ACCOUNTS
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A Practical Guide for Estimating Rates of Heterolysis Reactions[†]

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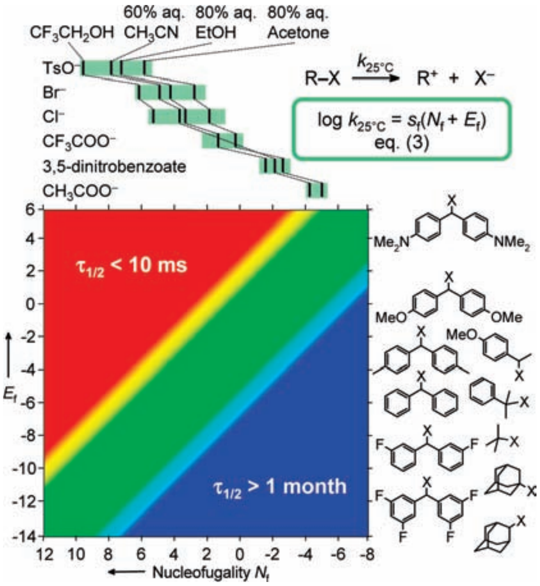

Chemists are well trained to recognize what controls relative reactivities within a series of compounds. Thus, it is well-known how the rate of ionization of R−X is affected by the stabilization of the carbocation R$^+$, the nature of the leaving group X$^-$, or the solvent ionizing power. On the other hand, when asked to estimate the half-life of the ionization of a certain substrate in a certain solvent, most chemists resign. This question, however, is crucial in daily laboratory practice. Can a certain substrate R−X be handled in alcoholic or aqueous solution without being solvolyzed? Can a biologically active tertiary amine or azole be released by ionization of a quaternary ammonium ion? In this Account, we describe a straightforward means of addressing such experimental concerns.

A semiquantitative answer to these questions is given by the correlation equation log $k_{25\,°C} = s_f(N_f + E_f)$, in which carbocations R$^+$ are characterized by the electrofugality parameter E_f, and leaving groups X$^-$ in a certain solvent are characterized by the nucleofugality parameter N_f and the nucleofuge-specific sensitivity parameter s_f. As s_f is typically around 1 ($0.8 < s_f < 1.2$), ionization half-lives of around 1 h at 25 °C can be expected when $E_f + N_f = -4$.

This correlation equation is formally analogous to the linear free energy relationship that was used to derive the most comprehensive nucleophilicity and electrophilicity scales presently available (Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles. *J. Am. Chem. Soc.* **2001**, *123*, 9500−9512). By subjecting 628 solvolysis rate constants $k_{25\,°C}$ for different benzhydryl derivatives (aryl$_2$CH−X) to a least-squares minimization on the basis of the correlation equation, we obtained and tabulate here (i) the electrofugality parameters E_f for 39 benzhydrylium ions and (ii) the nucleofuge-specific parameters N_f and s_f for 101 combinations of common leaving groups and solvents.

We show that the E_f parameters of the reference electrofuges can be used to determine N_f and s_f for almost any combination of leaving group and solvent. The nucleofuge-specific parameters of the reference systems can analogously be used to derive the electrofugalities E_f of other types of carbocations.

While it has long been recognized that good nucleophiles are not necessarily poor nucleofuges, it is now reported that there is also no general inverse relationship between electrophilicity and electrofugality. Although more electrophilic methyl- and methoxy-substituted benzhydrylium ions are generally weaker electrofuges, the inverse relationship between electrophilicity and electrofugality breaks down in the series of amino-substituted benzhydrylium ions.

Because neither differential solvation of the carbocations nor steric effects are explicitly considered by this treatment, predictions for substrates not belonging to the benzhydrylium series are only reliable within a factor of 10. This is hardly acceptable to physical organic chemists, who are used to high precision within narrow groups of compounds. The synthetic chemist, however, who is seeking orientation in a reactivity range of 25 orders of magnitude, might appreciate the simplicity of this approach, which only requires considering the sum $E_f + N_f$ or consulting our summary graphs.

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Introduction

A universally valid ranking of leaving group abilities does not exist. The same reasons that prevent the construction of general nucleophilicity and electrophilicity scales[1] also inhibit the construction of general nucleofugality and electrofugality scales. While it is well recognized that *absolute* ionization rates of substrates R−X are strongly affected by the nature of the solvent,[2,3] it has to be noted that also *relative* leaving group abilities of groups X^- (k_1, Scheme 1) are solvent-dependent.[4−6] Furthermore, ground-state effects, that is, electronic as well as steric interactions between leaving groups and other substituents at the reaction center, are variable (e.g., anomeric effect,[7−9] back strain[10,11]) and account for the dependence of the relative leaving group abilities of X^- on the nature of the electrofuges R^+. For these reasons, relative leaving group abilities have to be defined with respect to a certain solvent and a certain electrofuge.

Even if it is acknowledged that neither general nucleofugality nor general electrofugality scales can exist, the question arises whether there is a way of estimating the order of magnitude of the ionization rate of a certain substrate R−X in a certain solvent.

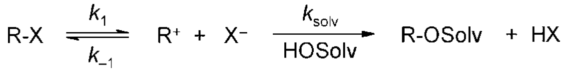
The classical way of predicting the influence of solvents on solvolysis rate constants is the Winstein−Grunwald eq 1,[2] where k is the rate constant under consideration, k_0 is the rate constant in 80% aqueous ethanol, Y is the solvent ionizing power (defined as log k of *tert*-butyl chloride), and m is a substrate-specific term, describing the sensitivity of the solvolysis rate constant on variation of the solvent ($m = 1$ for *tert*-butyl chloride).

$$\log(k/k_0) = mY \qquad (1)$$

Numerous alternative Y-scales have later been reported[5,12] to give better correlations with various types of substrates than the original Y-scale. Without judging the merit of these correlations, it is obvious that they focus on relative and not on absolute ionization rates, which are needed in daily laboratory practice.

Recently, we have suggested to solve this problem by developing comprehensive nucleofugality and electrofugality scales,[13] using an approach similar to that which gave access to the most comprehensive nucleophilicity and electrophilicity scales presently available.[1,14] By defining differently substituted benzhydrylium ions as reference electrofuges, the steric environment of the reaction center was kept constant while the stabilization of the resulting benzhydrylium ions was varied by many orders of magnitude.

SCHEME 1. Simplified Solvolysis Scheme



$$\text{R-X} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{R}^+ + \text{X}^- \xrightarrow[\text{HOSolv}]{k_{\text{solv}}} \text{R-OSolv} + \text{HX}$$

As illustrated in Scheme 2, one can employ acceptor-substituted benzhydrylium ions as reference electrofuges for differentiating the nucleofugalities of good leaving groups, methyl- and methoxy-substituted benzhydrylium ions for comparing leaving groups of intermediate reactivity, and amino-substituted benzhydrylium ions for characterizing poor leaving groups.

Determination of Ionization Rate Constants

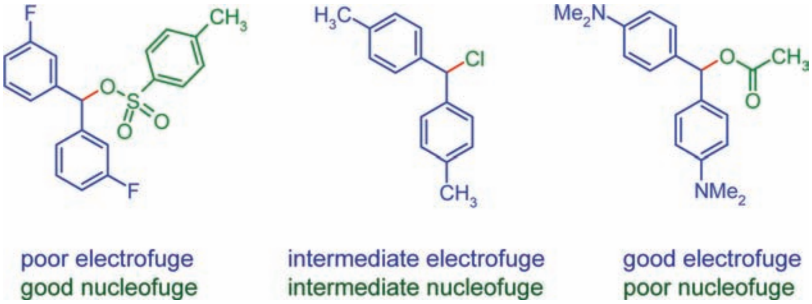
Most rate constants reported in the literature are in the experimentally most easily accessible range between 10^{-2} and 10^{-5} s^{-1} (half-lives 1 min to 1 day). Since in conventional S_N1 reactions a slow ionization step is followed by the fast trapping of the carbocation by the solvent, k_1 has usually been derived from the rate of formation of the acid HX,[15] which can be determined conductimetrically or titrimetrically as described in the literature.[16] Though this procedure disregards potential cation−anion combinations at the ion-pair stage, as demonstrated by Winstein and Goering with a variety of methods (e.g., racemization of optically active substrates or isotopomerization),[16] first-order rate constants referring to the rates of formation of HX are generally considered to be a good approximation for the ionization rate constants k_1 and are collected in Table S5 (Supporting Information).

Problems arise, however, when highly stabilized carbocations are produced in the solvolysis reactions. As already noted by Ingold et al.,[17] deviations from first-order kinetics are observed in such cases, because now also diffusionally equilibrated carbocations R^+ are not quantitatively trapped by the solvent but can recombine with the leaving group X^- (external ion return). Since the concentration of X^- increases during the course of the reaction, the degree of reversibility increases with the degree of conversion.[17,18]

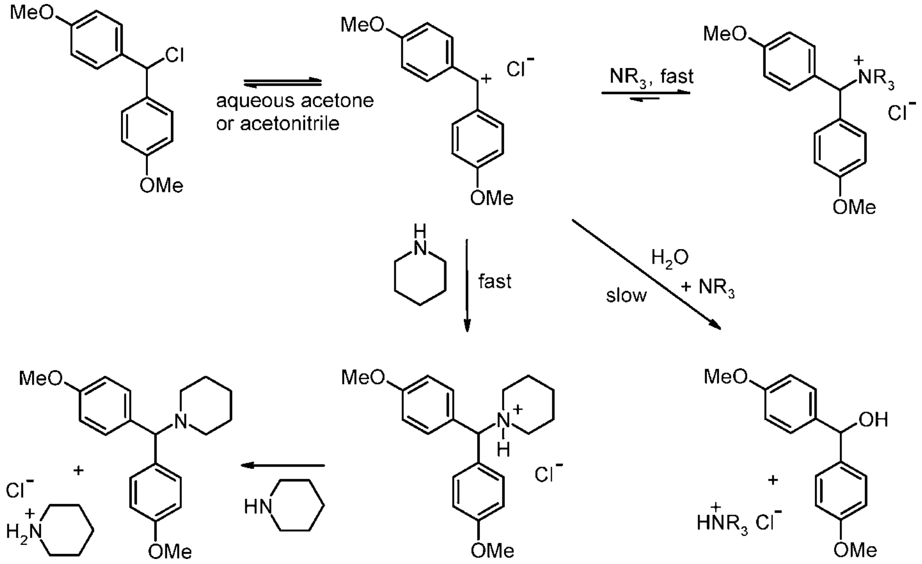
While external ion return has commonly been suppressed by N_3^- additives,[16] we have recently reported that external ion return can also be inhibited by adding nucleophilic amines, which quantitatively trap the intermediate carbenium ions without turning on the S_N2 mechanism (Scheme 3).[19] This method allows one to determine ionization rate constants on the millisecond time scale by using stopped-flow techniques with conductometric detection, thus giving access to a barely investigated field of carbocation chemistry.[20]

As shown in Figure 1, the conductometric rate constants, which were determined in a stopped-flow instrument by mix-

SCHEME 2. Substrates with Adjusted Electrofugal and Nucleofugal Properties



SCHEME 3. Heterolysis of 4,4′-Dimethoxybenzhydryl Chloride in Aqueous Solutions of Secondary and Tertiary Amines



ing a solution of the benzhydryl chloride in acetone with a solution of the amines in aqueous acetone, increase significantly with increasing concentrations of various amines. From the leveling of k_{obs} at 13.6−17.4 s^{-1}, corresponding to half-lives of 40−51 ms, we have excluded the occurrence of S_N2 reactions. 2,6-Lutidine, a stronger base than pyridine, does not increase the conductometric rate constant, indicating that the amines do not act as Brønsted bases, but suppress common ion return by trapping the intermediate carbenium ions with formation of benzhydryl ammonium ions (Scheme 3).

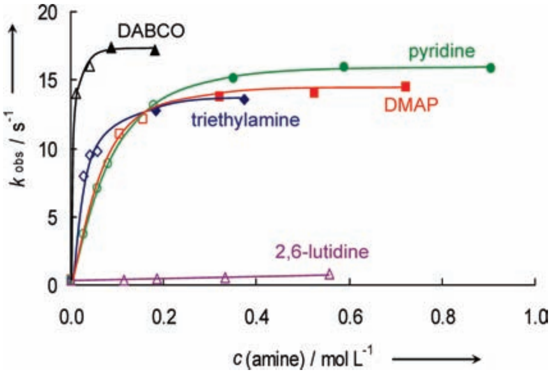
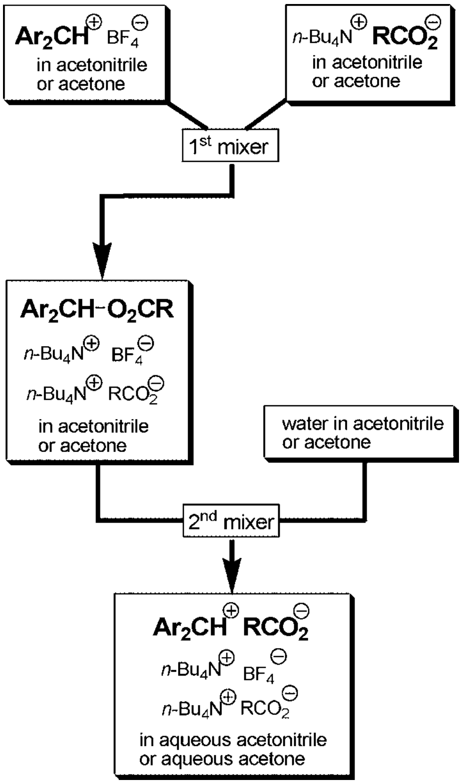


FIGURE 1. Observed rate constants of the solvolysis of 4,4′-dimethoxybenzhydryl chloride (0.018 M^{-1}) in 90% aqueous acetone in the presence of variable concentrations of different amines (open symbols represent kinetics that are not of first-order). (Reprinted with permission from ref 19. Copyright 2009 American Chemical Society.)

The similar, but not identical, heights of the plateaus observed with different amines indicate that the collapse of ion-pairs, in contrast to external ion return, cannot be completely suppressed by the amines. It should be noted that the plateau for pyridine is somewhat higher than that of the 10^3 times stronger nucleophile DMAP. As the reactions of the 4,4′-dimethoxybenzhydryl cation with these amines are diffusion-limited,[1,19] the relative nucleophilicities of the amines are not relevant for the rates of trapping the carbocations.

A further experimental technique has been developed for studying the ionization rates of benzhydrylium carboxylates Ar_2CH-O_2CR, which are derived from highly stabilized benzhydrylium ions. Due to the low stability of these esters, they cannot be isolated as pure compounds, and the double-mixing technique illustrated in Scheme 4 was employed to determine their ionization rates.[21] In the first mixer of a stopped-flow instrument, a solution of $Ar_2CH^+BF_4^-$ in acetonitrile or

SCHEME 4. Generation and Subsequent Ionization of Benzhydryl Carboxylates in a Double-Mixing Stopped-Flow Spectrometer (Reprinted with permission from ref 21. Copyright 2008 American Chemical Society)



acetone was combined with an excess of $n\text{Bu}_4\text{N}^+\text{RCO}_2^-$ in the same solvent to give a colorless solution of the covalent ester Ar_2CH-O_2CR. Combination of this solution with an equal volume of aqueous acetonitrile or acetone in a second mixer leads to regeneration of the colored benzhydrylium ion, which is monitored photometrically. Salt effects on the rates of these ionizations are negligible in the concentration ranges investigated[21] in line with observations by Hojo et al.[22]

Correlation Analysis

The most comprehensive nucleophilicity scale presently available is based on eq 2.[1,14,23]

$$\log k(20\ °\text{C}) = s(N + E) \tag{2}$$

It has been demonstrated that the solvent-dependent, nucleophile-specific parameters N and s, which are generally derived from the rates of the reactions of the corresponding nucleophiles with benzhydrylium ions of variable electrophilicity E, can be employed to predict rate constants for the reactions of a variety of carbenium ions and Michael acceptors with π-, n- and σ-nucleophiles.[1,14,23]

Equation 3, which characterizes electrofuges by one parameter (E_f) and nucleofuges by two (N_f and s_f) can analogously be used to correlate ionization rate constants of substrates with widely variable reactivity.[13] As solvent variation affects the leaving group abilities of different groups X^- quite differently, the nucleofuge-specific parameters N_f and s_f are generally defined for pairs of leaving groups and solvents, for example, for Cl^- in EtOH or for $CH_3CO_2^-$ in 60% aqueous acetonitrile. As most solvolysis rate constants have been measured at 25 °C, the reference temperature for eq 3 differs from that for eq 2.

$$\log k(25\ °\text{C}) = s_f(N_f + E_f) \tag{3}$$

A set of 39 benzhydrylium ions **E1**−**E39** have been selected as reference electrofuges (Table 1), and combinations of common leaving groups with commonly used solvents were defined as reference nucleofuges (**N1**−**N101**, see below). Solvolysis rate constants of substrates composed of the electrofuges **E1**−**E39** and the nucleofuges **N1**−**N101** are listed in Table S5 (Supporting Information).

The electrofugality of the 4,4′-dimethoxybenzhydrylium ion **E25** was defined as zero, E_f(**E25**) = 0.0, and the slope for Cl^- in EtOH was set to one, s_f(**N22**) = 1.0. With these fixations, the first-order rate constants listed in Table S5 (Supporting Information) were subjected to a least-squares fit according to eq 3, and $\Sigma\Delta^2$ as defined in eq 4 was minimized to yield the optimized parameters E_f (Table 1) as well as N_f and s_f (Table 2).[24] Slight deviations of these parameters from previously published values are due to the extended data basis for the parameters in this work.

$$\Sigma\Delta^2 = \Sigma(\log k_{\text{solv}} - \log k_{\text{calc}})^2 = \Sigma(\log k_{\text{solv}} - s_f(N_f + E_f))^2 \tag{4}$$

The good fit of these correlations is illustrated by Figure 2, and the small deviations between calculated and experimental rate constants (average factor of 1.1) are listed in Table S5 (Supporting Information).

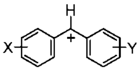
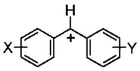
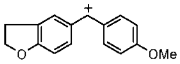
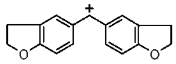
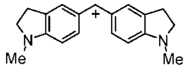
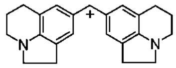
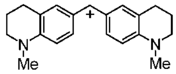
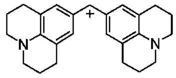
When different solvolysis rate constants were reported for the same substrate under the same conditions, and we were unable to unequivocally select one or the other, we generally used that rate constant for the final correlation which agreed best with the value calculated by eq 3.

Like eq 2, eq 3 has an untypical format of a linear free energy relationship. As both N_f and s_f are nucleofuge-specific parameters, eq 3 is equivalent to eq 5 where E_f and s_f are the same as in eq 3 and $N_f' = s_f N_f$.

$$\log k(25\ °\text{C}) = N_f' + s_f E_f \tag{5}$$

What is the difference between eqs 3 and 5? None, if one is going to calculate ionization rate constants log k from

TABLE 1. Reference Electrofuges

	Electrofuges  		Electro-fugality E_f [a]
No.	X =	Y =	
E1	3,5-Cl_2	3,5-Cl_2	−12.93
E2	3,5-F_2	3,5-F_2	−12.60
E3	3,5-Cl_2	3-Cl	−11.20
E4	3,5-F_2	3-F	−10.88
E5	3-Cl	3-Cl	−9.55
E6	3-F	3-F	−9.26
E7	4-NO_2	H	−9.20
E8	3-Cl	4-Cl	−8.15
E9	3-Cl	H	−7.69
E10	3-F	H	−7.53
E11	4-Cl	4-Cl	−6.91
E12	4-Br	H	−6.62
E13	4-Cl	H	−6.44
E14	H	H	−6.03
E15	3-Me	H	−5.73
E16	4-F	H	−5.72
E17	4-OPh	4-NO_2	−5.60
E18	3,5-Me_2	H	−5.43
E19	4-Me	H	−4.63
E20	4-OPh	H	−3.52
E21	4-Me	4-Me	−3.44
E22	4-OMe	H	−2.09
E23	4-OMe	4-Me	−1.32
E24	4-OMe	4-OPh	−0.86
E25	4-OMe	4-OMe	0.00
E26			0.61
E27			1.07
E28	4-$N(Ph)_2$	4-$N(Ph)_2$	1.78
E29	4-$N(CH_2CF_3)(Ph)$	4-$N(CH_2CF_3)(Ph)$	1.79
E30	4-$N(CH_3)_2$	H	2.38
E31	4-$N(CH_2CH_2)_2O$	4-$N(CH_2CH_2)_2O$	3.03
E32	4-$N(CH_2CF_3)(CH_3)$	4-$N(CH_2CF_3)(CH_3)$	3.13
E33	4-$N(Ph)(CH_3)$	4-$N(Ph)(CH_3)$	3.46
E34			4.83
E35	4-$N(CH_3)_2$	4-$N(CH_3)_2$	4.84
E36			5.05
E37			5.22
E38	4-$N(CH_2)_4$	4-$N(CH_2)_4$	5.35
E39			5.61

[a] For nucleofuges used to determine the E_f parameters, see Table S1 in the Supporting Information.

either N_f, s_f, and E_f (eq 3) or N_f', s_f, and E_f (eq 5)! It is trivial that a straight line can alternatively be expressed by the intercept on the y-axis (N_f' in eq 5) or on the x-axis (N_f in eq 3). As the authors are aware of the difficulties that some readers have with the unconventional form of eq 3,[25] ref 26 explains in detail why it is more convenient in practice to use eq 3 instead of eq 5.

Electrofugalities of Benzhydrylium Ions

Figure 3 shows a linear correlation between the electrofugality parameters and $\Sigma\sigma^+$. In line with previous investigations of Tsuno and Fujio,[27] highly unsymmetrically substituted systems (**E17**, **E30**) deviate positively from the correlation line, because in these cases the aryl ring with the weaker electron donor is twisted out of the plane and allows the aryl ring with the better electron donor to get into full conjugation with the carbenium center.

One can recognize a linear correlation between electrofugality E_f and electrophilicity E in the right part of Figure 4, which refers to methyl- and alkoxy-substituted benzhydrylium ions ($-2 < E < 6$). In this range, ionization rates (as expressed by E_f) decrease linearly with increasing electrophilic

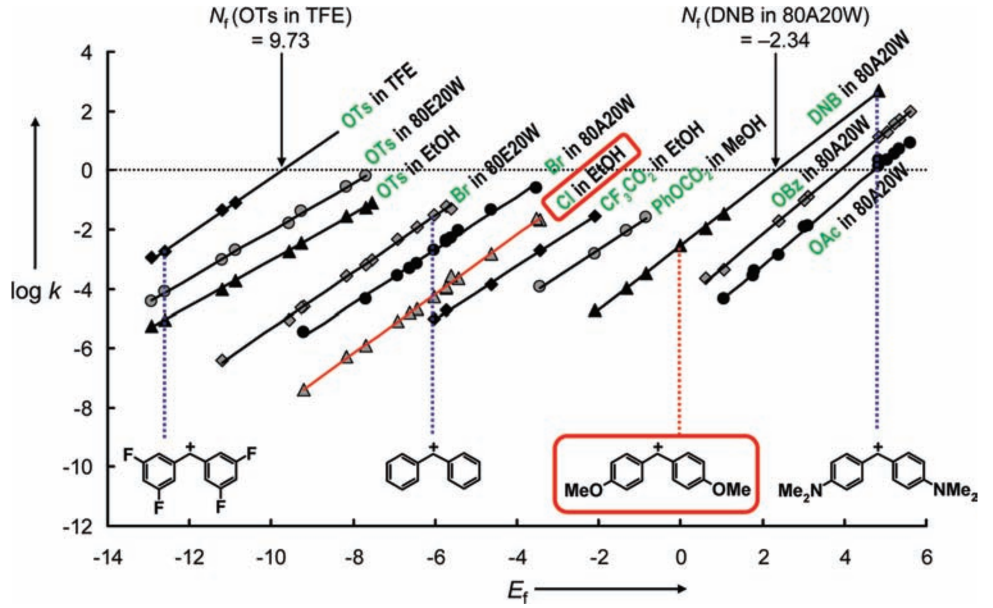


FIGURE 2. Plots of solvolysis rate constants log *k* (at 25 °C) for benzhydryl halides and various esters vs the electrofugality parameters E_f of benzhydrylium ions (determination of N_f as the negative intercepts on the abscissa and s_f as the slopes of the correlations). Mixtures of solvents are given as (v/v); A = acetone, E = ethanol, TFE = 2,2,2-trifluoroethanol, and W = water.

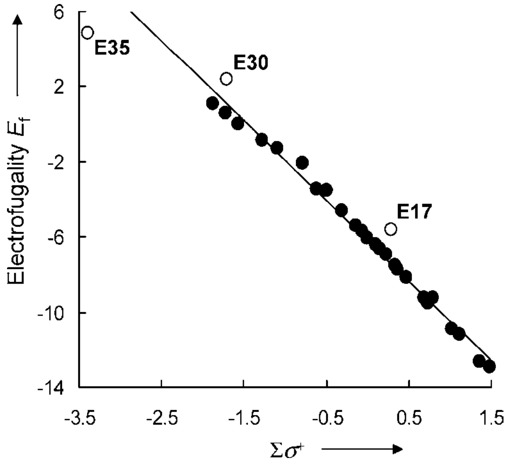


FIGURE 3. Correlation of the electrofugality parameters E_f of benzhydrylium ions (**E1**−**E27**, Table 1) with Hammett σ^+ constants (from refs 28 and 29). $E_f = -4.26\Sigma\sigma^+ - 6.19$, $n = 27$, $r^2 = 0.9916$; the deviating points (○) are not included in the correlation.

reactivity (*E*). The linear correlation breaks down for amino-substituted benzhydrylium ions ($E < -2$). The bis(dihydrofuranyl)-substituted benzhydrylium ion **E27**, for example, reacts 10^3 times faster with nucleophiles than the bis(diphenylamino)-substituted analogue **E28** (electrophilicity *E*), but the rates of their formation by ionization of the corresponding carboxylates differ by only a factor of 5 (electrofugality E_f). Furthermore, benzhydrylium ions **E35** and **E36**, which differ by almost 3 orders of magnitude in electrophilicity, are generated with almost identical rates (comparable electrofugality).

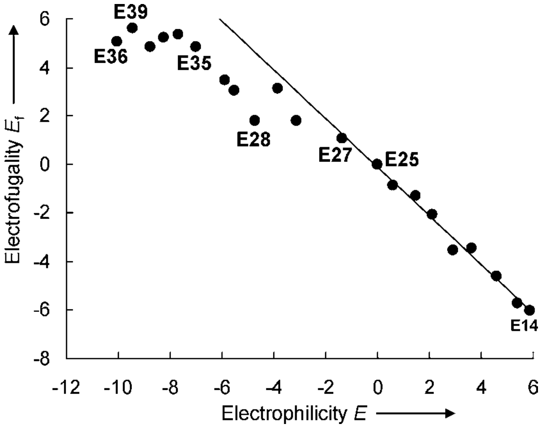


FIGURE 4. Correlation between electrophilicity (from ref 14) and electrofugality.

An alternative illustration of the breakdown of the correlation between E_f and *E* is presented in Figure 5 which compares two series of directly measured rate constants. One can clearly see that the rates of the reactions of the benzhydrylium ions **E34**−**E39** with 4-methylimidazole[30] (the same is true for reactions with any other nucleophile in various protic or aprotic solvents) do not give any information about the relative rates of ionization of the corresponding benzhydryl acetates.

Why are electrofugalities not always inversely correlated with electrophilicities? Figure 6 shows that the Gibbs energy diagrams for the hydrolyses of methyl- and dimethylamino-substituted benzhydryl derivatives, which proceed with similar rates, differ significantly. Whereas the transition state of the ionization of 4,4-dimethylbenzhydryl chloride (**E21-Cl**) is carbocation-like, the transition state of the ionization of the bis(dimethylaminophenyl)methyl acetate (**E35-OAc**) is not

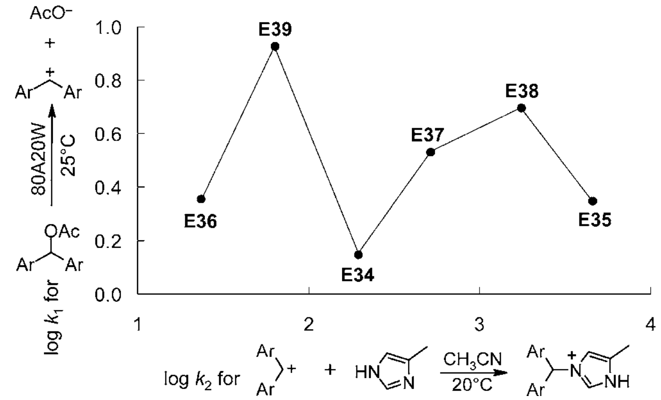


FIGURE 5. Plot of the first-order rate constants log k_1 for the solvolysis reactions of benzhydryl acetates in 80% aqueous acetone versus the second-order rate constants log k_2 of the combination reactions of benzhydrylium ions with 4-methylimidazole (a 7:3 mixture of 4-methyl and 5-methyl-1-benzhydrylimidazole was isolated, from ref 30).

carbocation-like. In order to compare ionization processes of similar rates, the change from less to more stabilized carbocations has to be accompanied by a change from good to weak leaving groups.

From the diffusion-controlled reactions of methyl substituted benzhydrylium ions with Cl^- and Br^-, we had concluded that the combinations of these ions occur without barrier.[31] According to the principle of microscopic reversibility, there can also not be a barrier for the reverse reaction (ionization process), and the transition states for the ionization of the methyl-substituted benzhydryl chlorides correspond to the Gibbs energies of the resulting carbocations (Figure 6, left). Since in these cases the ionization rate constants reflect the stabilities of the carbocations, electrofugalities are inversely correlated with the corresponding electrophilicities.

As highly stabilized carbocations are not generated through carbocation-like transition states (Figure 6, right), the Gibbs activation energies $\Delta G^\ddagger$ of the corresponding ionization processes are not solely controlled by the stabilization of the carbocations but also by the intrinsic barriers, the relative magnitudes of which are difficult to predict. As a result, electrofugalities are not any longer the reverse of the electrophilicities, as discussed in detail in ref 21. An analogous situation has recently been observed in correlations between the electrofugalities and electrophilicities of tritylium ions.[32]

The benzhydrylium ions listed in Table 1, which cover a reactivity range of 18 orders of magnitude, can now be used as reference electrofuges to characterize nucleofuges in a reactivity range of more than 25 orders of magnitude, because common kinetic methods allow one to measure ionization rate constants from 10^{-6} to 10^{2} s^{-1}. When selecting suitable reference electrofuges, it should be noted, however, *that one or several of the chlorine-substituted benzhydryl compounds* **E1**, **E3**, **E5**, **E8**, *and* **E9** *caused severe skin irritations*. We advise that these substrates should be avoided and replaced by the corresponding fluoro-derivatives **E2**, **E4**, **E6**, and **E10**, which have similar reactivities, but so far did not show any harmful effects.[33]

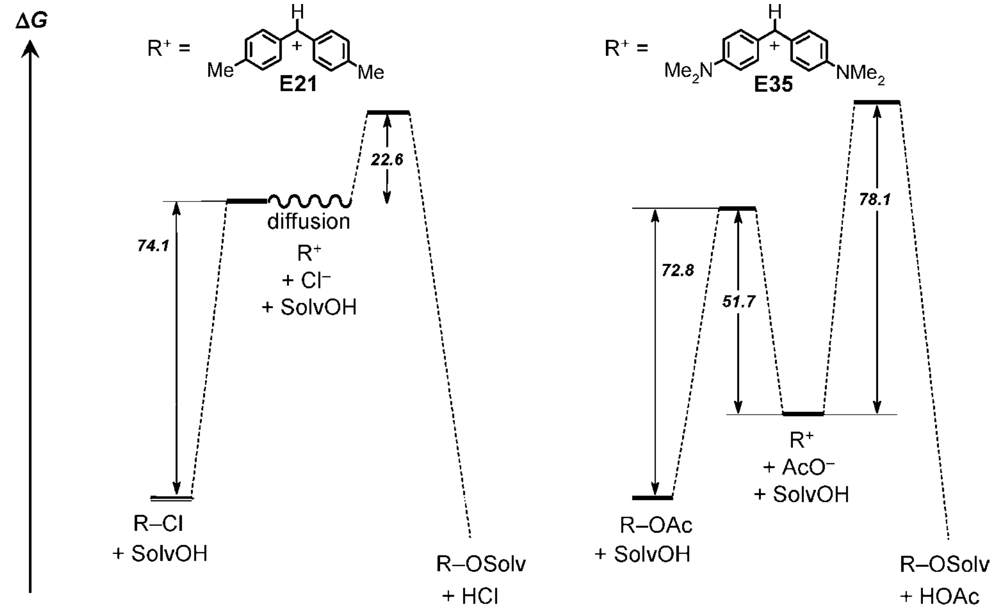


FIGURE 6. Gibbs energy profiles for the solvolyses of $(4\text{-}CH_3C_6H_4)_2CHCl$ (**E21-Cl**) in 80% aqueous ethanol and $(4\text{-}Me_2NC_6H_4)_2CHOAc$ (**E35-OAc**) in 90% aqueous acetone (at 25 °C, ΔG in kJ mol^{-1}).[31] In both solvolysis reactions, the ionization step is rate-determining, because the recombination of R^+ with the leaving group X^- is slower than the subsequent irreversible reaction with the solvent due to the low concentration of X^-.

TABLE 2. Reference Nucleofuges

Entry	Leaving group[a]	Solvent[b]	N_f/s_f[c]
N1	OTs	TFE	9.73/0.94
N2		M	7.33/0.82
N3		80E20W	7.45/0.80
N4		E	6.09/0.78
N5		60AN40W	7.97/0.82
N6		80A20W	6.00/0.83
N7		90A10W	5.38/0.89
N8	OMs	80E20W	7.49/0.84
N9		E	5.82/0.80
N10		60AN40W	7.70/0.83
N11		80A20W	5.85/0.84
N12	Br	TFE	6.19/0.95
N13		M	4.23/0.99
N14		80E20W	4.36/0.95
N15		E	2.93/0.93
N16		60AN40W	5.23/0.99
N17		80A20W	3.01/0.90
N18		90A10W	2.29/1.01
N19	Cl	TFE	5.54/0.85
N20		M	2.91/0.99
N21		80E20W	3.24/0.99
N22		E	1.82/1.00
N23		60AN40W	3.84/0.96
N24		80AN20W	2.96/1.00
N25		90AN10W	2.23/1.08
N26		60A40W	3.30/0.97
N27		80A20W	2.03/1.05
N28		90A10W	1.14/1.11
N29	HFB	60M40W	3.06/0.84
N30		70M30W	2.71/0.84
N31		80M20W	2.33/0.84
N32		90M10W	2.09/0.89
N33		M	1.52/0.90
N34		60E40W	2.30/0.86
N35		70E30W	1.99/0.86
N36		80E20W	1.80/0.88
N37		90E10W	1.37/0.88
N38		E	0.77/0.93
N39		50A50W	2.31/0.87
N40		60A40W	1.86/0.88
N41		70A30W	1.52/0.91
N42		80A20W	1.01/0.91
N43	TFA	70M30W	2.47/0.81
N44		80M20W	2.13/0.83
N45		90M10W	1.75/0.84
N46		60E40W	2.11/0.82
N47		70E30W	1.83/0.84
N48		80E20W	1.42/0.82
N49		E	0.34/0.89
N50		50A50W	2.03/0.81
N51		60A40W	1.66/0.86
N52		70A30W	1.23/0.88
N53		80A20W	0.65/0.88
N54		90A10W	0.21/0.97
N55	PhOCO$_2$	80M20W	–0.33/0.81
N56		90M10W	–0.61/0.85
N57		M	–0.95/0.90
N58		60E40W	–0.40/0.81
N59		70E30W	–0.57/0.85
N60		80E20W	–0.74/0.90
N61		90E10W	–0.91/0.96
N62		50A50W	–1.06/0.77
N63		60A40W	–1.39/0.83
N64		70A30W	–1.73/0.88
N65	DNB	80E20W	–1.43/0.98
N66		E	–2.05/1.09
N67		60AN40W	–2.06/0.97
N68		60A40W	–2.20/0.90
N69		80A20W	–2.34/1.10
N70		90A10W	–2.68/1.13
N71	MeOCO$_2$	80M20W	–1.43/0.94
N72		90M10W	–1.66/0.97
N73		M	–2.00/1.01
N74		60E40W	–1.59/0.89
N75		70E30W	–1.74/0.93
N76		80E20W	–1.96/0.95
N77		90E10W	–2.20/0.98
N78		50A50W	–2.13/0.86
N79		60A40W	–2.56/0.88
N80		70A30W	–2.83/0.94
N81	PNB	80E20W	–2.78/0.95
N82		60AN40W	–3.30/0.91
N83		80AN20W	–3.41/0.98
N84		60A40W	–2.79/1.11
N85		80A20W	–3.40/1.16
N86		90A10W	–3.70/1.17
N87	^{i}BuOCO$_2$	60E40W	–2.04/0.89
N88		90E10W	–2.46/0.98
N89		50A50W	–2.51/0.87
N90	^{t}BuOCO$_2$	60E40W	–2.91/0.89
N91		80E20W	–3.12/0.96
N92		60AN40W	–3.28/0.96
N93		60A40W	–3.62/0.94
N94	BzO	60AN40W	–3.92/1.02
N95		80AN20W	–4.19/1.12
N96		60A40W	–3.89/1.15
N97		80A20W	–4.46/1.17
N98	AcO	60AN40W	–4.18/1.08
N99		80AN20W	–4.52/1.11
N100		60A40W	–4.05/1.17
N101		80A20W	–4.73/1.18

[a] Leaving groups: HFB = heptafluorobutyrate, TFA = trifluoroacetate, DNB = 3,5-dinitrobenzoate, and PNB = 4-nitrobenzoate. [b] Mixtures of solvents are given as (v/v); A = acetone, AN = acetonitrile, E = ethanol, M = methanol, TFE = 2,2,2-trifluoroethanol, and W = water. [c] For electrofuges used to determine the N_f and s_f parameters, see Table S2 in the Supporting Information.

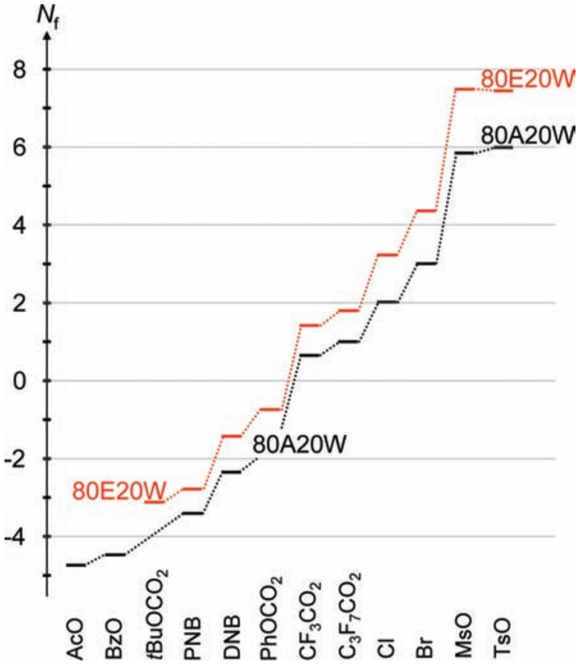


FIGURE 7. Nucleofugality scale. PNB = 4-nitrobenzoate, DNB = 3,5-dinitrobenzoate, A = acetone, and E = ethanol, W = water.

Nucleofugalities of the Reference Nucleofuges

The nucleofugality parameters N_f and s_f of the reference nucleofuges **N1**−**N101** which have been used to derive the E_f values of the reference electrofuges **E1**−**E39** are summarized in Table 2. Figure 7 illustrates an increase of nucleofugality by 11 units in N_f from acetate to tosylate in 80% aqueous acetone. As s_f is generally close to 1, this difference corresponds to an increase of reactivity by a factor of 10^{11}, or relative half-lives ranging from 1 s to 3000 years.

Though the small differences in s_f are difficult to explain, a trend appears to be general: In a series of solvents in which only the ratio organic component/water is changed, s_f decreases slightly with increasing amount of water, as exemplified in Figure 8.[15,34]

As this trend is also observed for solvolyses of benzhydryl chlorides in aqueous acetonitrile and aqueous acetone, that is, substrates where the recombination of leaving groups with carbocations is diffusion-controlled, the change of s_f cannot be due to a change of the ionic character of the transition state. The absence of a barrier between substrates and ions implies that the ionic character is fully developed in the transition states, and the smaller s_f values in the water-rich solvent mixtures indicate that the differences in carbocation stabilization which are observed in the less polar, water-poor solutions are slightly attenuated in the more polar, water-rich solutions. From the small differences of s_f, one can conclude that differential solvation of the carbocations, that is, the differences of the solvation energies of differently stabilized benzhydrylium ions, are rather small.

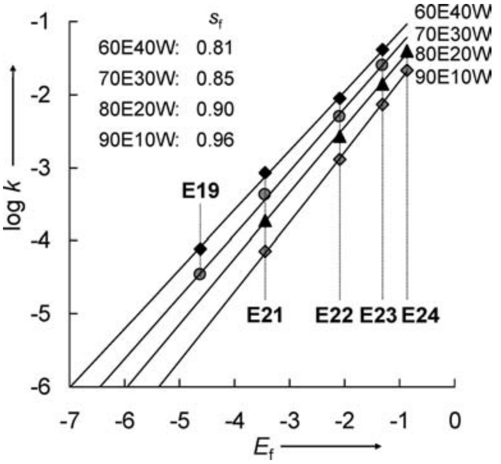


FIGURE 8. Plots of the observed first-order rate constants k (at 25 °C) for the solvolyses of benzhydryl phenyl carbonates[15] in aqueous ethanol (solvents given as v/v) against the electrofugality parameters E_f of the benzhydrylium ions.

At present, we do not yet know the rate constants for the combinations of benzhydrylium ions with tosylate or trifluoroacetate anions under the conditions of the solvolysis reactions. We, therefore, cannot confirm the assumption that the smaller values of s_f in these reaction series are due to transition states in which the carbocationic character is not yet fully developed.

Characterization of Further Nucleofuges

The availability of electrophilicity parameters for a series of electrofuges of widely differing reactivity (Table 1) now allows us to characterize nucleofugalities of almost any leaving group X^- or X.

If a series of rate constants are available for a certain leaving group in a certain solvent, which refer to benzhydrylium ions of significantly different electrofugality, one can plot the first-order rate constants log k_1 for these solvolysis reactions against the electrofugality parameters E_f from Table 1. As shown for three examples in Figure 9, the nucleofugality parameters N_f are then obtained as the negative intercepts on the abscissa (E_f axis) and the s_f parameters correspond to the slopes of these correlations. In this way, the N_f and s_f parameters listed in Table 3 have been calculated from the solvolysis rate constants listed in Table S6 of the Supporting Information.

In several cases, heterolysis rate constants k_1 cannot be measured directly, but they are accessible from the second-order rate constants k_2 of the reverse reactions (combination

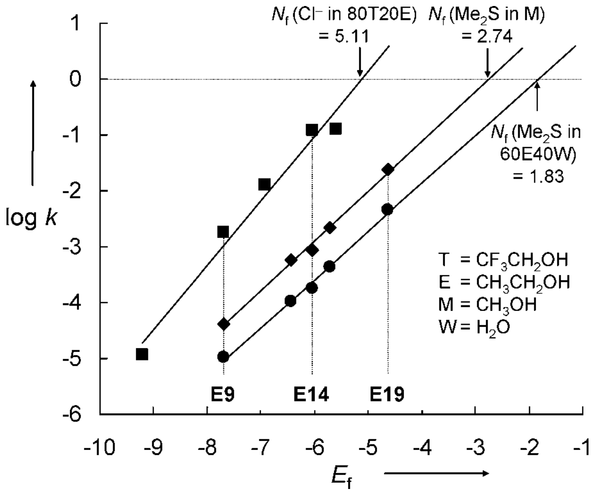


FIGURE 9. Plots of the first-order rate constants k (at 25 °C) of the solvolyses of benzhydryl chlorides and benzhydryl dimethylsulfonium ions against the electrofugality parameters E_f.

TABLE 3. Nucleofugality Parameters of Further Nucleofuges

leaving group X⁻ or X	solvent[a]	N_f/s_f
OMs	TFE	9.84/1.00
Br	80M20W	5.34/1.00
	90M10W	4.83/0.99
	70E30W	4.83/0.96
	90E10W	3.73/0.93
	50A50W	5.11/0.93
	60A40W	4.67/0.97
	70A30W	3.96/0.95
	60T40E	5.14/1.08
	80T20E	5.86/1.15
Cl	80M20W	4.12/1.00
	90M10W	3.56/0.99
	60E40W	4.09/0.97
	70E30W	3.63/0.96
	90E10W	2.62/0.98
	50A50W	4.26/1.03
	70A30W	2.72/1.00
	40T60E	3.45/1.04
	60T40E	4.44/1.16
	80T20E	5.11/1.15
	2-propanol	0.41/0.93
Me$_2$S	M	2.74/0.89
	80M20W	2.40/0.89
	60M40W	2.06/0.85
	E	2.40/0.87
	80E20W	1.96/0.86
	60E40W	1.83/0.86
AcO	80M20W	−3.92/0.91
	60M40W	−3.59/0.87
DNB	90E10W	−1.54/1.06
	70A30W	−2.28/0.98

[a] Mixtures of solvents are given as (v/v); A = acetone, AN = acetonitrile, E = ethanol, M = methanol, TFE or T = 2,2,2-trifluoroethanol, and W = water.

of nucleophile and electrophile) and the corresponding equilibrium constants K by using eq 6.

$$k_1 = k_2 / K \tag{6}$$

TABLE 4. Nucleofugality Parameters of Further Nucleofuges, s_f Fixed to 1.00 (Determined at 20 °C unless Noted Otherwise)

leaving group X⁻ or X	solvent[a]	N_f[b]
$\underline{S}$CN	AN	(1.89)
SC$\underline{N}$	AN	(−3.09)
(4-MeOC$_6$H$_4$)$_3$P	CH$_2$Cl$_2$	(−5.91)
(4-MeC$_6$H$_4$)$_3$P	CH$_2$Cl$_2$	(−5.20)
Ph$_3$P	CH$_2$Cl$_2$	(−4.44)
(4-ClC$_6$H$_4$)$_3$P	CH$_2$Cl$_2$	(−2.93)
azide	45M55AN	(−3.81)
	91M9AN	(−3.85)
	91E9AN	(−4.38)
nitrite	AN	(−3.76)
DMAP	CH$_2$Cl$_2$	(−5.32)
	AN	(−6.29)
4-(1-pyrrolidinyl)pyridine	CH$_2$Cl$_2$	(−5.33)
4-methoxypyridine	CH$_2$Cl$_2$	(−2.80)
4-methylpyridine	CH$_2$Cl$_2$	(−1.91)
pyridine	CH$_2$Cl$_2$	(−0.99)
DABCO	AN	(−1.00)
$\underline{S}$O$_2$Ph[c]	50AN50W	(−4.69)
	60AN40W	(−4.87)
S$\underline{O}_2$Ph	DMSO	(−3.10)
1-methylimidazole	AN	(−6.29)
1-phenylimidazole	AN	(−5.59)
1-methylbenzimidazole	AN	(−6.01)
isoquinoline	AN	(−3.04)

[a] Mixtures of solvents are given as (v/v); AN = acetonitrile, E = ethanol, M = methanol, TFE or T = 2,2,2-trifluoroethanol, and W = water. [b] Slope s_f fixed to 1.00. [c] At 25 °C.

As the heterolysis rate constants obtained in this way (Table S7, Supporting Information) do not allow a wide variation of electrofuges for characterizing a certain nucleofuge, a reliable determination of s_f is not possible in such cases. Therefore, estimates of N_f were derived from eq 3 by setting s_f = 1.00 (Table 4). As shown in Table S7 (Supporting Information), the agreement between calculated and experimental rate constants obtained in this way is again satisfactory (average factor 1.5), and significant deviations (factor 3 and 6) are only found for two phosphines.

Conclusions

The correlation eq 3, where electrofuges (carbocations) are characterized by one (E_f) and nucleofuges (combinations of leaving groups and solvents) are characterized by two parameters (N_f and s_f) predicts the ionization rates of benzhydryl derivatives with high precision. The 39 benzhydrylium ions in Table 1, which cover a reactivity range of 18 orders of magnitude, and the 101 combinations of common leaving groups and solvents in Table 2, which cover a reactivity range of 15 orders of magnitude, can be used as references to derive the reactivity parameters N_f, s_f, and E_f of other nucleofuges and electrofuges, respectively. Though the correlations are of lower quality when other types of carbocations are considered, the analysis of a smaller set of data has shown that eq 3 also works well for other types of aryl substituted carbenium ions.[35] Application of eq 3 for deriving electrofugality parameters from the solvolysis rate constants of *tert*-butyl chlorides and bromides and of 1-adamantyl chloride, bromide, tosy-

TABLE 5. Solvolysis Half-Lives for Benzhydryl Derivatives

$\tau_{1/2}$	k_1/s^{-1}	$s_f(N_f + E_f)$
1 min	1.2×10^{-2}	−1.9
1 h	1.9×10^{-4}	−3.7
1 day	8.0×10^{-6}	−5.1
1 month	2.6×10^{-7}	−6.6

late, trifluoroacetate, and dimethylsulfonium ion and the corresponding N_f and s_f parameters from Table 2 yielded electrofugalities E_f for the tertiary carbenium ions which varied by two units.[35] As a consequence, k_{exp}/k_{calc} ranges from 0.1 to 10, which we consider tolerable for qualitative predictions by a 3-parameter equation covering a reactivity range of more than 25 orders of magnitude. Table 5 can, therefore, be employed for estimating solvolysis half-lives for most S_N1 active substrates from E_f, N_f, and s_f. However, a severe failure of eq 3 must be expected for the generation of α-alkoxy- and α-amino-substituted carbenium ions, because in these cases geminal interactions between the alkoxy or the amino group with the leaving group will modify the ground state energies.[7]

A graphical illustration of these relationships is shown in Figure 10, where nucleofugalities increase from bottom to top, electrofugalities increase from top to bottom, and systems with $N_f + E_f = -4$ are set at the same level. As s_f typically ranges from 0.8 to 1.2, eq 3 predicts heterolysis half-lives from 0.3 to 5 h for combinations of electrofuges and nucleofuges at the same level; such combinations can easily be studied kinetically. More important, however, is

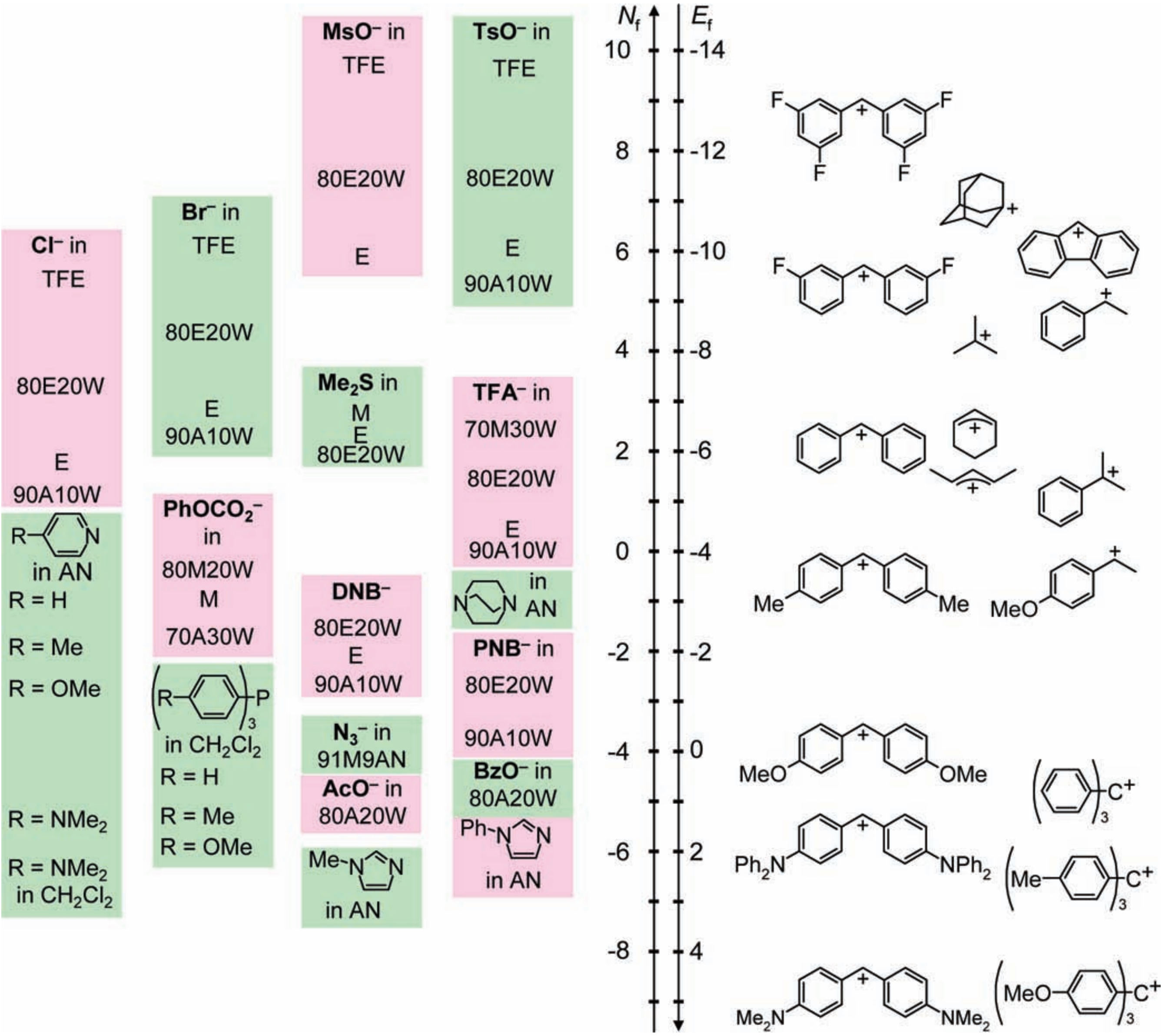


FIGURE 10. Semiquantitative model for heterolysis reactions: Combinations of electrofuges and nucleofuges at the same level cleave with a half-life of approximately 1 h.

another aspect of Figure 10: When the electrofuges are located several units above the nucleofuge in Figure 10, one can be confident that the heterolysis of such a combination will not occur at room temperature. If, however, a nucleofuge is located several units above an electrofuge, a substrate consisting of these two fragments will experience a very fast heterolytic cleavage. It will then be difficult or impossible to handle such a compound in the corresponding solvent. An alternative illustration of this behavior is given in the colored diagram of the Conspectus.

The reactivity parameters of the reference electrofuges in Table 1 and the reference nucleofuges in Table 2 can now be used to determine nucleofugalities N_f/s_f of almost any leaving group/solvent pair and electrofugalities of almost any carbocation in order to develop a semiquantitative basis of heterolytic processes.

Many of the rate constants used for these correlations have been determined by Dr. Sandra Jurić, Christoph Nolte, Dr. Heike F. Schaller, Dr. Andre Streiter, and Dr. Alexander Tishkov. Their contributions as well as financial support by the Deutsche Forschungsgemeinschaft (Ma 673/20-3) and the Ministry of Science, Education and Sports of the Republic of Croatia (Grant No. 006-0982933-2963) is gratefully acknowledged. We thank Dr. Armin R. Ofial for helpful discussions.

Supporting Information Available. Correlations of log *k* versus E_f and list of rate constants. This information is available free of charge via the Internet at http://pubs.acs.org/.

BIOGRAPHICAL INFORMATION

Nicolas Streidl obtained his Ph.D. (2010) with Herbert Mayr in München, Germany. His interests include quantitative approaches to organic reactivity with focus on heterolysis reactions.

Bernard Denegri received his B.S. and Ph.D. (O. Kronja, 2009) in chemistry from the Faculty of Science (University of Zagreb, Croatia). He is currently a Research and Teaching Assistant at the Faculty of Pharmacy and Biochemistry (University of Zagreb).

Olga Kronja received her Ph.D. in 1988 (S. Borčić, Zagreb, Croatia), and after postdoctoral studies (M. Saunders, Yale University, 1990−1992) she was appointed at the Faculty of Pharmacy and Biochemistry (University of Zagreb) as an Assistent Professor (1992), Associate Professor (1999), and Professor (2005). Her scientific interests are physical organic chemistry, particularly solvolytic reactions, kinetic and equilibrium isotope effects, and carbocation chemistry.

Herbert Mayr obtained his Ph.D. in 1974 (R. Huisgen, LMU München, Germany), and after postdoctoral studies (G. A. Olah, Cleveland) he completed his habilitation in 1980 (P. v. R. Schleyer, Erlangen, Germany). After professorships in Lübeck and Darmstadt, he returned to the LMU München in 1996. He is a member of the Bavarian Academy of Sciences and the Deutsche Akademie der Naturforscher Leopoldina, and he received the Liebig Denkmünze of the GDCh. He is developing quantitative approaches to polar organic reactivity.

FOOTNOTES

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[†] In memory of Professor Yuho Tsuno.

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