

How Fast Do R–X Bonds Ionize? A Semiquantitative Approach

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Abstract: The correlation equation $\log k_{25^\circ\text{C}} = s_f(N_f + E_f)$, where s_f and N_f are nucleofuge-specific parameters referring to leaving group/solvent combinations and E_f are electrofuge-specific parameters referring to the incipient carbocation R^+ , are used to predict ionization rate constants of alkyl derivatives R–X. We show how to employ

the E_f parameters of reference electrofuges and the s_f and N_f parameters of reference nucleofuges reported in the preceding article for determining fur-

ther s_f , N_f , and E_f parameters. Since s_f is usually close to 1.0, one comes to the semiquantitative rule that at 25 °C, compounds R–X for which $N_f + E_f > -2$ will solvolyze with half-lives of less than a minute, while the solvolysis half-lives will exceed 1 month if $N_f + E_f < -6.5$.

Keywords: carbocations • kinetics • nucleophilic substitution • reaction mechanisms • solvent effects

Introduction

Ionization processes as depicted in Equation (1), are key steps in many synthetic transformations.



The factors that are responsible for the *relative* rates of ionization, for example, the reactivity series depicted in Scheme 1, are familiar to any organic chemist.^[1]

- Influence of alkyl groups
 $\text{CH}_3\text{CH}_2\text{Br} \ll (\text{CH}_3)_2\text{CH-Br} < (\text{CH}_3)_3\text{CBr}$
- Influence of leaving groups
 $\text{R-OH} \ll \text{R-Cl} < \text{R-Br} < \text{R-I}$
- Influence of solvents
 $90\% \text{ aq. acetone} < 50\% \text{ aq. acetone} < \text{water}$

Scheme 1. Relative $\text{S}_{\text{N}}1$ reactivities.

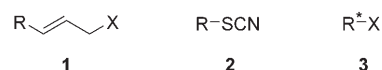
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However, most chemists have problems in estimating absolute $\text{S}_{\text{N}}1$ reactivities and cannot easily assess approximate reaction times, even for simple systems, such as the half-life of *tert*-butyl chloride in ethanol at 25 °C (answer: 93 days).^[2] However, such knowledge is important in many situations of everyday laboratory practice, as illustrated by the following examples.

Can a substrate RX be purified by chromatography or crystallization in alcoholic solution without being solvolyzed? Does RX tolerate synthetic transformations of R in aqueous or alcoholic solutions without solvolysis of the R–X bond? Can one isolate and manipulate compounds **1** or **2** without the occurrence of allylic rearrangements or of thiocyanate/isothiocyanate rearrangements, respectively? Are enantiopure compounds **3** configurationally stable, or do they racemize in dipolar protic or nonprotic media?



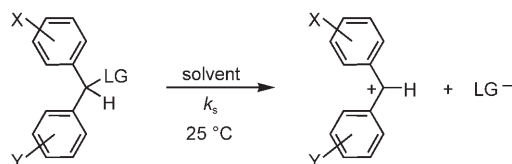
While we know that, *in principle*, all these reactions *may* occur, we often do not know whether they *actually will* occur under certain conditions. Clearly, numerous parameters have to be considered when accurate answers to these questions are required. While several scales that correlate solvolysis rate constants of certain substrates with empirical solvent parameters have been published,^[2–9] they cannot easily be applied to predict ionization rates of R–X in gen-

eral. This article demonstrates that, in a variety of reference solvents and solvent mixtures, semiquantitative rate constants for the heterolysis of R–X bonds can be derived from just two parameters: nucleofugality N_f and electrofugality E_f .

In the preceding article^[10] we have demonstrated that Equation (2) is suitable for the calculation of heterolysis rate constants of benzhydryl derivatives in various solvents (Scheme 2).

$$\log k_{25^\circ\text{C}} = s_f(N_f + E_f) \quad (2)$$

where k is the first-order rate constant (s^{-1}), s_f is the nucleofuge-specific slope parameter, N_f is the nucleofugality parameter, and E_f is the electrofugality parameter.



Scheme 2. LG = leaving group.

We studied the solvolysis rates of a large variety of benzhydrylium tosylates, bromides, chlorides, trifluoroacetates, 3,5-dinitrobenzoates, and 4-nitrobenzoates in standard solvents and subjected the solvolysis rate constants to a correlation analysis on the basis of Equation (2), and thus obtained E_f values for a series of benzhydrylium ions, which are considered as reference electrofuges, as well as N_f and s_f values for several combinations of leaving groups and solvents, which are considered as reference nucleofuges.^[10] Here, we demonstrate how to employ these reactivity parameters for characterizing further electrofuges and nucleofuges, and show how to use these data for answering the questions raised above.

Results and Discussion

Characterization of further nucleofuges

Nucleofugalities of chloride and bromide in different solvents: Solvolysis rates of benzhydrylium chlorides and bromides have been investigated in a manifold of solvents,^[7,11,12] and the corresponding rate constants are given in the Supporting Information. As depicted in Figure 1, the isopropanolysis rate constants of benzhydrylium chlorides, as well as the corresponding solvolysis rate constants in 90% aqueous methanol (90M) and 70% aqueous acetone (70A), correlate well with the corresponding electrofugality parameters E_f reported in the preceding article.^[10] The same is true for solvolysis rate constants in other solvents, and the N_f and s_f parameters summarized in Table 1 and depicted in Scheme 3 have been obtained as the negative intercepts on the abscissa and the slopes of analogous correlations, respectively.

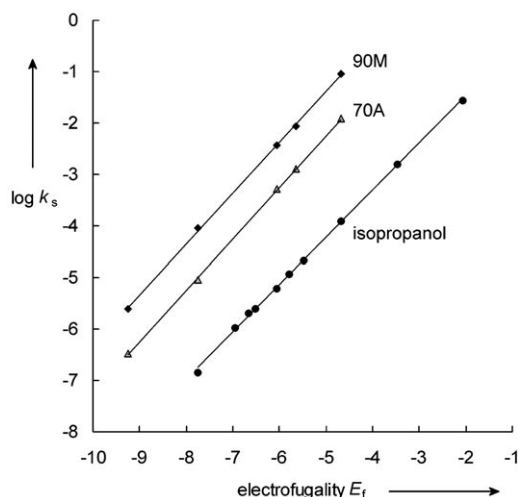
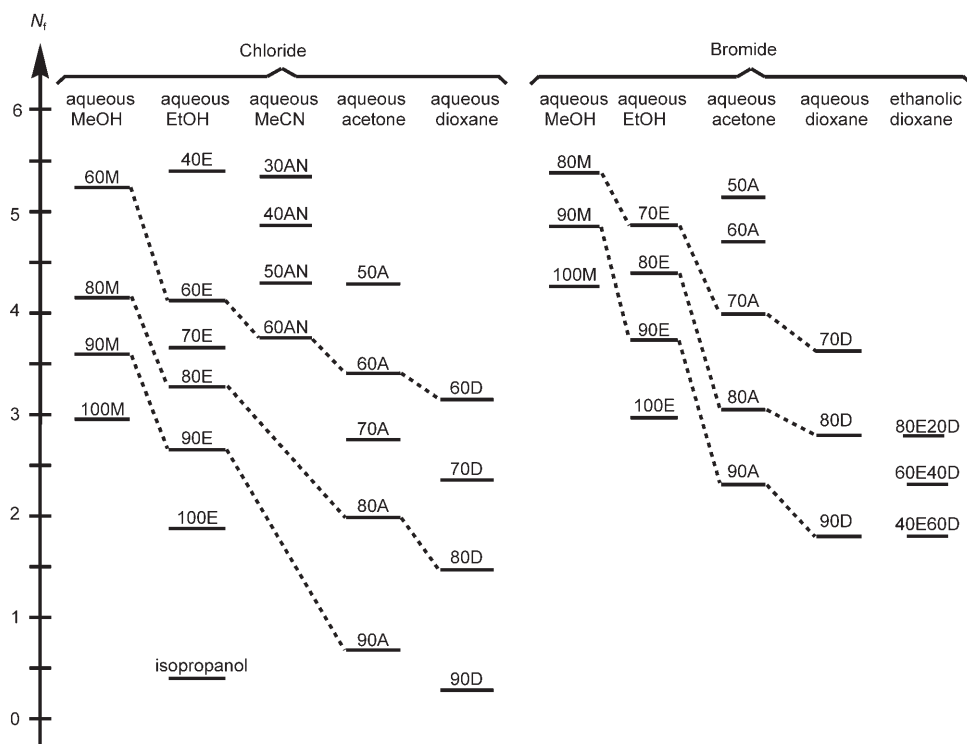


Figure 1. Correlation of the rate constants for the solvolysis reactions of benzhydrylium chlorides in 90% aq. methanol (90M), 70% aq. acetone (70A), and isopropanol^[7,11,12] with the electrofugalities E_f of the benzhydrylium ions from ref. [10].

Table 1. Nucleofugality parameters N_f and s_f for chloride and bromide in various solvents.

Solvent ^[a]	N_f (s_f) ^[b]	
	Chloride	Bromide
100M	2.95 (0.98) ^[c]	4.27 (0.98) ^[c]
90M10W	3.59 (0.99)	4.86 (0.98)
80M20W	4.16 (1.00)	5.38 (0.99)
60M40W	5.25 ^[d]	
100E	1.87 (1.00) ^[c]	2.97 (0.92) ^[c]
90E10W	2.66 (0.98)	3.75 (0.93)
80E20W	3.28 (0.98) ^[c]	4.39 (0.94) ^[c]
70E30W	3.64 (0.96)	4.86 (0.96)
60E40W	4.11 (0.97)	
40E60W	5.40 ^[d]	
isopropanol	0.39 (0.92)	
90A10W	0.69 (0.99) ^[c]	2.31 (1.00) ^[c]
80A20W	1.98 (1.02) ^[c]	3.04 (0.90) ^[c]
70A30W	2.75 (1.00)	3.99 (0.95)
60A40W	3.41 (0.98)	4.71 (0.97)
50A50W	4.29 (1.02)	5.15 (0.92)
90D10W	0.28 ^[d]	1.69 ^[d]
80D20W	1.48 ^[d]	2.80 ^[d]
70D30W	2.36 ^[d]	3.63 ^[d]
60D40W	3.16 ^[d]	
60AN40W ^[e]	3.75 ^[d]	
50AN50W ^[e]	4.30 ^[d]	
40AN60W ^[e]	4.87 ^[d]	
30AN70W ^[e]	5.34 ^[d]	
40E60D		1.71 ^[d]
60E40D		2.32 ^[d]
80E20D		2.77 ^[d]
100T	5.56 (0.82) ^[c]	6.20 (0.92) ^[c]
80T20E	5.14 (1.14)	5.89 (1.14)
60T40E	4.47 (1.15)	5.18 (1.08)
40T60E	3.49 (1.04)	4.47 ^[d]

[a] Mixtures of solvents are given as (v/v) unless specified. Solvents: A = acetone, AN = acetonitrile, D = 1,4-dioxane, E = ethanol, M = methanol, T = 2,2,2-trifluoroethanol, W = water. [b] Nucleofugality parameters N_f and s_f were derived from $\log k_s$ vs E_f correlations unless otherwise noted. The solvolysis rate constants that were employed for the correlations and the corresponding references are given in the Supporting Information (Table S1). [c] From ref. [10]. [d] N_f parameters were calculated from a single solvolysis rate constant of $\text{Ph}_2\text{CH}-\text{Cl}$ or $\text{Ph}_2\text{CH}-\text{Br}$ by using Equation (2) and assuming $s_f=1$. [e] Mixtures of solvents are given as (w/w).



Scheme 3. Nucleofugality parameters N_f for chloride and bromide in various solvents. Solvents: A=acetone, AN=acetonitrile, D=1,4-dioxane, E=ethanol, M=methanol. In general, solvent mixtures are given as (v/v); however, solvents that contain acetonitrile (AN) refer to (w/w). Data from Table 1.

Since the slope parameters s_f given in Table 1 do not differ significantly from 1, one may expect a relationship between the nucleofugalities N_f for Cl in different solvents and the solvent-ionizing power Y , which was defined by Winstein and Grunwald as the ratio of solvolysis rates of *tert*-butyl chloride ($m=1$) in a given solvent and in 80% aqueous ethanol ($Y=0$) at 25 °C [Eq. (3)].^[2]

$$\log(k/k_0) = mY \quad (3)$$

While Equation (3) was initially assumed to be applicable to all types of S_N1 solvolyses, it was soon realized that deviations from Equation (3) were not only due to nucleophilic solvent participation in the rate-determining step, but were also due to variable solvation, particularly of alkyl and aryl groups, of the developing carbocations.^[13–20] As a consequence, a number of Y scales of solvent-ionizing power have been established,^[5–7,14a,15,21,22] each of which was developed in an attempt to render reliable predictions of solvolysis rate constants for structurally related compounds.

With this background, it is not surprising that the nucleofugality parameters N_f of Table 1, which were derived from benzhydryl solvolysis rates, correlate better with Y scales derived from the secondary benzyl derivatives **4–6** (Figure 2)^[5–7] than with Y scales based on *tert*-alkyl derivatives.

The fact that different types of solvents are on the same correlation line indicates that, in the transition state, the in-

cident secondary benzyl cations arising from **4–6** experience the same changes in solvation as the incipient benzhydrylium ions. The different slopes for different leaving groups reflect the different demands of anions for solvent stabilization, which decrease in the order $Cl^- > Br^- \approx OTs^- > CF_3CO_2^- > DNB^-$ ($OTs^- = p$ -tosylate, $DNB^- = 3,5$ -dinitrobenzoate), as discussed in the preceding article.^[10]

Analogous plots of $N_f(Cl^-)$ and $N_f(Br^-)$ against Y scales derived from *tert*-butyl^[14a] and adamantyl^[21] species give rise to separate lines for each binary solvent pair (Figure 3). The same type of dispersion was reported by Winstein, Fainberg, and Grunwald for a plot of $\log k$ for the benzhydryl chloride solvolysis vs $Y(tBuCl)$.^[15] While the origin of the dispersion, which implies that benzhydryl solvolysis rates decrease in the order aqueous MeOH >

aqueous EtOH > aqueous acetone in solvents of the same $Y(tBuCl)$ values, was not clear at that time, Kevill rationalized the dispersion by differential solvation of π -conjugated and nonconjugated carbocations.^[23]

As a consequence of the correlations shown in Figures 2 and 3, the nucleofugality parameters N_f derived from benzhydryl solvolyses can be expected to yield reliable predictions of ionization rates for solvolyses yielding π -delocalized carbocations. On the other hand, deviations of one to two orders of magnitude can be expected when alkyl-substituted carbenium ions are generated. In view of the systematic deviations shown in Figure 3, corrections are feasible;^[23] however, for the sake of clarity and simplicity, we will not introduce correction terms and rather will tolerate the deviations for saturated systems.

Nucleofugalities of further leaving groups: While the influence of solvents on the ionization rates has been one of the most intensely studied topics of physical organic chemistry for more than half a century,^[21,22,24] there are relatively few investigations on the nucleofugalities of different leaving groups. The need for such data in daily practice has been the impetus for establishing Equation (2). We now demonstrate how to derive such parameters from published solvolysis rate constants.

For benzhydryl fluoride, solvolysis rate constants of $6.63 \times 10^{-8} \text{ s}^{-1}$ (80% aq. acetone)^[25] and $2.75 \times 10^{-7} \text{ s}^{-1}$ (80% aq. ethanol)^[26] have been reported (25 °C). With $E_t(Ph_2CH^+) =$

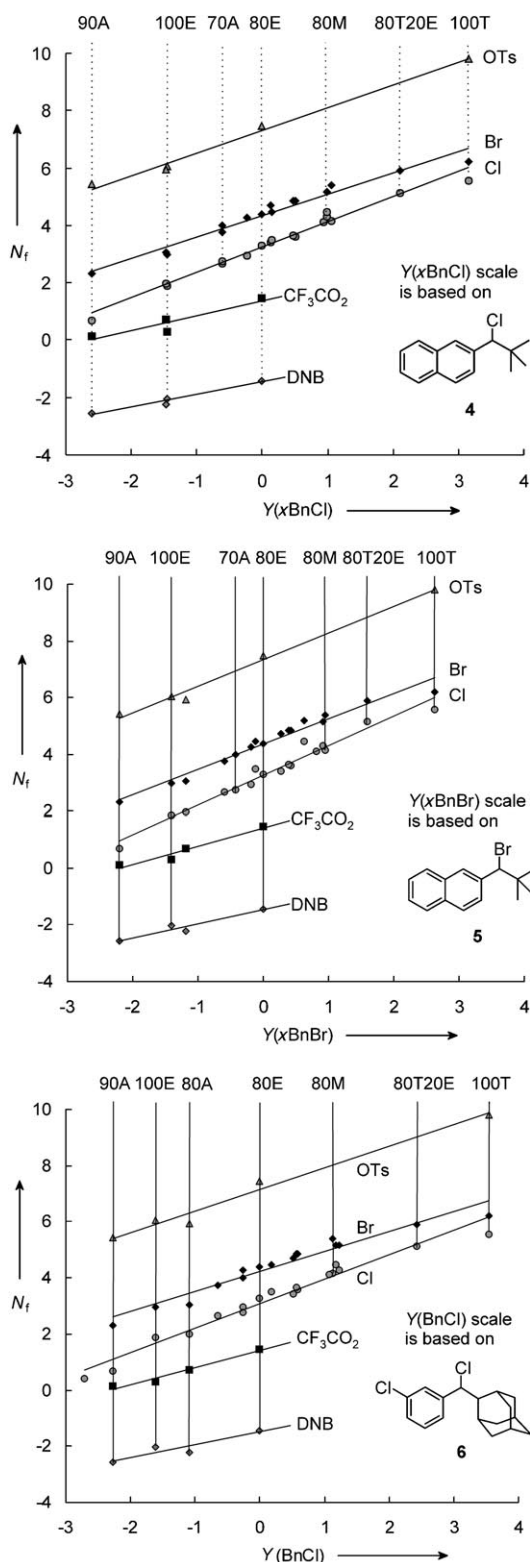


Figure 2. Correlations of the nucleofugality parameters N_f for various leaving groups with three different Y scales (OTs = *p*-tosylate, DNB = 3,5-dinitrobenzoate). Mixtures of solvents are defined as shown in Scheme 3.

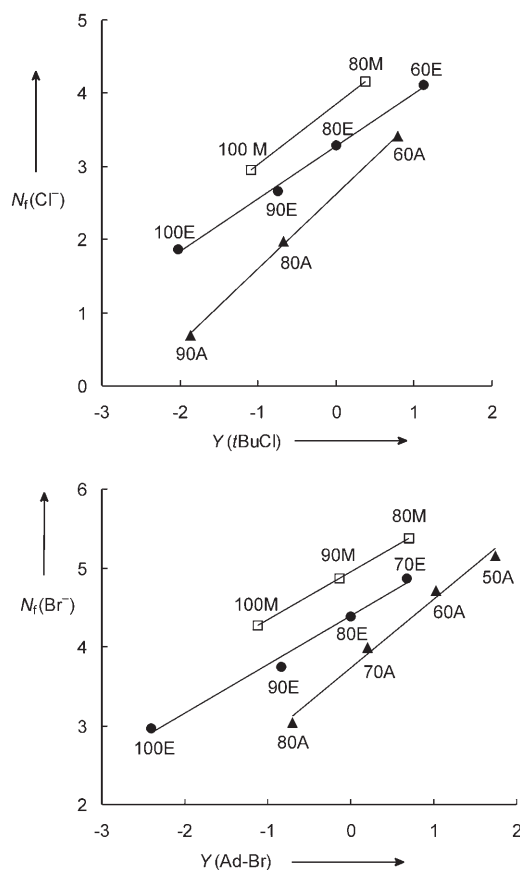


Figure 3. Dispersion of the nucleofugality parameters N_f derived from benzhydryl solvolysis rates as exemplified in the plots of $N_f(\text{Cl}^-)$ vs $Y(\text{tBuCl})$ and $N_f(\text{Br}^-)$ vs $Y(\text{Ad-Br})$.

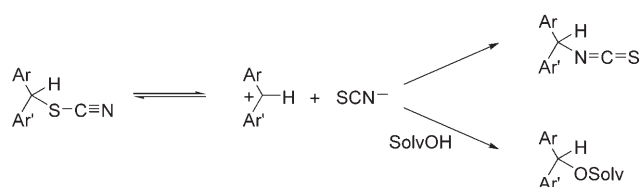
$-6.05^{[10]}$ and the assumption of $s_f=1.00$, one calculates $N_f=-1.13$ for fluoride in 80% aqueous acetone and $N_f=-0.51$ for fluoride in 80% aqueous ethanol, that is, nucleofugalities that are three to four orders of magnitude lower than those of chloride in the corresponding solvents. Hughes, Streitwieser, and Noyce estimated a Cl/F ratio of 10^5 for the solvolysis rate constants of the corresponding *tert*-butyl and 1-phenylethyl halides, respectively, in 80% aqueous ethanol.^[27,28]

Solvolysis studies of the parent benzhydrylium mesylate in 80% aqueous ethanol (80E) at -17.1 to $0.8^\circ\text{C}^{[29]}$ allowed the extrapolation $k_{25^\circ\text{C}}=14.8\text{ s}^{-1}$ from which $N_f=7.22$ for MsO^- in 80E was calculated with the assumption of $s_f=1.00$. A value of $N_f=7.53$ would be calculated if $s_f=0.79$ was assumed as for tosylate. This small difference illustrates the low sensitivity of the N_f parameters on s_f and confirms that mesylate in 80E has a similar nucleofugality as tosylate. From the ethanolysis rate constant of the parent benzhydrylium mesylate at 25°C (0.82 s^{-1}) a nucleofugality of $N_f(\text{MsO}^-/\text{EtOH})=5.96$ was calculated for $s_f=1.00$ and of $N_f=5.94$ for $s_f=0.75$.^[30] Similar leaving group abilities of tosylate and mesylate have been reported previously by Bentley and Brown for secondary alkyl derivatives^[31] and estimated by Noyce.^[32]

Bunton and Henty studied the solvolysis of benzhydrylium toluene-*p*-sulfinate in 60% aqueous dioxane (60D40W). They observed a solvolysis rate constant of $k = 1.42 \times 10^{-6} \text{ s}^{-1}$ at 25 °C.^[33] With an assumed $s_f = 1.00$, a nucleofugality of $N_f = 0.20$ can be calculated for the toluene-*p*-sulfinate leaving group in 60D40W. This value is consistent with the poor leaving group ability of toluene-*p*-sulfinate in 60D40W compared to Cl^- in the same solvent, which undergoes heterolysis 1000 times faster.^[33]

From acetolysis rates of benzhydryl 2,4-dinitrophenolate and benzhydryl 2-nitro-4-cyanophenolate at 49–78 °C,^[34] one can calculate $k_{25^\circ\text{C}} = 1.12 \times 10^{-6} \text{ s}^{-1}$ and $7.96 \times 10^{-7} \text{ s}^{-1}$, respectively, from which $N_f = 0.10$ for 2,4-dinitrophenolate and $N_f = -0.05$ for 2-nitro-4-cyanophenolate in acetic acid are calculated when $s_f = 1.0$ is assumed. From these numbers one can derive that 2,4-dinitrophenolates of benzhydrylium systems with weak electron-donating substituents should solvolyze with moderate rates at 25 °C. This would allow one to examine whether $s_f \approx 1$ also holds for phenolate leaving groups.

Isomerizations, racemizations, and solvolysis reactions of benzhydryl thiocyanates (Scheme 4) were studied intensively



Scheme 4.

in the 1960s in order to elucidate the role of different ion pairs and free ions in these processes.^[35–39]

From the isomerization rates of bis(*p*-tolyl)methyl thiocyanate ($k_{25^\circ\text{C}} = 8.79 \times 10^{-5} \text{ s}^{-1}$) and diphenylmethyl thiocyanate ($k_{25^\circ\text{C}} = 1.65 \times 10^{-7} \text{ s}^{-1}$, from experiments at 70–90 °C) in acetonitrile, one can calculate $s_f = 1.06$ and $N_f = -0.37$ for thiocyanate in acetonitrile.^[35] Since the bis(*p*-tolyl)methyl cation and the parent benzhydrylium ion are known to react 5–10 times faster with the S terminus of thiocyanate than with the N terminus,^[40] the N_f value reflecting the ionization step should be approximately one unit larger. Comparable nucleofugality parameters can be derived for thiocyanate in 95% aqueous acetone, where an isomerization rate constant of $5.33 \times 10^{-5} \text{ s}^{-1}$ and a solvolysis rate constant of $1.32 \times 10^{-5} \text{ s}^{-1}$ have been observed for bis(*p*-tolyl)methyl thiocyanate at 25 °C.^[37]

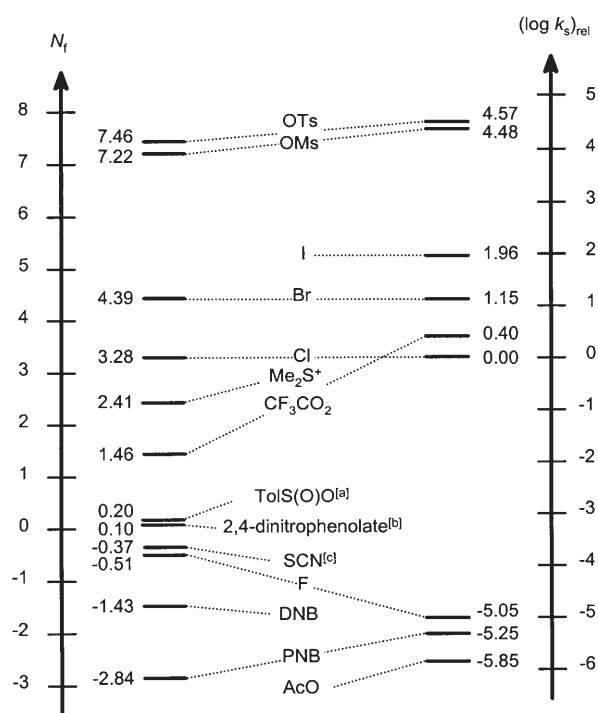
The leaving group ability of dimethylsulfide from the benzhydryl dimethylsulfonium ion has been studied in a large variety of solvents. In accordance with findings for other neutral leaving groups,^[22] the rate constants vary only slightly with the solvent, namely, from 10^{-4} s^{-1} in 20–80% aqueous dioxane to $57 \times 10^{-4} \text{ s}^{-1}$ in 97% hexafluoroisopropanol. Rate constants^[41] and nucleofugalities of dimethylsulfide in the selected standard solvents are given in Table 2, assuming $s_f = 1.0$.

Table 2. Solvolysis rate constants k_s of $\text{Ph}_2\text{CHS}^+\text{Me}_2$ and nucleofugalities N_f of SMe_2 in various solvents (assumption $s_f = 1.0$).

Solvent ^[a]	k_s ^[b] [s^{-1}]	N_f
90A	2.81×10^{-4}	2.50
100E	4.60×10^{-4}	2.71
80A	2.29×10^{-4}	2.41
100M	7.88×10^{-4}	2.95
80E	2.30×10^{-4}	2.41

[a] Solvent mixtures are given as (v/v); solvents: 90A = 90% aq. acetone, 80A = 80% aq. acetone, 100E = ethanol, 80E = 80% aq. ethanol, 100M = methanol. [b] At 25 °C, from ref. [41].

There is a relatively good agreement between the nucleofugality parameters N_f determined in this work and the relative solvolysis rates of 1-phenylethyl esters reported by Noyce and Virgilio^[28] (Scheme 5); however, trifluoroacetate



Scheme 5. Comparison of the nucleofugality parameters N_f (25 °C) and the relative solvolysis rates of 1-phenylethyl esters $(\log k_s)_{\text{rel}}$ (75 °C, from ref. [28]) for various leaving groups in 80% aq. ethanol (v/v) (if not stated otherwise). [a] In acetic acid. [b] In 60% aq. dioxane. [c] R–SCN heterolysis in acetonitrile. DNB = 3,5-dinitrobenzoate, PNB = 4-nitrobenzoate, OTs = *p*-tosylate, OMs = mesylate.

seems to be a much better leaving group on the Noyce scale than on the N_f scale.

The discrepancy is caused largely by the smaller s_f value for trifluoroacetate ($s_f = 0.82$ for $\text{CF}_3\text{CO}_2/80\text{E}20\text{W}$) compared to chloride ($s_f = 0.98$ for $\text{Cl}/80\text{E}20\text{W}$).^[10] As already seen in the benzhydrylium series,^[10] the preference of Cl^- over CF_3CO_2^- as a leaving group decreases with decreasing stabilization of the carbocations. An extrapolation of these results indicates that R–Cl and R–OCOCF₃ will solvolyze with identical rates in 80% aqueous ethanol at $E_f = -12.6$ in

the benzhydrylium series. The similar reactivities of 1-phenylethyl chloride and trifluoroacetate reported by Noyce^[28] are, therefore, within the range of the confidence limit of Equation (2) for $E_f(\text{PhCH}^+\text{CH}_3) = -8.44$ (see below). In addition, O-acyl cleavage may become attractive for trifluoroacetates that undergo $\text{S}_{\text{N}}1$ solvolysis very slowly.^[42]

Electrofugalities of other carbenium ions: As discussed above, relative electrofugalities depend somewhat on the nature of the leaving groups as well as on the types of solvents. Differential steric and electronic interactions between R and X in the RX substrates, as well as differential solvation of differently delocalized carbocations, have been suggested to be responsible for the deviations from the correlations shown in Figures 2 and 3.

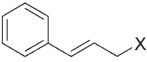
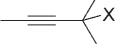
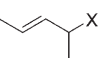


In order to examine the scope of Equation (2) for variable R groups, we have used it to calculate E_f for a variety of carbocations from the solvolysis rates of the corresponding chlorides and bromides in standard solvents. Entries 1–9 of Table 3^[43–58] demonstrate that, for aryl-substituted carbenium ions, the agreement in E_f is generally better than ± 0.4 . Somewhat larger deviations of up to ± 0.5 were observed when π -conjugation is less extended, as in propargyl and allyl systems (entries 10–12). The largest scatter in E_f (± 1.0) was found for the *tert*-butyl cation.

Since the deviations in different solvents are in the same direction for *tert*-butyl chloride and bromide, which are considered as models for other 1,1-dimethylalkyl halides,^[59] one can conclude that the deviations shown in Table 3 are not predominantly due to the

Table 3. Electrofugalities E_f of R^+ derived from solvolysis rate constants k_s of R-X ($\text{X} = \text{Cl, Br}$) in different solvents.

Entry	R-X	X/Solvent ^[a]	$N_f^{[b]}$	$s_f^{[b]}$	$k_s^{[c]}$ [s^{-1}]	Ref.	Individual $E_f^{[d]}$
1		Cl/90A	0.69	0.99	4.84×10^{-10}	[7]	-10.10
		Cl/100E	1.87	1.00	7.10×10^{-9}	[7]	-10.02
		Cl/80A	1.98	1.02	6.80×10^{-9}	[7]	-9.99
		Cl/100M	2.95	0.98	1.16×10^{-7}	[7]	-10.03
		Cl/80E	3.28	0.98	1.99×10^{-7}	[7]	-10.12
		Br/90A	2.31	1.00	4.40×10^{-8}	[6]	-9.67
		Br/100E	2.97	0.92	2.79×10^{-7}	[6]	-10.09
		Br/80A	3.04	0.90	4.63×10^{-7}	[6]	-10.08
		Br/100M	4.27	0.98	5.57×10^{-6}	[43]	-9.63
		Br/80E	4.39	0.94	7.03×10^{-6}	[43]	-9.87
2		Cl/90A	0.69	0.99	3.40×10^{-3}	[44]	-3.18
		Cl/100E	1.87	1.00	2.17×10^{-2}	[5b]	-3.53
		Cl/80A	1.98	1.02	7.21×10^{-2}	[5b]	-3.10
		Cl/100M	2.95	0.98	3.94×10^{-1}	[44]	-3.36
		Cl/80E	3.28	0.98	1.55	[44]	-3.09
3		Cl/100E	1.87	1.00	1.65×10^{-7}	[45]	-8.65
		Cl/80A	1.98	1.02	6.80×10^{-7}	[46]	-8.03
		Cl/100M	2.95	0.98	2.26×10^{-6}	[14b]	-8.71
		Cl/80E	3.28	0.98	1.00×10^{-5}	[47a]	-8.38
		Br/100E	2.97	0.92	6.28×10^{-6}	[14c]	-8.62
		Br/100M	4.27	0.98	5.10×10^{-5}	[14c]	-8.65
		Br/80E	4.39	0.94	2.02×10^{-4}	[47b]	-8.32
4		Cl/90A	0.69	0.99	3.04×10^{-6}	[48]	-6.26
		Cl/100E	1.87	1.00	1.67×10^{-5}	[48, 49]	-6.65
		Cl/80A	1.98	1.02	6.61×10^{-5}	[48]	-6.08
		Cl/100M	2.95	0.98	2.90×10^{-4}	[44]	-6.56
		Cl/80E	3.28	0.98	1.16×10^{-3}	[44]	-6.28
		Br/90A	2.31	1.00	5.89×10^{-5}	[44]	-6.54
		Br/100E	2.97	0.92	2.35×10^{-4}	[44]	-6.91
		Br/80A	3.04	0.90	8.57×10^{-4}	[44]	-6.45
		Br/100M	4.27	0.98	3.31×10^{-3}	[44]	-6.80
Br/80E	4.39	0.94	9.69×10^{-3}	[44]	-6.53		
5		Cl/90A	0.69	0.99	4.28×10^{-4}	[50]	-4.09
		Cl/100E	1.87	1.00	1.64×10^{-3}	[50]	-4.66
		Cl/80A	1.98	1.02	7.09×10^{-3}	[50]	-4.09
		Cl/100M	2.95	0.98	5.05×10^{-2}	[50]	-4.27
		Cl/80E	3.28	0.98	1.53×10^{-1}	[50]	-4.11
6		Cl/90A	0.69	0.99	1.67×10^{-5}	[51]	-5.52
		Cl/100E	1.87	1.00	3.71×10^{-5}	[51]	-6.30
		Cl/80A	1.98	1.02	2.15×10^{-4}	[51]	-5.58
		Cl/100M	2.95	0.98	7.33×10^{-4}	[51]	-6.15
		Cl/80E	3.28	0.98	1.78×10^{-3}	[51]	-6.09
7		Cl/90A	0.69	0.99	1.24×10^{-4}	[52]	-4.64
		Cl/100E	1.87	1.00	3.80×10^{-4}	[51]	-5.29
		Cl/80A	1.98	1.02	1.79×10^{-3}	[51]	-4.67
		Cl/100M	2.95	0.98	5.11×10^{-3}	[52]	-5.29
		Cl/80E	3.28	0.98	1.73×10^{-2}	[51]	-5.08
8		Cl/90A	0.69	0.99	1.94×10^{-6}	[52]	-6.46
		Cl/100E	1.87	1.00	6.86×10^{-6}	[52]	-7.03
		Cl/80A	1.98	1.02	2.52×10^{-5}	[50]	-6.49
		Cl/100M	2.95	0.98	8.00×10^{-5}	[52]	-7.13
		Cl/80E	3.28	0.98	2.60×10^{-4}	[50]	-6.94

Table 3. (Continued)

Entry	R-X	X/Solvent ^[a]	$N_f^{[b]}$	$s_f^{[b]}$	$k_s^{[c]}$ [s ⁻¹]	Ref.	Individual $E_f^{[d]}$
9		Cl/100E	1.87	1.00	8.39×10^{-7}	[53]	-7.95
		Cl/80A	1.98	1.02	2.15×10^{-6}	[53]	-7.54
		Cl/100M	2.95	0.98	8.51×10^{-6}	[53]	-8.12
		Cl/80E	3.28	0.98	4.73×10^{-5}	[53]	-7.69
		Br/100E	2.97	0.92	1.56×10^{-5}	[54]	-8.19
		Br/80A	3.04	0.90	2.87×10^{-5}	[54]	-8.09
		Br/100M	4.27	0.98	1.13×10^{-4}	[54]	-8.30
		Br/80E	4.39	0.94	4.78×10^{-4}	[54]	-7.92
10		Cl/100E	1.87	1.00	7.56×10^{-6}	[55]	-6.99
		Cl/80A	1.98	1.02	6.02×10^{-5}	[55]	-6.12
		Cl/100M	2.95	0.98	8.77×10^{-5}	[55]	-7.09
		Cl/80E	3.28	0.98	5.42×10^{-4}	[56]	-6.61
11		Cl/90A	0.69	0.99	3.5×10^{-5}	[55]	-5.19
		Cl/100E	1.87	1.00	4.57×10^{-5}	[55]	-6.21
		Cl/80A	1.98	1.02	5.64×10^{-4}	[55]	-5.17
		Cl/100M	2.95	0.98	5.8×10^{-4}	[55]	-6.25
		Cl/80E	3.28	0.98	4.3×10^{-3}	[55]	-5.69
12		Br/90A	2.31	1.00	2.23×10^{-4}	[30]	-5.96
		Br/100E	2.97	0.92	2.09×10^{-4}	[30]	-6.97
		Br/80A	3.04	0.90	2.30×10^{-3}	[30]	-5.97
		Br/80E	4.39	0.94	1.16×10^{-2}	[30]	-6.45
13		Cl/90A	0.69	0.99	1.27×10^{-7}	[14a]	-7.66
		Cl/100E	1.87	1.00	8.60×10^{-8}	[14a]	-8.94
		Cl/80A	1.98	1.02	1.97×10^{-6}	[14a]	-7.57
		Cl/100M	2.95	0.98	7.53×10^{-7}	[14a]	-9.20
		Cl/80E	3.28	0.98	9.26×10^{-6}	[14a]	-8.42
		Br/90A	2.31	1.00	1.27×10^{-5}	[57]	-7.21
		Br/100E	2.97	0.92	4.40×10^{-6}	[14c]	-8.79
		Br/80A	3.04	0.90	1.10×10^{-4}	[2,58]	-7.44
		Br/100M	4.27	0.98	3.44×10^{-5}	[14c]	-8.82
		Br/80E	4.39	0.94	3.58×10^{-4}	[14c]	-8.06

[a] Solvent mixtures are given as (v/v); solvents: 90A=90% aq. acetone, 80A=80% aq. acetone, 100E=ethanol, 80E=80% aq. ethanol, 100M=methanol. [b] From ref. [10]. [c] At 25°C. [d] Individual E_f parameters were calculated from $E_f = [(\log k_s)/s_f] - N_f$ for each reaction. [e] E_f was obtained from all available solvolysis rate constants for a certain R⁺ by minimizing $\Sigma \Delta^2 = \Sigma (\log k_s - s_f(N_f + E_f))^2$, standard deviations refer to the differences between the individual E_f parameters and the optimized E_f for R⁺.

variation of the leaving group. The lower electrofugality calculated for *t*Bu⁺ in alcoholic media compared to in acetone/water mixtures reflects the different solvation of localized and π -delocalized carbocations in the different solvents, as previously noted in the discussion of Figure 3.^[23]

Not many solvolysis rate constants are available that allow systematic comparisons of Cl⁻ and Br⁻ with other types of leaving groups. Scheme 5 implies that 1-phenylethyl solvolyses are affected by leaving group variation in a similar way as benzhydryl solvolyses over a wide range of reactivity. Analogously, Bentley, Christl, and Norman have demonstrated that the *p*-tosylate/*p*-nitrobenzoate ratio of 3.3×10^9 determined for benzhydryl derivatives in 80% aqueous ethanol at 25°C remains almost constant for 1-adamantyl, *tert*-butyl, 7-norbornenyl, and 2-norbornyl derivatives.^[29]

Solvolysis reactions of α -*tert*-butyl-substituted benzyl chlorides, bromides, and tosylates yield E_f parameters that agree within two orders of magnitude for each of the electrofuges (Table 4).^[7,60-62] The fact that the tosylates of these

sterically strained compounds are on the low-reactivity end is surprising in view of the high steric demand of the tosyloxy group.^[63]

For the 9-fluorenyl cation, electrofugality parameters E_f can be calculated with maximum deviations of ± 1.0 from the corresponding chloride, bromide, and tosylate in a variety of solvents employing rate constants that cover five orders of magnitude.

Perhaps the most convincing demonstration of the applicability of Equation (2) to other types of carbocations comes from solvolysis rates of a variety of 1-adamantyl esters that have been studied in a variety of solvents. As shown in Table 5,^[9,64-66] rate constants extending over more than six orders of magnitude can be used to arrive at $E_f = -11.1 \pm 0.7$, thus demonstrating the applicability of E_f and N_f/s_f parameters to semiquantitatively predict heterolysis rate constants of a large variety of substrates.

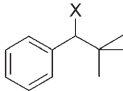
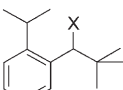
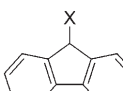
How fast do R-X bonds ionize? It has long been known that the experimentally determined solvolysis rate constants are complex quantities

that, in the case of fast consecutive reactions, become identical to the ionization rates.^[68] Recently, we reported quantitative Gibbs energy profiles for solvolysis reactions that allow us to identify cases in which solvolysis rate constants reflect the ionization rates.^[69]

Since first-order rate constants k are related to the reaction half-lives $\tau_{1/2}$ by $\tau_{1/2} = (\ln 2)/k$, Equation (2) can be employed to estimate the half-lives of solvolyses of R-X in various solvents (Table 6).

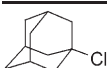
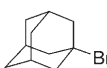
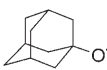
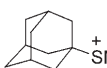
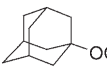
In this and the preceding article, it has been shown that s_f is usually close to 1,^[10] and deviations from 1 can be neglected in semiquantitative treatments as long as s_f is multiplied by relatively small numbers. This is generally the case when applying Equation (2) since measured solvolysis rate constants are usually between $10^{-6} < k_s < 10^{-2} \text{ s}^{-1}$ (see reference [10]). One can, therefore, neglect s_f for practical applications and estimate absolute heterolysis rate constants by considering only the electrofugality E_f and the nucleofugality N_f , as depicted in Figure 4.

Table 4. Comparison of carbocation electrofugalities E_f derived from solvolysis rates of sterically demanding benzyl as well as fluorenyl tosylates, bromides, and chlorides in different solvents (25 °C).

R-X	X	k_s [s ⁻¹]	Solvent ^[a]	Individual E_f ^[b]	Ref.
 $E_f = -11.70 \pm 0.72$ ^[c]	OTs	1.50×10^{-6}	90A	-11.96	[60]
		1.21×10^{-5}	80A	-12.01	[60]
		6.14×10^{-6}	100E	-13.00	[60]
	Br	1.07×10^{-4}	80E	-12.49	[60]
		1.25×10^{-2}	TFE	-11.96	[60]
		6.22×10^{-8}	80A	-11.05	[61]
 $E_f = -10.67 \pm 0.79$ ^[c]	OTs	3.48×10^{-5}	80A	-11.44	[61]
		3.08×10^{-4}	80E	-11.90	[61]
		1.26×10^{-1}	TFE	-10.83	[61]
	Br	1.38×10^{-6}	80E	-10.62	[61]
		1.18×10^{-6}	100M	-10.32	[61]
		1.04×10^{-3}	TFE	-9.44	[61]
 $E_f = -9.92 \pm 0.60$ ^[c]	OTs	3.42×10^{-4}	90A	-9.31	[62]
		2.66×10^{-3}	80A	-9.12	[62]
		3.34×10^{-3}	100E	-9.35	[62]
	Br	6.71×10^{-2}	80E	-8.95	[62]
		2.45×10^{-6}	80E	-10.36	[62]
		1.22×10^{-6}	100M	-10.30	[62]
	Cl	1.05×10^{-4}	TFE	-10.52	[62]
		5.86×10^{-9}	80A	-10.05	[7]
		3.01×10^{-7}	80E	-9.93	[7]
		5.92×10^{-5}	TFE	-10.72	[7]

[a] Solvent mixtures are given as (v/v); solvents: 90A=90% aq. acetone, 80A=80% aq. acetone, 100E=ethanol, 80E=80% aq. ethanol, 100M=methanol, TFE=2,2,2-trifluoroethanol. [b] Individual E_f parameters were calculated from $E_f = [(\log k_s)/s_f] - N_f$ for each reaction. [c] E_f was obtained from all available solvolysis rate constants for a certain R⁺ by minimizing $\Sigma \Delta^2 = \Sigma (\log k_s - s_f(N_f + E_f))^2$, standard deviations refer to the differences between the individual E_f parameters and the optimized E_f for R⁺.

Table 5. Solvolysis rates of 1-adamantyl derivatives with different leaving groups in various solvents (25 °C).

R-X	k_s [s ⁻¹]	Solvent ^[a]	Individual E_f ^[b]	Ref.
	7.6×10^{-9}	80E	-11.6	[9]
	5.41×10^{-6}	97T	-12.0	[9]
	2.8×10^{-7}	80E	-11.4	[9]
	9.5×10^{-5}	97T	-10.6	[9]
	4.03×10^{-3}	80E	-10.5	[64]
	4.40×10^{-5}	100E	-11.9	[64]
	4.61×10^{-4}	80A	-10.1	[64]
	4.16×10^{-5}	90A	-10.3	[64]
	6.61×10^{-10}	80E	-11.6	[65]
	5.97×10^{-9}	80E	-11.5	[66]
	1.28×10^{-9}	80A	-10.8	[66]

[a] Solvent mixtures are given as (v/v); solvents: 90A=90% aq. acetone, 80A=80% aq. acetone, 100E=ethanol, 80E=80% aq. ethanol, 97T=97% aq. 2,2,2-trifluoroethanol. [b] Individual E_f parameters were calculated from $E_f = [(\log k_s)/s_f] - N_f$ for each reaction. An $E_f = -11.1 \pm 0.7$ was obtained from all available solvolysis rate constants for the 1-adamantyl ion by minimizing $\Sigma \Delta^2 = \Sigma (\log k_s - s_f(N_f + E_f))^2$, the standard deviation refers to the differences between the individual E_f parameters and the optimized E_f for R⁺.

Heterolyses of R-X, which correspond to the blue range in Figure 4, will be so slow that they cannot be observed at room temperature. Ionizations of substrates in the red range will be so fast that solutions of the corresponding substrates can hardly be prepared at room temperature. Although the borderlines between these ranges (green→yellow→red and green→blue in Figure 4) depend somewhat on s_f , clearly the green range is the most easily accessible for kinetic investigations of ionization processes.

Figure 4 combined with the E_f and N_f parameters presented in this and the preceding article^[10] can now be used to answer the questions raised at the start. Substrates located in the blue range are stable enough to tolerate short-time exposure to the corresponding solvents for purification or synthetic transformations without undergoing solvolysis or racemization. Regioselectivities of

Table 6. Solvolysis half-lives for benzhydryl halides.

$\tau_{1/2}$	k_s [s ⁻¹]	$s_f(N_f + E_f)$
1 min	1.2×10^{-2}	-2.0
1 hour	1.9×10^{-4}	-3.7
1 day	8.0×10^{-6}	-5.1
1 month	2.6×10^{-7}	-6.6

the reactions of ambident carbenium ions (allyl or propargyl cations) with nucleophiles or of ambident anions with carbenium ions will be thermodynamically controlled if the products are in the red range and kinetically controlled if the products are in the blue range. Because blue and red cover the largest area of Figure 4, there remains only the relatively small green range that requires more subtle consideration.

Since the electrofugalities E_f of a large variety of carbenium ions can easily be derived from the numerous solvolysis rates published in the literature, we will focus our future work on the determination of nucleofugalities of leaving groups that are relevant in organic synthesis.

In combination with an analogous treatment of electrophile/nucleophile combinations,^[70,71] it has thus become possible to semiquantitatively describe the rates of two of the most important processes in organic chemistry.

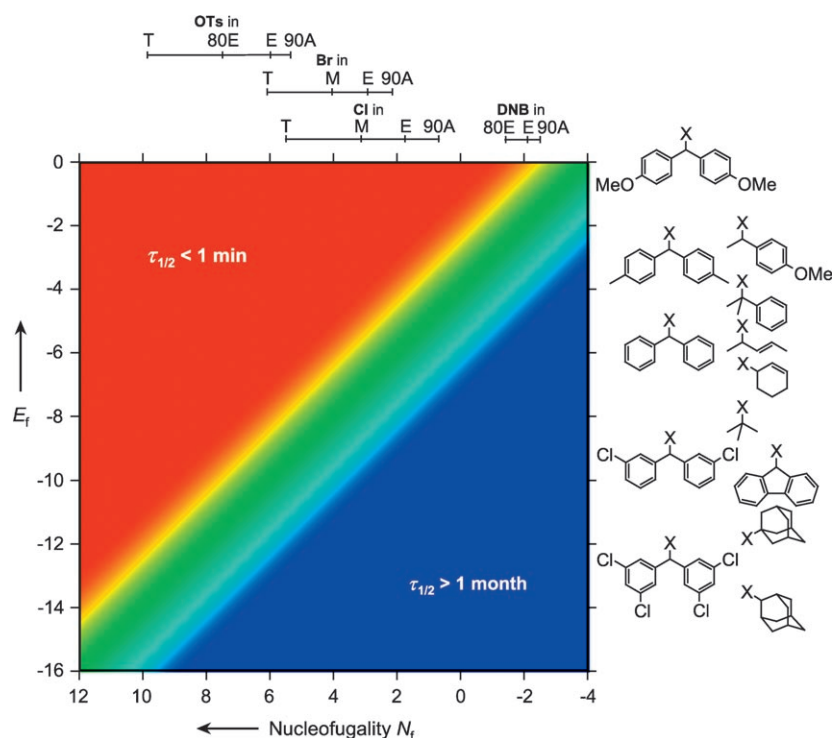


Figure 4. From high reactivity to inertness: A semiquantitative model for predicting S_N1 half-reaction times. Solvent mixtures are given as (v/v); solvents: 90A = 90% aq. acetone, E = ethanol, 80 E = 80% aq. ethanol, M = methanol, T = 2,2,2-trifluoroethanol (OTs = *p*-tosylate, DNB = 3,5-dinitrobenzoate).

Acknowledgements

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