8
acenaphthane	−0.76	4	−1.0
pyrene	−0.68	1	−1.6
ferrocene	−1.30	1	2.6
o-carborane	0.31	1	−8.3
m-carborane	0.23	1	−7.8
1,6-methano[10]annulene	−0.80	2	−0.8

[a] Carbocyclic compounds, ref 12; heterocyclic compounds, ref 13.

previously been characterized by σ^+ or σ^+_{arene} parameters (Table 4). With these data it becomes possible to predict absolute rate constants for the electrophilic attack at such arenes, for which only relative reactivities have yet been determined. It should be noted that eq 3 may alternatively be used to calculate σ^+ parameters of alkenes, allylsilanes, silyl enol ethers, and other aliphatic π-systems from their *N* values, which would render an analogous comparison.

Table 5. Comparison between Calculated (k_{calc}) and Experimentally Observed (k_{obs}) Rate Constants of Various Electrophilic Aromatic Substitutions

electrophile	E^a	nucleophile	N^b	$\log k_{calc}$,^{c} L mol^{-1} s^{-1}	$\log k_{obs}$, L mol^{-1} s^{-1}
$Fe(CO)_3(C_6H_7)^+$	−8.00	thiophene	−0.4	−8.4	−7.8^d
		N,N-dimethylaniline	5.6	−2.4	−2.0^d
$Fe(CO)_3(2\text{-MeOC}_6H_6)^+$	−9.17	*N*-methylindole	6.9	−2.3	−1.0^e
		N,N-dimethylaniline	5.6	−3.6	−1.9^e
$4\text{-NO}_2C_6H_4N_2^+$	−5.1	*N*-methylindole	6.9	1.8	0.8^f
$4\text{-CNC}_6H_4N_2^+$	−5.5			1.4	0.6^f
$4\text{-ClC}_6H_4N_2^+$	−6.7			0.2	−0.9^f
$C_6H_5N_2^+$	−7.2			−0.3	−1.6^f
$4\text{-CH}_3C_6H_4N_2^+$	−7.7			−0.8	−2.2^f
$4\text{-CH}_3OC_6H_4N_2^+$	−8.4			−1.5	−2.6^f
$C_6H_5N_2^+$	−7.2	*N*-methylpyrrole (**1a**)	6.18^g	−1.0	1.2^h
$4\text{-CH}_3C_6H_4N_2^+$	−7.7			−1.5	0.6^h
$4\text{-CH}_3OC_6H_4N_2^+$	−8.4			−2.2	−0.07^h

^{a} *E* parameters for $Fe(CO)_3$-stabilized cations, see ref 6; *E* parameters for diazonium ions, see ref 29. ^{b} Table 4. ^{c} Calculated by eqs 2 and 3 with $s = 1$. ^{d} Reference 10. Kinetics studied in nitromethane at 25 °C. Extrapolation to 20 °C was made with the assumption $\Delta S^{\ddagger} = -100$ J mol^{-1} K^{-1}. ^{e} Reference 10. Kinetics studied in nitromethane at 20 °C. ^{f} Reference 16. Kinetics studied in acetonitrile at 25 °C. ^{g} Table 3. ^{h} Reference 17. Kinetics studied in water at 20 °C.

For the reactions of electrophiles with some of the arenes listed in Table 4, rate constants have been reported in the literature. Comparison of these data with the rate constants calculated by eqs 2 and 3 provides a test of the reliability of our approach.
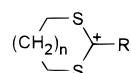
Table 5 lists previously published electrophilicity parameters of tricarbonyliron coordinated cyclohexadienylium ions and diazonium ions as well as nucleophilicity parameters of arenes derived from their σ^+-parameters by eq 3. With the assumption $s = 1$, one can calculate the corresponding rate constants by eq 2. Comparison of the two columns on the right of Table 5 shows that calculated and observed rate constants show a mean deviation of 1.33 logarithmic units (=factor of 20) with a maximum deviation of 2.3 logarithmic units (=factor of 200). Such deviations are typical for our semiquantitative approach, which for the sake of simplicity and generality neglects steric as well as solvent effects.

Conclusion

The preceding discussion has shown that the *N* parameters derived in this work provide approximate absolute rate constants for electrophilic aromatic substitutions. The synthetic chemist can, therefore, use these data for predicting the possibility of certain synthetic transformations. In analogy to Figure 2, Figure 4 lists nucleophiles and electrophiles ordered by their reactivity parameters *N* and *E*. Electrophiles and nucleophiles located at the same level fulfill the condition $N + E = -5$. According to eq 2, the second-order rate constant of their combination at 20 °C will be $\log k = -5s$ which corresponds to rate constants between 10^{-6} and 10^{-3} L mol^{-1} s^{-1}, since the overwhelming majority of nucleophiles is characterized by slope parameters of $0.6 < s < 1.2$.^{6} Assuming an average concentration of 1 mol L^{-1} for the reactant used in excess, this corresponds to half-reaction times of 12 min to 8 days, i.e., to slow reactions at room temperature. It can, therefore, be expected that electrophiles will react with all nucleophiles located below themselves in Figure 4. The applicability of this method for describing reactions of cationic electrophiles with aliphatic π-systems has already been demonstrated.^{6,18} We will now analyze some electrophilic substitutions of arenes and heteroarenes on the basis of Figure 4.

Reactions with Dithiocarbenium Ions. In previous work, we have determined the electrophilicity parameters

E of the heterocyclic cations **6**, which have been employed

	n	R		E
	0	Ph	**6a**	-6.25
	1	Ph	**6b**	-6.82
	1	H	**6c**	-2.17

as acylium equivalents.^{19} These electrophiles have been reported to react with *N,N*-dialkylanilines and with indoles,^{20} in accord with the relative positions of these electrophiles and nucleophiles in Figure 4. The corresponding reaction of **6c** with benzo[*b*]thiophene ($N = -2.5$) represents a borderline case and could not be achieved.^{20d}

Mannich reactions with pyrroles and indoles have long been known to proceed smoothly,^{21} in accord with the location of these arenes far below the *N,N*-dimethyliminium ion (Figure 4).^{22} Since furan is positioned on the same level as $Me_2N^+{=}CH_2$, a slow aminomethylation can be expected. This prediction is nicely corroborated by the experimental findings. While furan reacts with the *N,N*-dimethyliminium chloride within 5 d in acetonitrile at room temperature,^{23a} no reaction takes place under classical Mannich conditions in aqueous solution.^{23b} The lower concentration of the in situ generated iminium ions as well as their stabilization by CH-hydrogen bridging^{24} may account for the failure of the aminomethylation.

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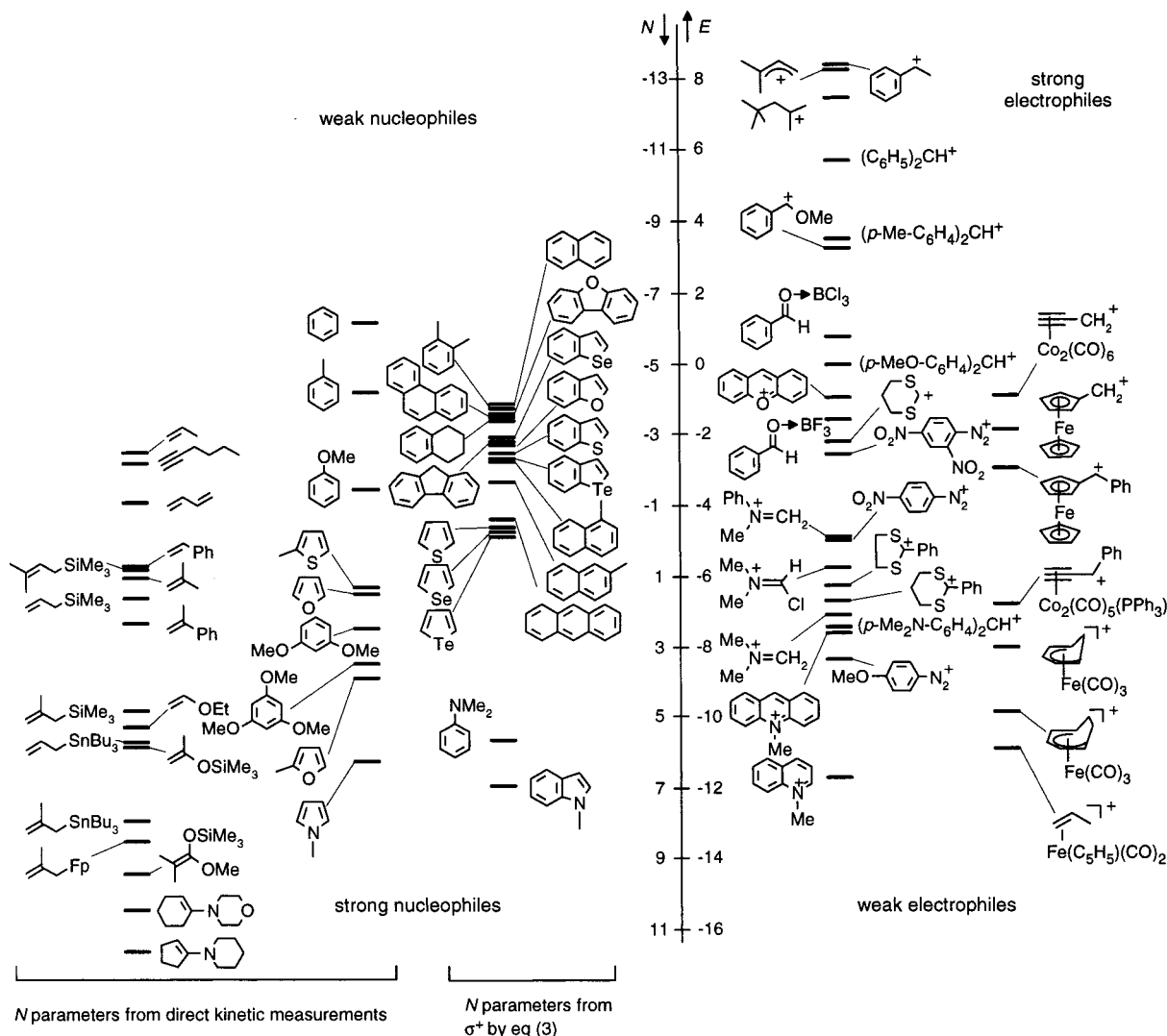
Figure 4. Electrophilicity and nucleophilicity scales.

The borderline situation of the aminomethylations of thiophenes, which can be seen from Figure 4, has also been reported by Dowle et al.: While thiophene did not react under classical Mannich conditions, prolonged heating of 2-methylthiophene and thiophene with N,N-dimethyliminium chloride in refluxing acetonitrile (up to 24 h) gave 77 and 55% of the corresponding Mannich bases, respectively.[25]

Vilsmeier–Haack reactions of arenes with dimethylformamide and POCl$_3$ are useful formylation reactions which are also of industrial importance.[26] As indicated by the position of the N,N-dimethylchloroiminium ion (E = −5.8) in Figure 4,[22] this intermediate reacts with 2-methylthiophene or furan at room temperature but with thiophene only at elevated temperatures.[27] While naphthalene (N = −3.8) and benzo[b]thiophene (N = −2.5) have been reported not to react under Vilsmeier–Haack conditions,[27] heating of anisole (N = −1.56) with

N,N-dimethylchloroiminium chloride at 100 °C for 24 h gave less than 5% of p-anisaldehyde (see relative positions in Figure 4).[28] The yield could be improved by using the more electrophilic agent **7** which is produced from dimethylformamide and pyrophosphoryl chloride (P$_2$O$_3$Cl$_4$).[28]

7
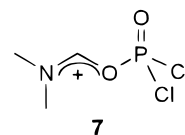
Azo Couplings. Recently we have determined the electrophilicities of a variety of arenediazonium ions,[29] some of which are listed in Figure 4. In the preceding section we have already compared the directly measured rate constants for azo couplings with N-methylindole and N-methylpyrrole with the k values derived from eqs 2 and 3 (Table 5). The well-known fact that benzenediazonium ions couple with N,N-dimethylaniline[30] but not with naphthalene[31] can also be derived from Figure 4.

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The semiquantitative approach in Figure 4 also rationalizes that benzene does not even couple with the 2,4-dinitrobenzenediazonium ion, the most electrophilic diazonium ion investigated by us ($E = -2.5$). Figure 4 suggests reactions of this diazonium ion with thiophene and 2-methylthiophene. These azo couplings, for which rate constants of 1.3×10^{-3} L mol^{-1} s^{-1} and 7.8×10^{-2} L mol^{-1} s^{-1} are predicted by eq 2, are not observed, however. Radical processes with loss of nitrogen take place, and arylation of the thiophenes instead of azo-coupling is observed.[32] On the other hand, 2-*tert*-butyl-thiophene, which should have a similar nucleophilicity as 2-methylthiophene, was found to undergo azo-couplings, as expected on the basis of Figure 4.[33]

These observations illustrate an important feature of our analysis: eq 2 and Figure 4 provide an estimate for the rate constants of electrophile−nucleophile combinations which proceed with rate-determining formation of one new σ-bond in the initial step. One cannot exclude, however, that nature finds alternative, more attractive pathways which proceed faster than those considered by our analysis. To explain these observations, we assume that an electron-transfer process from thiophene and 2-methylthiophene to the 2,4-dinitrobenzenediazonium ion is faster than the azo coupling, the rate of which can be calculated by eq 2.

A similar situation is encountered in the reaction of the 2,4-dinitrobenzenediazonium ion with furan: Depending on the reaction conditions, either a product derived from electrophilic attack of the diazonium ion at furan or an arylation product was observed,[34] indicating that the rate of electron transfer is comparable to that of the polar process.

It can, therefore, be concluded that a large variety of electrophilic aromatic substitutions can satisfactorily be summarized by the reactivity scales depicted in Figure 4 but that predicted electrophile nucleophile combinations (i.e. nucleophile below electrophile in Figure 4) may be outstripped by faster alternative processes.

Experimental Section

General. The heteroarenes **1a**−**d** are commercially available and were distilled prior to use (GC > 99%). The carbenium precursors **2a**$^+$BF$_4$$^-$, **2a**$^+OTf^-$, **2b**-OAc, **2c**-OMe, and **2d**-Cl

were synthesized by following known literature procedures.[35] Trimethylsilyl triflate (TMSOTf) is commercially available. The ZnCl$_2$·OEt$_2$ complex was prepared according to ref 7c.

All reactions were run under an atmosphere of dry nitrogen in dichloromethane, which was freshly distilled from CaH$_2$ prior to use. ^{1}H NMR spectra (300 or 400 MHz) were referenced to CDCl$_3$ ($\delta = 7.26$). ^{13}C NMR spectra (75.5 or 100 MHz) were calibrated with CDCl$_3$ ($\delta = 77.0$). DEPT, HETCOR, H,H-COSY, and COLOCS experiments were used to assign the signals (see Supporting Information).

General Procedure for the Reactions of 2-X with 1. In a flame-dried 50-mL Schlenk flask **2-X** (1 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL). By means of a syringe, 2 mmol of the Lewis acid specified in Table 1 was added to yield a deeply colored solution of the carbenium salt. Addition of **1** (3−15 equiv; see Table 1) led to slow decolorization of the solution. After completion of the reaction, the mixture was vigorously stirred with 15 mL of half-concentrated ammonia. The two layers were separated, and the aqueous layers were extracted with CH$_2$-Cl$_2$ (3 × 30 mL). The combined organic layers were washed with three 30-mL portions of saturated aqueous solution of ammonium chloride and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the products were purified by column chromatography (silica gel 60) or recrystallization. Details of the purification and complete characterization of the products **3a**−**k** and **4a**−**e** are given in the Supporting Information.

Kinetics. All kinetic investigations were run under an atmosphere of dry nitrogen. The kinetic procedures have been published elsewhere.[7a] Details of the kinetic experiments can be found in the Supporting Information.

Note Added in Proof. It has just been shown (Richard, J. P.; Szymanski, P.; Williams, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 10372−10378) that the nucleophilicity parameters N presented in this article can be used to rationalize selectivities of solvolytically generated carbocations.

Supporting Information Available: Tables with concentrations and rate constants of the individual kinetic experiments and text providing characterization (including ^{1}H and ^{13}C NMR data) data for compounds **3a**−**l** and **4a**−**e** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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