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Do general nucleophilicity scales exist?[†]

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Comprehensive nucleophilicity scales including π-, n- and σ-nucleophiles have been constructed using benzhydrylium ions and structurally related quinone methides as reference electrophiles. It is shown how the correlation (Eqn (1)) log $k_{20°C} = s(E + N)$, where s and N are nucleophile-specific parameters and E is an electrophile-specific parameter, has recently been employed to characterize further classes of nucleophiles (phosphines, amines, isonitriles, trifluoromethanesulfonyl-substituted carbanions) and electrophiles (2-benzylideneindan-1,3-diones and benzylidenebarbituric acids). Practical applications of the reactivity parameters E, N and s for developing Friedel–Crafts alkylations in neutral alcoholic or aqueous solution and for characterizing nucleophilic organocatalysts will be discussed. Eventually, a new correlation equation will be presented, which includes Eqn (1), the Ritchie equation (nucleophilic additions to stabilized carbocations), and the Swain–Scott equation (nucleophilic substitutions of methyl halides) as special cases. Copyright © 2008 John Wiley & Sons, Ltd.

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The answer to the title question is plain: A general nucleophilicity scale cannot exist! It is well-known that carbocations and protons show selectivities towards alkenes, arenes and amines, which differ considerably from those of metal cations or halogens X_2. In this lecture it will be shown, however, that useful rankings of nucleophiles can be made on the basis of kinetic experiments, when only carbon electrophiles are considered as reaction partners.

One of the major problems experienced in daily life is also encountered in chemical kinetics: You never have the proper tools (Fig. 1). Every kineticist has made this experience: One has an excellent idea. But when attempting to check it, one realizes that the reaction is either too fast or too slow for the available kinetic equipment.

In order to eliminate this problem we set up working stations that cover all conceivable time regimes for bimolecular reactions: Conventional kinetics – we use submersible probes with fibre optics – for reactions which take 10 s to several days, stopped-flow techniques for reactions from 10 ms to several seconds, and nanosecond Laser-flash spectroscopy which allows us to reach the diffusion limit, that is, to study the fastest possible bimolecular reactions in solution (Fig. 2).

In the next step, we have selected a reference electrophile [$(p\text{-MeOC}_6H_4)_2CH^+$], a reference solvent ($CH_2Cl_2$), and a reference temperature (20 °C) for constructing a comprehensive nucleophilicity scale applicable to these conditions. Figure 3 illustrates the limitations of this approach. Whereas one can differentiate the nucleophilic reactivities of slightly activated arenes and alkenes, allylsilanes, allylstannanes and silylated enol ethers under these conditions, more reactive and less reactive nucleophiles cannot be characterized with this reference electrophile. Nonactivated arenes and alkenes on the very left of Fig. 3 do not react at all, while carbanions and enamines on the very right react with the same rates: The rate constants for the very fast reactions are not determined by the rate of the bond-forming step, but by the rates with which the molecules diffuse through the solution. The consequence is obvious: A single electrophile allows one to compare only a rather limited group of compounds, which differ by less than 14 orders of magnitude in reactivity. Whichever electrophile will be selected as reference, most nucleophiles will always be outside of this window.[1]

For that reason, we have decided to select not one, but more than 30 structurally related electrophiles, each of which allows one to compare a different group of nucleophiles. Imagine a nucleophile that undergoes a diffusion-controlled reaction with the most electrophilic carbocation shown in Fig. 4; it will react within minutes with the ditolylcarbenium ion, within a day with the dianisylcarbenium ion and within a couple of thousand years with Michler's hydrol blue. The reaction with the weakest electrophile shown in Fig. 4 is expected to require approximately a million times the age of the universe.

When we want to determine the reactivity of a rather weak nucleophile, for example, toluene, we can study the rates of its reactions with strong electrophiles. Electrophiles in the medium range can be used for characterizing nucleophiles of intermediate reactivity, and weak electrophiles may be used for characterizing strong nucleophiles. We are presently extending these scales towards even weaker electrophiles and expect that we will soon arrive at an electrophilicity scale that covers 40 orders of magnitude.

The core for these reactivity scales has been established in 2001/2002.[2–4] Figure 5 shows rate constants (log k) for the

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reactions of each of the reference electrophiles (benzhydrylium ions and structurally related quinone methides) with a series of carbon nucleophiles. The vertical lines in Fig. 5 correspond to 29 nucleophilicity scales, each one with respect to another electrophile. A least-squares minimization procedure according to Eqn (1) was then employed to arrange the vertical lines in a way that the measured rate constants match the diagonal lines optimally. Rate constants greater than 10^7–$10^8\,M^{-1}\,s^{-1}$ deviate from the linear correlations, because the diffusion limit is approached, and are not considered for the construction of the correlation lines. Details of the correlation method have been reported previously.[2]

$$\log k_{20\,^\circ\mathrm{C}} = s(N + E) \qquad (1)$$

Figure 1. You never have the proper tools (Reproduced by permission of Werner Tiki Küstenmacher, Gröbenzell, Germany)

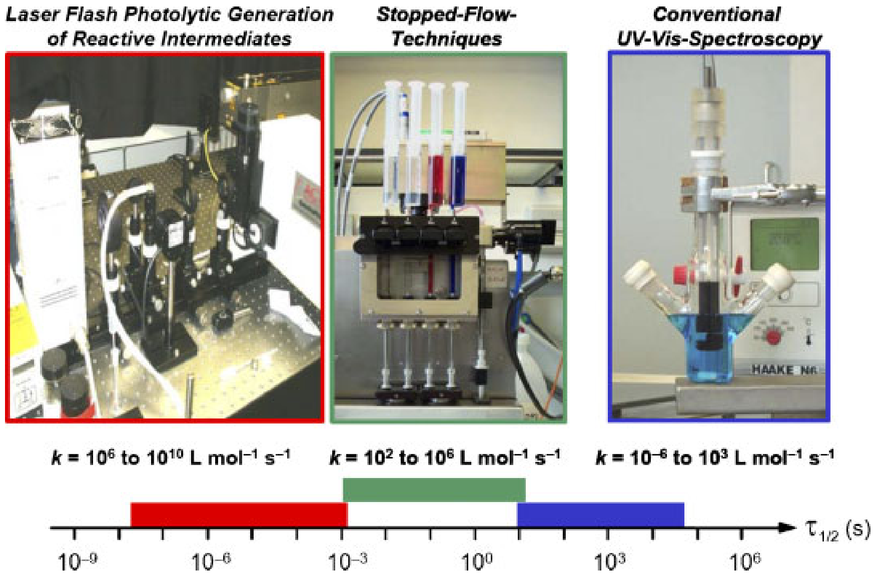


Figure 2. Tools for following the kinetics of a reaction

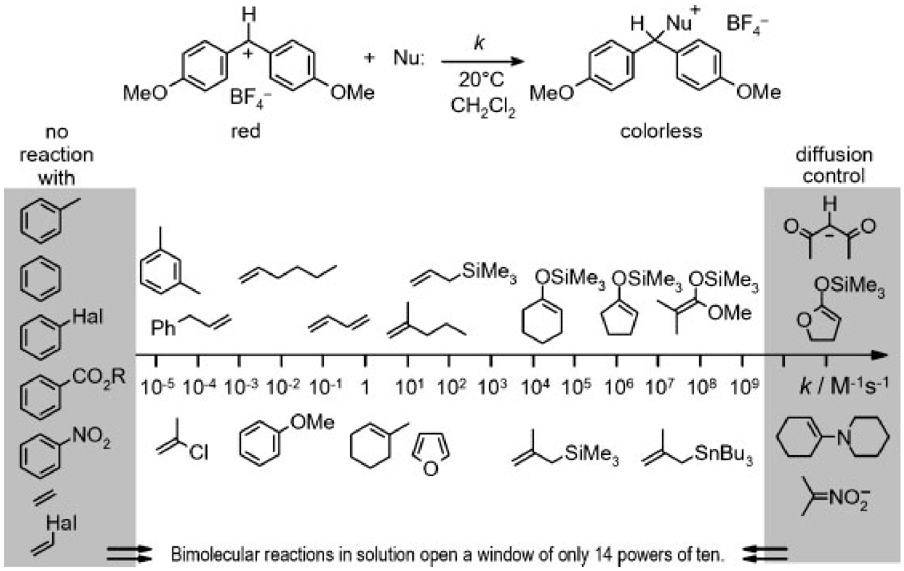


Figure 3. Construction of a nucleophilicity scale with respect to a certain electrophile in a certain solvent at a given temperature

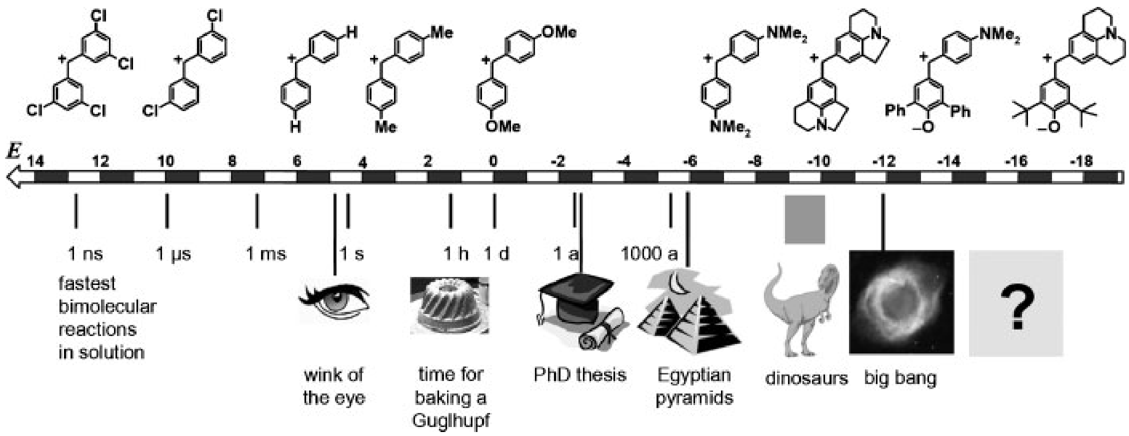


Figure 4. The benzhydrylium scale: Basis for a quantitative model of polar organic reactivity

Each of the electrophiles is thus characterized by an electrophilicity parameter E and each of the nucleophiles is characterized by the nucleophilicity parameter N (= negative intercept on the abscissa) and the slope parameter s. For historic reasons (our work started with kinetics of the reactions of carbocations with alkenes) the bis(4-methoxyphenyl)carbenium ion was assigned $E = 0$ and 2-methylpent-1-ene was assigned $s = 1.0$. We have previously discussed that it is advantageous to characterize nucleophilicities by N, the intercept on the abscissa (instead by the intercept on the ordinate), because the intercept on the x-axis, other than that on the y-axis, is always within or close to the experimentally relevant range.[5–8]

One referee raised the question whether linear free energy relationships should work over such a wide range. As mentioned earlier,[9,10] we are also astonished by these long linear ranges. The Leffler–Hammond effect should cause a downward- bending and the frontier orbital effect should cause an upward-bending as one moves from bottom left to top right in Fig. 5. We thus need two nonlinear effects which compensate each other to explain the long linear correlations. Not satisfactory! Theoreticians are challenged to provide a better explanation.

The electrophilicity scale established in 2001/2002 (Fig. 6) has been employed in the following years to identify the reactivities of numerous classes of nucleophiles by plotting log k against the electrophilicity parameters E of Fig. 6 and determining N and s according to Eqn (1) by least squares minimization. Because this topic has already been reviewed,[1] we will now demonstrate the

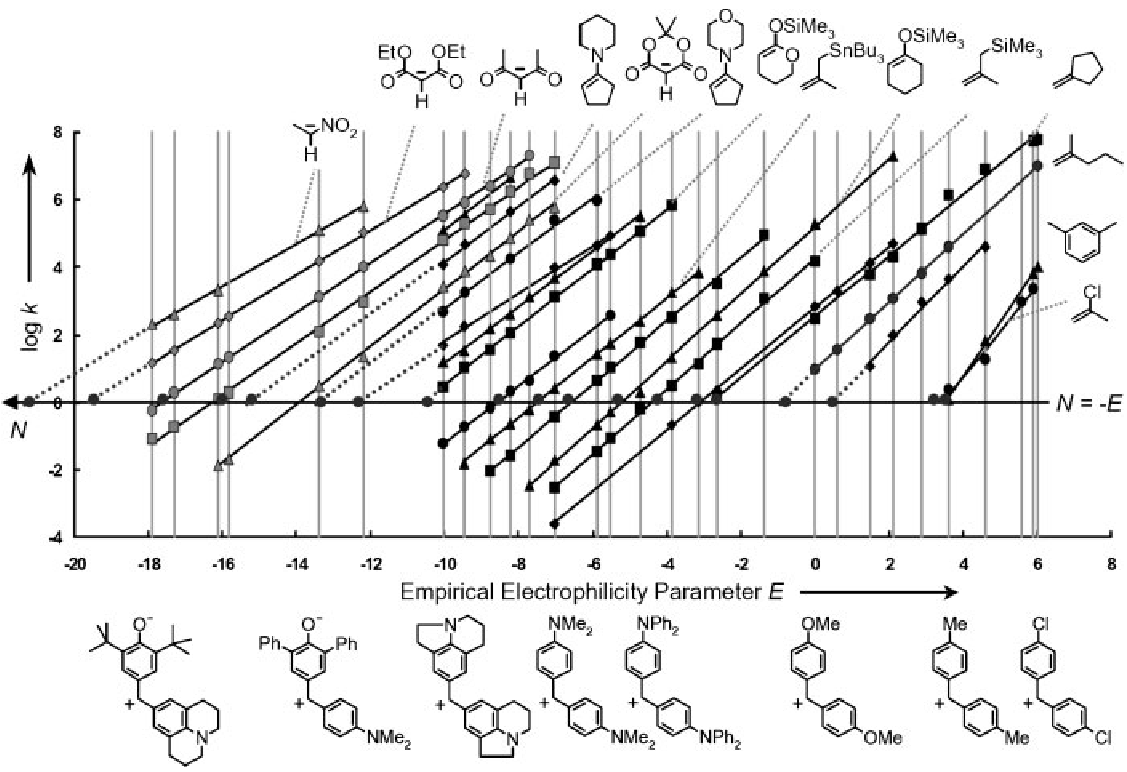


Figure 5. Fit of second-order rate constants for electrophile nucleophile combinations (20 °C) to Eqn (1)

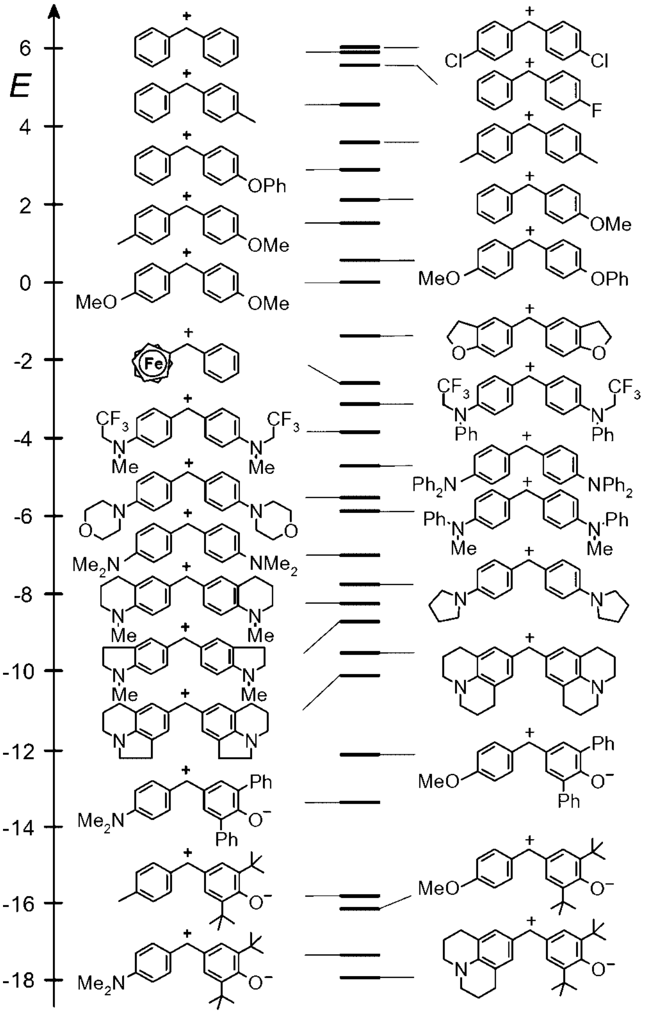


Figure 6. Benzhydrylium ions and structurally related quinone methides as reference electrophiles

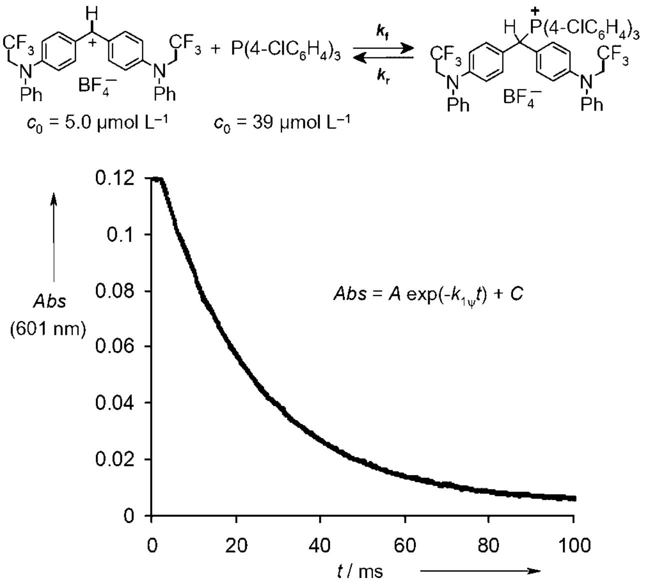


Figure 7. Exponential decay of absorbance during the reaction of a benzhydrylium ion and a triarylphosphane (dichloromethane, 20 °C)

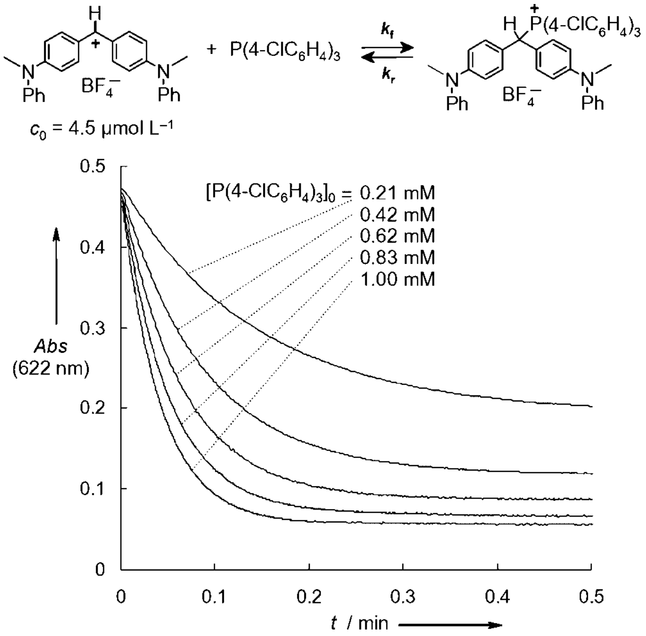


Figure 8. Effect of phosphane concentration on the decay of absorbance during the reaction with a benzhydrylium ion (dichloromethane, 20 °C)

method of determining the nucleophile-specific parameters *N* and *s* with examples published since the appearance of that review and will discuss applications of the scales.

When a benzhydrylium salt is mixed with a high excess of a triarylphosphane,[11] a fast, exponential decay of the benzhydrylium absorbance is observed (Fig. 7). When less electrophilic benzhydrylium ions are employed, a complete consumption of the benzhydrylium ions is only observed at very high phosphane concentrations (Fig. 8) due to the reversibility of these reactions.

Experiments of this type have then been performed with different phosphanes and different benzhydrylium ions. For the evaluation, log *k* was plotted versus *E*, and the negative intercepts on the abscissa yield the nucleophilicity parameters *N* which allow us to compare the nucleophilic reactivities of phosphanes with those of carbanions, enamines and enol ethers (Fig. 9).

Extensive studies of the reactivities of amines, amino acids and simple di- and tripeptides in water were performed analogously.[12,13] Plots of log *k* versus the electrophilicity parameters *E* of the benzhydrylium ions were linear, and the negative intercepts on the abscissa again provided the nucleophilicity parameters *N* of amines which can now be compared with those of carbanions and enamines (Fig. 10).

The order of the nucleophilicities *N* of amines is in full accord with the results of previous kinetic investigations.[14–18] By determining their reactivities towards benzhydrylium ions, it has become possible to include *N*-nucleophiles in the comprehensive nucleophilicity scales based on Eqn (1). Our investigations corroborate that pK_{aH} is a very poor measure for relative amine nucleophilicities. Thus, aniline is much more nucleophilic than ammonia despite its 10^5-fold lower basicity. On the other hand, secondary amines are 10^2–10^3 times more nucleophilic than typical primary alkyl amines despite the fact that their pK_{aH} values are almost identical (Fig. 11).

The benzhydrylium method has recently been employed to characterize the nucleophilicities of isocyanides (Fig. 12).[19,20] We

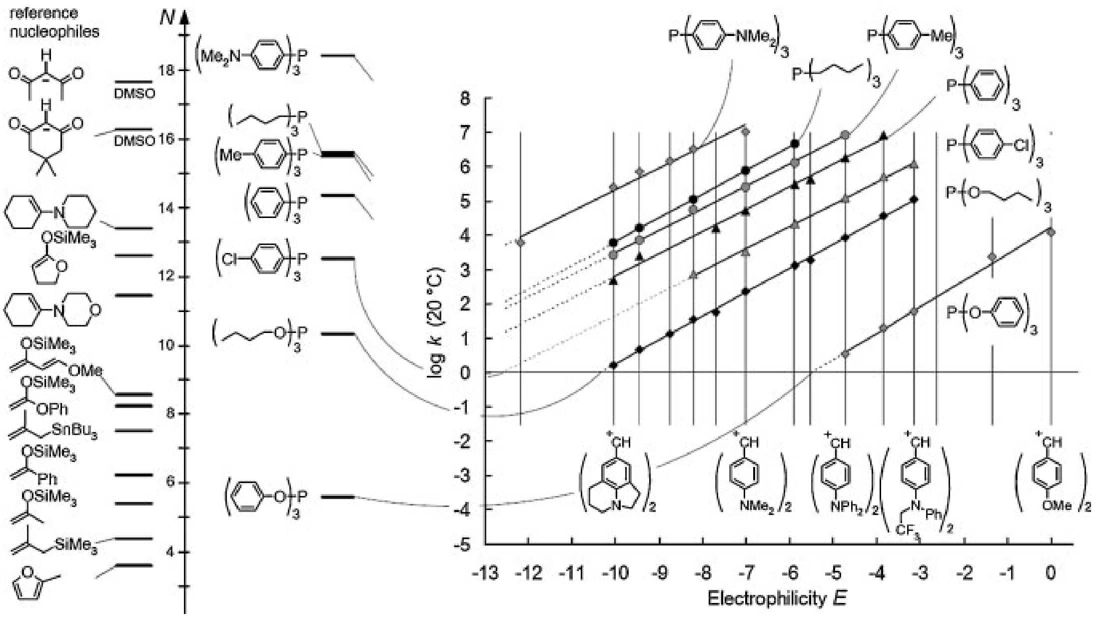


Figure 9. Determination of nucleophilicity parameters for P-nucleophiles

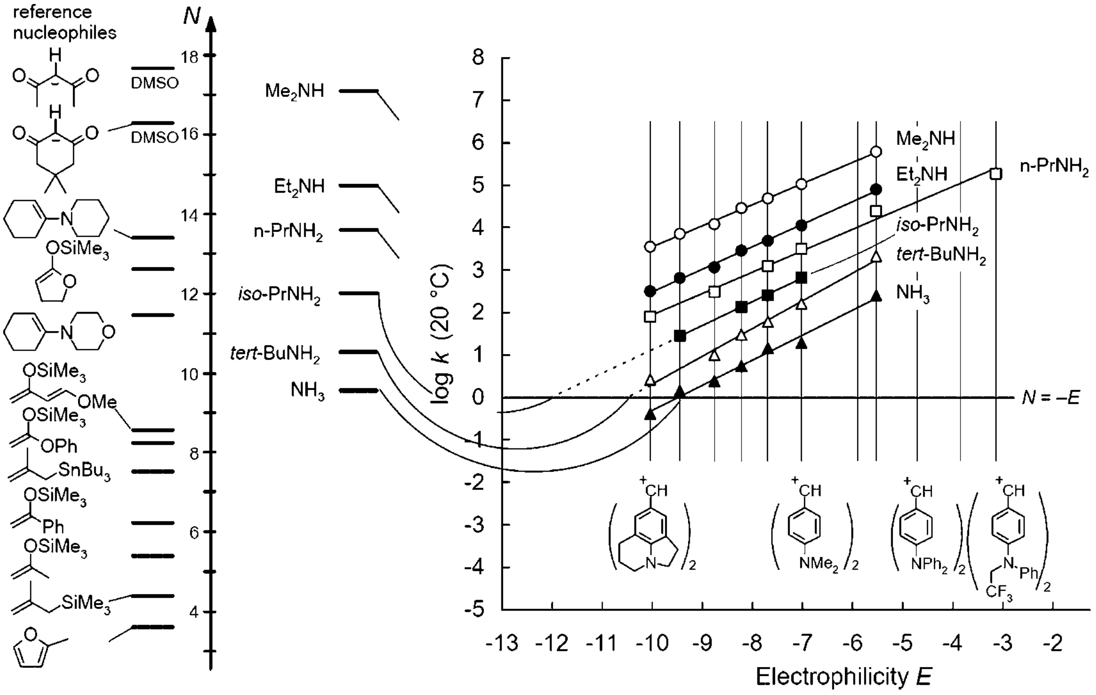


Figure 10. Determination of nucleophilicity parameters for primary and secondary amines in water

find an exponential decay of the benzhydrylium absorbances, when benzhydrylium ions are combined with a large excess of isocyanides. From the slopes of the linear plots of the pseudo-first-order rate constants versus the isocyanide concentrations we obtain the second-order rate constants, and trapping of the initial reaction products with silylated ketene acetals proves that the reaction, which we have monitored photometrically, is the formation of the nitrilium ions (Fig. 12).

The same type of experiment is now done with different isonitriles and different benzhydrylium ions, and one can see that the nucleophilic reactivities of isonitriles are only slightly affected by the substituents. The nucleophilicities of isonitriles are comparable to those of allylsilanes and silylated enol ethers (Fig. 13).

Stefan Berger[21] investigated the nucleophilicities of trifluoromethanesulfonyl-stabilized carbanions, which have previously

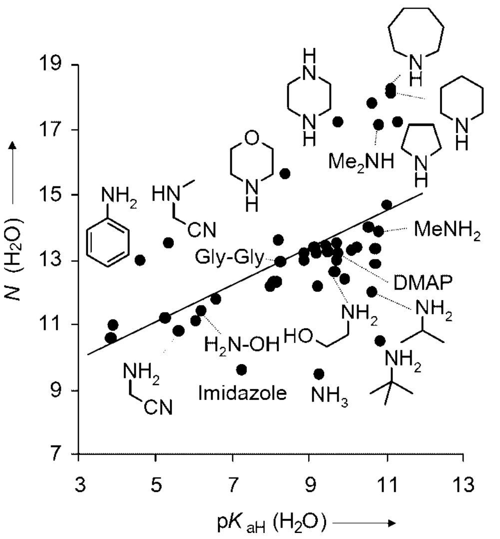


Figure 11. Correlation of nucleophilicity N and Brønsted basicity pKa_H of amines in water

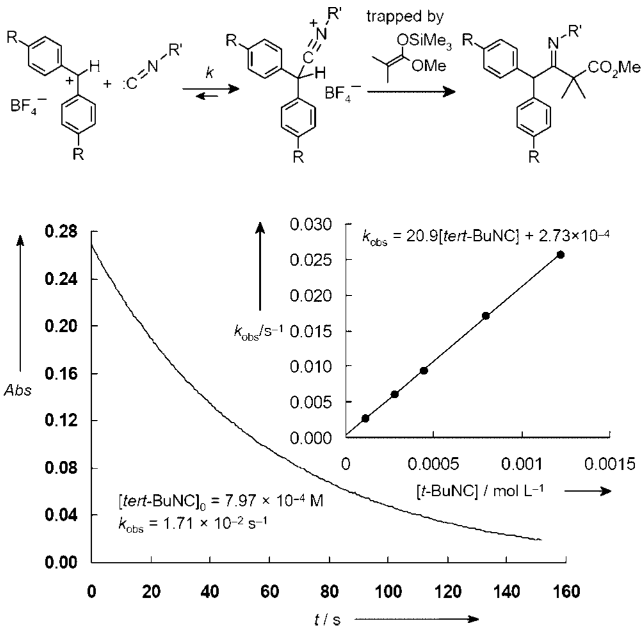


Figure 12. Absorption decay at 593 nm for the reaction of Ar_2CH^+ BF_4^- (R = $N(CH_3)CH_2CF_3$) with *tert*-butyl isocyanide (dichloromethane, 20 °C)

been reported by Terrier to have unique properties, because the conjugate CH acids (sulfones) are more acidic in DMSO than in water.[22–24] One can see that the plots of log k versus E (Fig. 14) are similar to the correlations discussed above. The magnitudes of the N and s parameters are comparable to those of other stabilized carbanions.

We were astonished, however, by the location of these carbanions in an N versus pK_{aH} plot (Fig. 15). It is well-known that even within the class of carbanions the relationship between nucleophilicity and Brønsted basicity is rather poor.[25,26] Because Terrier had shown that the trifluoromethanesulfonyl group does not stabilize carbanions by resonance effects and that these carbanions have an sp^3-hybridized carbanion centre,[22–24] we had expected their reactions with electrophiles to have low intrinsic barriers with the consequence that these carbanions appear at the upper edge of this ‘correlation corridor’. The opposite is true: All trifluoromethanesulfonyl-substituted carbanions sit at the lower edge of the ‘correlation corridor’, that is, these carbanions react via *high* intrinsic barriers. We have concluded therefore that in DMSO the major contribution to the intrinsic barriers for these reactions comes from the desolvation

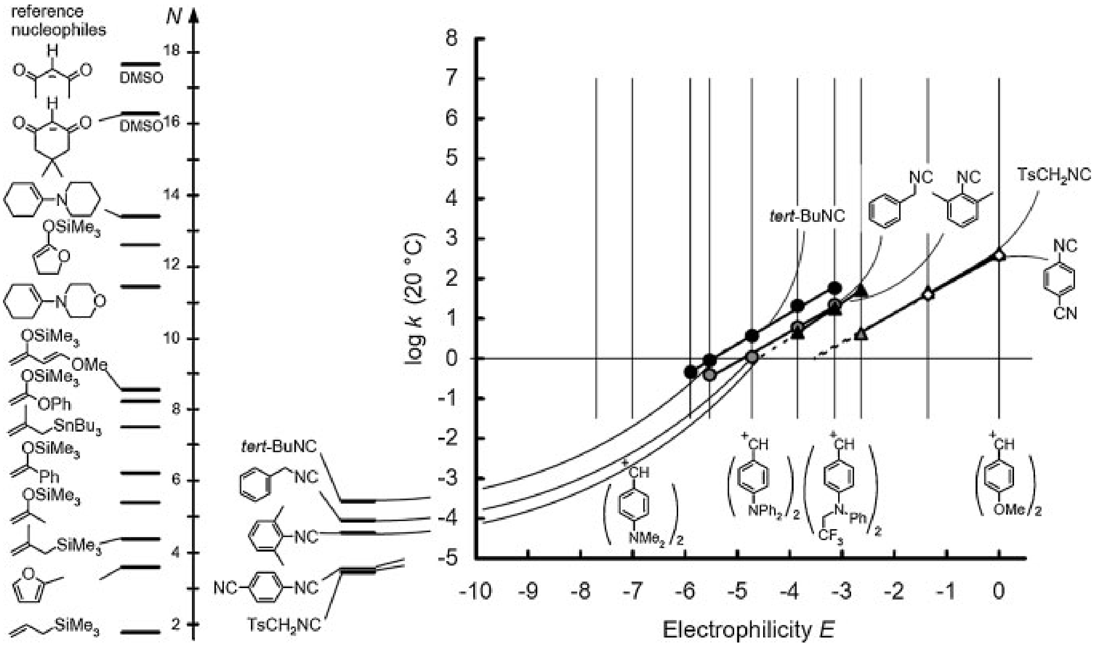


Figure 13. Determination of nucleophilicity parameters for isocyanides in dichloromethane

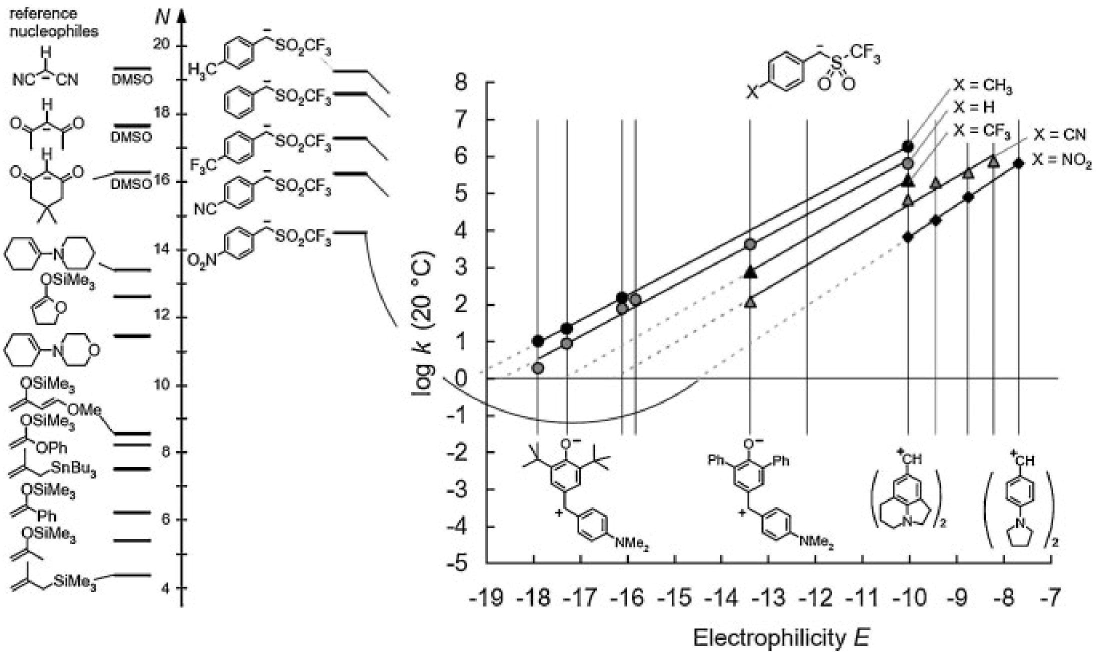


Figure 14. Determination of nucleophilicity parameters for trifluoromethanesulfonyl-stabilized carbanions in DMSO

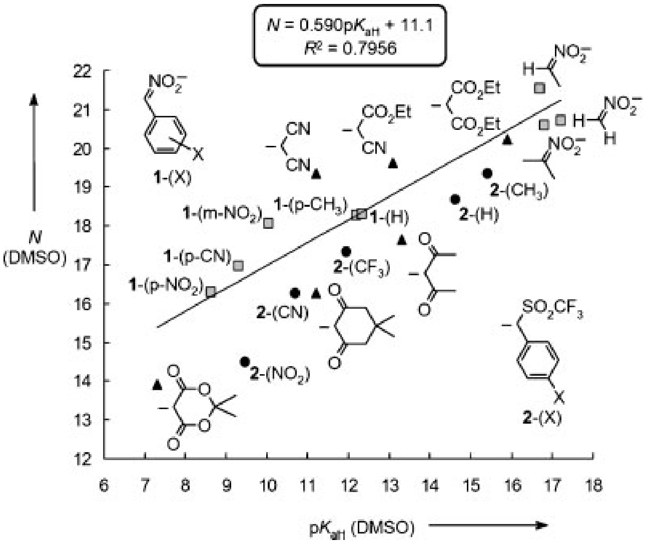


Figure 15. Correlation between nucleophilicity *N* and Brønsted basicity pKa_H of carbanions in DMSO

of the carbanions and not from the nonperfect synchronization of resonance stabilization.[21]

Figure 16 summarizes that the benzhydrylium method allows us to directly compare reactivities of nucleophiles of widely differing structure.[27–31] In a variety of studies, we have shown that this order of nucleophilicities also holds for reactions with other types of carbocations (excluding exceedingly bulky systems such as tritylium ions) though the correlations are now of lower quality.[8,32]

Figures 17 and 18 show examples how to use these scales in practice. Figure 17 compares nucleophilicities of π-systems with those of solvents.[33] Because the nucleophilicity parameters of solvents refer to first-order rate constants, we called them N_1. If 1 M solutions of the π-nucleophiles are considered, the two scales become directly comparable, and one can see that many π-systems are more nucleophilic than 2,2,2-trifluoroethanol (TFE) and that several of them are even more nucleophilic than water.

We had, therefore, concluded that it should be possible to generate carbocations under S_N1 conditions in aqueous or alcoholic solution and trap the intermediate carbocations by π-systems which are more nucleophilic than the corresponding solvents. Friedel–Crafts alkylations in neutral aqueous or alcoholic solutions should result (Fig. 18). This has, indeed, been realized.

When *p*-methoxybenzyl chloride was added to solutions of xylene, mesitylene or anisole in trifluoroethanol buffered by NH_4HCO_3, good yields of Friedel–Crafts products have been obtained.[34,35] Because arenes have higher *s* parameters, these products were isolated even when the *N* values of the arenes were slightly smaller than *N* of trifluoroethanol (Fig. 19).

Indoles and pyrroles are so nucleophilic that they even trap carbocations which are generated under S_N1 conditions in aqueous acetone (Fig. 20).[36] Treatment of these hetarenes with allyl bromides in aqueous acetone in the presence of ammonium hydrogencarbonate as an acid quencher yielded the products of electrophilic aromatic substitution in good yields. It will be hard to find conditions for the allylation of indoles and pyrroles which are milder than those described in Fig. 20. It has to be mentioned, however, that the reaction is not highly regioselective, and that in most cases the preferred β-attack is accompanied by approximately 10% of α-attack.

It has been shown that the nucleophilicity parameters derived from reactions with benzhydrylium ions (e.g. Fig. 16) also hold for reactions with electron-deficient arenes[37,38] and ordinary Michael acceptors[39] though these correlations are of lower quality than those used for the characterization of nucleophiles (e.g. Figs 5, 9, 10, 13 and 14). Two more recently investigated groups of Michael acceptors are benzylideneindan-1,3-diones[40] and benzylidenebarbituric and -thiobarbituric acids.[41] Figures 21 and 22 illustrate that plots of (log *k*)/*s* versus *N* are

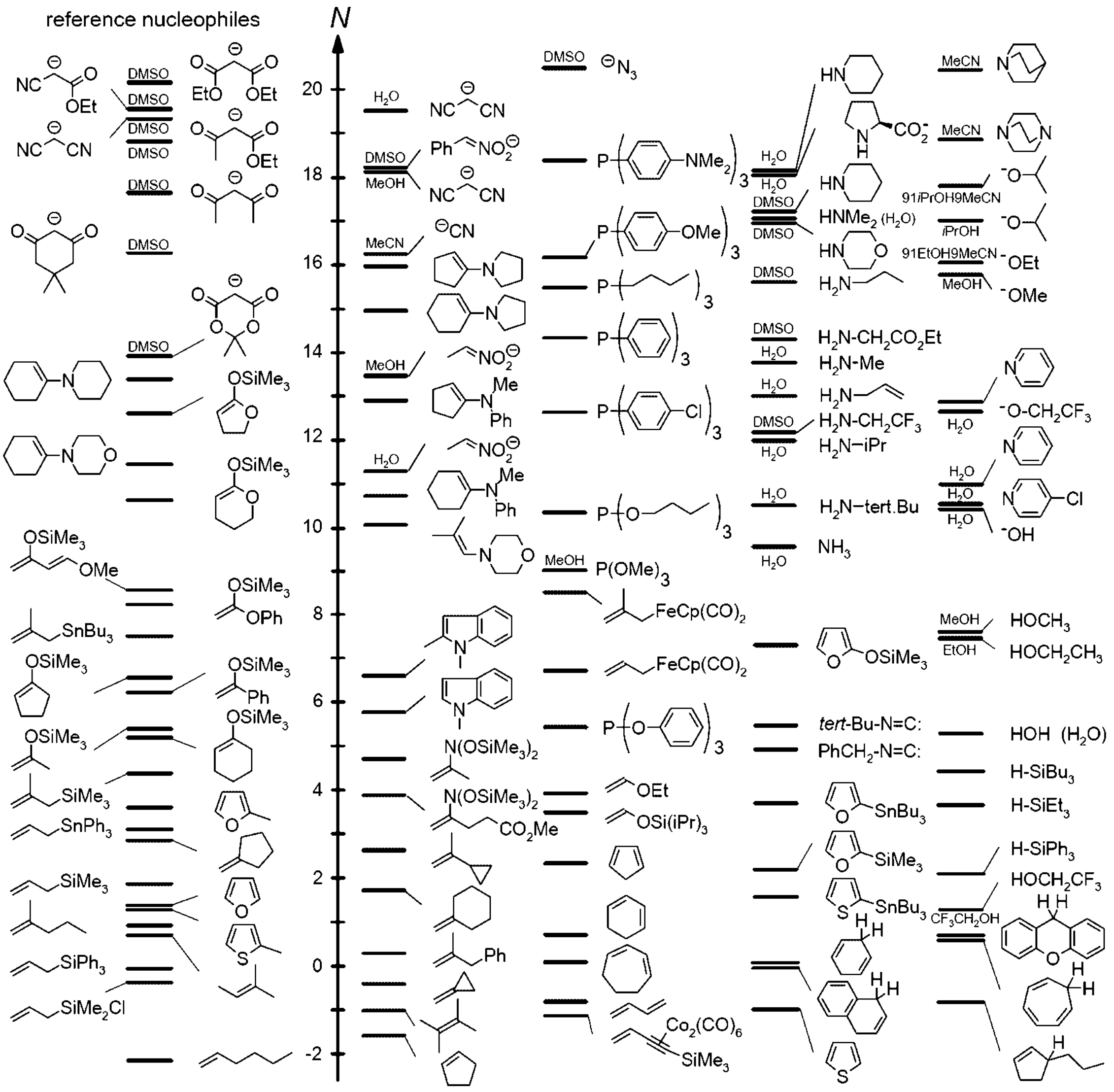


Figure 16. Comparison of the reactivities of different types of nucleophiles (in dichloromethane if not mentioned otherwise; mixtures of solvents are given as v/v)

linear with slopes of 1.0 as required by Eqn (1). We can thus assume that the nucleophilicity parameters N and s derived by the benzhydrylium ion method also hold for a large variety of reactions with Michael acceptors.

Figures 21 and 22 show that the rate constants for trifluoromethanesulfonyl substituted carbanions as well as for the 1-nitroethyl and the 2-nitropropyl anion are generally below the correlation lines. Asghar and Crampton[42] reported that these types of carbanions also react more slowly than expected with sterically demanding electrophiles such as 1,3,5-trinitrobenzene and assigned these deviations to steric effects. Because benzylidene-indan-1,3-diones, benzylidene-barbituric and benzylidene-thiobarbituric acid can be expected to have larger steric requirements than the benzhydrylium ions which were used as reference electrophiles for calibrating the nucleophilicity parameters of these carbanions, steric effects may also account for some of the deviations from the correlation lines in Figs 21 and 22.

Combinations of nucleophiles with electrophiles are the key-steps of many organocatalytic cycles as illustrated for the Baylis–Hillman reaction in Fig. 23 (steps 1 and 2). We, therefore, set out to employ the benzhydrylium tool for examining the efficiency of organocatalysts.[43–45]

Figure 24 shows that N and s for DMAP (4-dimethylaminopyridine) can be determined from the second-order rate constants (determined by the stopped-flow technique) of the reactions of DMAP with benzhydrylium ions of $-10 \leq E \leq -7$.[43] We failed, however, to determine the nucleophilicities of DABCO (1,4-diazabicylo[2.2.2]octane) and quinuclidine analogously. Benzhydrylium ions with $E > -9$ reacted so fast that they could not be followed by the stopped-flow method while carbocations with $E < -9$ did not react at all with DABCO and quinuclidine. Therefore, ns-laser flash techniques have been employed to measure the reactivities of the bicyclic amines. Figure 24 shows that they react 10^3 times faster than DMAP.[44,45]

On the other hand, Fig. 25 shows that the equilibrium constants determined with respect to benzhydrylium ions follow just the opposite order. DMAP, the considerably weaker nucleophile, is a 650-fold stronger Lewis base than DABCO.[44,45] In summary, DABCO is a 10^3 times better nucleophile and a 10^6

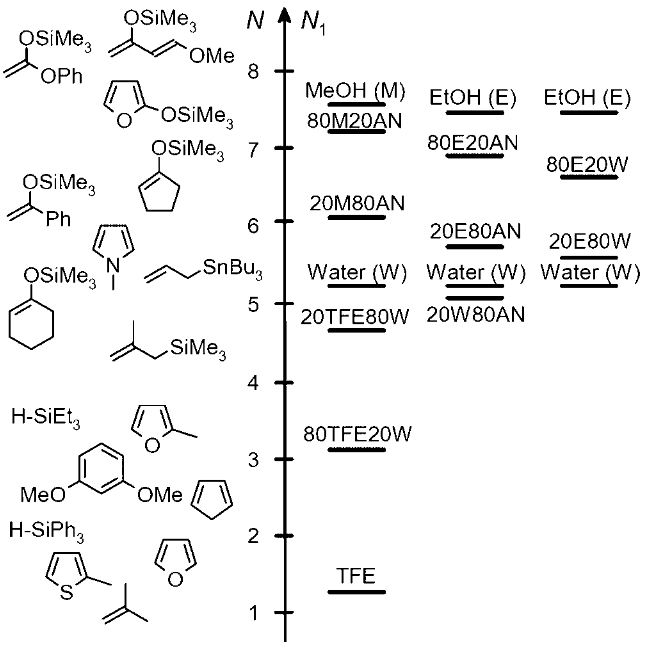


Figure 17. Comparison of the nucleophilicities of π-nucleophiles and solvents (AN: acetonitrile, TFE: 2,2,2-trifluoroethanol; mixtures of solvents are given as v/v)

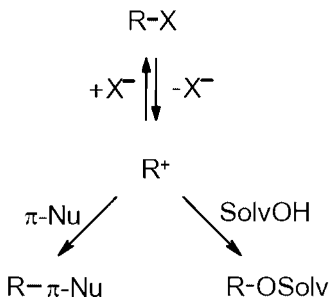


Figure 18. Acid-free Friedel–Crafts alkylations: Trapping of the intermediates of S_N1 solvolysis reactions by π-nucleophiles

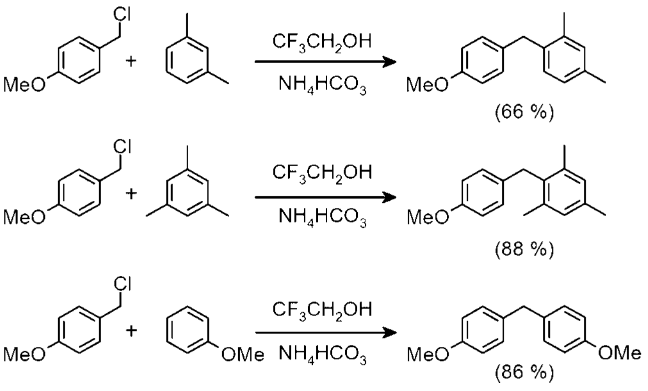


Figure 19. Electrophilic benzylations in buffered trifluoroethanol solutions

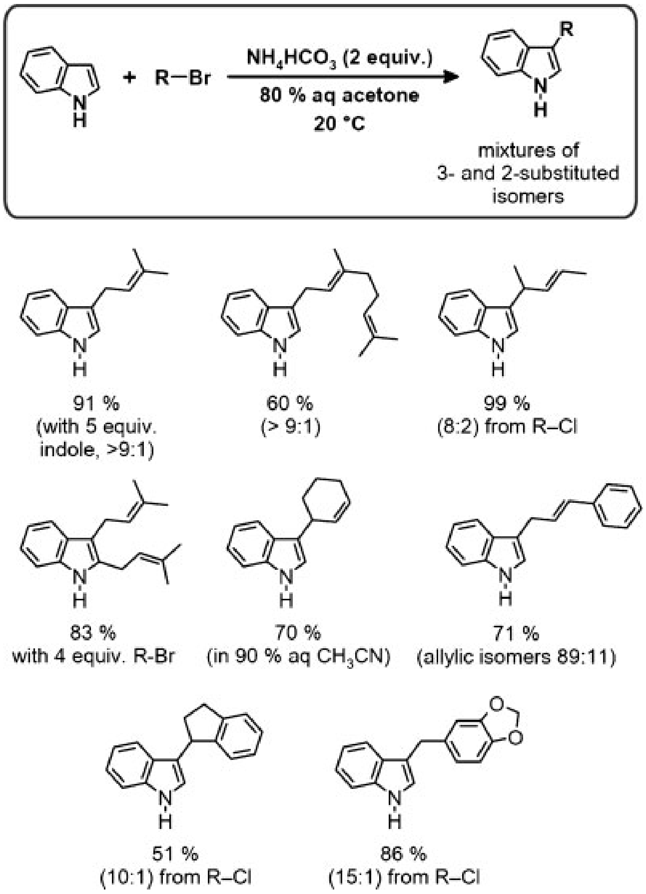


Figure 20. Allylations and benzylations of indole

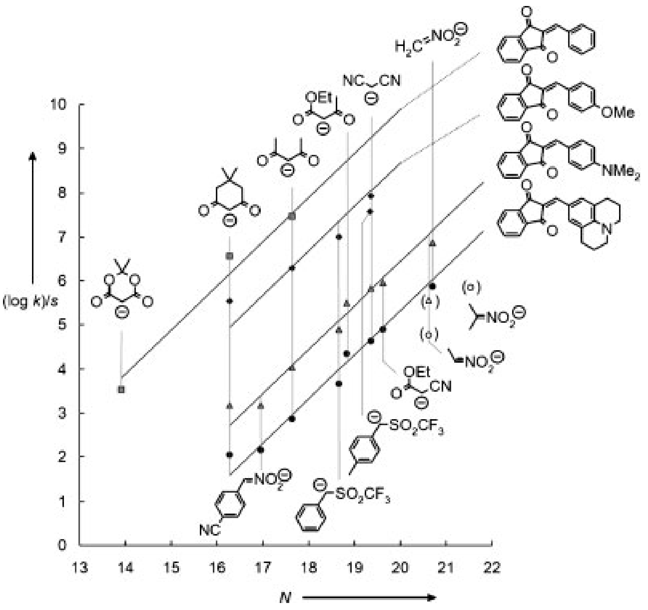


Figure 21. Correlation of (log *k*)/*s* with the nucleophilicity parameter *N* for the reactions of four 2-benzylideneindan-1,3-diones with carbanions in DMSO at 20 °C. The correlation lines are fixed at a slope of 1.0, as required by Eqn (1). Rate constants for reactions with the anions of 2-nitropropane ($N = 20.61$) and of nitroethane ($N = 21.53$) are put in parentheses because they were not included for the calculation of the correlation lines

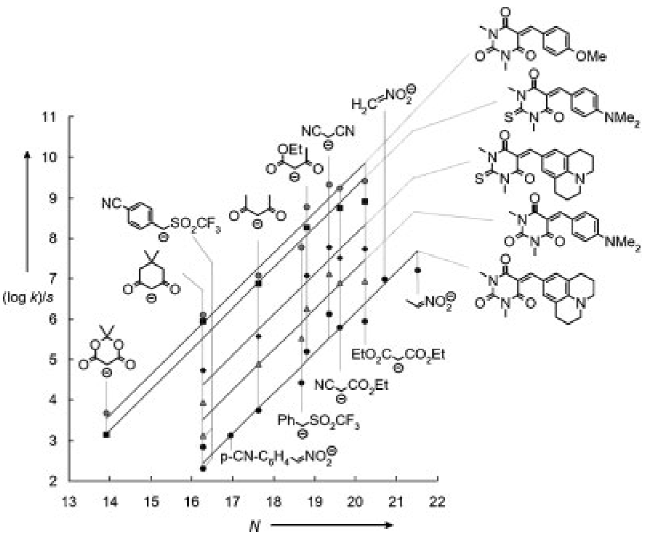


Figure 22. Plot of (log *k*)/*s* versus *N* for the reactions of benzylidene barbituric and thiobarbituric acids with selected carbanions (DMSO, 20 °C). The correlation lines are fixed at a slope of 1.0, as required by Eqn (1)

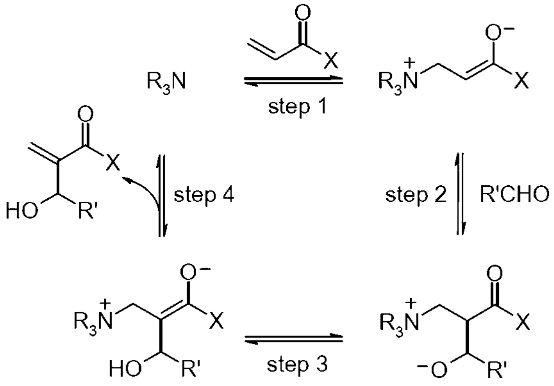


Figure 23. Catalytic cycle for an amine-catalyzed Baylis–Hillman reaction

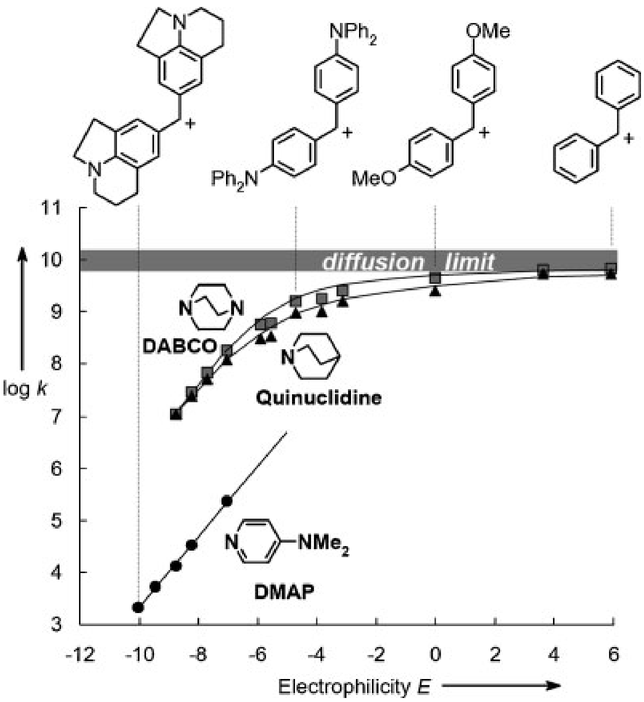
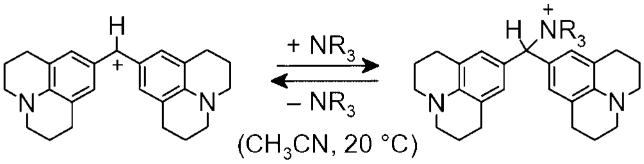


Figure 24. Characterization of the nucleophilicities of organocatalysts (in acetonitrile at 20 °C)



NR₃	*K* (L mol⁻¹)	$\Delta_r G°$ (kJ mol⁻¹)
DABCO	4 × 10¹	–9.0
DMAP	2.6 × 10⁴	–24.8

Figure 25. Comparison of the carbon basicities of DABCO and DMAP

times better nucleofuge than DMAP. If side reactions, initiated by these amines are unimportant, one can conclude that DABCO will be the superior organocatalyst in Baylis–Hillman reactions if the rates of addition (step 1) or elimination (step 4) are crucial but that DMAP will be superior if reactivity is controlled by the concentration of the zwitterionic intermediate.[46,47]

Hoz and Speizman[48] as well as Pross[49] pointed out that the relative reactivities of CN^-, OH^- and N_3^- in water towards carbocations (Ritchie's N_+) are opposite to those towards methyl halides (Swain-Scott *n*) and concluded that nucleophilicity with respect to C_{sp2} centres is not related to nucleophilicity with respect to C_{sp3} centres. This conclusion was contradicted by Richard who reported linear correlations between Ritchie's N_+ and Swain–Scott's *n* parameters.[50] Analogously, Bunting found that the reactivities of amines towards the *N*-methyl-4-vinylpyridinium ion (C_{sp2}-electrophile) correlate linearly with the reactivities towards methyl 4-nitrobenzene-sulfonate (C_{sp3}-electrophile).[15]

Figure 26 plots (log *k*)/*s* for the reactions of O-, N-, P- and C-nucleophiles with the *S*-methyl-dibenzothiophenium ion towards the nucleophilicity parameters *N*. A good linear correlation over a wide range of reactivity is observed,[51,52] showing that the nucleophilicity parameters *N* and *s*, which have been derived from reactions with benzhydrylium ions, are also relevant for S_N2 reactions of these nucleophiles. A similar correlation has been reported for reactions with methyl iodide.[51,52]

However, the slope of the correlation shown in Fig. 26 does not equal 1 as required by Eqn (1), indicating that the benzhydrylium-based nucleophile-specific parameters *N* and *s* can only be applied for S_N2 reactions when an additional, electrophile-specific slope parameter s_E is added.[51,52] For the same reason as

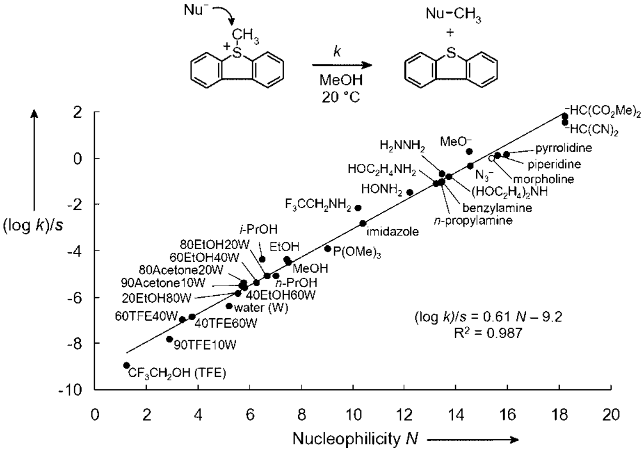


Figure 26. Reactions of the *S*-methyldibenzothiophenium ion with solvents and solutions of nucleophiles in methanol (rate constants are from References [33,51–53])

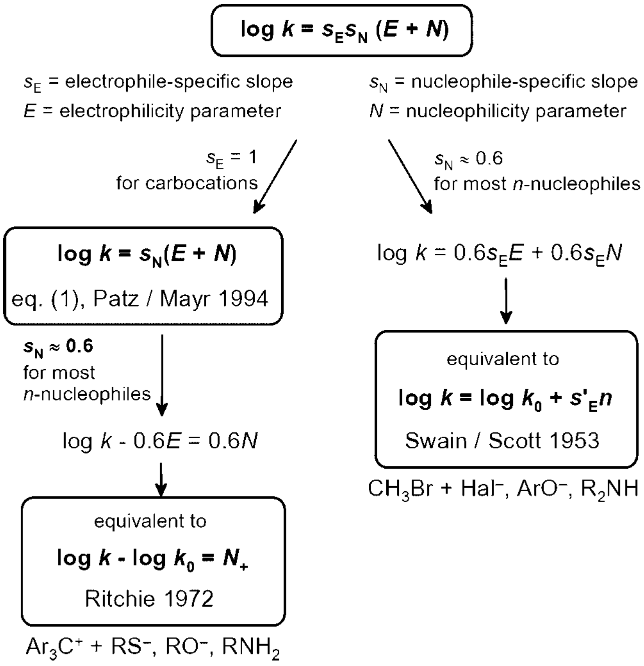


Figure 27. Relationships between the different correlation equations for electrophile nucleophile combinations

discussed in the context of Fig. 5, s_E is put before the parentheses which comprise the sum of *E* and *N*. For the sake of clarity, the nucleophile-specific parameter *s* defined in Eqn (1) is now renamed as s_N, but it should be emphasized that no new parameterization is performed and that the nucleophile-specific parameters *N* and *s* which have been derived from reactions with benzhydrylium ions can now be employed for describing S_N2 reactions. The analogy of this correlation with the extended Winstein–Grunwald equation,[54–56] which also employs nucleophile- and electrophile-specific sensitivity parameters is obvious.

Figure 27 shows that the general correlation equation given on top simplifies to Eqn (1) if only reactions of nucleophiles with carbocations are considered ($s_E = 1$). In previous work,[32] we have already reported that most of the nucleophiles studied by Ritchie have nucleophile-specific slope parameters of $s_N \approx 0.6$. Figure 27 shows that substitution of this value into our 1994 correlation (Eqn (1)) converts it into the Ritchie equation. Interestingly, water has a higher value of $s_N = 0.89$ than most other nucleophiles with a lone pair of electrons. Therefore, water which was originally selected as the reference nucleophile by Ritchie ($N_+ = 0$), does not match the Ritchie equation well. Ritchie[57] noticed this behaviour during the development of his scales and later replaced water by hydroxide ($N_+ = 4.75$) as the reference nucleophile.

Swain and Scott[58] also predominantly used nucleophiles with $s_N \approx 0.6$ for their studies of S_N2 reactions. When s_N is substituted by this number in the general equation on top of Fig. 27, an expression is obtained which is equivalent to the Swain–Scott equation.

It has thus been shown that the Ritchie and the Swain–Scott equations are special cases of the general relationship on top of Fig. 27. Future work has to concentrate on merging of these correlations and interpretations of the physical basis of s_E, s_N, *E* and *N*.

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