Nucleophilicity Scales

DOI: 10.1002/anie.200600542

Towards a General Scale of Nucleophilicity?**

Thanh Binh Phan, Martin Breugst, and Herbert Mayr*

Dedicated to Professor Dieter Enders on the occasion of his 60th birthday

The development of quantitative scales of nucleophilicity has intrigued chemists for more than 50 years.^[1] The optimistic start in the 1950s, which delivered the Swain–Scott equation $[Eq. (1)]^{[2]}$ and the Edwards equation^[3] was followed by a period of disillusionment in the 1960s, when more and more factors were identified which had to be considered for a quantitative description of nucleophilicity.^[4]

 [*] Dr. T. B. Phan, M. Breugst, Prof. Dr. H. Mayr Department Chemie und Biochemie Ludwig-Maximilians-Universität München Butenandtstrasse 5–13 (Haus F), 81377 München (Germany) Fax: (+49) 89-2180-77717 E-mail: herbert.mayr@cup.uni-muenchen.de

[**] Financial support by the Deutsche Forschungsgemeinschaft (Ma673/21-1) and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank F. Brotzel and Dr. A. R. Ofial for helpful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Angew. Chem. Int. Ed. 2006, 45, 3869-3874

© 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

InterScience 3869

Communications

 $\log \left(k/k_{\rm H_2O} \right) = s'_{\rm E} n$

 $n = \text{nucleophilicity constant} (n_{\text{H}_2\text{O}} = 0)$ (1)

 $s'_{\rm E}$ = sensitivity of electrophile $(s'_{\rm CH_3Br} = 1)^{[5]}$

The culmination of the pessimistic view was reached in 1968, when Pearson reported that the reactivities of nucleophiles towards *trans*-[Pt(py)₂Cl₂] (py = pyridine) did not correlate with any of the nucleophilicity parameters known at that time and finally concluded: "*At present it is not possible to predict quantitatively the rates of nucleophilic displacement reactions if a number of substrates of widely varying properties are considered*."^[6]

Only four years later, Ritchie reported a correlation of astonishing simplicity [Eq. (2)],^[7] which claims that the relative reactivities of a variety of nucleophiles toward carbocations and diazonium ions can be described by a single, electrophile-independent nucleophilicity parameter N_+ .

$$\lg\left(k/k_{\rm o}\right) = N_{+} \tag{2}$$

The impact of this so-called constant selectivity relationship has significantly been augmented by the work of Kane-Maguire and Sweigart et al. who showed that Equation (2) holds also for the reactions of cationic metal π -complexes with a variety of nucleophiles.^[8,9]

The most extensive nucleophilicity scale,^[10,11] presently available, has been derived from the rate constants of the reactions of benzhydrylium ions with alkenes, arenes, enol ethers, ketene acetals,^[12] enamines,^[13] allyl element compounds,^[14] transition-metal π -complexes,^[15] diazoalkanes,^[16] and delocalized carbanions^[17-19] (π -nucleophiles), amines,^[20] alcohols,^[21] alkoxides,^[22] phosphanes,^[23] inorganic anions^[24-27] (*n*-nucleophiles), and a variety of hydrides^[28-31] (σ -nucleophiles); these rate constants were subjected to a least-squares minimization on the basis of Equation (3)^[10,11] in which *k* is the second-order rate constant at 20 °C and *E* is a nucleophileindependent electrophilicity parameter.

$$\lg k = s_{\rm N}(E+N) \tag{3}$$

It has been shown that the electrophile-independent nucleophile-specific N and s_N parameters^[5] derived in this way can be employed for predicting the rates of reactions of the corresponding nucleophiles with carbocations,^[10,11] cationic metal- π -complexes,^[10,11] as well as electron-deficient alkenes^[32] and arenes.^[33,34] Their applicability to S_N2 type reactions has not yet been examined.

Recently, we have found that the nucleophilicity parameters N for aqueous and alcoholic solvents, which we derived from the rates of decay of benzhydrylium ions in these solvents,^[21] correlate linearly with Kevill's $N_{\rm T}$ parameters.^[35] Because the $N_{\rm T}$ parameters reflect the rates of solvolysis of the S-methyldibenzothiophenium ion (1) in the corresponding solvents, that is, the rates of $S_{\rm N}2$ reactions, we were prompted to examine whether the nucleophilicity parameters N and $s_{\rm N}$ derived from Equation (3) are generally applicable to bimolecular nucleophilic substitutions. We now demonstrate that this is the case for a variety of substrates and suggest a general correlation equation which includes Equations (1)–(3) as special cases.

The reactions of 1 with nucleophiles proceed with changes in the UV spectrum as exemplified in Figure 1 for the reaction of 1 with the azide ion. The decrease of the absorbance at 271 nm owing to the consumption of 1 is accompanied by the increase of the absorbances at 285 nm and 325 nm as a result of the formation of dibenzothiophene (2).



Figure 1. UV spectra during the reaction of 1 with sodium azide (in MeOH, 20°C) at t=0, 1, 2, 4, 8, 16, and 47 min; $[1]_0=6.05 \times 10^{-5}$ m, $[N_3^{-1}]_0=3.51 \times 10^{-3}$ m.

As the nucleophiles were generally employed in high excess over **1**, first-order rate constants k_{obs} [Eq. (4)] can be derived from the exponential decay of [**1**] (absorbance at 271 nm). The formation of product **2** can be monitored by the exponential increase of the absorbances at 285 and 325 nm.

$$\mathbf{d}[\mathbf{1}]/\mathbf{d}t = -k_{\rm obs}[\mathbf{1}] \tag{4}$$

The least-squares fits of the time-dependent absorbances A to the single-exponential function $A_t = A_0 \exp(-k_{obs}t) + C$ (for 271 nm) and $A_t = A_{end}[1 - \exp(-k_{obs}t)] + C$ (for 285 and 325 nm) gave rise to identical first-order rate constants $k_{obs} = 1.83 \times 10^{-3} \text{ s}^{-1}$ at any of these three wavelengths (Figure 2). Details of the kinetic investigations are given in the Supporting Information.

As indicated by Equation (5), the second-order rate constants k_2 for the reactions of **1** with the nucleophiles listed in Table 1 were obtained from the slopes of k_{obs} versus [Nu] plots.

$$k_{\rm obs} = k_2 [\rm Nu] + k_{\rm MeOH}$$
⁽⁵⁾

The small values of the intercepts of these plots (see Supporting Information) indicate that the competing reaction of **1** with the solvent methanol is negligible. This observation



Figure 2. Monitoring of the reaction of **1** with sodium azide depicted in Figure 1 at three different wavelengths (methanol, 20°C).

is in accord with the first-order rate constant for the reaction of **1** with methanol (Table 1), which was reported by $\text{Kevill}^{[36]}$ and which is corroborated in this work.

For several nucleophiles used in this work, N and s_N parameters were not available. These parameters were derived from the kinetics of the reactions of the corresponding nucleophiles with the benzhydrylium reference electrophiles,^[10] following the procedure described in the literature.^[22] For technical reasons, these reactions could not be studied in pure methanol and were performed in the presence of 9% acetonitrile (see footnotes of Table 1). Details of the kinetic experiments are given in the Supporting Information.

Figure 3 shows that the correlation of $(\lg k)/s_N$ versus *N* for the reactions of the sulfonium ion **1** with C-, N-, O-, and Pnucleophiles, which covers 20 units of the logarithmic nucleophilicity scale, is linear with a slope of 0.6. Although the relevance of the benzhydrylium-based parameters *N* and s_N for this S_N2 reaction is thus demonstrated, the non-unity slope indicates that Equation (3) is not applicable because variation of the nucleophiles affects the reactivities toward **1** by only 60% of the amount that is observed in the reactions with benzhydrylium ions (slope = 1.00).

A similar correlation is found for the reactions of different types of charged and neutral nucleophiles with iodomethane in methanol (Figure 4).

While the paucity of data in a narrow reactivity range do not allow a discussion of the slope of the graph in Figure 4, it can be seen that in both correlations (Figures 3 and 4) the absolute deviations from the correlation lines are generally smaller than one order of magnitude despite the large variety of nucleophiles employed. It can thus be deduced that the order of nucleophilicities toward electrophilic C_{sp^3} and C_{sp^2} centers is not fundamentally different.

This conclusion may be surprising because the contrasting reactivity orders $CN^- > HO^- > N_3^-$ (towards CH_3Br) and $CN^- < HO^- < N_3^-$ (towards Ar_3C^+) have been considered as an indication that nucleophilicities toward C_{sp^3} and C_{sp^2} centers are controlled by different factors.^[41] It should be noted, however, that CN^- and HO^- are of similar reactivity toward both types of electrophiles, and it is only N_3^- which deviates significantly (Table 2).

In agreement with our findings, more comprehensive comparisons had already come to the conclusion that

Table 1: Rate constants for the reactions of 1 with nucleophiles (in methanol, 20° C).

Nucleophiles	Ν	s _N	k
(MeO ₂ C) ₂ CH ⁻	18.24 ^[a]	0.644 ^[a]	1.41×10 ^{1 [b,c]}
(NC) ₂ CH ⁻	18.21 ^[a]	0.686 ^[a]	1.13×10^{1} [b,c]
pyrrolidine	15.97 ^[d]	0.627 ^[d]	1.25 ^[b]
piperidine	15.63 ^[d]	0.644 ^[d]	1.16 ^[b]
morpholine	15.40 ^[d]	0.643 ^[d]	9.9×10 ^{-1 [b,e]}
azide	14.54 ^[f]	0.822 ^[f]	5.08×10 ^{-1 [b]}
methoxide	14.51 ^[g]	0.680 ^[g]	1.50 ^[b]
diethanolamine	13.71 ^[d]	0.670 ^[d]	2.92×10 ^{-1 [b]}
hydrazine	13.47 ^[d]	0.702 ^[d]	3.24×10 ^{-1 [b]}
benzylamine	13.46 ^[d]	0.624 ^[d]	2.25×10^{-1} [b]
<i>n</i> -propylamine	13.41 ^[d]	0.657 ^[d]	2.01×10^{-1} [b]
ethanolamine	13.23 ^[d]	0.646 ^[d]	1.91×10^{-1} [b]
hydroxylamine	12.23 ^[d]	0.663 ^[d]	1.07×10^{-1} [b]
imidazole	10.41 ^[d]	0.696 ^[d]	1.09×10^{-2} [b]
2,2,2-trifluoroethylamine	10.20 ^[d]	0.917 ^[d]	1.02×10^{-2} [b]
trimethylphosphite	9.04 ^[d]	0.698 ^[d]	1.80×10^{-3} [b]
methanol	7.54 ^[h,i]	0.92 ^[h,i]	7.23×10^{-5} [j]
ethanol	7.44 ^[h,i]	0.90 ^[h,i]	1.14×10 ⁻⁴ [j]
propan-1-ol	7.05 ^[h,k]	0.80 ^[h,k]	8.50×10 ^{-5 [I]}
80E20W ^[m]	6.68 ^[h,i]	0.85 ^[h,i]	4.84×10 ⁻⁵ [j]
propan-2-ol	6.49 ^[h,k]	0.96 ^[h,k]	6.42×10 ^{-5 [I]}
60E40W ^[m]	6.28 ^[h,i]	0.87 ^[h,i]	1.99×10 ⁻⁵ [j]
40E60W ^[m]	5.81 ^[h,i]	0.90 ^[h,i]	8.91×10 ^{-6 [j]}
80A20W ^[m]	5.77 ^[h,n]	0.87 ^[h,n]	2.06×10 ⁻⁵ [j]
90A10W ^[m]	5.70 ^[h,n]	0.85 ^[h,n]	2.14×10 ⁻⁵ [j]
20E80W ^[m]	5.54 ^[h,i]	0.94 ^[h,i]	3.32×10^{-6} [j]
water	5.20 ^[h,i]	0.89 ^[h,i]	2.03×10^{-6} [j]
40T60W ^[m]	3.77 ^[h,i]	0.88 ^[h,i]	8.97×10 ^{-7 [j,o]}
60T40W ^[m]	3.42 ^[h,i]	0.90 ^[h,i]	5.11×10 ^{-7 [j,p]}
90T10W ^[m]	2.93 ^[h,i]	0.88 ^[h,i]	1.36×10^{-7} [j,q]
2,2,2-trifluoroethanol	1.23 ^[h,i]	0.92 ^[h,i]	5.66×10 ^{-9 [j]}

[a] From reference [37]. [b] Second-order rate constant $[M^{-1}s^{-1}]$, this work; see Supporting Information. [c] In 91/9 (v/v) methanol/acetonitrile. [d] Reactivity parameters N and s_N refer to second-order rate constants in 91/9 (v/v) methanol/acetonitrile, this work; see Supporting Information. [e] Only two data points were available for the determination of k $[M^{-1}s^{-1}]$. [f] In 91/9 (v/v) methanol/acetonitrile, from ref. [38]. [g] In 91/9 (v/v) methanol/acetonitrile, from ref. [22]. [h] Reactivity parameters N and s_N refer to first-order rate constants. [] From ref. [21]; [j] First-order rate constants in [s⁻¹] at 25.1 °C, from ref. [36]. [k] Reactivity parameters of 91/9 (v/v) alcohol/acetonitrile mixtures, from ref. [22]. [l] First-order rate constant in $[s^{-1}]$, this work, for details see Supporting Information. [m] Mixtures of solvents are given as (v/v); solvents: A = acetone, E = ethanol, T = 2,2,2-trifluoroethanol, W = water. [n] From ref. [39]. [o] Rate constant for 50T50W (w/w) [=42T58W (v/v)]. [p] Rate constant for 70T30W (w/w) [=63T37W (v/v)]. [q] Rate constant for 90T10W (w/w) [=87T13W (v/v)].

nucleophilicities toward C_{sp^3} and C_{sp^2} centers are closely related. Bunting and co-workers, for example, reported that the rate constants of the reactions of about 60 amines with methyl *p*-nitrosulfonates correlate linearly with the corresponding reactivities toward 4-vinylpyridinium ions.^[44] Analogous orders of nucleophilicities toward carbocations and haloalkanes have also been claimed by Richard and coworkers^[45] who noted that only N_3^- and α -effect nucleophiles deviate strongly from the linear correlation between Ritchie's N_+ and Swain and Scott's *n* constants (Figure 5).

These reports and preliminary data for $S_N 2$ reactions with further haloalkanes^[46] indicate that the benzhydryl-cation-

Communications



Figure 3. Correlation of $(\lg k)/s_N$ for the reactions of 1 with various solvents and with solutions of nucleophiles in methanol versus the nucleophilicity parameters *N*. Nucleophile-specific parameters s_N and *N* as well as rate constants *k* (\blacksquare in s⁻¹, \bullet and \odot in M^{-1} s⁻¹) from Table 1; the rate constant for morpholine (\odot) was not used for the correlation; mixtures of solvents are given as v/v; solvents: A=acetone, E=ethanol, T=2,2,2-trifluoroethanol, W=water.



Figure 4. Reactions of iodomethane with methanol and with solutions of various nucleophiles in methanol (*N* and s_N parameters from Table 1; rate constants of the reactions with iodomethane at 25 °C from ref. [6, 40]). In ref. [6] the rate constant for the reaction of P(OMe)₃ with iodomethane is reported to be of lower reliability than the other rate constants.

Table 2: Swain–Scott (n) and Ritchie (N_+) nucleophilicity constants of the cyanide, hydroxide, and azide ions in water.

Nucleophiles	$n(CH_3Br)^{[a]}$	$N_{+} (Ar_{3}C^{+})^{[b]}$
CN ⁻	5.10	4.12
HO⁻	4.20	4.75
N_3^-	4.00	7.54

[a] From ref. [42]; [b] From ref. [43].

based nucleophilicity parameters N and s_N are also suitable for many S_N^2 type reactions. We, therefore, suggest extending Equation (3) by an electrophile-specific parameter s_E to arrive at the general Equation (6) (see Scheme 1), which includes the empirical correlations given in Equations (1)–(3) as special cases.^[47]

If only reactions of nucleophiles with carbocations are considered, the electrophile-specific slope parameter $S_{\rm E}$ becomes 1 and Equation (6) transforms into Equation (3) (Scheme 1, left). We have already discussed that Equation (3) simplifies to Ritchie's constant selectivity relationship [Eqs. (2a) or (2)] if only reactions of carbocations with nucleophiles of $s_{\rm N} \approx 0.6$, for example, CN⁻, HO^- , MeO^- , RNH_2 are considered.^[20] Water, originally selected as the reference nucleophile of the Ritchie relationship,^[7] was later reported to deviate from the constant selectivity relationship in Equation (2).^[43,48] We have recently shown that this deviation is due to the slope parameter $s_N(H_2O) = 0.89^{[21]}$ which



Figure 5. Correlation between Ritchie N_+ and Swain–Scott *n* parameters (from ref. [45]); entries for the azide ion and for α -effect nucleophiles (\bigcirc) were not considered for the correlation.

differs from those of the other nucleophiles studied by Ritchie. Note, however, that other groups of reactions, for example, reactions of terminal alkenes ($s_{\rm R} = 1$) with carbocations ($s_{\rm E} = 1$) also constitute discrete sets of constant selectivity relationships which can be described by Equation (2).^[49]

The Swain–Scott equation [Eq. (1)] was derived from rate constants for S_N2 reactions of haloalkanes and related compounds with *n*-nucleophiles of $s_N \approx 0.6$. Substitution of this value into Equation (6) yields Equation (1a) which is equivalent to the Swain–Scott relationship (Scheme 1, right).

While it is tempting to consider Equation (6) as *the* equation for describing polar organic reactivity, it should be emphasized that the scope and limitations of Equation (6)

3872 www.angewandte.org

© 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Scheme 1. General equation [Eq. (6)] for electrophile–nucleophile combinations and its relation to other more specialized correlation equations.

have not yet been explored. As the nucleophilicity parameters N and s_N have been derived from reactions with carbon electrophiles whereas the electrophilicity parameters E and $s_{\rm E}$ have been derived from reactions with carbon nucleophiles, Equation (6) should only be applied to reactions where at least one of the reaction centers in either electrophile or nucleophile is carbon. Even then, deviations are to be expected, if stabilizing or destabilizing geminal substituent interactions are created or destroyed in the transition state. Thus, carboxonium ions react faster with alcohols than predicted by Equations (3) or (6) (anomeric product stabilization).^[50] On the other hand, Ritchie's observation that the N_{+} parameters for heteronucleophiles defined by Equation (2) are also applicable to reactions with diazonium ions^[7,43,51] indicates that in certain cases Equation (6) may also hold for combinations of heteroelectrophiles with heteronucleophiles.

We hope that the possibility to describe a large variety of organic reactions by a single empirical correlation [Eq. (6)] will stimulate further activities to unveil the physical basis of electrophilicity and nucleophilicity.

Received: February 9, 2006 Published online: April 28, 2006

Keywords: kinetics · linear free energy relationships · nucleophiles · reaction mechanisms · reactivity scales

- Nucleophilicity (Eds.: M. Harris, S. P. McManus), American Chemical Society, Washington, DC, 1987, (Adv. Chem. Ser. 215).
- [2] C. G. Swain, C. B. Scott, J. Am. Chem. Soc. **1953**, 75, 141–147.
- [3] a) J. O. Edwards, J. Am. Chem. Soc. 1954, 76, 1540–1547; b) J. O. Edwards, J. Am. Chem. Soc. 1956, 78, 1819–1820.
- [4] J. F. Bunnett, Annu. Rev. Phys. Chem. 1963, 14, 271–290; see also reference [1].

 1821.

 licity parameters
 [12] a) T. Tokuyasu, H. Mayr, Eur. J. Org. Chem. 2004, 2791–2796;

 ons with carbon
 b) A. D. Dilman, H. Mayr, Eur. J. Org. Chem. 2005, 1760–1764.

319-326.

1984, 84, 525-543.

DBintro.html.

4971

222

[13] a) A. D. Dilman, S. L. Ioffe, H. Mayr, J. Org. Chem. 2001, 66, 3196–3200; b) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, Chem. Eur. J. 2003, 9, 2209–2218.

[5] In the original literature, $s'_{\rm E}$ in Equation (1) and $s_{\rm N}$ in Equa-

[6] R. G. Pearson, H. Sobel, J. Songstad, J. Am. Chem. Soc. 1968, 90,

[7] a) C. D. Ritchie, Acc. Chem. Res. 1972, 5, 348–354; b) C. D. Ritchie, P. O. I. Virtanen, J. Am. Chem. Soc. 1972, 94, 4966–

[8] L. A. P. Kane-Maguire, E. D. Honig, D. A. Sweigart, Chem. Rev.

[9] R. D. Pike, D. A. Sweigart, Coord. Chem. Rev. 1999, 187, 183-

[10] a) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker,

[11] a) H. Mayr, M. Patz, Angew. Chem. 1994, 106, 990-1010; Angew. Chem. Int. Ed. Engl. 1994, 33, 938-957; b) H. Mayr, B.

B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, J. Am. Chem. Soc. 2001, 123, 9500–9512; b) For a comprehensive

listing of nucleophilicity parameters N and electrophilicity

parameters E, see http://www.cup.uni-muenchen.de/oc/mayr/

Kempf, A. R. Ofial, Acc. Chem. Res. 2003, 36, 66-77; c) H.

Mayr, A. R. Ofial in Carbocation Chemistry (Eds.: G. A. Olah,

G. K. S. Prakash), Wiley, Hoboken, NJ, **2004**, chap. 13, pp. 331–358; d) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, 77, 1807–

modified the symbols used in the literature.

tion (3) are both termed s. Because use of the same symbol for different properties would lead to confusion herein, we have

- [14] F. Dulich, K.-H. Müller, A. R. Ofial, H. Mayr, *Helv. Chim. Acta* 2005, 88, 1754–1768.
- [15] a) H. Mayr, K.-H. Müller, *Collect. Czech. Chem. Commun.* 1999, 64, 1770–1779; b) H. Mayr, O. Kuhn, C. Schlierf, A. R. Ofial, *Tetrahedron* 2000, 56, 4219–4229.
- [16] T. Bug, M. Hartnagel, C. Schlierf, H. Mayr, Chem. Eur. J. 2003, 9, 4068-4076.
- [17] a) R. Lucius, H. Mayr, Angew. Chem. 2000, 112, 2086–2089; Angew. Chem. Int. Ed. 2000, 39, 1995–1997; b) R. Lucius, R. Loos, H. Mayr, Angew. Chem. 2002, 114, 97–102; Angew. Chem. Int. Ed. 2002, 41, 91–95.
- [18] T. Bug, T. Lemek, H. Mayr, J. Org. Chem. 2004, 69, 7565-7576.
- [19] T. Bug, H. Mayr, J. Am. Chem. Soc. 2003, 125, 12980-12986.
- [20] S. Minegishi, H. Mayr, J. Am. Chem. Soc. 2003, 125, 286-295.
- [21] S. Minegishi, S. Kobayashi, H. Mayr, J. Am. Chem. Soc. 2004, 126, 5174-5181.
- [22] T. B. Phan, H. Mayr, Can. J. Chem. 2005, 83, 1554-1560.
- [23] B. Kempf, H. Mayr, Chem. Eur. J. 2005, 11, 917-927.
- [24] R. Loos, S. Kobayashi, H. Mayr, J. Am. Chem. Soc. 2003, 125, 14126-14132.
- [25] A. A. Tishkov, H. Mayr, Angew. Chem. 2005, 117, 145–148; Angew. Chem. Int. Ed. 2005, 44, 142–145.
- [26] S. Minegishi, R. Loos, S. Kobayashi, H. Mayr, J. Am. Chem. Soc. 2005, 127, 2641–2649.
- [27] A. A. Tishkov, U. Schmidhammer, S. Roth, E. Riedle, H. Mayr, Angew. Chem. 2005, 117, 4699–4703; Angew. Chem. Int. Ed. 2005, 44, 4623–4626.
- [28] H. Mayr, G. Lang, A. R. Ofial, J. Am. Chem. Soc. 2002, 124, 4076–4083.
- [29] H. Mayr, N. Basso, G. Hagen, J. Am. Chem. Soc. 1992, 114, 3060-3066.
- [30] H. Mayr, N. Basso, Angew. Chem. **1992**, 104, 1103–1105; Angew. Chem. Int. Ed. Engl. **1992**, 31, 1046–1048.
- [31] M. A. Funke, H. Mayr, Chem. Eur. J. 1997, 3, 1214-1222.
- [32] T. Lemek, H. Mayr, J. Org. Chem. 2003, 68, 6880-6886.

Communications

- [33] a) F. Terrier, S. Lakhdar, R. Goumont, T. Boubaker, E. Buncel, *Chem. Commun.* **2004**, 2586–2587; b) F. Terrier, S. Lakhdar, T. Boubaker, R. Goumont, *J. Org. Chem.* **2005**, *70*, 6242–6253.
- [34] G. Ya. Remennikov, B. Kempf, A. R. Ofial, K. Polborn, H. Mayr, J. Phys. Org. Chem. 2003, 16, 431–437.
- [35] D. N. Kevill in Advances in Quantitative Structure-Property Relationship, Vol. 1 (Ed.: M. Charton), JAI, Greenwich, 1996, pp. 81–115.
- [36] D. N. Kevill, S. W. Anderson, J. Org. Chem. 1991, 56, 1845-1850.
- [37] T. B. Phan, H. Mayr, Eur. J. Org. Chem. 2006, in press.
- [38] T. B. Phan, H. Mayr, J. Phys. Org. Chem. 2006, in press.
- [39] B. Denegri, S. Minegishi, O. Kronja, H. Mayr, Angew. Chem. 2004, 116, 2353-2356; Angew. Chem. Int. Ed. 2004, 43, 2302-2305.
- [40] For the reaction of MeOH with MeI at 25 °C, the first-order rate constant $k = 3.3 \times 10^{-9} \text{ s}^{-1}$ from ref. [6] as well as N = 7.54 and $s_N = 0.92$ from ref. [21] were used.
- [41] a) A. Pross in *Theoretical and Physical Principles in Organic Reactivity*, Wiley, New York, **1995**, p. 232; b) S. Hoz in *Nucleophilicity* (Eds.: M. Harris, S. P. McManus), American Chemical Society, Washington, DC, **1987**, pp. 181–194.
- [42] J. Koskikallio, Acta Chem. Scand. 1969, 23, 1477-1489.
- [43] C. D. Ritchie, Can. J. Chem. 1986, 64, 2239-2250.
- [44] J. W. Bunting, J. M. Mason, C. K. M. Heo, J. Chem. Soc. Perkin Trans. 2 1994, 2291–2300.
- [45] J. P. Richard, M. M. Toteva, J. Crugeiras, J. Am. Chem. Soc. 2000, 122, 1664–1674.
- [46] T. B. Phan, H. Mayr, unpublished results.
- [47] Because s_E and E are nucleophile independent, and s_N and N are electrophile independent, Equation (6) is equivalent to $\lg k = s_N E' + s_E N'$, where $E' = s_E E$ and $N' = s_N N$. For the same reasons discussed for Equation (3) (see ref. [11]), the parameters E' and N' are less convenient in practical use. Hence, we prefer to use the version of Equation (6) shown in Scheme 1.
- [48] a) C. D. Ritchie, J. Am. Chem. Soc. 1975, 97, 1170–1179;
 b) C. D. Ritchie, M. Sawada, J. Am. Chem. Soc. 1977, 99, 3754–3761; c) C. D. Ritchie, J. E. Van Verth, P. O. I. Virtanen, J. Am. Chem. Soc. 1982, 104, 3491–3497; d) C. D. Ritchie, J. Am. Chem. Soc. 1984, 106, 7187–7194.
- [49] H. Mayr, Angew. Chem. 1990, 102, 1415-1428; Angew. Chem. Int. Ed. Engl. 1990, 29, 1371-1384.
- [50] a) The Anomeric Effect and Associated Stereoelectronic Effects (Ed.: G. R. J. Thatcher), ACS Symp. Ser. 1993, 539; b) E. Juaristi, G. Cuevas, Tetrahedron 1992, 48, 5019–5087.
- [51] C. D. Ritchie, P. O. I. Virtanen, J. Am. Chem. Soc. 1972, 94, 1589–1594.