

Nucleophilic Reactivities of Carbanions in Water: The Unique Behavior of the Malodinitrile Anion

Thorsten Bug and Herbert Mayr*

Contribution from the Department Chemie der Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13 (Haus F), D-81377 München, Germany

Received June 23, 2003; E-mail: Herbert.Mayr@cup.uni-muenchen.de

Abstract: The kinetics of the reactions of nine carbanions **1a–i**, each stabilized by two acyl, ester, or cyano groups, with benzhydrylium ions in water were investigated photometrically at 20 °C. Because the competing reactions of the benzhydrylium ions with water and hydroxide ions are generally slower, the second-order rate constants of the reactions of the benzhydrylium ions with the carbanions can be determined with high precision. The rate constants thus obtained can be described by the Ritchie equation, $\log(k/k_0) = N_+$ (eq 1), which allows us to calculate Ritchie N_+ parameters for a series of stabilized carbanions, for example, malonate, acetoacetate, malodinitrile, etc., and compare them with those of other n -nucleophiles in water (hydroxide, amines, azide, thiolates, etc.). Because the Ritchie relationship (eq 1) is a special case of the more general relationship $\log k = s(N + E)$ (eq 4), the reactivity parameters N and s for the carbanions **1a–i** can also be calculated and compared with the nucleophilic reactivities of a large variety of n -, π -, and σ -nucleophiles, including reactivities of carbanions in dimethyl sulfoxide. While the acyl and ester substituted carbanions are approximately 3 orders of magnitude less reactive in water than in dimethyl sulfoxide, the malodinitrile anion (**1i**) shows almost the same reactivity in both solvents. Correlations between the nucleophilic reactivities of carbanions with the pK_a values of the corresponding CH acids reveal that the malodinitrile anion (**1i**) is considerably more nucleophilic than was expected on the basis of its pK_a value. This deviation is assigned to the exceptionally low Marcus intrinsic barriers of the reactions of the malodinitrile anion (**1i**).

Introduction

Ritchie's discovery that the rates of the reactions of stabilized carbocations and diazonium ions with a large variety of nucleophiles can be described by the so-called "constant selectivity relationship" (eq 1) led to the conclusion that nucleophilicity is an intrinsic property of the reagents, dependent on the medium but independent of the nature of the reaction partner.¹

$$\log(k/k_0) = N_+ \quad (1)$$

$\log k_0$ = electrophile-dependent parameter

N_+ = nucleophile-dependent parameter

A large variety of nucleophiles, for example, amines, alcohols, alkoxides, thiolates, have been characterized in this way.² Remarkably, cyanide was the only carbon nucleophile investigated by Ritchie, despite the fact that carbanions are the nucleophiles of greatest interest to organic chemists.³ We have now determined the nucleophilic reactivities of carbanions in water each stabilized by two cyano, ester, or keto groups, and we compare the results with Ritchie's N_+ values of heteronucleophiles as well as with the nucleophilic reactivities of these

carbanions in DMSO.⁴ As in our previous investigations, benzhydrylium ions were employed as reference electrophiles (Table 1), which allows us to link the data obtained in this investigation to the reactivity scales of uncharged π -nucleophiles⁵ and hydride donors.^{6,7} For the determination of the nucleophilicity parameters of the tertiary carbanions **1d** and **1h**

- (3) (a) Bates, R. B.; Ogle, C. A. In *Carbanion Chemistry-Reactivity and Structure Concepts in Organic Chemistry*; Hafner, K., Lehn, J.-M., Rees, C. W., Schleyer, P. v. R., Trost, B. M., Zahradnik, R., Eds.; Springer-Verlag: Berlin, 1983; Vol. 17. (b) Buncl, E.; Durst, T. *Comprehensive Carbanion Chemistry*, pts. A, B, and C; Elsevier: New York, 1980, 1984, 1987. (c) Snieckus, V. *Advances in Carbanion Chemistry*; JAI: Greenwich, 1992, 1996; Vols. 1 and 2. (d) Heathcock, C. H.; Winterfeldt, E.; Schlosser, M. In *Modern Synthetic Methods – Topics in Carbanion Chemistry*; Scheffold, R., Ed.; VCHA and VCH: Basel and Weinheim, 1992. (e) Trofimov, B. A. *J. Heterocycl. Chem.* **1999**, 36, 1469–1490. (f) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.1–1.7. (g) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, 58, 1–23. (h) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, 78, 275–316.
- (4) (a) Lucius, R.; Mayr, H. *Angew. Chem.* **2000**, 112, 2086–2089; *Angew. Chem., Int. Ed.* **2000**, 39, 1995–1997. (b) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem.* **2002**, 114, 97–102; *Angew. Chem., Int. Ed.* **2002**, 41, 91–95.
- (5) (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, 36, 66–77. (b) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.-Eur. J.* **2003**, 9, 2209–2218. (c) Bug, T.; Hartnagel, M.; Schlierf, C.; Mayr, H. *Chem.-Eur. J.* **2003**, 9, 4068–4076.
- (6) (a) Funke, M.-A.; Mayr, H. *Chem.-Eur. J.* **1997**, 3, 1214–1222. (b) Mayr, H.; Basso, N.; Hagen, G. *J. Am. Chem. Soc.* **1992**, 114, 3060–3066. (c) Mayr, H.; Lang, G.; Ofial, A. R. *J. Am. Chem. Soc.* **2002**, 124, 4076–4083.
- (7) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, 123, 9500–9512.

(1) (a) Ritchie, C. D. *Acc. Chem. Res.* **1972**, 5, 348–354. (b) Ritchie, C. D. *Can. J. Chem.* **1986**, 64, 2239–2250.

(2) See refs 10–25 in ref 1b.

Table 1. Electrophilicity Parameters E , and $\log k_0$ Values of the Reference Electrophiles Employed for Determining the Nucleophilicities of the Carbanions **1a–i**

	electrophile	E	$\log k_0^a$	$\lambda_{\max} / \text{nm}$
2a		-7.02^b	-2.64	604^a
2b		-7.69^b	-3.08	611^a
2c		-8.22^b	-3.34	618^a
2d		-8.76^b	-3.73	614^a
2e		-10.04^b	-4.44	630^a
2f		-15.83^c	-	371^d
2g		-17.90^c	-	521^d

^a In water from ref 8. ^b From ref 7. ^c From ref 4b. ^d In DMSO from ref 9.

Table 2. Rate Constants of the Reactions of Benzhydrylium Tetrafluoroborates with Water and OH^- in Water

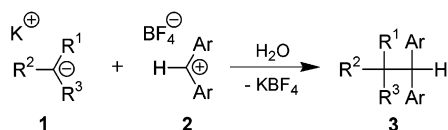
electrophile	$k_{1\psi, \text{W}} / \text{s}^{-1}$	$k_{2, \text{OH}} / \text{L mol}^{-1} \text{s}^{-1}$
2a	$2.6 \times 10^{-2}^a$	$1.31 \times 10^2^b$
2b	$5.57 \times 10^{-3}^b$	$4.85 \times 10^1^b$
2c	$2.20 \times 10^{-3}^b$	$2.36 \times 10^1^c$
2d		$1.08 \times 10^1^b$
2e		2.16^b

^a From ref 11. ^b From ref 8. ^c Calculated with N and s from ref 8 and eq 4.

in DMSO, the quinone methides **2f** and **2g** were used as additional electrophiles, as in previous kinetic investigations of carbanions in DMSO (Table 1).^{4a}

Results

Preparative Investigations. The reactions of the carbanions **1** with the benzhydrylium salts **2**– BF_4^- in water produce the [1:1] addition products **3**. As shown in Table 3, reaction products of the combinations of the carbanions **1a–i** with one or two of the benzhydrylium salts **2a–e**– BF_4^- have been isolated and characterized as described in the Supporting Information.



Kinetic Investigations. All reactions reported in this Article followed second-order kinetics, first order with respect to the carbanion **1a–i** concentration and first order with respect to electrophile **2a–g** concentration. Because the carbanions **1a–i** were usually employed in excess over the carbocations, their concentration can be considered to be constant, resulting in pseudo-first-order kinetics with an exponential decay of the

Table 3. Second-Order Rate Constants of the Reactions of the Carbanions **1a–i** with Benzhydrylium Tetrafluoroborates (**2a–e**)– BF_4^- in Water at 20 °C and Listing of the Characterized Products

carbanion	electrophile	$k_{2, \text{C}} / \text{L mol}^{-1} \text{s}^{-1}$	product	yield / % ^a
	2a	1.04×10^3	-	-
	2b	3.90×10^2	3ab	23
	2d	7.61×10^1	-	-
	2e	1.29×10^1	3ae	62
	2a	2.50×10^3	3ba	30
	2b	7.03×10^2	-	-
	2d	1.53×10^2	-	-
	2e	2.30×10^1	-	-
	2a	2.12×10^4	3ca	85
	2c	3.00×10^3	-	-
	2e	2.41×10^2	-	-
	2a	1.14×10^5	3da	94
	2c	1.29×10^4	-	-
	2e	9.36×10^2	-	-
	2a	8.49×10^4	3ea	38
	2c	2.23×10^4	-	-
	2e	1.54×10^3	-	-
	2a	3.88×10^5	3fa	68
	2c	6.46×10^4	-	-
	2e	5.09×10^3	-	-
	2a	9.61×10^5	3ga	58
	2c	1.64×10^5	-	-
	2e	1.01×10^4	-	-
	2a	$1.76 \times 10^5^b$	3ha	38
	2c	$5.65 \times 10^4^b$	-	-
	2e	$5.78 \times 10^3^b$	-	-
	2a	6.73×10^6	3ia	57
	2c	1.56×10^6	-	-
	2e	1.50×10^5	-	-

^a Yields not optimized. ^b Uncertain value; see text.

electrophile **2** concentration (eq 2).

$$-\text{d}[\mathbf{2}]/\text{d}t = k_{1\psi, \text{obs}}[\mathbf{2}] \quad (2)$$

In all reactions of the benzhydrylium ions with carbanions in water, competing reactions of the carbocations with hydroxide and water have to be considered. The observed pseudo-first-order rate constants $k_{1\psi, \text{obs}}$ reflect the reaction of the electrophile with the carbanion ($k_{1\psi, \text{C}^-}$), OH^- ($k_{1\psi, \text{OH}^-}$), and water ($k_{1\psi, \text{W}}$) (eq 3).

$$k_{1\psi, \text{obs}} = k_{1\psi, \text{C}^-} + k_{1\psi, \text{OH}^-} + k_{1\psi, \text{W}} \quad (3)$$

$$= k_{2, \text{C}^-}[\text{C}^-] + k_{2, \text{OH}^-}[\text{OH}^-] + k_{1\psi, \text{W}}$$

$$k_{1\psi} = k_{1\psi, \text{obs}} - k_{2, \text{OH}^-}[\text{OH}^-] = k_{2, \text{C}^-}[\text{C}^-] + k_{1\psi, \text{W}} \quad (3.1)$$

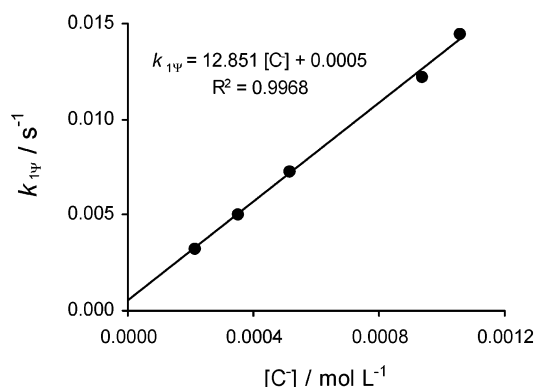


Figure 1. Determination of the second-order rate constant $k_{2,C^-} = 12.9 \text{ L mol}^{-1} \text{ s}^{-1}$ for the reaction of **2e** with deprotonated dimedone (**1a**) in water at 20 °C.

Table 4. Second-Order Rate Constants of the Reactions of the Carbanions **1d,h** with the Electrophiles **2e**–**BF₄[−]** and **2f,g** in DMSO at 20 °C and Listing of the Characterized Products

carbanion	electrophile	$k_2 / \text{L mol}^{-1} \text{ s}^{-1}$	product	yield / % ^a
	2e	1.09×10^6	3de	27
	2f	7.02×10^1	-	-
	2f	4.08×10^3	3hf	39
	2g	1.59×10^2	-	-

^a Yields not optimized.

$[C^-]$ is the concentration of the carbanion, which was generated from the CH acid with KOH. The concentrations of the carbanions $[C^-]$ and of the hydroxide $[OH^-]$ are calculated¹⁰ from $[OH^-]_0$, $[CH \text{ acid}]_0$, and pK_a as described on p S12 of the Supporting Information. With the already published k_{2,OH^-} values⁸ (Table 2) and the calculated concentrations $[OH^-]$, the partial pseudo-first-order rate constants $k_{1\psi,OH^-}$ can be calculated.

The slopes of the plots ($k_{1\psi} = k_{1\psi,obs} - k_{1\psi,OH^-}$) (eq 3.1) versus $[C^-]$ correspond to the second-order rate constants k_{2,C^-} , as shown in Figure 1 and in the Supporting Information. The intercepts, which correspond to the reactions of the benzhydrylium ions with water, are negligible, in accord with the directly measured reactivities toward water listed in the middle column of Table 2. As explicitly shown in the Supporting Information, only in some experiments with **1h** does $k_{1\psi,OH^-}$ reach an order of magnitude similar to that of $k_{1\psi,C^-}$, while in all other cases $k_{1\psi,OH^-} \ll k_{1\psi,C^-}$ with the consequence that usually $k_{1\psi} \approx k_{1\psi,obs}$.

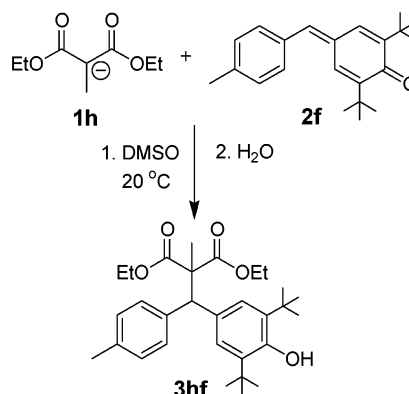
The pK_a values for the conjugate CH acids of **1a–f** and of **1i** have repeatedly been determined in the literature and agree within ± 0.2 units in pK_a . Because of the high acidities of these compounds ($pK_a \leq 11.2$, see Table 5), the errors in calculated carbanion concentrations as well as in k_{2,C^-} and N resulting from the uncertainties of pK_a are negligible. For diethyl malonate, we used a pK_a value of 12.9¹² which is consistent with other data, with the consequence that the resulting N value can also be considered as reliable. Because the pK_a value for diethyl

Table 5. pK_a Values of the Conjugate CH Acids of the Carbanions **1a–i** in Water and DMSO

carbanion	$pK_a(\text{H}_2\text{O})$	$pK_a(\text{DMSO})$	$pK_a(\text{DMSO}) - pK_a(\text{H}_2\text{O})$
dimedone (1a)	5.3 ^a	11.2 ^b	5.9
Meldrum's acid (1b)	4.8 ^a	7.3 ^b	2.5
acetylacetone (1c)	9.0 ^c	13.3 ^d	4.3
3-methylacetylacetone (1d)	10.8 ^e	15.1 ^f	4.3
ethyl cyanoacetate (1e)	11.2 ^g	13.1 ^h	1.9
ethyl acetylacetate (1f)	10.7 ⁱ	14.2 ^b	3.5
diethyl malonate (1g)	12.9 ^c	16.4 ^d	3.5
diethyl methylmalonate (1h)	13.1 ^j	18.7 ^d	5.6
malodinitrile (1i)	11.2 ^c	11.1 ^d	−0.1

^a From ref 23. ^b From ref 24. ^c From ref 12. ^d From ref 25. ^e From ref 26. ^f From ref 27. ^g From ref 28. ^h From ref 29. ⁱ From ref 30. ^j From ref 13.

Scheme 1. Reaction of the Tertiary Carbanion **1h** with the Quinone Methide **2f** in DMSO



methylmalonate in water has not been determined experimentally, the value of 13.1 calculated by ACD Software was employed.¹³ Because of the lack of independent confirmation, the resulting k_{2,C^-} and N values for **1h** should be considered as less reliable.

Rate constants for the reactions of the carbanions **1a–i** with electrophiles in water are given in Table 3.

To compare the nucleophilicities of all carbanions from Table 3 in water with the corresponding data in DMSO, it was necessary to complete the previously published data set in DMSO^{4b} by determining the nucleophilic reactivities of **1d** and **1h** in this solvent (Table 4). Scheme 1 shows the isolated addition product **3hf** which was obtained from the quinone methide **2f** and the tertiary carbanion **1h** in DMSO.

Discussion

Figure 2 shows that the reactions of the carbanions **1a–i** with benzhydrylium ions follow Ritchie's eq 1, not worse and not better than the nucleophiles initially studied by Ritchie.¹

The N_+ values in water for the carbanions **1a–i** (Figure 3), which correspond to the abscissa of Figure 2, have been calculated from the Ritchie correlation (eq 1) using the $\log k_0$ values⁸ listed in Table 1.

These N_+ values can be compared with N_+ of other nucleophiles determined by Ritchie.¹ It is remarkable that the

(8) Minegishi, S.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 286–295.

(9) Lucius, R. Dissertation, Ludwig-Maximilians-Universität München, 2001.

(10) Evans, A. G.; Hamann, S. D. *Trans. Faraday Soc.* **1951**, *47*, 34–40.

(11) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966–3972.

(12) Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants: A Laboratory Manual*, 3rd ed.; Chapman and Hall: London, 1984; pp 137–160.

(13) From *SciFinder Scholar* 2002: Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 (1994–2003 ACD).

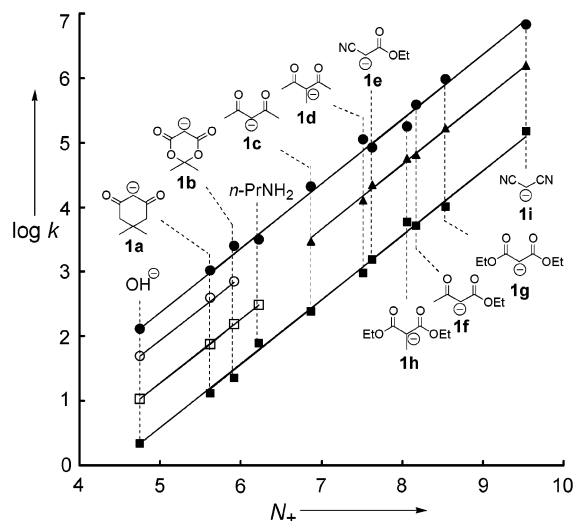


Figure 2. Analysis of the rate constants for the reactions of benzhydrylium ions with the carbanions **1a–i** in water according to the Ritchie formalism (eq 1). Data for OH^- and $n\text{-PrNH}_2$ are from ref 8. Each correlation line corresponds to one benzhydrylium ion: ● (**2a**), ○ (**2b**), ▲ (**2c**), □ (**2d**), ■ (**2e**).

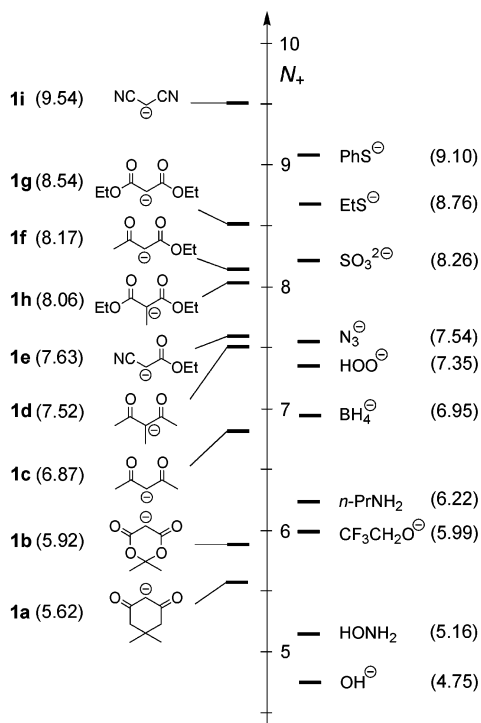


Figure 3. Comparison of the N_+ values in water for the carbanions **1a–i** with those of other nucleophiles. N_+ of PhS^- , EtS^- , N_3^- , BH_4^- , and OH^- from ref 1b; N_+ of SO_3^{2-} , HOO^- , $n\text{-PrNH}_2$, $\text{CF}_3\text{CH}_2\text{O}^-$, and HONH_2 from ref 8.

carbanions of dimedone (**1a**) and Meldrum's acid (**1b**), the least reactive carbanions of this series, are considerably more reactive than OH^- in water (Figure 3). The thiolate anions (EtS^- and PhS^-) are more nucleophilic than most carbanions of this series, only exceeded by the malodinitrile anion (**1i**).

Numerous investigations of the reactions of carbocations with π -nucleophiles (alkenes,¹⁴ arenes¹⁵) and hydride donors (silanes,^{6b,16} stannanes,¹⁷ aminoboranes,^{6a} unsaturated hydrocarbons^{6c}) have shown that Ritchie's two-parameter eq 1 is insufficient to properly describe the rate constants of all of these reactions.^{5a,18}

Excellent correlations were obtained, however, by employing

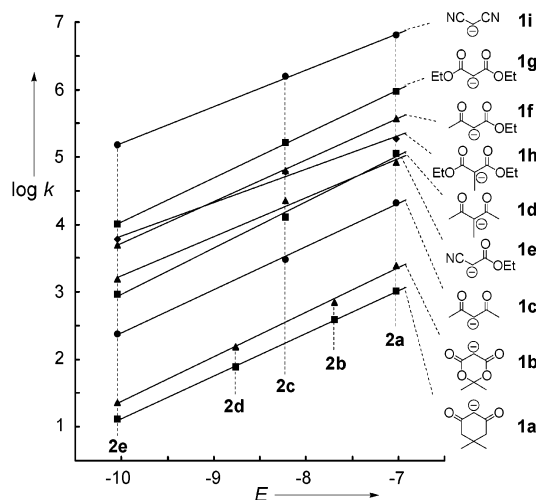


Figure 4. Correlation of the rate constants (20 °C) for the reactions of the carbanions **1a–i** with the benzhydrylium tetrafluoroborates (**2a–e**)- BF_4^- in water toward the electrophilicity parameters E .

eq 4, which differs from eq 1 by an additional parameter, the nucleophile-specific slope parameter s .

$$\log k(20^\circ\text{C}) = s(N + E) \quad (4)$$

s = nucleophile-specific slope parameter

N = nucleophilicity parameter

E = electrophilicity parameter

Because eq 1 is a special case ($s = \text{constant}$) of the more general relationship (4), eq 4 has recently been employed for linking Ritchie's nucleophilicity parameters to the nucleophilicity scales for π -systems and hydride donors.⁸ It has previously been discussed that eq 4 is equivalent to $\log k = Nu + sE$ with $Nu = sN$; for practical reasons, however, it is preferable to use the nucleophilicity parameters N instead of Nu .¹⁸

In analogy to previous investigations,⁷ we have plotted the rate constants of the reactions of the carbanions **1a–i** with the benzhydrylium ions **2a–e** in water against the corresponding electrophilicity parameters E . The reactivity parameters N and s as defined by eq 4 were then derived (Figure 4).

While the nucleophilicity sequences expressed by N_+ (Figure 2) and by N (Figure 4) are similar, the two scales are not perfectly proportional to each other: While N_+ (eq 1) reflects the averaged relative reactivities of the nucleophiles toward the electrophiles investigated in this work, N (eq 4) reflects the extrapolated reactivity order of nucleophiles toward variable

- (14) (a) Mayr, H.; Schneider, R.; Schade, C.; Bartl, J.; Bederke, R. *J. Am. Chem. Soc.* **1990**, *112*, 4446–4454. (b) Mayr, H.; Schneider, R.; Irrgang, B.; Schade, C. *J. Am. Chem. Soc.* **1990**, *112*, 4454–4459. (c) Mayr, H.; Schneider, R.; Grabis, U. *J. Am. Chem. Soc.* **1990**, *112*, 4460–4467. (d) Mayr, H. *Angew. Chem.* **1990**, *102*, 1415–1428; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1371–1384. (e) Irrgang, B.; Mayr, H. *Tetrahedron* **1991**, *47*, 219–228. (f) Roth, M.; Schade, C.; Mayr, H. *J. Org. Chem.* **1994**, *59*, 169–172. (g) Mayr, H.; Hartnagel, M. *Liebigs Ann. Chem.* **1996**, 2015–2018.
- (15) (a) Mayr, H.; Bartl, J.; Hagen, G. *Angew. Chem.* **1992**, *104*, 1689–1691; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1613–1615. (b) Gotta, M. F.; Mayr, H. *J. Org. Chem.* **1998**, *63*, 9769–9775.
- (16) Basso, N.; Görs, S.; Popowski, E.; Mayr, H. *J. Am. Chem. Soc.* **1993**, *115*, 6025–6028.
- (17) Mayr, H.; Basso, N. *Angew. Chem.* **1992**, *104*, 1103–1105; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1046–1048.
- (18) (a) Mayr, H.; Patz, M. *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957. (b) Mayr, H.; Patz, M.; Gotta, M. F.; Ofial, A. R. *Pure Appl. Chem.* **1998**, *70*, 1993–2000. (c) Mayr, H.; Kuhn, O.; Gotta, M. F.; Patz, M. *J. Phys. Org. Chem.* **1998**, *11*, 642–654.

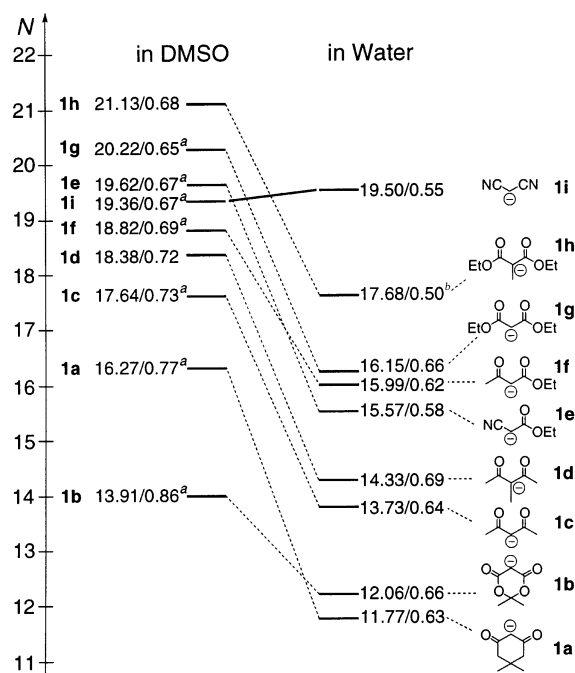


Figure 5. Comparison of the nucleophilicity and slope parameters (N/s) for the carbanions **1a–i** in water and in DMSO. (a) Data are from ref 4b. ^b Uncertain value; see text.

(hypothetical) electrophiles which react with rate constants of $1 \text{ L mol}^{-1} \text{ s}^{-1}$ ($\log k = 0$). As discussed previously,⁸ the N parameters thus derived can be employed for a direct comparison with the reactivities of nucleophiles which do not follow eq 1, for example, alkenes and arenes.

The rate constants for the reactions of carbanions with benzhydrylium ions in water (Table 3) are from 1 to 3 orders of magnitude smaller than the corresponding values in DMSO (Figure 5).^{4b} We assign these differences predominantly to different carbanion solvation and not to carbocation solvation because similar solvent effects are observed for the reactions of carbanions with benzhydrylium ions and quinone methides. Thus, the reaction of ethyl cyanoacetate (**1e**) with the benzhydrylium ion **2e** and with the neutral electrophiles **2f,g** is 5 times slower in methanol than in DMSO.¹⁹

Figure 5 shows that the nucleophilicity parameters N of all carbonyl and ester stabilized carbanions are about 2–4 units smaller in water than in DMSO, corresponding to rate ratios $k(\text{DMSO})/k(\text{H}_2\text{O})$ of 10^2 – 10^4 . Hydrogen bonding to the negatively charged oxygen atoms may account for the lower reactivities of these carbanions in water.

However, the deprotonated malodinitrile (**1i**) behaves differently. It possesses nearly the same N parameter in water and in DMSO. The small reactivity difference toward the electrophile **2e** ($k(\text{DMSO})/k(\text{H}_2\text{O}) = 12$) is due to the difference in the slope parameter s . The remarkably small influence of the solvent on the nucleophilicity of the malodinitrile anion **1i** is in accord with the small degree of charge delocalization in cyano substituted carbanions,^{20,21} which results in little hydrogen bond stabilization and identical $\text{p}K_{\text{a}}$ values of malodinitrile in water

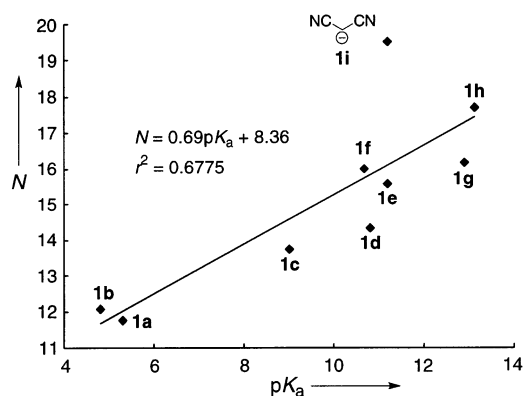


Figure 6. Plot of the nucleophilicity parameter N versus $\text{p}K_{\text{a}}$ of the corresponding acids of the carbanions **1a–i** (water, 20 °C).

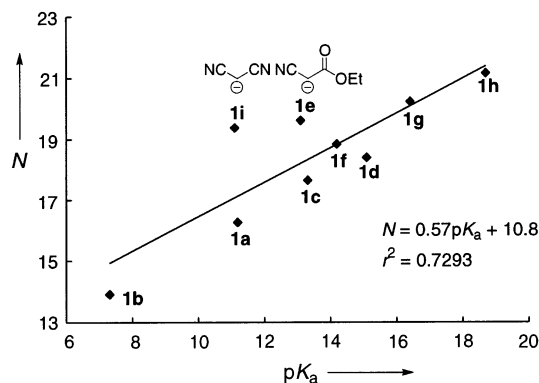


Figure 7. Plot of the nucleophilicity parameter N versus $\text{p}K_{\text{a}}$ of the corresponding acids of the carbanions **1a–i** (DMSO, 20 °C).

and in DMSO (Table 5).²² All other CH acids of this investigation are significantly more acidic in water than in DMSO.

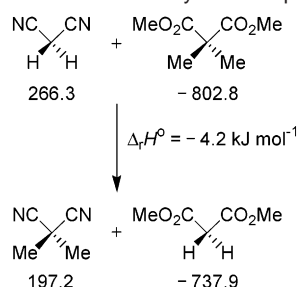
The reactivity parameters N of the carbanions **1a–i** in water determined in this work and the corresponding $\text{p}K_{\text{a}}$ values can be used for correlations between reactivity and Brønsted basicity.³¹ Good correlations may be expected because the nucleophiles are of the same type (carbanions)³² and the nucleophile-specific slope parameters s according to eq 4 differ only slightly ($0.50 \leq s \leq 0.69$, H_2O). Both correlations of N versus $\text{p}K_{\text{a}}$ in water (Figure 6) as well as in DMSO (Figure 7), are of poor quality, however.

The deprotonated malodinitrile (**1i**), in particular, is considerably more reactive in both solvents than expected on the basis of its $\text{p}K_{\text{a}}$ value. Thus, the malodinitrile anion is again unique.

Because Figures 6 and 7 correlate nucleophilicity toward carbon with basicity toward protons, one cannot a priori exclude a thermodynamic origin for this observation. Rüchardt had indeed reported that the destabilizing inverse anomeric effect

- (19) Phan Thanh, B.; Mayr, H., unpublished results.
 (20) Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327–6334.
 (21) (a) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715–726. (b) Abboto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449–455.

- (22) Bernasconi, C. F.; Bunnell, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 2900–2903.
 (23) Feith, B.; Weber, H.-M.; Maas, G. *Chem. Ber.* **1986**, *119*, 3276–3296.
 (24) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
 (25) Bordwell, F. G.; Harrelson, J. A., Jr.; Satish, A. V. *J. Org. Chem.* **1989**, *54*, 3101–3105.
 (26) Pearson, R. G.; Mills, J. M. *J. Am. Chem. Soc.* **1950**, *72*, 1692–1694.
 (27) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767.
 (28) Dale, J.; Morgenlie, S. *Acta Chem. Scand.* **1970**, *24*, 2408–2418.
 (29) Bordwell, F. G.; Branca, J. C.; Bares, J. E.; Filler, R. *J. Org. Chem.* **1988**, *53*, 750–782.
 (30) Eidinoff, M. L. *J. Am. Chem. Soc.* **1945**, *67*, 2072–2073.
 (31) Brønsted, J. N.; Pedersen, K. Z. *Phys. Chem.* **1924**, *108*, 185–235.
 (32) Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; American Chemical Society: Washington, DC, 1987.

Scheme 2. Effect of Methyl Substitution on the Geminal Interaction of Two Ester or of Two Cyano Groups^a

^a Gas-phase thermochemical data are from ref 33 (nitrile) and ref 35 (esters). Values correspond to $\Delta_f H^\circ$ in kJ mol^{-1} .

of geminal nitrile groups is attenuated by the presence of alkyl groups.³³ The magnitude of this effect is given by $\Delta_r H^\circ$ of the isodesmic reaction in Scheme 2, which indicates that the replacement of the methylene protons by methyl groups stabilizes malodinitrile only slightly more than methyl malonate.³⁴ The small value of $\Delta_r H^\circ$ in Scheme 2 excludes differences between carbon and proton basicities of malodinitrile and malonic ester anions as the origin for the exceptionally high nucleophilicity of the malodinitrile anion.

One has to assume, therefore, that the intrinsic barrier for the reaction of the malodinitrile anion (**1i**) is significantly lower than that for the other carbanions of this study. This conclusion is in accord with Bernasconi's report that the malodinitrile anion (**1i**) undergoes Michael additions with lower intrinsic barriers than most other carbanions.³⁶ The well-known fact that cyano-carbons differ from most CH acids in the sense that their proton-transfer reactions are almost "normal" in the Eigen sense^{37,38} again indicates low intrinsic barriers.^{21a} Both phenomena have been attributed to the small degree of resonance stabilization in the malodinitrile anion^{21,39} which results in little transition state imbalance⁴⁰ of its reactions with electrophiles. Bernasconi's "Principle of Nonperfect Synchronization"^{38,41} which relates the magnitudes of intrinsic barriers with the degree of resonance stabilization of the reagents has previously been used to explain the high intrinsic reactivity of the malodinitrile anion with Michael acceptors as well as its fast proton-transfer reactions. Analogous rationalizations can be used to explain the exceptionally high reactivity of the malodinitrile anion toward carbocations.

We have thus shown on a statistical basis that $\text{p}K_a$ values are poor guides for predicting nucleophilic reactivities of carbanions and that the exceptional high nucleophilicity of malodinitrile anion (**1i**) is found in water as well as in DMSO.

Experimental Section

Materials. Water was distilled and passed through a Milli-Q water purification system. Dimethyl sulfoxide (DMSO, Fluka, puriss., stored over molecular sieve, $\text{H}_2\text{O} \leq 0.01\%$) and acetonitrile (Fluka, for HPLC, $\geq 99.9\%$) were used without further purification.

Benzhydrylium tetrafluoroborates⁷ and quinone methides^{9,42} were prepared as described.

Potassium salts of diethyl methylmalonate and 3-methylacetylacetone were synthesized in analogy to literature reports.^{9,27}

Potassium hydroxide was purchased as an aqueous solution (Merck, $c = 0.1 \text{ M} \pm 0.1\%$; Aldrich, $c = 0.5073 \text{ M}$ (volumetric standard)). Meldrum's acid (Acros, 98%), dimedone (Acros, 99%), diethyl malonate (Fluka, $\geq 99\%$), ethyl cyanoacetate (Fluka, $\geq 99\%$), malodinitrile (Lancaster, 99%), ethyl acetoacetate (Fluka, $\geq 99\%$), acetylacetone (Merck, $\geq 99.5\%$), diethyl methylmalonate (Fluka, $\geq 99\%$), and 3-methylacetylacetone (Fluka, $\geq 99\%$) were from commercial sources. Liquids were distilled before use. Solids were used without further purification.

Kinetics. The reactions of benzhydrylium ions with carbanions were studied in aqueous solution and in DMSO, whereas the reactions of quinone methides were only studied in DMSO. The rates of the reactions of the colored electrophiles with the carbanions **1a–i** were measured photometrically. In aqueous solutions, all carbanions were generated by treatment of the corresponding acids with KOH. The reactions in DMSO were carried out with stock solutions of the potassium salts of the CH acids.

For slow reactions ($\tau_{1/2} > 10 \text{ s}$), the decrease of the absorbances of the benzhydrylium ions was measured in a thermostated flask with an immersion UV–vis probe using a working station as already described.^{14b,43} We used a J&M TIDAS diode array spectrophotometer which was controlled by Labcontrol Spectacle software and connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) via fiber optic cables and standard SMA connectors. The temperature of solutions during all kinetic studies was kept constant ($20 \pm 0.2^\circ \text{C}$) by using a circulating bath thermostat and monitored with a thermocouple probe that was inserted into the reaction mixture.

Fast reactions ($\tau_{1/2} < 10 \text{ s}$ at 20°C) were studied with a stopped-flow spectrophotometer system (Hi-Tech SF-61DX2 spectrophotometer controlled by Hi-Tech Kinet Asyst2 software) as described previously.^{7,44} The kinetic runs were initiated by mixing equal volumes of solutions of the carbanion and the electrophile. Carbanion concentrations higher than the electrophile concentration were employed, resulting in pseudo-first-order kinetics with an exponential decay of the electrophile. First-order rate constants were obtained by least-squares fitting of the absorbance data (averaged from at least four kinetic runs at each nucleophile concentration) to the single-exponential $A_t = A_0 \exp(-k_{1\text{p,obs}}t) + C$.

In the cases of the weak CH acids **1g** and **1h**, the concentration of the corresponding carbanion is smaller than that of the electrophiles. The exponential decays of the electrophile concentrations indicate, however, the constancy of $[\text{C}^-]$, implying that the deprotonation of the CH acid used in large excess is fast as compared to the reaction of the benzhydrylium cations with carbanion and hydroxide.

Because of the poor solubility of the benzhydrylium tetrafluoroborates in water, it was necessary to employ up to 1.6% (v/v) of acetonitrile as a cosolvent for the kinetic investigations in water. In previous work with other anionic nucleophiles, it has already been shown that the small amount of acetonitrile does not affect the observed rate constants.⁸

- (33) Beckhaus, H.-D.; Dogan, B.; Pakusch, J.; Verevkin, S.; Rüchardt, C. *Chem. Ber.* **1990**, *123*, 2153–2159.
 (34) Thermodynamic data for the exchange of only one methyl group are not available.
 (35) Verevkin, S.; Dogan, B.; Beckhaus, H.-D.; Rüchardt, C. *Angew. Chem.* **1990**, *102*, 693–695; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 674–676.
 (36) Bernasconi, C. F.; Zitomer, J. L.; Fox, J. P.; Howard, K. A. *J. Org. Chem.* **1984**, *49*, 482–486.
 (37) (a) Eigen, M. *Angew. Chem.* **1963**, *75*, 489–508; *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19. (b) Hojatti, M.; Kresge, A. J.; Wang, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 4023–4028. (c) For the analogous behavior of HCN, see: Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107*, 7117–7126.
 (38) Bernasconi, C. F. *Acc. Chem. Res.* **1992**, *25*, 9–16.
 (39) Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981–988.
 (40) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948–7960.
 (41) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301–308. (b) Bernasconi, C. F. *Tetrahedron* **1989**, *45*, 4017–4090. (c) Bernasconi, C. F. *Adv. Phys. Org. Chem.* **1992**, *119*–238.

- (42) Evans, S.; Nesvadba, P.; Allenbach, S. (Ciba-Geigy AG), EP 744392, 1996 [*Chem. Abstr.* **1997**, *126*, 46968v].
 (43) Dilman, A. D.; Ioffe, S. L.; Mayr, H. *J. Org. Chem.* **2001**, *66*, 3196–3200.
 (44) Mayr, H.; Ofial, A. R. *Einsichten – Forschung an der LMU München* **2001**, *20*, 30–33.

In some experiments with electrophile **2a** in water, small quantities of benzenesulfonic acid were added to avoid the reaction of **2a** with water prior to mixing the solutions of the reactants.

Acknowledgment. Dedicated to Professor Manfred T. Reetz on the occasion of his 60th birthday. We thank Stefanie Mugrauer for performing experiments with **1a** and **1b** and Clemens Schlierf for preparative investigations. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Syntheses and characterization of the products **3** of the reactions of carbanions **1** with electrophiles **2**. Tables containing the concentrations and rate constants of the individual kinetic experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA036838E