

π -Nucleophilicity in Carbon–Carbon Bond-Forming Reactions

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ABSTRACT

Which electrophiles react with which nucleophiles? The correlation $\log k_{20\text{ }^\circ\text{C}} = s(E + N)$, in which electrophiles (carbocations, metal- π -complexes, diazonium ions) are characterized by one (E) and nucleophiles are characterized by two parameters (N , s), proved to be applicable for a wide variety of electrophile–nucleophile combinations. Since the introduction of this correlation in 1994 (*Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957), numerous new reagents have been characterized, and in 2001 (*J. Am. Chem. Soc.* **2001**, *123*, 9500–9512), a new method of parametrization was proposed that facilitates a continuous extension of the data sets without the need for reparametrization of existing data. This Account adjusts the N and s parameters of all presently characterized π -nucleophiles (arenes, alkenes, organometallics) to the new parametrization and illustrates how to employ the resulting reactivity scales for analyzing synthetic and mechanistic problems in organic and macromolecular chemistry. Predictions of absolute rate constants, inter- and intramolecular selectivities, and analyses of reaction mechanisms are discussed. We outline how new compounds can be added to the scales and present our view on the scope and limitations of this approach to polar organic reactivity.

Introduction

The electrophilic attack of carbocations or related electrophiles at aromatic and nonaromatic π -systems represents the key step of many synthetically important reactions. Friedel–Crafts alkylations and acylations,¹ Prins reactions,² Hosomi–Sakurai allylations,³ Mukaiyama aldol cross-couplings,⁴ Nicholas propargylations,⁵ Mannich aminoalkylations,⁶ and Tsuji–Trost allylations⁷ are just a few examples (Scheme 1).

Is it possible to describe the rates of all of these reactions and of many more carbon–carbon bond-forming reactions with a single set of parameters? Can one define electrophilicity and nucleophilicity parameters from

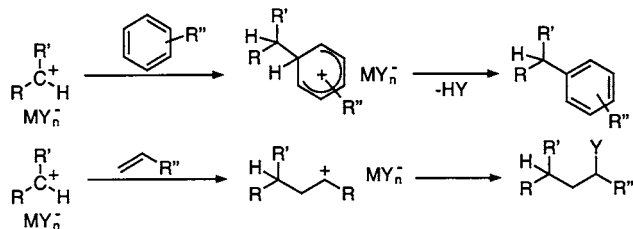
Herbert Mayr studied chemistry at the LMU München and gained his doctorate in 1974 under Rolf Huisgen. He did postdoctoral studies with George A. Olah in Cleveland, Ohio, and joined Paul v. R. Schleyer in Erlangen, where he habilitated in 1980. After professorships in Lübeck and Darmstadt, he returned to München in 1996. His interests are the development of quantitative approaches to organic reactivity, their applications to organic and macromolecular synthesis, and the theoretical basis of the underlying principles.

Bernhard Kempf is pursuing his Ph.D. with Herbert Mayr in München. His interests are kinetic and equilibrium studies on reactive nucleophiles.

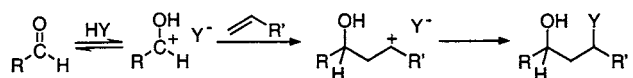
Armin R. Ofial studied chemistry at the TU Darmstadt with Alarich Weiss and Herbert Mayr (doctoral degree, 1996). Since 1997, he has been a Research Associate at the LMU München. His interests are reactions of iminium ions and chemical kinetics.

Scheme 1

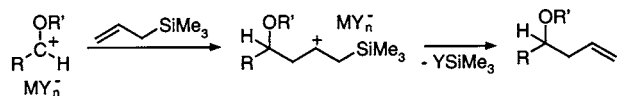
Friedel–Crafts type reactions



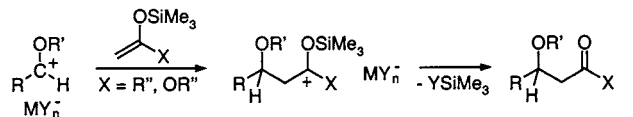
Prins reaction



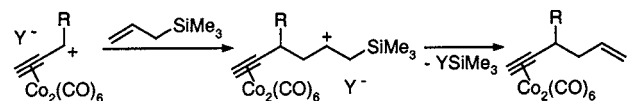
Hosomi–Sakurai allylation



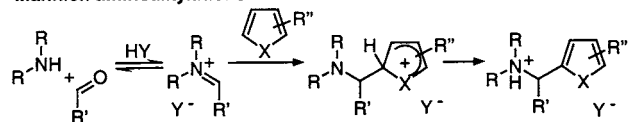
Mukaiyama aldol cross coupling



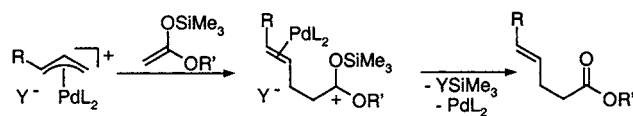
Nicholas propargylation



Mannich aminoalkylations



Tsuji–Trost allylation



which one can derive that iminium ions react with furan but not with benzene and that allylsilanes react with hexacarbonyldicobalt-coordinated propargylium ions but not with allylpalladium complexes?

In 1994, we demonstrated that one parameter for electrophiles (E) and two parameters for nucleophiles (N and s) are sufficient to quantitatively describe the rates of a large variety of electrophile–nucleophile combinations:⁸

$$\log k = s(N + E) \quad (1)$$

where s is a nucleophile-specific parameter, N is a nucleophilicity parameter, and E is an electrophilicity parameter.

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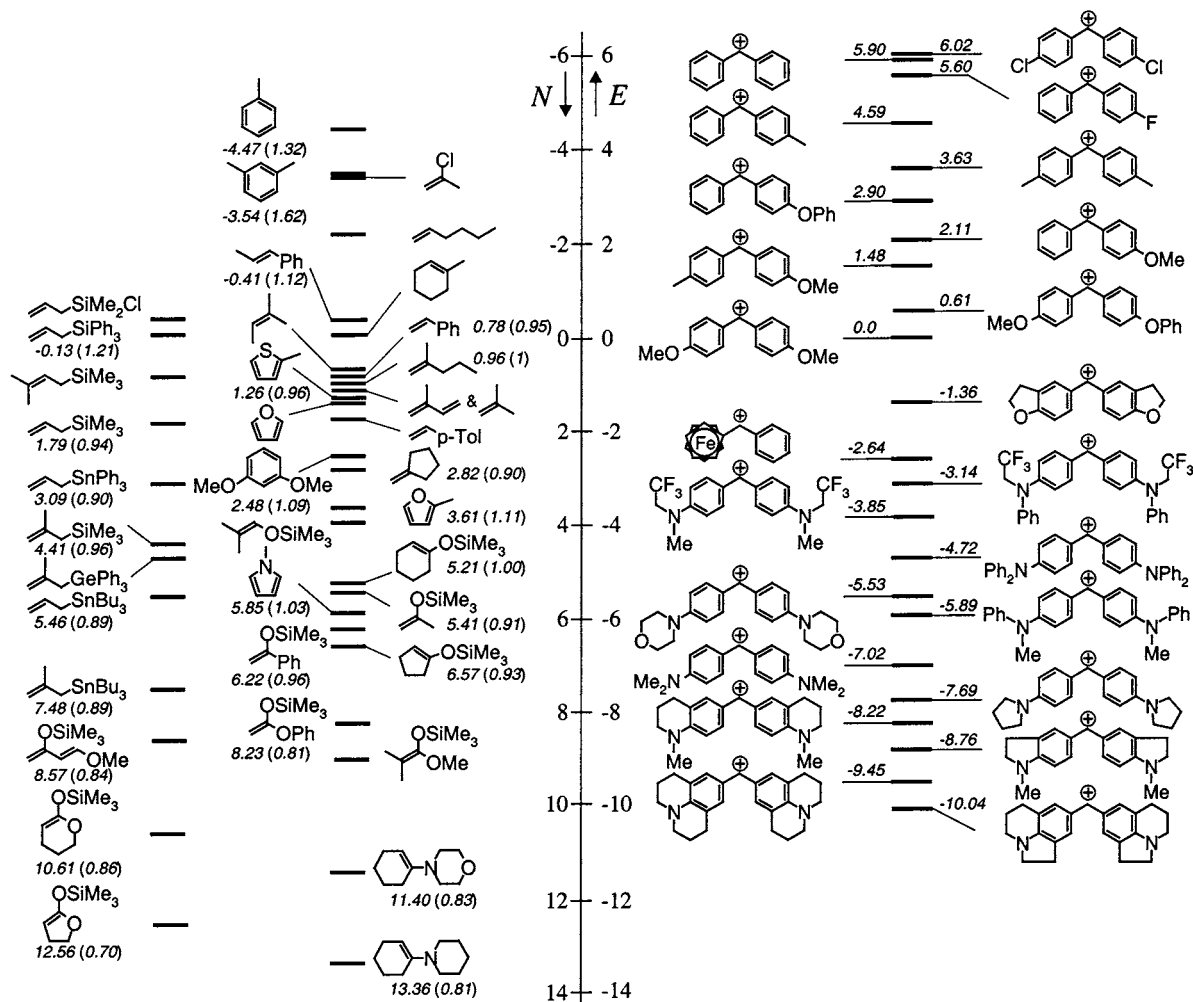


FIGURE 1. Compilation of all basis set compounds used for the determination of E , N , and s . Reactivity parameters of the recommended reference compounds are explicitly listed (s in parentheses).⁹

Numerous new reagents have been characterized since then, and in order to cope with the steadily increasing amount of quantitative data, we recently introduced a more systematic way of parametrization by defining reference compounds.⁹ Though the originally published parameters^{8a} were only slightly altered by the alternative approach,⁹ a revision and update of the whole set of reactivity parameters appeared necessary. In this Account, we present the comprehensive list of reactivity parameters for π_{cc} -nucleophiles so far determined and complement it with a table of revised electrophilicity parameters for carbocations and related electrophiles.

How the Reactivity Scales Are Constructed

Reference Compounds. Twenty-three diarylcarbenium ions, with identical environment of the electrophilic reaction center (Figure 1, right), have been defined as the electrophile basis set. Variation of the para and meta substituents alters their electrophilicities by 16 orders of magnitude: a nucleophile that reacts with the parent benzhydrylium ion at the top of Figure 1 within 1 min would require 20 billion years to react with the bis-(lilolidin-8-yl)carbenium ion at the bottom. A comparable reactivity range is covered by the basis set nucleophiles

listed on the left side of Figure 1, which are arranged according to increasing nucleophilicity from top to bottom. One thus arrives at a representation where the nucleophiles at the top do not react with the electrophiles at the bottom, while the nucleophiles at the bottom react with the electrophiles at the top with diffusion control. Nucleophiles and electrophiles located on similar levels in Figure 1 combine with activation control at measurable rates.

All available second-order rate constants with $k < 10^8 \text{ M}^{-1} \text{ s}^{-1}$ (20 °C) for the reactions of the nucleophiles in the left part of Figure 1 with the electrophiles on the right were subjected to a correlation analysis on the basis of eq 1 by defining $E[(p\text{-MeOC}_6\text{H}_4)_2\text{CH}^+] = 0$ and $s(2\text{-methyl-1-pentene}) = 1$. Though most of these rate constants refer to dichloromethane solution, the small solvent dependence of these rate constants^{10,11} prompted us to include also data that were only available for other solvents (e.g., acetonitrile) without correction. Using the least-squares method, E parameters for the 23 benzhydryl cations and N and s parameters for 39 π -nucleophiles were thus derived from 209 rate constants. Figure 2, in which each correlation line corresponds to the reactions of a certain nucleophile with a series of diarylcarbenium ions, il-

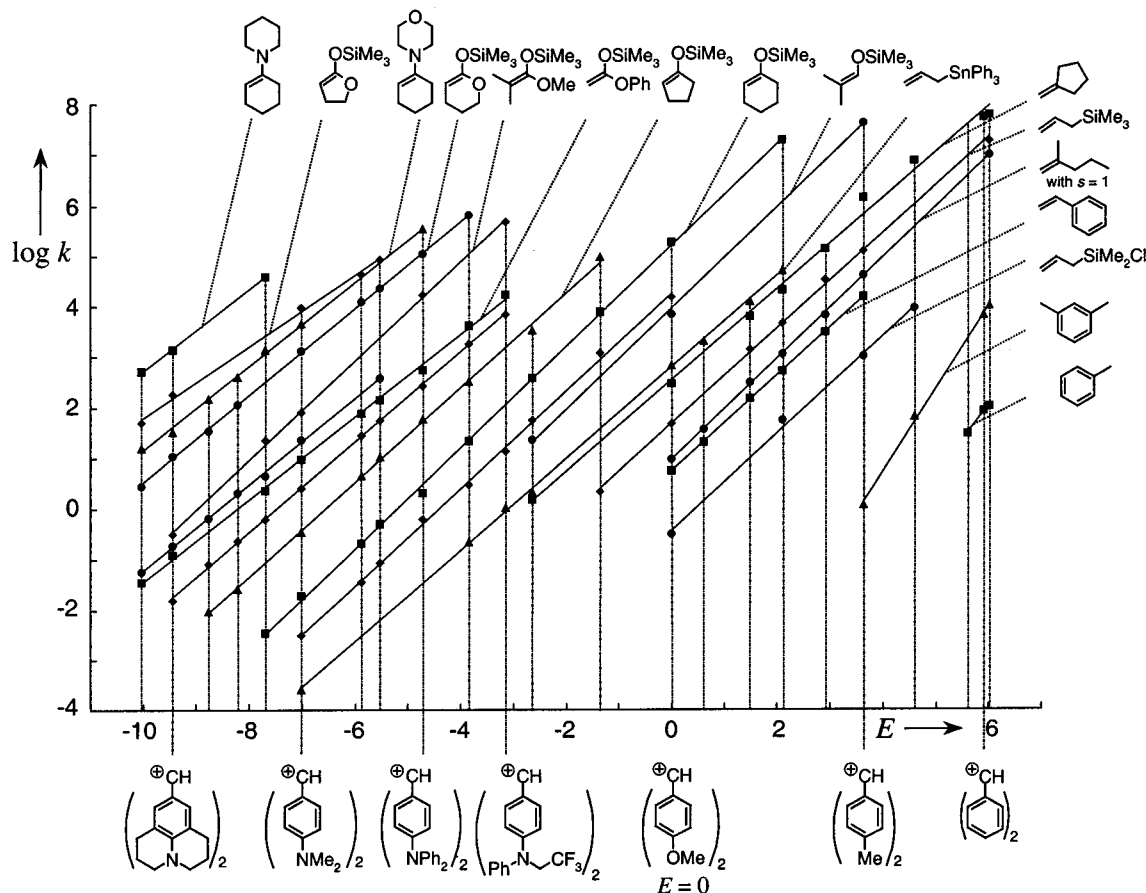


FIGURE 2. Plot of $\log k(20\text{ }^\circ\text{C})$ for the reactions of benzhydryl cations with several π -nucleophiles versus the E parameters of the benzhydryl cations.⁹ Seven of 23 reference electrophiles are depicted below the abscissa.

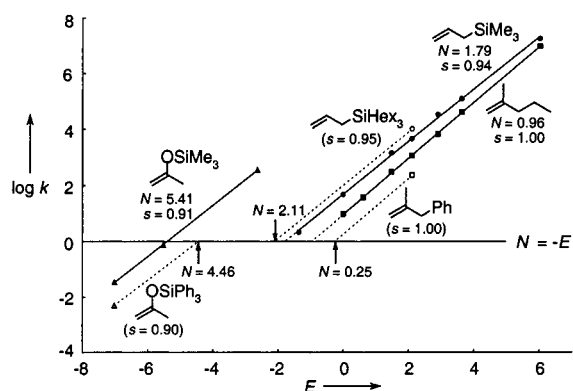
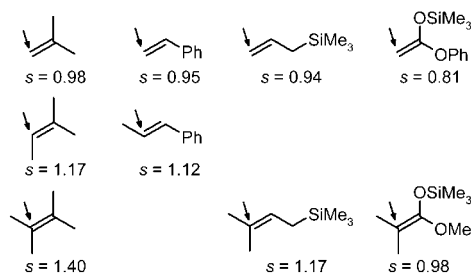


FIGURE 3. Determination of nucleophilicity parameters N from single rate constants.

illustrates the high quality of the correlations: though electrophile as well as nucleophile reactivities cover 16 orders of magnitude, the standard deviation between experimental and calculated rate constants is only a factor of 1.19. Only half of the correlations that have been employed for the determination of the reactivity parameters listed in Figure 1 are depicted in Figure 2.

All basis set carbocations shown in Figure 1 are recommended as references for characterizing further nucleophiles, but the variable availability and unlike ease of handling prompted us to select 26 of the 39 basis set nucleophiles in Figure 1 as reference compounds that we recommend as reaction partners for the characterization

Scheme 2. Influence of Methyl Substitution on the Slope Parameters s of π -Nucleophiles



of further electrophiles. The reference nucleophiles are marked by numerical values of N and s in Figure 1.

Nucleophilicity Scales. It is impracticable to derive N parameters for any nucleophile of interest from kinetic investigations with a series of benzhydrylium ions following the procedure described for the construction of Figure 2. However, Figures 1 and 2 indicate that structurally related nucleophiles, particularly when they have analogous substituents at the position of electrophilic attack, are characterized by closely similar s parameters. One can, therefore, derive an approximate value of N for a certain nucleophile from a single rate constant by assuming the slope parameter s as determined for structurally related nucleophiles. Figure 3 illustrates how N parameters of 2-methyl-3-phenylpropene, allyltriethylsilane, and 2-(triphenylsiloxy)propene can be calculated from single rate

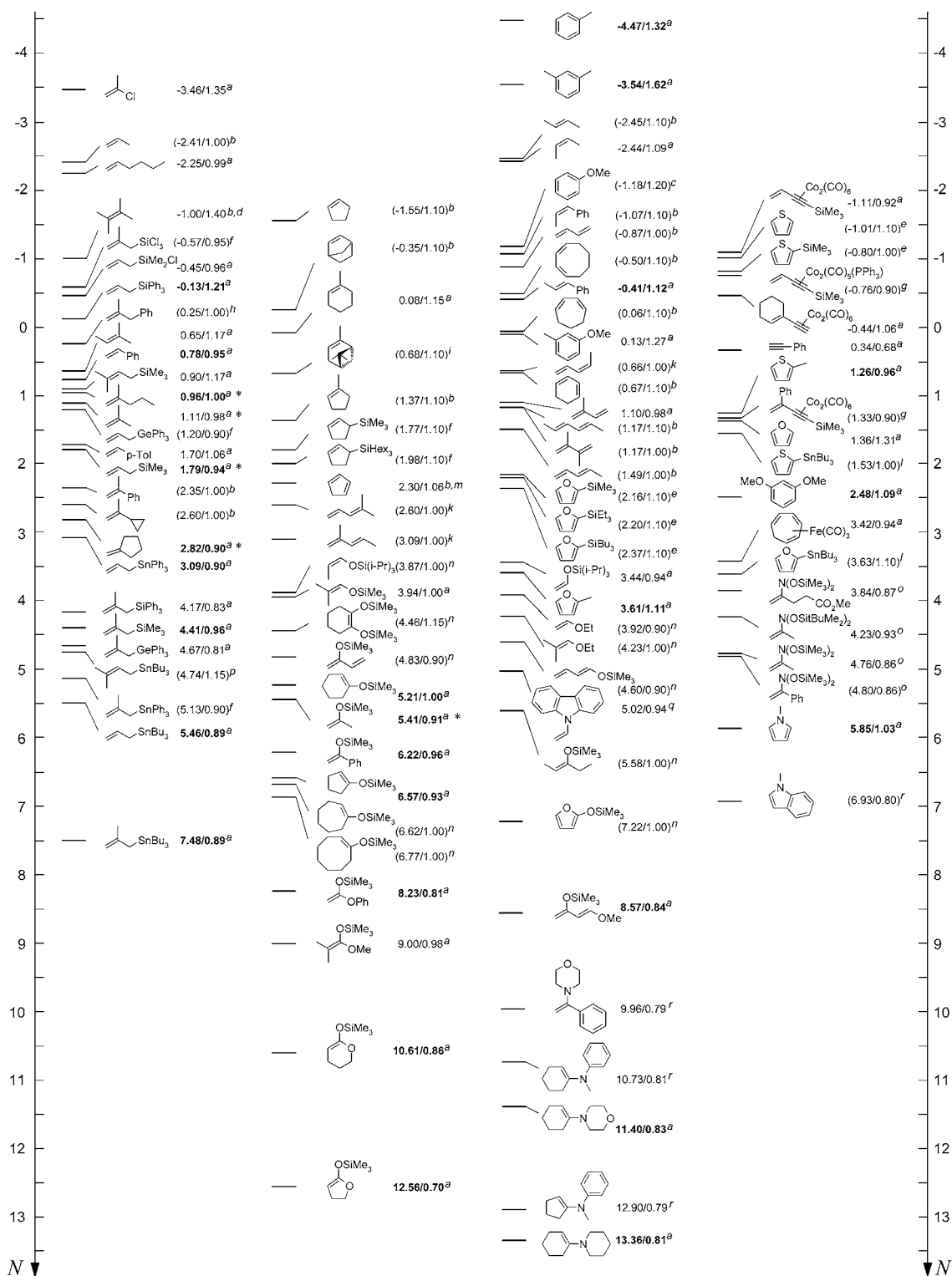


FIGURE 4. Nucleophilicity and slope parameters N/s for π -nucleophiles. Reference compounds are in bold; parentheses indicate estimated values of s . For nucleophiles marked with an asterisk, additional reactivity parameters of structurally analogous compounds are listed in Table 1. ^a From ref 9. ^{b–r} For details of the kinetic measurements, see ^bref 13, ^cref 14, ^dref 15, ^eref 16, ^fref 11, ^gref 17, ^href 18, ⁱref 19, ^kref 20, ^lref 21, ^mref 22, ⁿref 23, ^oref 24, ^pref 25, ^qref 26, and ^rref 27.

constants by employing s parameters similar to those for 2-methyl-1-pentene, allyltrimethylsilane, and 2-(trimethylsilyloxy)propene, respectively.

Though the origin of (the nucleophile-specific parameter) s is not fully understood at present,¹² it is obvious that the introduction of methyl groups at the position of

electrophilic attack leads to an increase of s , as shown by the comparisons in Scheme 2. This fact has to be considered when estimating s .

The closer $\log k$ is to 0, the smaller is the uncertainty in N introduced by estimating s . However, in view of the small range of s values found for a large variety of

Table 1. Nucleophilic Reactivities of Further 2-Methyl-1-alkenes, Allyl Silanes, Methylenecycloalkanes, and Silyl Enol Ethers

π -nucleophile	<i>N/s</i>	π -nucleophile	<i>N/s</i>	π -nucleophile	<i>N/s</i>	π -nucleophile	<i>N/s</i>
	(0.06/1.00) ^a		(-0.47/0.90) ^{b,c}		(1.27/0.95) ^d		3.78/0.79 ^e
	(0.54/1.00) ^a		(1.65/0.90) ^b		1.79/0.94^e		(4.46/0.90) ^f
	0.96/1.00^e		2.82/0.90^e		(1.80/0.95) ^d		5.38/0.85 ^e
	(0.97/1.00) ^a		(1.66/0.90) ^b		(1.93/0.95) ^d		(5.41/0.90) ^f
	(1.00/1.00) ^a		(2.24/0.90) ^b		(2.04/0.95) ^d		5.41/0.91^e
	1.11/0.98^e		(3.16/0.90) ^b		(2.09/0.95) ^d		(5.58/0.90) ^f
	(0.54/1.00) ^g		(2.57/0.90) ^b		(2.11/0.95) ^d		
	(1.14/1.00) ^g		(2.82/0.90) ^b		(1.69/1.10) ^d		
	(1.69/1.00) ^g		(2.33/0.90) ^b		(1.94/1.10) ^d		
	(1.58/1.00) ^g		(1.52/0.90) ^b		(3.15/1.15) ^d		
			(1.69/0.90) ^b				

^a For details of the kinetic measurements, see ref 13. ^b For details of the kinetic measurements, see ref 28. ^c Extrapolated from a rate constant determined at -70 °C assuming $\Delta S^\ddagger = -120$ J mol⁻¹ K⁻¹. ^d For details of the kinetic measurements, see ref 11. ^e From ref 9. ^f For details of the kinetic measurements, see ref 23. ^g For details of the kinetic measurements, see ref 18.

nucleophiles (Figure 1), it appears to be unlikely that the method of one-point calibrations introduces large uncertainties into *N*.

All π -nucleophiles thus characterized are summarized in Figure 4^{9,11,13–27} and Table 1.^{9,11,13,18,23,28} The different sources of the parameters are indicated by different printing, as outlined in the caption of Figure 4.

Some of the nucleophiles listed in Figure 4 and Table 1 have equivalent positions for electrophilic attack, and one might consider statistical corrections to be appropriate. However, symmetrical alkenes, like 2-butenes or 2,3-dimethyl-2-butene, may be approached by electrophiles in the center of the π -bond, and the decision whether to introduce statistical factors or not would depend on the knowledge of the exact reaction mechanism. To avoid this ambiguity, we generally define *N* parameters for a certain compound and not for a certain position. For the sake of consistency, *N* parameters of arenes also refer to a certain compound, not to a specific position. Since *N* parameters and Hammett's σ^+ parameters are linked by the correlation shown in Figure 5, one can derive approximate *N* parameters of arenes from σ^+ parameters reported in the literature²⁹ (Table 2). The slight deviation of the correlation in Figure 5 from that reported in ref 30 is again a consequence of the new parametrization.⁹

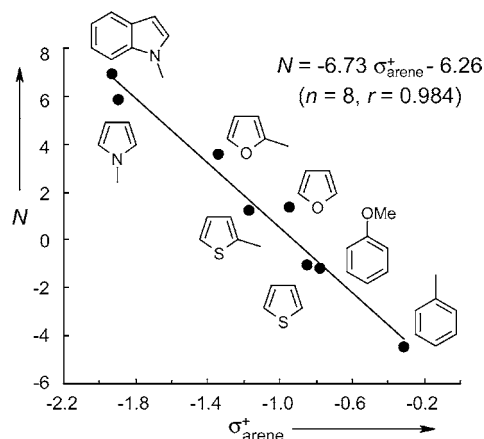


FIGURE 5. Correlation between the nucleophilicity parameters *N* and σ^+ arene.

Electrophilicity Scales. Equation 1 can analogously be used for determining the parameter *E* of a certain electrophile from log *k* for its reaction with a reference nucleophile defined in Figure 1 and the *N* and *s* parameters of this nucleophile. Though knowledge of a single rate constant with respect to a reference nucleophile is, in principle, sufficient for the calculation of an electrophilicity parameter *E* by eq 1, rate constants with respect to several reference nucleophiles are needed to examine

Table 2. Estimated Nucleophilicity Parameters for Various Iso- and Heterocyclic Arenes Derived from σ^+ arene Using the Correlation in Figure 5

arene	σ^+ arene ^a	position	<i>N</i>
ethyl benzoate	0.32	3	-8.4
<i>o</i> -carborane	0.31	1	-8.3
<i>m</i> -carborane	0.23	1	-7.8
bromobenzene	0.15	4	-7.2
iodobenzene	0.14	4	-7.2
chlorobenzene	0.12	4	-7.0
benzene	0.00	1	-6.3
fluorobenzene	-0.08	4	-5.7
isopropylbenzene	-0.33	4	-4.0
naphthalene	-0.35	1	-3.9
dibenzothiophene	-0.37	4	-3.7
<i>o</i> -xylene	-0.37	4	-3.7
phenanthrene	-0.39	3	-3.6
dibenzofuran	-0.40	4	-3.5
benzocycloheptane	-0.40	7	-3.5
benzocyclopentane	-0.41	5	-3.5
tetralin	-0.41	6	-3.5
2-methylphenanthrene	-0.42	9	-3.4
1-methylphenanthrene	-0.44	9	-3.3
biphenylene	-0.47	2	-3.1
benzo[<i>b</i>]selenophene	-0.48	2	-3.0
fluorene	-0.48	2	-3.0
benzo[<i>b</i>]furan	-0.49	2	-2.9
benzo[<i>b</i>]thiophene	-0.54	3	-2.6
2-methylfluorene	-0.55	7	-2.5
1-methylnaphthalene	-0.57	4	-2.4
benzo[<i>b</i>]tellurophene	-0.58	2	-2.3
2-methylnaphthalene	-0.64	1	-1.9
pyrene	-0.68	1	-1.6
2-bromothiophene	-0.72	5	-1.4
acenaphthene	-0.76	4	-1.1
1,6-methano[10]annulene	-0.80	2	-0.8
anthracene	-0.81	9	-0.8
selenophene	-0.88	2	-0.3
tellurophene	-0.90	2	-0.2
ferrocene	-1.30	1	2.5
aniline	-1.47	4	3.7
<i>N,N</i> -dimethylaniline	-1.74	4	5.5

^a From ref 29.

the validity of eq 1 for the reactions under consideration. Electrophilicity parameters *E* derived from reactions with more than one reference nucleophile were obtained by minimizing $\Delta^2 = \sum(\log k_i - s_i(E + N_i))^2$ and are accompanied by standard deviations and the numbers of examples in Figure 6.^{9,26,31–37} *E* parameters for electrophiles, which are based on reactions with a single reference nucleophile (single-point calibrations), are included in Figure 6 only when structurally related electrophiles have been demonstrated to follow eq 1.

How the Scales Can Be Employed

Does a Certain Reaction Take Place? Countless combinations of electrophiles with nucleophiles can be imagined, and the key question when considering a certain synthetic transformation is whether it will take place at all. This question is closely related to the expected reaction rates.

The half-life of a bimolecular reaction with equal initial concentrations of the reactants (*c*₀) is $\tau_{1/2} = 1/(kc_0)$. A mixture that is 1 M in both reactants, therefore, requires a second-order rate constant of $k > 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ to give 50% conversion in less than 3 h. For a slope parameter of $0.7 < s < 1.2$, this condition is fulfilled when $E + N > -5.7$ to -3.3 . Considerations of that type have previously

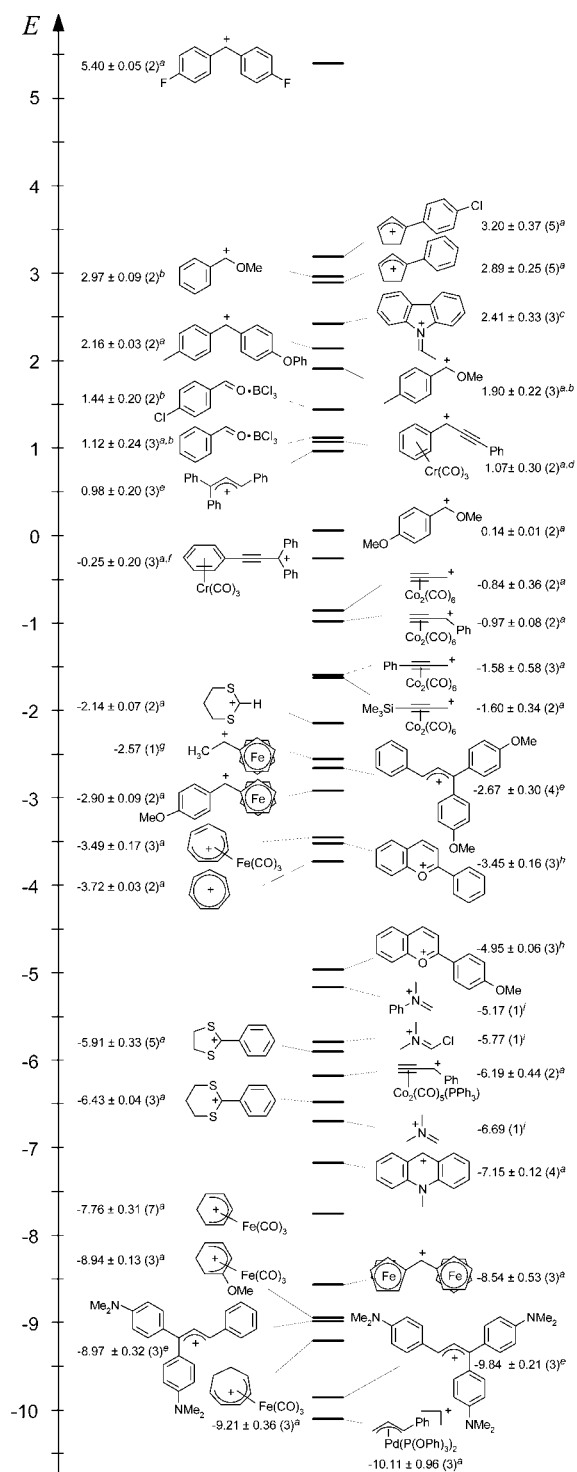


FIGURE 6. Electrophilicity parameters for carbocationic electrophiles, with standard deviations and numbers of experiments in parentheses, as calculated from rate constants given in ^aref 9, ^bref 31, ^cref 26, ^dref 32, ^eref 33, ^fref 34, ^gref 35, ^href 36, and ⁱref 37. For *E* parameters of reference benzhydrylium ions, see Figure 1.

led to the rule of thumb that electrophiles can be expected to react with nucleophiles at room temperature when $E + N > -5$.⁸ Figures 4 and 6 can be used to derive this information, and in borderline cases it is advisable also to consider *s* when estimating reaction times.

We have used this qualitative rule for summarizing the synthetic potential of heterosubstituted carbenium ions

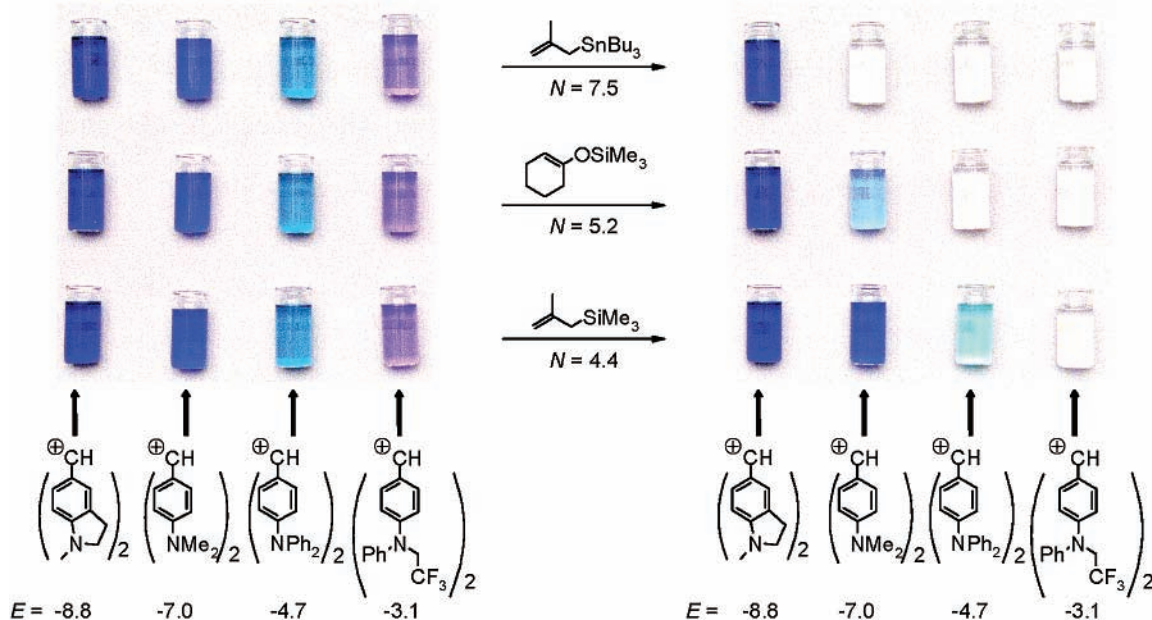


FIGURE 7. Quick test of nucleophilicity.

as well as that of cationic metal- π -complexes. Hexacarbonyldicobalt-coordinated propargyl cations ($E = -1$ to -2) thus have been reported to react with nucleophiles of $N > -3$,³⁸ and the tricarbonyliron-coordinated cyclohexadienylum ion ($E = -7.8$) was reported to react readily with nucleophiles of $N > 3$.^{38,39} In accord with this analysis, the reaction of $(\text{CO})_3\text{Fe}(\text{C}_6\text{H}_7)^+$ with allyltrimethylsilane ($N = 1.79$) required several hours of heating at 60°C ,⁴⁰ and the reactions of this electrophile with furan ($N = 1.36$) or 2-methylthiophene ($N = 1.26$) are very slow at 45°C .⁴¹ Inspection of these scales even allowed us to verify carbon-carbon bond-forming reactions of Nicholas' cations that had previously been reported not to take place.^{5,38}

The reactivity parameters presented in Figures 4 and 6 provide a bridge between the chemistry of different functional groups. According to Figure 4, allyltriphenylstannane ($N = 3.09$), vinyl triisopropylsilyl ether ($N = 3.44$), 2-methylfuran ($N = 3.61$), and tricarbonylironcycloheptatriene ($N = 3.42$), representatives of different classes of compounds, have similar N parameters.⁹ Let us now assume that one observes the reaction of a novel electrophile with one of these compounds. One can then expect that this electrophile will also react with other nucleophiles of similar or of higher nucleophilicity N . Without the need of a single kinetic experiment, one can estimate $E \geq -8$ for this electrophile and thus employ Figures 4 and 6 on an entirely qualitative basis. Since the same E and N parameters hold for different classes of compounds, the borderlines between classical disciplines as aliphatic, aromatic, and coordination chemistry become permeable.

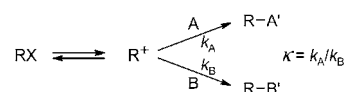
A semiquantitative nucleophilicity test is illustrated in Figure 7. A series of four reference electrophiles with $E = -8.8$, -7.0 , -4.7 , and -3.1 (Figure 7, left) are combined with reaction partners of different nucleophilicity. The photograph taken 1 min after the addition of the nucleophiles (Figure 7, right) reveals the reactivity order allylsi-

lane < silyl enol ether < allylstannane without the need of any quantitative measurements. In this way, nucleophiles of unknown reactivity can efficiently be characterized with a precision that suffices for many purposes. This simple test then allows one to predict numerous synthetic transformations of the corresponding nucleophile.

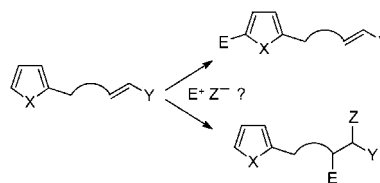
Inter- and Intramolecular Selectivity. Before establishing the methods for direct measurements of the rates of reactions of carbocations with alkenes, we had determined relative reactivities of alkenes by competition experiments.⁴² As expected, the competition constants κ derived from product ratios were generally identical to those calculated as the ratio of two independently determined second-order rate constants, k_A and k_B (Scheme 3). As a consequence, eq 1 can be used for predicting product ratios that result when carbocations are in situ generated in a mixture of two competing nucleophiles. More important in practice: the N and s values of Figure 4 also predict the preferred sites of electrophilic attack at bisnucleophiles possessing two or more π -systems (Scheme 4).

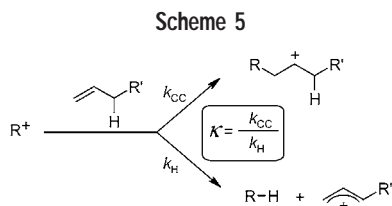
Since N and s values are available for a set of CH-hydride donors,⁴³ one can also analyze the question of whether the reaction of a carbocation with an unsaturated

Scheme 3



Scheme 4

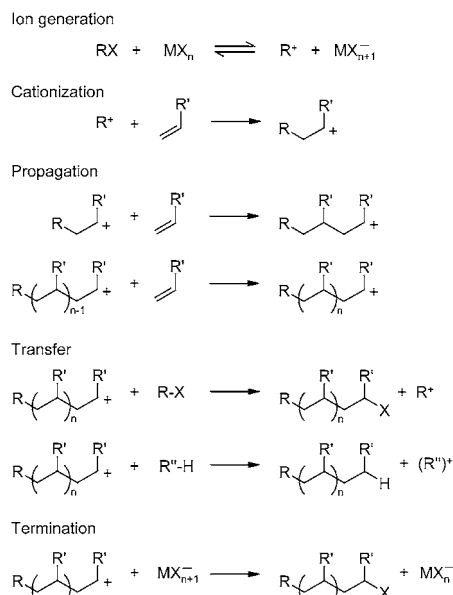




hydrocarbon will lead to carbon–carbon bond formation due to electrophilic attack at the π -bond or will result in allylic oxidation due to hydride abstraction (Scheme 5).

Furthermore, it is possible to derive N and s parameters for n -nucleophiles. With these numbers it becomes possible to conjecture whether a solvolitically generated carbocation can be intercepted by an external π -nucleophile before it is trapped by the solvent. Thus, Richard reported a limit of $N > 6$ for the trapping of the α -(N,N -dimethylthiocarbamoyl)-4-methoxybenzyl cation by π -nucleophiles in 50% aqueous acetonitrile.⁴⁴

It should be stressed, however, that the N parameters in Figure 4 must not be used to predict selectivities of very fast reactions. The linear correlation (1) holds only for reactions with $k < 10^8 \text{ M}^{-1} \text{ s}^{-1}$. At higher rates, the correlation lines shown in Figure 2 bend and asymptotically approach the diffusion limit, which is around $(2\text{--}4) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for reactions of carbocations with non-charged nucleophiles (Figure 8).⁴⁵ For carbocation anion combinations in organic solvents, the diffusion limit is at approximately $10^{10} \text{ M}^{-1} \text{ s}^{-1}$.^{46,47} As a consequence, intermolecular selectivity decreases when $s(E + N) > 8$ for one of the competing reactions and is completely lost when $s(E + N) > 10$ for both competing reactions. Since rate- and product-determining step are not necessarily identical,⁴⁸ it is not yet clear how intramolecular selectivities (e.g., regio- or stereoselectivities) change when diffusion control is reached.

Scheme 6

Carbocationic polymerizations are often initiated by mixtures of alkyl halides and Lewis acids, as shown in Scheme 6.⁴⁹

The reactivity parameters in Figures 1, 4, and 6 as well as in Table 1 can be used to calculate the rate constants for the cationization reactions and thus allow one to select suitable initiators for polymerizations.⁵⁰ In principle, propagation rate constants can also be determined by eq 1. However, it turned out that many carbocationic polymerizations occur with propagation rate constants greater than $10^8 \text{ M}^{-1} \text{ s}^{-1}$, i.e., in the curved ranges of Figure 8, outside the domain of eq 1.⁵¹ In such cases, eq 1 only predicts $k > 10^8 \text{ M}^{-1} \text{ s}^{-1}$ but does not provide more precise values. For the same reason, one cannot derive accurate

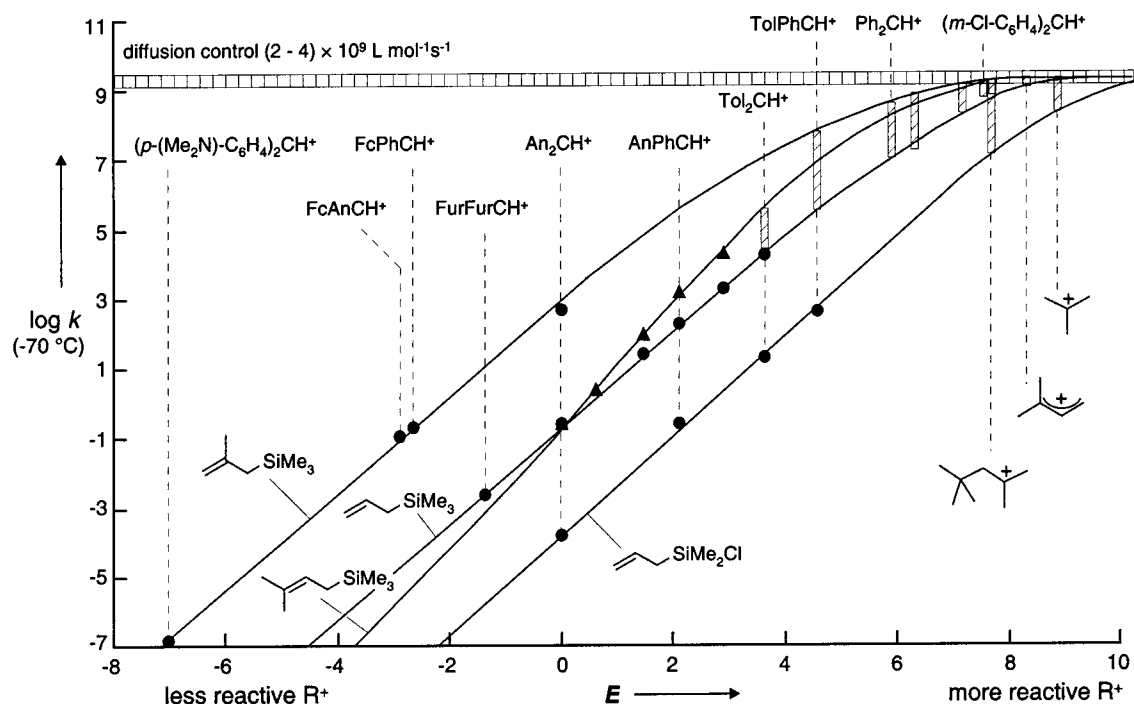


FIGURE 8. Diffusion control limits the domain of eq 1.

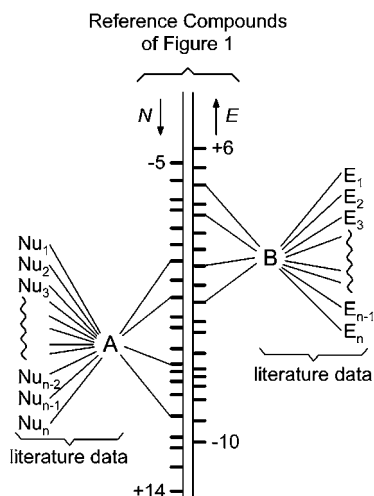


FIGURE 9. Method for linking reactivity data from the literature to the reference scales of Figure 1.

copolymerization parameters from the nucleophilicity parameters in Figure 4. Since only monomers with similar N parameters can be copolymerized by carbocationic processes, Figure 4 is useful, however, for the selection of potential monomer combinations in carbocationic polymerizations. Finally, the probability of hydride abstractions, one of the most important transfer processes, can be derived from the N and s parameters of hydride donors.⁴³

How the Scales Can Be Extended

The choice of reference electrophiles and of reference nucleophiles with fixed reactivity parameters (Figure 1) allows a continuous extension of the scales without the need for unending reparametrizations of previously calculated E , N , and s values. From the reactivity parameters listed in Figure 1, one can characterize N and s for further nucleophiles in the range $-4 < N < 16$, and further electrophiles with $-12 < E < 6$, following the procedures described in the sections, Nucleophilicity Scales and Electrophilicity Scales (above). Since the inclusion of new compounds does not affect other reactivity parameters, it is unproblematic to initially characterize further reagents by preliminary parameters obtained from one-point calibrations or correlation with other physical constants and eventually replace them later by more reliable values. This procedure has already been employed for the construction of Figures 4 and 6 and Tables 1 and 2, where the different origins of the data are specified.

The stepwise extension of the scales opens another possibility. There are abundant data on electrophile nucleophile combinations in the literature.⁵² Most of them report structure–reactivity relationships of a group of nucleophiles toward a standard electrophile **A** or of a group of electrophiles toward a standard nucleophile **B**. In such cases, one can determine the reactivity parameter E for compound **A** or N and s for compound **B** by the methods described above and thus link a large variety of isolated kinetic data to a common scale, as schematically shown in Figure 9.

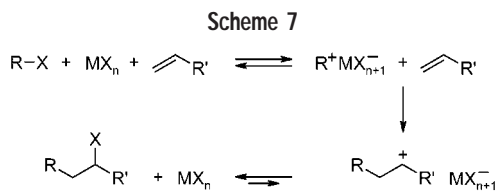
However, the reactivity domains covered by the reference compounds in Figure 1 limit the procedures described so far for the characterization of further compounds in ranges of approximately $-4 < N < 16$ and $-12 < E < 6$. To characterize more reactive as well as less reactive nucleophiles and electrophiles, an extension of the list of reference compounds in Figure 1 is needed.

Kinetic investigations of the reactions of stabilized carbanions with reference benzhydrylium ions ($E < -8$) and quinone methides have already shown that the downward extension of Figure 1 is unproblematic and can be done without changing the parameters given in Figure 1.⁵³ Extensive kinetic data on reactivities of enamines will soon be published that may also qualify as new reference nucleophiles for the characterization of weak electrophiles.²⁷

The extension beyond the upper border of Figure 1 appears to be more problematic, however, since we usually derive reactivity parameters from kinetic experiments with persistent carbocations. Since superacidic solutions are not suitable for such types of experiments, the kinetic methods used so far will permit only minor extensions into the domain of stronger electrophiles and weaker nucleophiles. Investigations of in situ generated carbocations by diffusion clock methods⁵⁴ have already been proven to provide approximate E values for highly electrophilic carbocations.⁵⁵ Pezacki's approach to derive electrophilic reactivities of laser-flash-generated carbocations from their reactions with donor-substituted arenes in fluorinated alcohols appears to be an attractive alternative.⁵⁶

Scope and Limitations

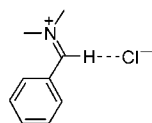
Steric Effects. Organic reactivity is generally described by a combination of electronic and steric effects. Why is this separation not considered in eq 1? In the series of benzhydryl cations that are defined as reference electrophiles in Figure 1, steric effects remain constant, and the change of electrophilicity by 16 orders of magnitude is entirely due to electronic effects. On the other hand, the N and s parameters of the reference nucleophiles in Figure 1 reflect a combination of steric and electronic effects, with the latter predominating. Since the reference benzhydrylium ions are of “intermediate size”, a single set of N and s parameters appeared to be sufficient for satisfactorily calculating reactivities toward most types of carbocations. Certainly, differential steric effects contribute significantly to the standard deviation of factor 2 that has been reported for reactions of various types of carbon electrophiles (excluding benzhydrylium ions) with the reference nucleophiles of Figure 1.⁹ When deviations in the rate constant up to a factor of 100 from the predictions of eq 1 are tolerated, corresponding to a noise level of 11 kJ mol⁻¹, most differential steric effects are included. Only when very bulky reagents are employed, steric effects become larger, and eq 1 will be misleading. Rather than introducing a steric term into eq 1, we prefer to keep the correlation simple and advise not to employ the reactivity scales for reactions of bulky compounds, e.g., tritylium



ions. The reagents listed in Figures 4 and 6 and Table 1 give an idea of the structural variety tolerated by eq 1.

Counterions and Solvents. The proper choice of counterions MX_{n+1}^- is crucial for the course of Lewis acid-induced reactions. [1:1]-Addition products can be produced from alkyl halides with alkenes only when an efficient transfer of X^- from MX_{n+1}^- to the newly formed carbocation occurs (Scheme 7).^{57,58} Otherwise, polymerizations of the alkenes take place.

The rate of attack of carbocations at π -nucleophiles, on the other hand, was demonstrated to be independent of the nature of the complex counterion for several types of nucleophiles,^{10,11,23} and reasons for the different role of counterions in carbocation and carbanion chemistry have been discussed.^{50a,59} For the reaction of the bis(julolidin-9-yl)methylum tetrafluoroborate (Figure 1, $E = -9.45$) with 1-morpholinocyclopentene in CH_2Cl_2 , it has been demonstrated that even in the presence of a high concentration of tetrabutylammonium chloride (30 mM), the addition rate constant was only 30% smaller than in the absence of the electrolyte.⁶⁰ Significant counterion effects have so far only been observed in reactions of iminium ions with nucleophiles,⁶⁰ where hydrogen bonding between $\text{H}-\text{C}_{\text{sp}^2}$ and halide anions has been demonstrated.⁶¹



The same reasons that account for the negligible influence of counterions on the rates of most reactions of carbocations with π -nucleophiles also explain the small importance of solvent effects. While ionization equilibria depend strongly on the nature of the solvent,⁶² variation of the solvents affects the rate constants of the reactions of carbocations with π -nucleophiles only slightly. Thus, the reaction of the bis(*p*-anisyl)carbenium ion with 2-methyl-1-pentene has been found to be 4 times faster in nitromethane than in dichloromethane, and the rate constants in 1,2-dichloroethane and nitroethane are in between.¹⁰ One can assume, therefore, that the solvent effects on most rate constants discussed in this Account disappear in the noise of the correlations. However, solvent donicity has a large influence on the electrophilicities of diazonium ions,^{63,64} and their E parameters have to be specified for a certain solvent.⁶⁵ Likewise, nucleophilicity parameters for amines, alcohols, and related n -nucleophiles strongly depend on the solvent and have to be specified for the corresponding medium.^{66,67}

Reaction Types. The nucleophilicity scales in Figure 4 and in Tables 1 and 2, which have been derived from reactions with benzhydrylium ions, have been demon-

strated also to hold for other types of carbon electrophiles, including various classes of carbocations and metal- π -complexes. Deviations are expected for $\text{S}_{\text{N}}2$ -type reactions, where making one σ -bond is coupled with breaking another σ -bond. Azo couplings with aromatic and olefinic π -systems follow eq 1,⁶⁵ and it has been discussed that the reactivities of differently substituted alkenes toward H_3O^+ and benzhydrylium ions show analogous trends.^{13,59} A more detailed analysis of protonation rates on the basis of the extended set of N parameters given in this Account appears to be timely.

It is obvious that brominations, sulfenylations, and other reactions with bridging electrophiles cannot be described by eq 1.⁶⁸ As discussed above, eq 1 has already been employed to describe hydride abstractions⁴³ as well as reactions of carbocations with n -nucleophiles.^{8a}

All nucleophiles listed in Figure 4 and Tables 1 and 2 have reaction centers similar to those of the reference nucleophiles in Figure 1, and all electrophiles listed in Figure 6 have reaction centers similar to those of the reference benzhydryl cations. For that reason, the reactivity parameters E , N , and s that have been derived from reactivities toward reference compounds can be expected to provide reasonable predictions for all possible combinations arising from these compilations. Deviations have to be expected, however, when heteronucleophiles (alcohols, amines) are combined with heteroelectrophiles (variable σ -bond energies) or heterosubstituted carbocations (anomeric effect). The wide-ranging reactivity scales presented in this work provide a basis to treat such effects quantitatively.

This Account is dedicated to Professor Klaus Hafner, who steadily encouraged these investigations, on the occasion of his 75th birthday. We thank all associates whose contributions laid the basis for these scales, particularly Dr. M. Patz who first recognized the potential of eq 1 for a quantitative description of polar organic reactions. Financial support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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