

Kinetics of electrophile–nucleophile combinations: A general approach to polar organic reactivity^{*,**}

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Abstract: Benzhydrylium ions (Ar_2CH^+) and structurally related quinone methides are employed as reference electrophiles for comparing the nucleophilicities of a large variety of compounds, e.g., alkenes, arenes, alkynes, allylsilanes, allylstannanes, enol ethers, enamines, diazo compounds, carbanions, transition-metal π -complexes, hydride donors, phosphanes, amines, alkoxides, etc., using the correlation equation $\log k (20^\circ\text{C}) = s(N + E)$, where s and N are nucleophile-dependent parameters and E is an electrophilicity parameter. The same equation was employed to derive the electrophilicity parameter E for different types of carbocations, cationic transition-metal π -complexes, typical Michael acceptors, and electron-deficient arenes. The E , N , and s parameters thus obtained can be used for predicting rates and selectivities of polar organic reactions.

Keywords: Kinetics; electrophilicity; nucleophilicity; linear free energy relationships; polar organic reactions.

INTRODUCTION

The problem is evident: Most organic reactions are combinations of electrophiles with nucleophiles. Yet, general scales for electrophilicity and nucleophilicity are not available [1].

Figure 1, which displays nucleophiles of large structural variety, illustrates the situation. Requests to order these compounds with respect to increasing nucleophilicity usually trigger two types of answers. While some chemists start ordering compounds within certain groups, e.g., toluene < anisole < *N,N*-dimethylaniline or 2-chloropropene < isobutylene < enol ethers or $\text{H}_2\text{O} < \text{HO}^-$, others vehemently reject the idea of constructing comprehensive nucleophilicity scales with reference to previous work by Parker, Pearson, and others who showed the dependence of relative nucleophilicities on many factors (e.g., reaction partner, solvent, and temperature), implying that a single general nucleophilicity scale cannot exist [1b,1d,2–4].

If the latter position is accepted, one might attempt to create a comprehensive nucleophilicity scale with respect to a certain electrophile in a given solvent at a certain temperature. The problems encountered during such an attempt are illustrated in Fig. 2.

The red bis(*p*-methoxy)benzhydrylium ion, for example, can be generated as a stable tetrachloroborate or triflate in dichloromethane at 20 °C [5–7], and it is possible to study the rates of its reactions with alkyl-substituted benzenes and ethylenes [5,6], electron-rich heteroarenes [8] and enol

*Paper based on a presentation at the 17th International Conference on Physical Organic Chemistry (ICPOC-17), Shanghai, China, 15–20 August 2004. Other presentations are published in this issue, pp. 1807–1921.

**Dedicated to Prof. Paul Ragué von Schleyer on the occasion of his 75th birthday.

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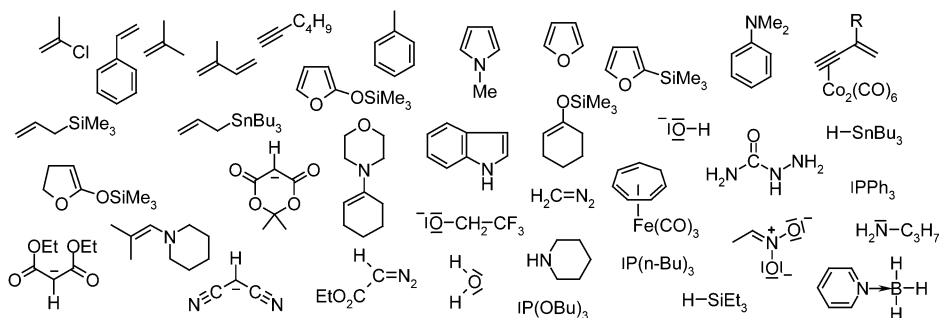


Fig. 1 Examples for the large structural variety of nucleophiles.

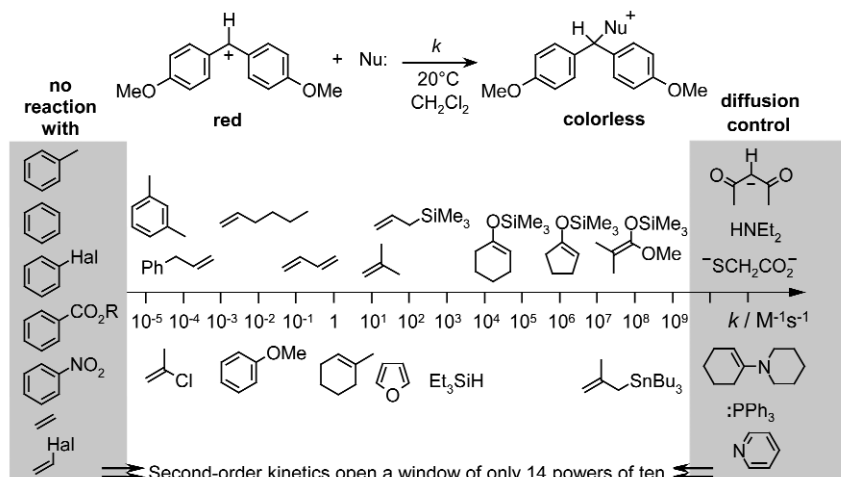


Fig. 2 Construction of a nucleophilicity scale with respect to a certain electrophile in a certain solvent at a given temperature.

ethers [9], trialkylsilanes [10,11], and ketene acetals [9] by conventional UV–vis spectroscopy or stopped-flow methods. Laser-flash techniques have been employed to investigate faster reactions [12–15], and it has been found that highly reactive nucleophiles comparable to amines, enamines, phosphanes, carbanions, and thiolate anions react with similar, diffusion-controlled rates. Since, on the other hand, nonactivated arenes and alkenes do not react at all at measurable rates at 20 °C, it is obvious that it is impossible to construct a comprehensive nucleophilicity scale with respect to a single electrophile.

Construction of reactivity scales for electrophiles and nucleophiles

For that reason, we selected a series of 29 *para*- and *meta*-substituted benzhydrylium ions and structurally related quinone methides as reference electrophiles and studied the kinetics of their reactions with a variety of carbon nucleophiles in dichloromethane (carbocations + neutral nucleophiles) or dimethyl sulfoxide (anions + neutral or positively charged electrophiles) by photometric monitoring of the consumption of the electrophiles [16–19]. By combining strong electrophiles with weak nucleophiles and weak electrophiles with strong nucleophiles, we arrived at second-order rate constants between 10^{-5} and $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ at 20 °C (Figs. 3 and 4) [20]. As pointed out previously, free and paired benzhydrylium ions react with equal rates [21], and carbanions were employed under conditions (K^+ or R_4N^+ salts with $c < 10^{-3} \text{ M}$ in DMSO) where ion-pairing was almost absent [18].

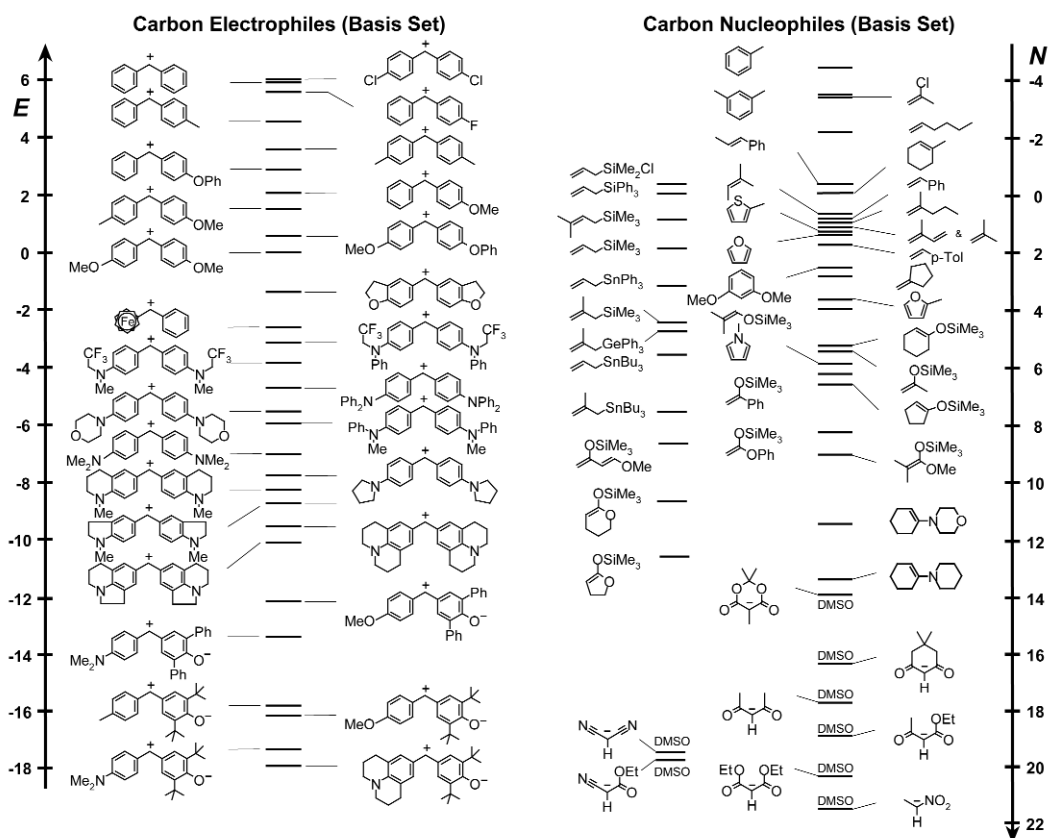


Fig. 3 Carbon electrophiles and carbon nucleophiles used for the construction of the reactivity scales.

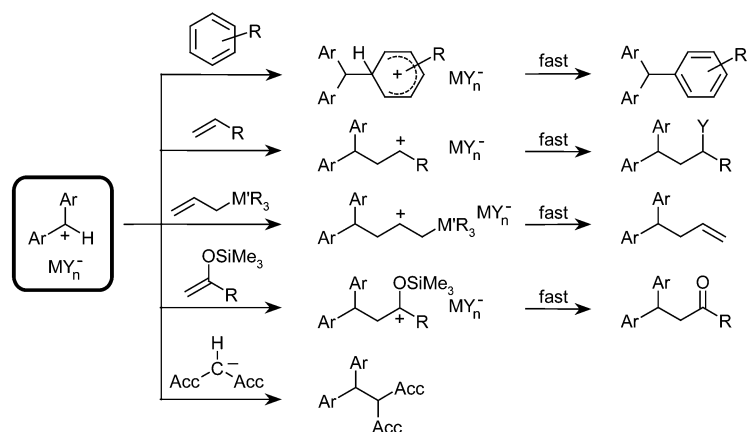


Fig. 4 Reactions of benzhydrylium ions Ar_2CH^+ with various types of carbon nucleophiles.

In this way, 29 nucleophilicity scales were obtained, one for each electrophile, which are depicted in Fig. 5. For the sake of clarity, formulas are only depicted for 8 of the 29 reference electrophiles. Least-squares analysis of the rate constants for the reactions of the 29 reference electrophiles with selected carbon nucleophiles gave the correlation lines shown in Fig. 5, where each electrophile is characterized by one parameter E [E for $(p\text{-MeOC}_6\text{H}_4)_2\text{CH}^+ = 0$] while nucleophiles are characterized by

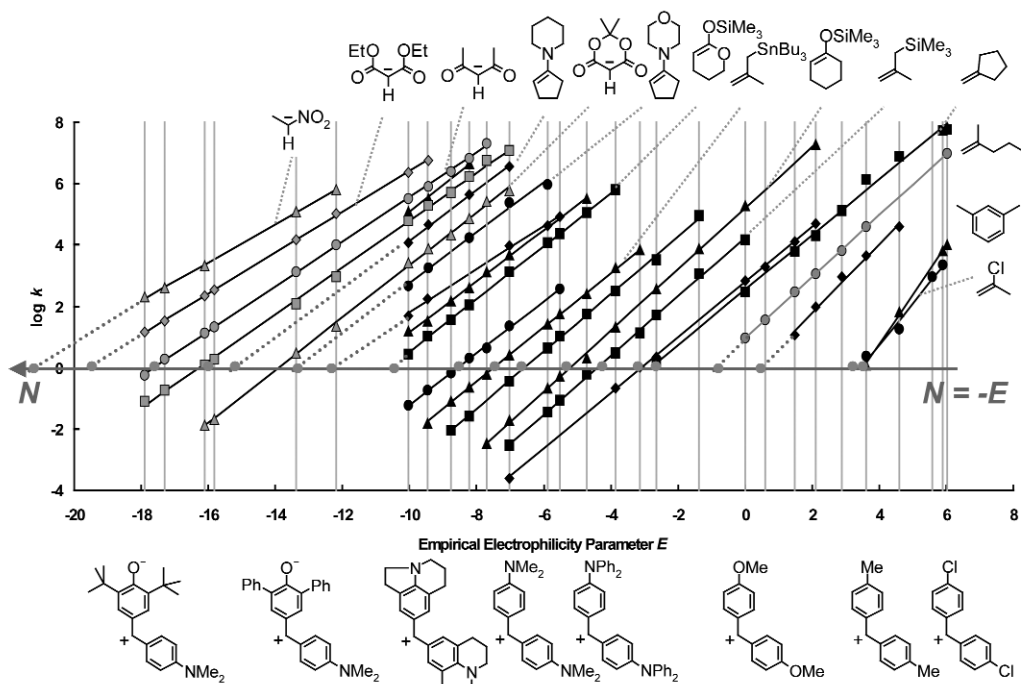


Fig. 5 Second-order rate constants for electrophile nucleophile combinations (20 °C).

two parameters N and s ($s = 1$ for 2-methyl-1-pentene). Equation 1 defines nucleophilicity N as the negative intercept of a correlation line with the abscissa. This definition of nucleophilicity is more suitable for practical applications than mathematically equivalent expressions which employ the intercept on the ordinate ($= sN$) for defining nucleophilicity [22–24].

$$\log k_{20\text{ }^\circ\text{C}} = s(N + E) \quad (1)$$

The N and E parameters employed for ordering the nucleophiles and electrophiles in Fig. 3 have been derived from this analysis [16,17,19]. The benzhydrylium ions and quinone methides, thus characterized by E , are now considered as reference electrophiles and can be employed for characterizing other types of nucleophiles.

Reactivities of various types of nucleophiles

Figure 6 shows, for example, that the second-order rate constants for the reactions of enamines with benzhydrylium ions correlate perfectly with their electrophilicity parameters E [7,17,25]. The intercepts on the abscissa yield the nucleophilicity parameters N which are depicted along with some reference nucleophiles on the left side of Fig. 6. One can see that enamines studied in this work span a reactivity range of 12 units in N corresponding to relative reaction times of 1 min to 30 000 years (for $s \approx 0.85$). The entries for the two indoles in the plot of Fig. 6 show another feature of our approach. As soon as some representatives of a new class of compounds have been demonstrated to follow eq. 1, it is not any longer necessary to study whole reactions series, but one can perform kinetic experiments with only one electrophile, assume a similar slope s , and arrive at a reasonable estimate for N [17].

Figure 7 shows an analogous procedure for identifying the nucleophilic reactivities of diazo compounds [26]. Though different types of products were isolated from different classes of diazo compounds, electrophilic attack of the carbocation at the diazo carbon is generally rate-determining, which leads to similar $\log k$ vs. E correlations as for other C-nucleophiles. While the qualitative nucleophilicity

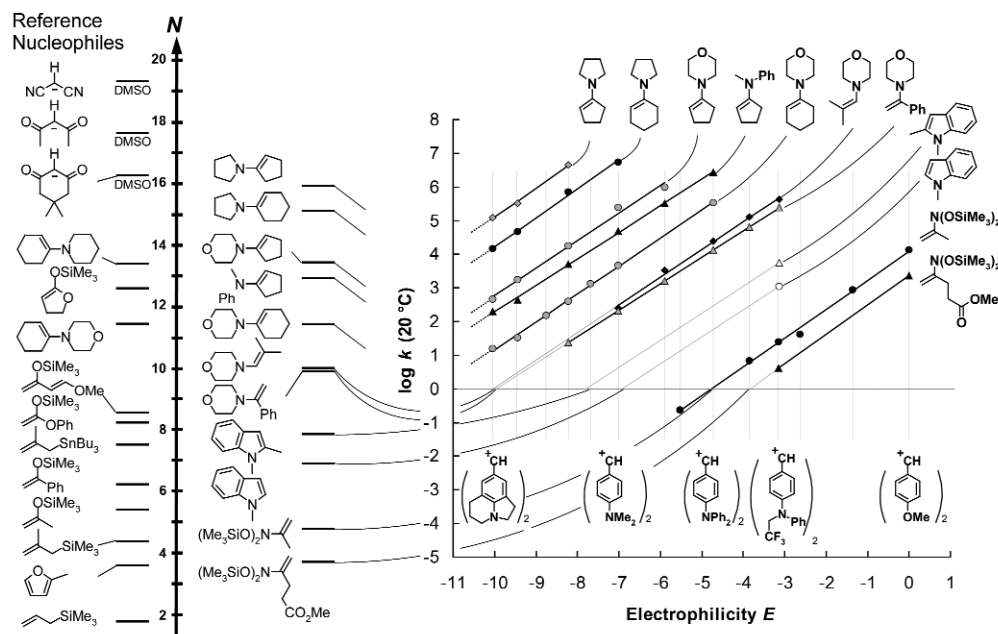


Fig. 6 Determination of nucleophilicity parameters for enamines [7,17,25].

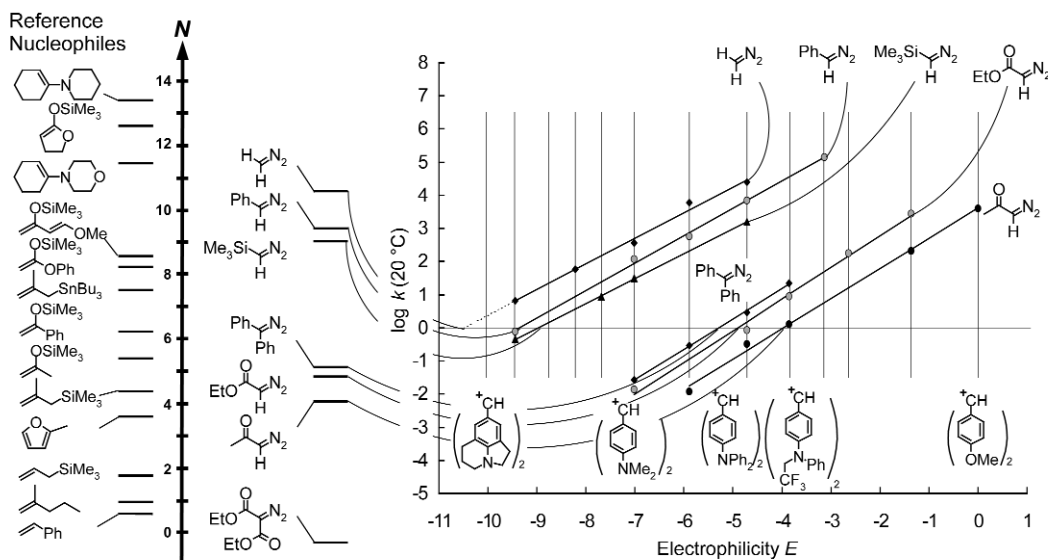


Fig. 7 Determination of nucleophilicity parameters for diazo compounds [26].

order of the diazo compounds, diazomethane > ethyl diazoacetate > ethyl diazomalonnate is in full accord with expectation [27], in addition, it now becomes possible to directly compare their nucleophilic reactivities with those of other π -systems. Thus, the nucleophilicity of diazomethane corresponds to that of moderately reactive enamines, ethyl diazoacetate is comparable to typical enol ethers, and ethyl diazomalonnate is comparable to 1,1-dialkylethylenes or styrene.

Many organic chemists have problems relating the nucleophilic reactivities of organometallic π -systems with those of typical organic compounds. The correlations in Fig. 8 show that they follow analogous relationships as the π -systems discussed before [17]. It is thus found that allyl-

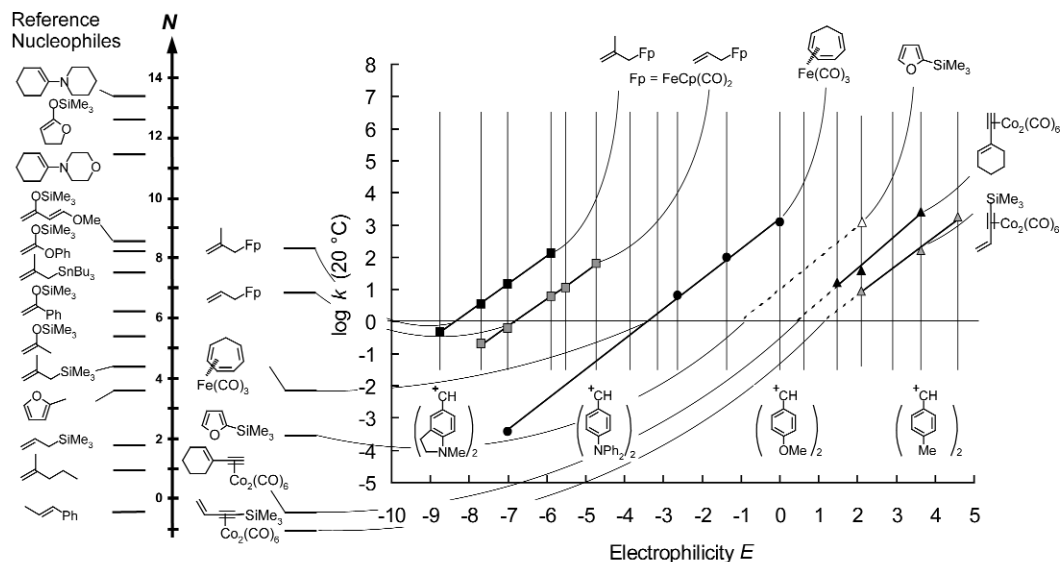


Fig. 8 Determination of nucleophilicity parameters for organometallic π -nucleophiles [28–31].

dicarbonylcyclopentadienyliron has a similar nucleophilicity as enol ethers [28] and that tricarbonyliron cycloheptatriene is comparable to 2-methylfuran [29]. Contrary to intuition, the hexacarbonyldicobalt enyne complexes are less nucleophilic than 1,1-dialkylethylenes; the fact that only reactions with fairly strong electrophiles have been reported for these enyne complexes is in accord with this finding [30]. When discussing the fact that 2-(trimethylsilyl)furan is less nucleophilic than 2-methylfuran, one has to consider that both compounds are attacked at the 5-position of furan, i.e., that one is comparing the α -effect of a trimethylsilyl and a methyl group [31]. The fact that ipso-attack is not observable at 2-(trimethylsilyl)furan shows that the stabilizing β -silyl effect is not yet largely developed in the transition states of the electrophilic attack, which has been explained by the orthogonality of the π -system and the $\sigma_{\text{C-Si}}$ -bond [31].

According to Fig. 9, the correlations for hydride-transfer reactions to benzhydrylium ions [10,11,16,32,33] are of similar quality as those for CC bond-forming reactions, but the slopes show larger differences: For that reason, crossings of correlation lines are encountered more often than in comparisons of π -nucleophiles, which implies a reversal of the relative reactivities of hydride donors upon variation of the hydride acceptor. If only crude estimates of relative reactivities are needed, however, the slopes s can be neglected also for these compounds, and the left part of Fig. 9 provides a semi-quantitative comparison of the reactivities of hydride donors and π -nucleophiles. While tributylstannane [11,16] and amineboranes [32] possess nucleophilicities comparable to ketene acetals [16], the C–H hydride donating ability of 1,4-cyclohexadiene [33] is in between the π -nucleophilicity of mono- and 1,1-dialkylated ethylenes.

As shown by Fig. 10, benzhydrylium ions can also be employed for comparing the nucleophilic reactivities of phosphanes and phosphites with each other as well as with carbon nucleophiles [34]. While tris(*p*-dimethylaminophenyl)phosphane has a nucleophilicity comparable to that of typical stabilized carbanions, triphenylphosphite is considerably less nucleophilic, comparable to enol ethers. It has to be noted, however, that predicted high rate constants for the reactions of carbocations with trivalent phosphorous compounds do not necessarily imply fast formation of phosphonium compounds. Since the initially formed quaternary phosphonium ions often cannot undergo irreversible consecutive reactions, they may redissociate into starting materials, and no reaction may take place macroscopically even if Fig. 10 suggests fast electrophile–nucleophile combinations. The availability of rate and equi-

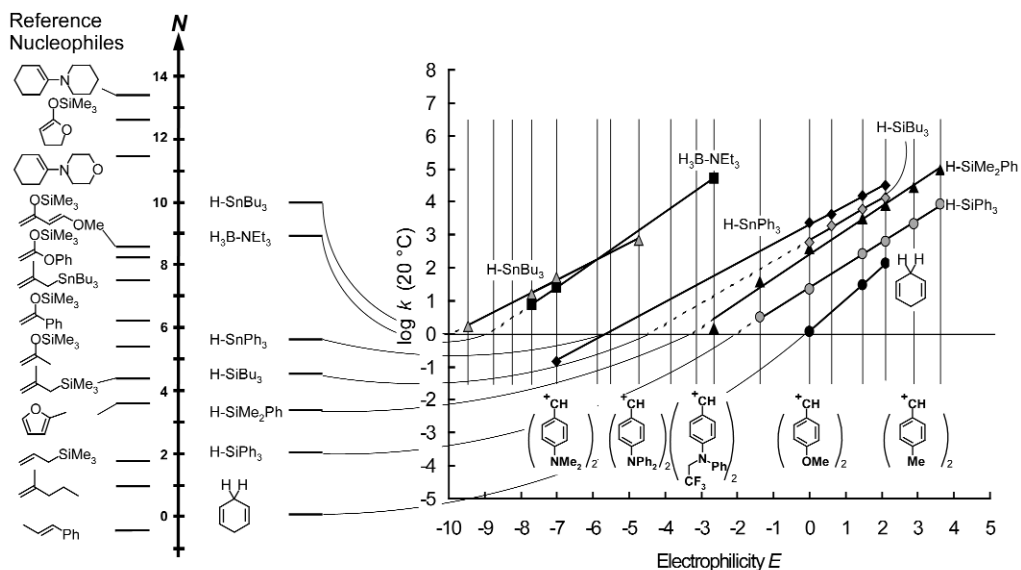


Fig. 9 Determination of nucleophilicity parameters for hydride donors [10,11,16,32,33].

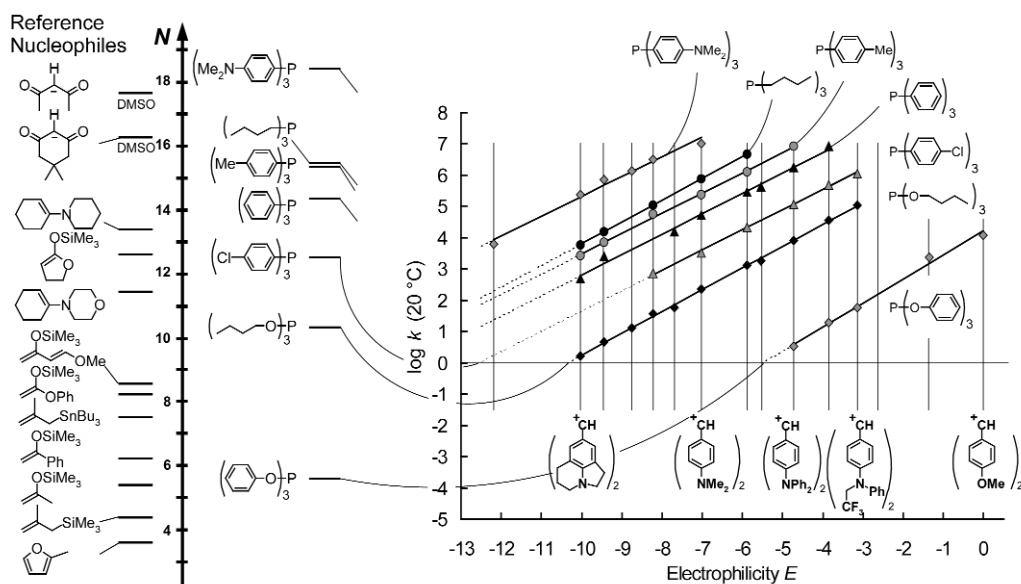


Fig. 10 Determination of nucleophilicity parameters for P -nucleophiles [34].

librium constants for several reactions of benzhydrylium ions with triarylphosphanes allowed us also to determine their Marcus intrinsic barriers of ca. 58 kJ mol⁻¹ [34].

While solvent effects on the nucleophilicities of neutral π -systems and hydride donors were found to be generally small [10,17,21,32,35], the nucleophilic reactivities of amines and of anions depend strongly on the solvent [36–38], and their N parameters are generally given with respect to a certain solvent (Fig. 11). In accord with Ritchie's studies on tritylium ions [37,39], primary alkyl amines are 10² to 10³ times more reactive in DMSO than in water and exceed the nucleophilicity of ammonia in water by several orders of magnitude [38]. The fact that the correlation line for water is considerably steeper than those for the other nucleophiles shown in Fig. 11 has been identified as the reason why Ritchie had

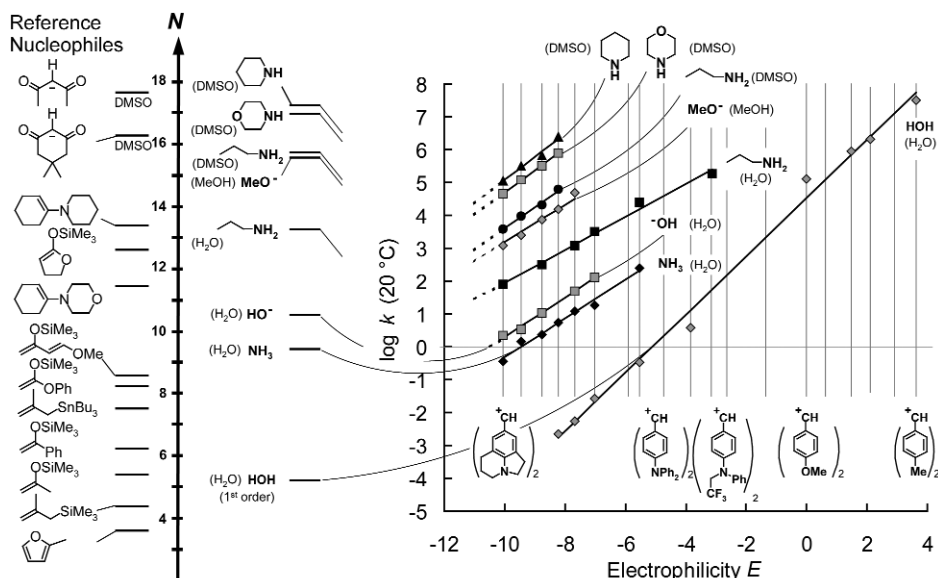


Fig. 11 Determination of nucleophilicity parameters for amines and alkoxides [38].

abandoned the usage of a single set of parameters for describing electrophile–nucleophile combinations in his 1986 review [37]. The observation that many π -systems have higher N parameters than water (Fig. 11, left) [40] suggested that solvolytically generated carbocationic intermediates may be intercepted by π -nucleophiles in aqueous solution and gave rise to a new methodology for Friedel–Crafts reactions in neutral aqueous or alcoholic solutions [41].

The possibility of comparing nucleophiles of widely variable reactivity allowed us to systematically explore the influence of solvents on carbanion nucleophilicities. Correlations comparable to those depicted in Figs. 6–11 gave rise to the N parameters for carbanions in water and DMSO [19,42–44]. The left side of Fig. 12 shows that ester- and keto-stabilized carbanions are more nucleophilic in DMSO than in water by approximately three units in N but that the nucleophilic reactivity of the malonodinitrile anion is hardly affected by variation of the solvent. Dramatic solvent effects were found for nitronate anions (Fig. 12, right) [44].

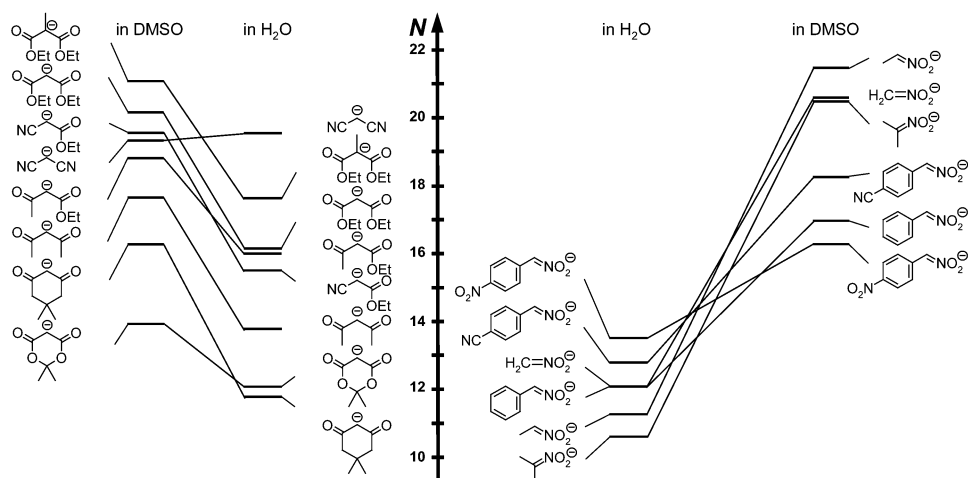


Fig. 12 Nucleophilicities of carbanions in DMSO and water [42–44].

While aliphatic nitronate anions in DMSO are among the strongest nucleophiles studied so far, they are so strongly solvated by hydrogen-bridging that aliphatic nitronate anions in water are among the weakest carbanionic nucleophiles, comparable to ketene acetals. The solvent effect on aromatic nitronates is much weaker, and the relative nucleophilicities of aromatic and aliphatic nitronates are reversed when changing from aqueous to DMSO solution. Furthermore, the solvent effect on the nucleophilicities of aromatic nitronates decreases with increasing electron-accepting ability of the *p*-substituents. As a consequence, the nucleophilic reactivities of aryl-substituted nitronates, which decrease in the order $H > p\text{-CN} > p\text{-NO}_2$ in DMSO are inverted in water, i.e., $p\text{-NO}_2 > p\text{-CN} > H$. The observation that more basic nitronate anions are less nucleophilic has previously been termed *nitroalkane anomaly* [45]. We have shown, however, that there is no systematic relationship between basicities and nucleophilicities of nitronate anions in water [44]. Because of the strong solvation of nitronate anions, the nucleophilic reactivities of all nitronate anions studied so far differ by less than a factor of 10^2 , and it depends on the accidental choice of compounds for comparison whether one observes increasing or decreasing nucleophilicity of nitronates when the pK_{Ha} values are increased.

As it is now possible to directly compare nucleophilicities of a large structural variety of compounds with respect to benzhydrylium ions and structurally related quinone methides as reaction partners (Fig. 13), the question arises as to how relevant these data are for reactions with other electrophiles.

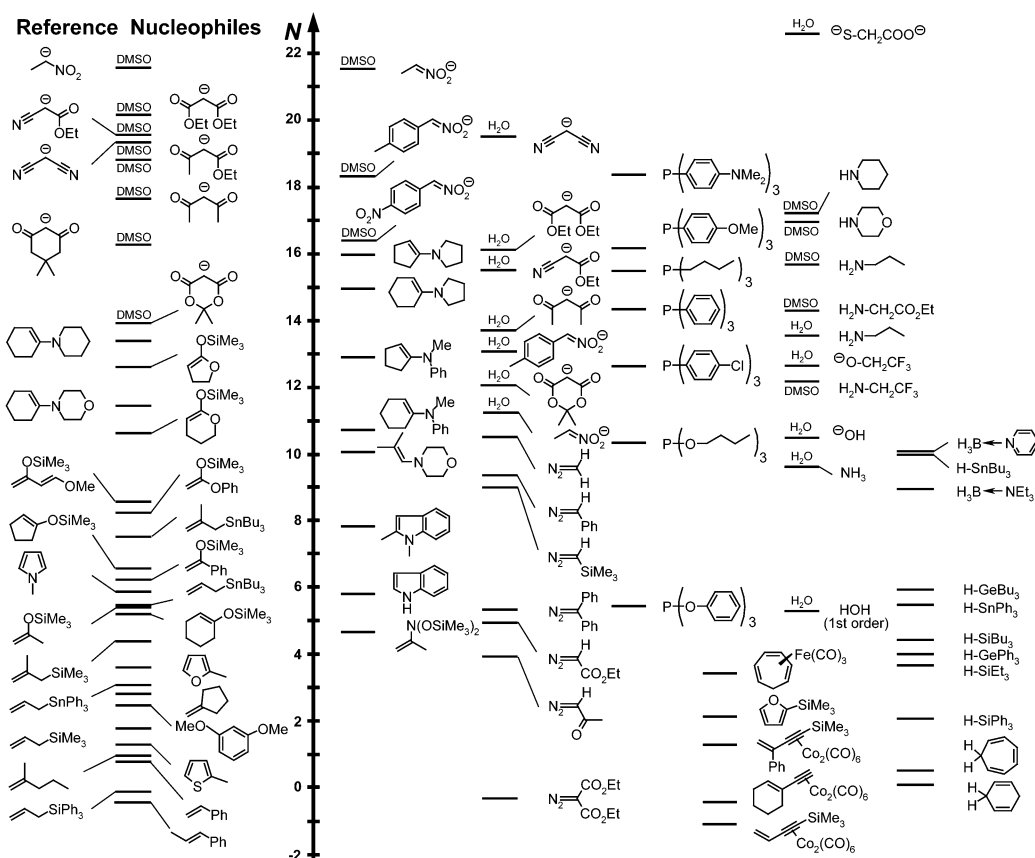


Fig. 13 Nucleophilicity parameters N for various types of nucleophiles (in CH_2Cl_2 , if not mentioned otherwise).

Reactivities of various types of electrophiles

Figure 14 plots $(\log k)/s$ for the reactions of triarylallyl cations [46], flavylum ions [47], and the *N*-methylacridinium ion [16,17] against the *N* parameters of *C*-nucleophiles. As expected, the correlations now show more scatter than those referring to benzhydrylium ions (see Figs. 6–11), but their quality is sufficient to derive the electrophilicity parameters *E* for these carbocations [17] and compare them with those of benzhydrylium ions, as shown on the right side of Fig. 14.

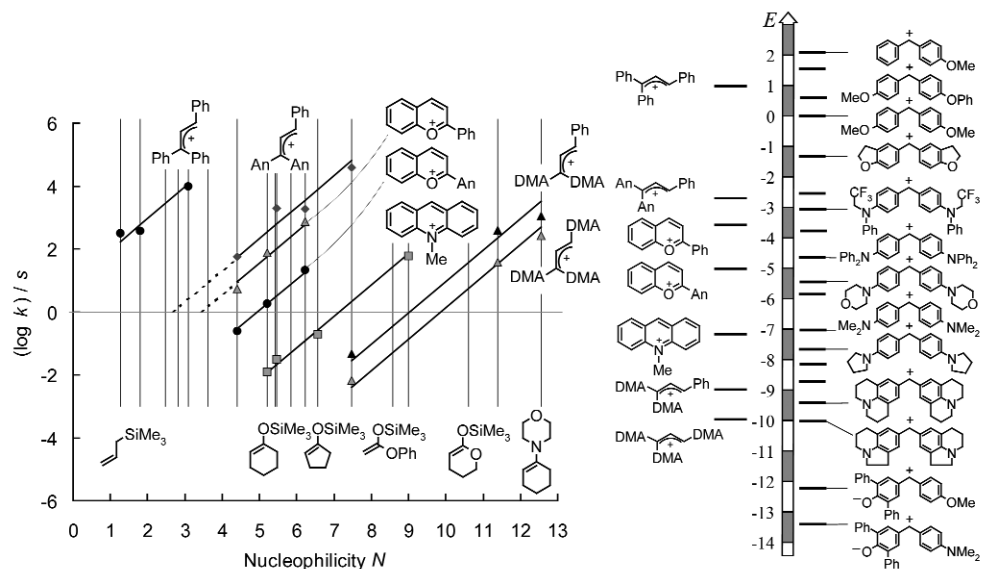


Fig. 14 Determination of the electrophilicities of further types of carbocations (An = 4-MeO-C₆H₄, DMA = 4-Me₂N-C₆H₄) [16,17,46,47].

An analogous analysis yields the electrophilicity parameters *E* for cationic metal π -complexes (Fig. 15) [17,48–51]. Our conclusion that the tricarbonyliron cyclohexadienylum ion is slightly less electrophilic than Michler's hydrol blue [(4-Me₂N-C₆H₄)₂CH⁺] [49] has previously been derived from the rates of their reactions with phosphanes by Sweigart and Alavosus [52]. While several hexacarbonyldicobalt-coordinated propargyl cations were found to have similar electrophilicities as the bis(*p*-methoxy)benzhydrylium ion, only slightly depending on the substituents at the propargylium fragment, substitution of one carbonyl group by the triphenylphosphane ligand reduces the electrophilic reactivity by a factor of almost one million [50].

Readers may be surprised by the fact that the correlation lines drawn in Figs. 14–17 often seem to deviate from the optimal correlation. This is most obvious for the two correlations in Fig. 15, which refer to only two data points. The reason why the correlation lines in these cases do not pass through the two points is the nature of eq. 1 [16,17,22] which only contains a nucleophile-specific slope parameter, *s*, and defines electrophiles by only one parameter, the electrophilicity *E*. Therefore, unity slope is enforced in all $(\log k)/s$ correlations of Figs. 14–17.

Figure 16 reveals that the reactions of carbanions with arylidenemalononitriles follow the same correlations as the corresponding reactions with the reference electrophiles defined in Fig. 3 [43]. The satisfactory fit shown in Fig. 16 does not only corroborate the wide applicability of the nucleophilicity parameters derived from reactions with benzhydrylium ions, but also permits an independent examination of the reliability of eq. 1. Since kinetics of the reactions of arylidenemalononitriles with amines and alkoxides have previously been reported by Bernasconi [53,54], it is now possible to compare predictions by eq. 1 with experimental data obtained in another laboratory. As discussed previously [16], the

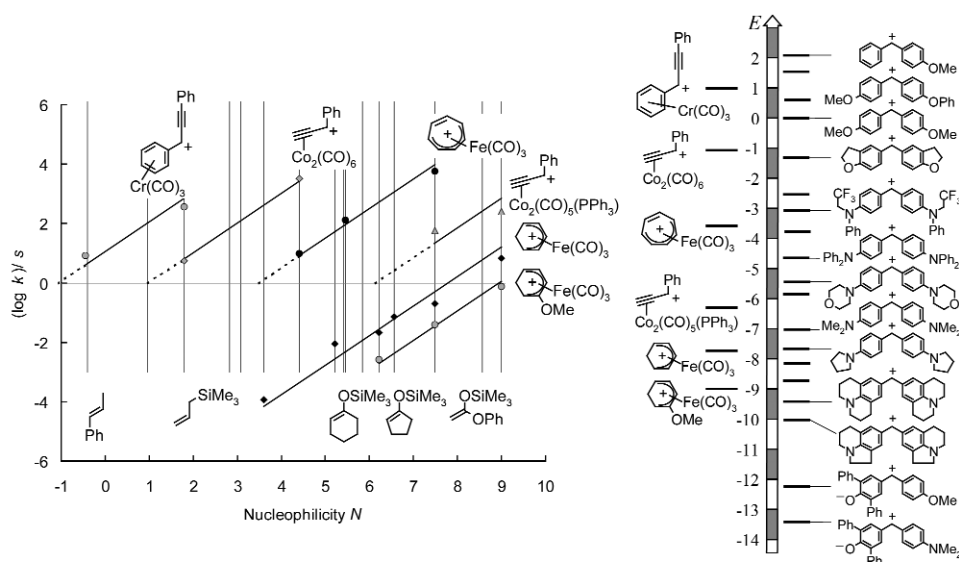


Fig. 15 Determination of the electrophilicities of cationic metal π -complexes [17,48–51].

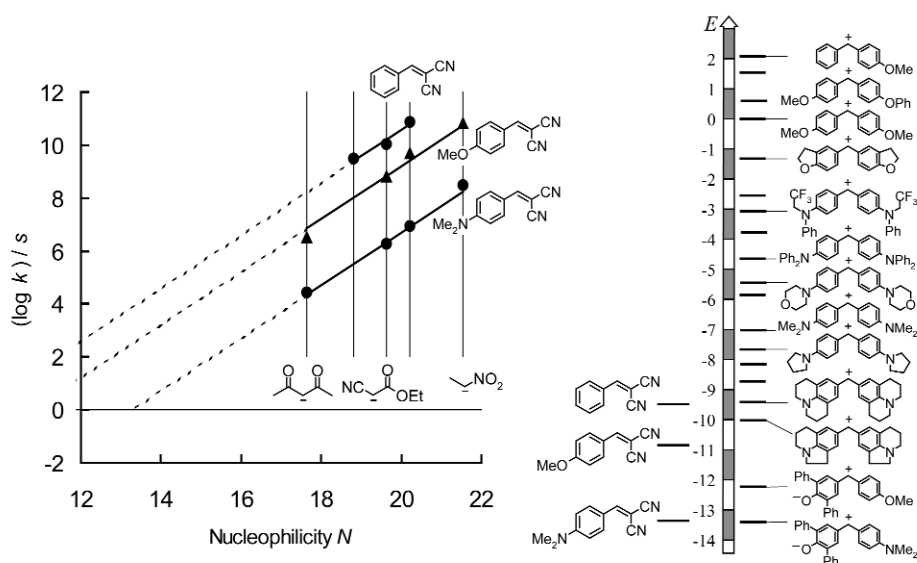


Fig. 16 Determination of the electrophilicities of arylidene malonitriles [43].

agreement between experimental and calculated rate constants is generally within a factor of 100, which we consider satisfactory in view of the more than 40 orders of magnitude covered by the reactivity scales presented in this report. Larger deviations have so far only been observed when very bulky reagents (e.g., tritylium ions) are considered [38a] or when a change in mechanism is involved [55,56].

Acceptor-substituted benzofuroxans and related compounds have been termed *superelectrophiles* because their electrophilic reactivity exceeds that of most other classes of neutral electrophiles significantly [57–60]. Terrier and coworkers have recently investigated the kinetics of the reactions of such electron-deficient arenes with enamines and pyrroles of known nucleophilicity parameters N and s [61,62]. In this way, 4,6-dinitrobenzofuroxan (= 4,6-dinitro-2,1,3-benzoxadiazole-1-oxide) has been shown to be 8 orders of magnitude more electrophilic than 1,3,5-trinitrobenzene, which quantitatively

reflects the superior electron-accepting ability of the furoxan substituent compared to a nitro group. These data can also be used to derive electrophilicity parameters E of these compounds (Fig. 17) and compare them with those of the reference electrophiles. With electrophilicity parameters $E \approx -5$, the most reactive compounds of this series are two orders of magnitude more electrophilic than Michler's hydrol blue [(4-Me₂N-C₆H₄)₂CH⁺] indicating a wide overlap of the reactivity ranges of charged and neutral electrophiles.

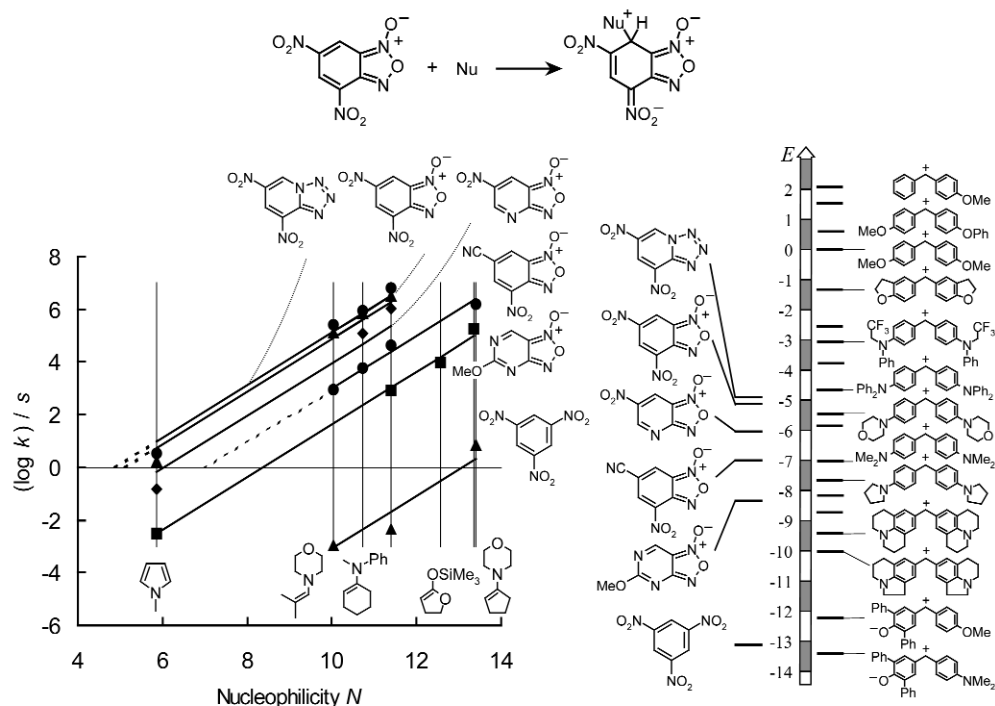


Fig. 17 Determination of the electrophilicities of electron-deficient arenes [61,62].

CONCLUSION AND OUTLOOK

We have shown that the reference electrophiles and nucleophiles depicted in Fig. 3 can be used to construct comprehensive nucleophilicity (Figs. 6–13) as well as electrophilicity scales (Figs. 14–17). With the E , N , and s values thus obtained, one cannot only derive whether a certain electrophile–nucleophile combination can be expected to take place at 20 °C ($E + N > -5$), but also when diffusion control will be reached [$s(N + E) > 9$], which is often associated with a loss of selectivity. Scope and limitations of this approach have been defined [16,17]. We are presently working on an extension of the reference scales in Fig. 3 by several orders of magnitude in both directions, which should further increase the predictive power of eq. 1.

Our endeavors to extend the classes of compounds and reactions covered by eq. 1 are accompanied by employing these data for examining theoretical concepts of organic reactivity, for example, the reactivity selectivity principle [63] or the hard and soft acids and bases (HSAB) concept for explaining ambident reactivity [13,64]. We furthermore attempt to elucidate the physical basis of these relationships by analyzing the relationship between kinetic barriers and thermodynamic driving force [65] as well as the role of electron-transfer processes [66] and hope that this contribution will not only stimulate experimentalists to include further classes of reagents into these scales, but also theoretical chemists to search for the origin of E , N , and s [65,67].

ACKNOWLEDGMENTS

We are indebted to all of our coworkers whose intellectual and experimental contributions made this report possible, and we are grateful to Prof. F. Terrier for the permission to include unpublished data in Fig. 17. We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

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