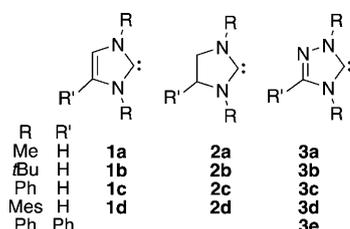


# N-Heterocyclic Carbenes: Organocatalysts with Moderate Nucleophilicity but Extraordinarily High Lewis Basicity\*\*

Biplab Maji, Martin Breugst, and Herbert Mayr\*

Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

Since the first isolation and characterization of stable N-heterocyclic carbenes (NHCs) by Arduengo and co-workers in 1991,<sup>[1]</sup> these compounds have attracted great interest in various fields of chemistry. As molecules with divalent carbon atoms, NHCs (e.g., **1–3**, Scheme 1) are not only of theoretical interest<sup>[2]</sup> but also of practical relevance as ligands in metal complexes<sup>[3]</sup> and as nucleophilic organocatalysts.<sup>[4]</sup>



Scheme 1. Important N-heterocyclic carbenes (NHCs).

Despite the extensive use of NHCs as organocatalysts, quantitative investigations of their catalytic activities are rare.<sup>[5]</sup> Since the relative reactivities of different nucleophiles towards electrophiles correlate only poorly<sup>[6]</sup> with the corresponding Brønsted basicities ( $pK_{\text{aH}}$ ),<sup>[7]</sup> we have recently employed benzhydrylium ions and structurally related quinone methides **4** (Table 1) with widely varying reactivities as reference compounds<sup>[8]</sup> to compare the nucleophilicities and Lewis basicities of various organocatalysts.<sup>[9]</sup>

It was demonstrated that the rates of the reactions of carbocations and Michael acceptors with  $n$ -,  $\pi$ -, and  $\sigma$ -nucleophiles can be described by the linear free-energy relationship in Equation (1), where electrophiles are charac-

$$\lg k_2 = s_N(N + E) \quad (1)$$

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Table 1: Benzhydrylium ions **4a–f** ( $\text{BF}_4^-$  salts) and quinone methides **4g–l** employed as reference electrophiles in this work.

Electrophile	$E^{\text{[a]}}$	$\lambda_{\text{max}}^{\text{[b]}}$ [nm]
	<b>4a</b> –7.02	611
	<b>4b</b> –7.69	618
	<b>4c</b> –8.22	626
	<b>4d</b> –8.76	622
	<b>4e</b> –9.45	637
	<b>4f</b> –10.04	635
	<b>4g</b> –12.18	411
	<b>4h</b> –13.39	499
	<b>4i</b> –15.83	362
	<b>4j</b> –16.11	384
	<b>4k</b> –17.29	460
	<b>4l</b> –17.90	492

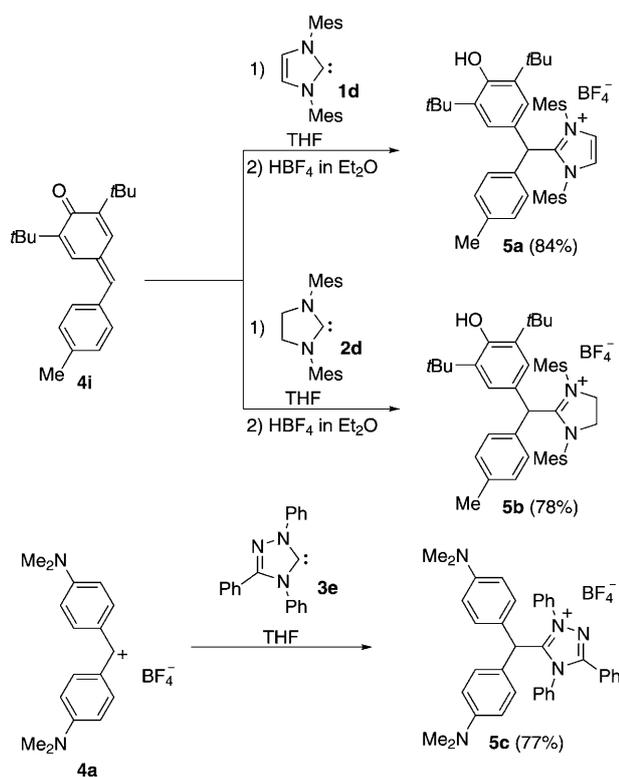
[a] Electrophilicity parameters  $E$  for **4a–f** from ref. [8c], for **4g–l** from ref. [8d]. [b] In THF.

terized by one solvent-independent electrophilicity parameter  $E$ , and nucleophiles are characterized by two solvent-dependent parameters, the nucleophilicity parameter  $N$ , and a nucleophile-specific sensitivity parameter  $s_N$ .<sup>[8]</sup>

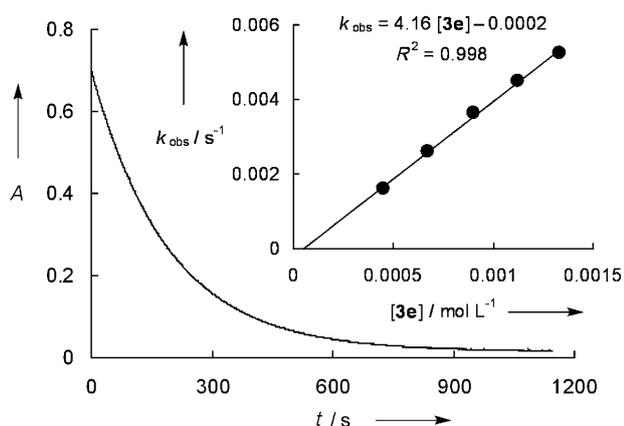
We now report on the use of the benzhydrylium methodology for characterizing the nucleophilicities of three representative NHCs (**1d**, **2d**, and **3e**) and for comparing them with other nucleophilic organocatalysts.

Representative combinations of the carbenes **1d**, **2d**, and **3e** with the reference electrophiles **4a** or **4i** showed the course of the reactions (Scheme 2). The products formed from **1d** and **2d** and the quinone methide **4i** in THF were subsequently treated with one equivalent of  $\text{HBF}_4$  to generate the salts **5a,b**, which were isolated and characterized as described in the Supporting Information. Addition of the Enders carbene **3e** to the blue solution of the benzhydrylium tetrafluoroborate **4a-BF<sub>4</sub>** in THF at ambient temperature led to decolorization and formation of the adduct **5c**, which has been isolated and characterized by X-ray crystallography.<sup>[10]</sup>

The kinetic investigations were performed in THF at 20 °C by photometrically monitoring the disappearance of the colored electrophiles **4** (Table 1, Figure 1).<sup>[11]</sup> The NHCs were used in high excess to achieve pseudo-first-order conditions. Because of the strong overlap of the UV bands of **4i** with those of its adducts with **1d**, **2d**, and **3e**, we were



**Scheme 2.** Products of the reactions of the NHCs **1d**, **2d**, and **3e** with reference electrophiles in THF.



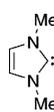
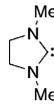
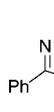
**Figure 1.** Exponential decay of the absorbance at 499 nm during the reaction of **3e** ( $1.33 \times 10^{-3} \text{ mol L}^{-1}$ ) with **4h** ( $3.98 \times 10^{-5} \text{ mol L}^{-1}$ ) at  $20^\circ\text{C}$  in THF ( $k_{\text{obs}} = 5.26 \times 10^{-3} \text{ s}^{-1}$ ). Insert: Determination of the second-order rate constant  $k_2 = 4.16 \text{ L mol}^{-1} \text{ s}^{-1}$  from the dependence of  $k_{\text{obs}}$  on the concentration of **3e**.

unable to determine the kinetics of these reactions. The first-order rate constants  $k_{\text{obs}}$  ( $\text{s}^{-1}$ ) were obtained by fitting the mono-exponential function  $A = A_0 \exp(-k_{\text{obs}}t) + C$  to the experimentally observed decay of the absorbances. The plots of  $k_{\text{obs}}$  against the concentrations of **1–3** were linear with negligible intercepts (Figure 1, insert) indicating a second-order rate law [Eq. (2)].

$$-\text{d}[\mathbf{4}]/\text{d}t = k_2[\text{carbene}][\mathbf{4}] \quad (2)$$

The slopes of these linear plots give the second-order rate constants  $k_2$  which are listed in Table 2. As the nucleophilicities of triphenylphosphane (**6**), 4-(dimethylamino)pyridine (DMAP, **7**), and diazabicyclo[5.4.0]undecene (DBU, **8**) have

**Table 2:** Second-order rate constants for the reactions of the NHCs **1d**, **2d**, and **3e** as well as  $\text{PPh}_3$  (**6**), DMAP (**7**), and DBU (**8**) with the reference electrophiles **4** in THF at  $20^\circ\text{C}$ .

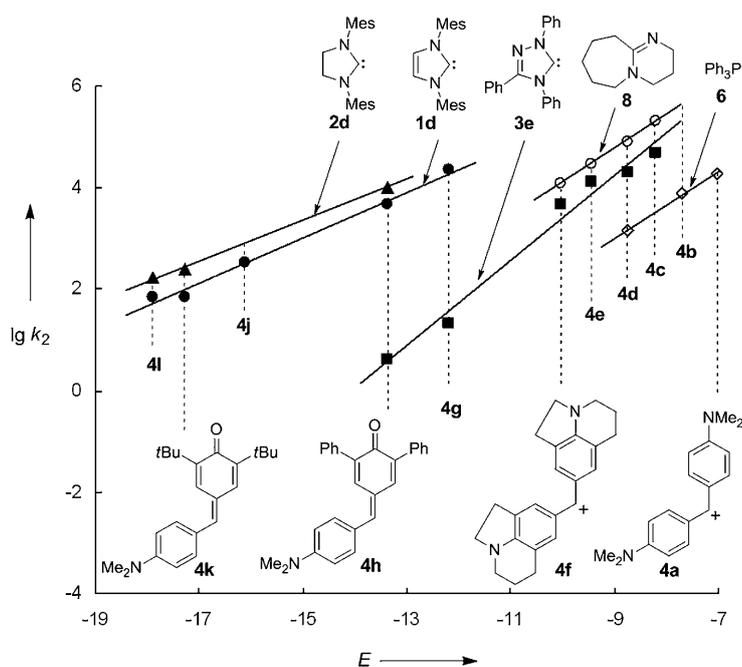
Nucleophile	$N$ , $s_N$	Electrophile	$k_2$ [ $\text{L mol}^{-1} \text{ s}^{-1}$ ]
 <b>1d</b>	21.72, 0.45	<b>4g</b>	$2.27 \times 10^4$
		<b>4h</b>	$4.64 \times 10^3$
		<b>4j</b>	$3.45 \times 10^2$
		<b>4k</b>	$7.03 \times 10^1$
		<b>4l</b>	$7.03 \times 10^1$
 <b>2d</b>	23.35, 0.40	<b>4h</b>	$1.04 \times 10^4$
		<b>4k</b>	$2.53 \times 10^2$
		<b>4l</b>	$1.69 \times 10^2$
		<b>4c</b>	$4.96 \times 10^4$
 <b>3e</b>	14.07, 0.84	<b>4d</b>	$2.08 \times 10^4$
		<b>4e</b>	$1.28 \times 10^4$
		<b>4f</b>	$4.91 \times 10^3$
		<b>4g</b>	$2.11 \times 10^1$
		<b>4h</b>	4.16
		<b>4i</b>	$1.93 \times 10^4$
 <b>6</b>	13.59, 0.66 <sup>[a]</sup>	<b>4a</b>	$1.93 \times 10^4$
		<b>4b</b>	$7.80 \times 10^3$
		<b>4d</b>	$1.42 \times 10^3$
 <b>7</b>	15.90, 0.66 <sup>[a]</sup>	<b>4a</b>	$7.14 \times 10^5$
		<b>4b</b>	$3.63 \times 10^5$
		<b>4c</b>	$1.18 \times 10^5$
		<b>4d</b>	$4.32 \times 10^4$
		<b>4e</b>	$2.21 \times 10^4$
		<b>4f</b>	$7.62 \times 10^3$
 <b>8</b>	16.12, 0.67 <sup>[a]</sup>	<b>4c</b>	$2.13 \times 10^5$
		<b>4d</b>	$8.12 \times 10^4$
		<b>4e</b>	$3.01 \times 10^4$
		<b>4f</b>	$1.24 \times 10^4$

[a] The  $N$  and  $s_N$  values of these nucleophiles in  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{CN}$  are slightly different: ref. [12].

previously only been determined in other solvents,<sup>[9]</sup> their reactivities towards the reference electrophiles **4** have now also been measured in THF solution (Table 2) to allow a comparison of the corresponding rate constants under the same conditions.<sup>[11]</sup>

Figure 2 shows linear plots of  $\lg k_2$  for the reactions of the NHCs **1d**, **2d**, and **3e** with the reference electrophiles **4** versus the previously published electrophilicity parameters  $E$  of **4a–l** (Table 1), from which the nucleophile-specific parameters  $N$  and  $s_N$  [Eq. (1)], listed in Table 2, have been derived. Small, but systematic deviations of the reactivities of **3e** from these correlations are noticed and are commented on page S16 of the Supporting Information.

Though the relative reactivities of the NHCs depend slightly on the nature of the reference electrophile, one can see in Figure 2 that the carbenes derived from imidazolium (**1d**) and imidazolinium (**2d**) salts are roughly  $10^3$  times more



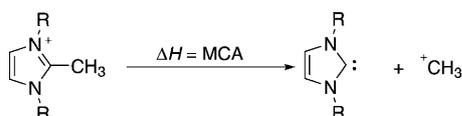
**Figure 2.** Plot of  $\lg k_2$  for the reactions of NHCs **1d**, **2d**, and **3e**,  $\text{PPh}_3$  (**6**), and DBU (**8**) with the reference electrophiles **4** in THF at 20°C versus their electrophilicity parameters.

nucleophilic than the Enders carbene **3e**, which in turn has a similar nucleophilicity as DMAP (**7**) and DBU (**8**).

This gradation of the rate constants differs significantly from that of the Lewis basicities of these compounds. While **3e** combines quantitatively with **4g** and **4h**,  $\text{PPh}_3$  (**6**) and DMAP (**7**) do not react at all with these two quinone methides, though Equation (1) predicts relatively high rate constants for these reactions. The corresponding reactions of DBU (**8**) with **4g** and **4h** proceed incompletely. The Arduengo carbenes **1d** and **2d** are so strong Lewis bases that they react quantitatively even with **4k** and **4l**, the weakest electrophiles of this series.

As all attempts to measure the equilibrium constants for the reactions of these NHCs with **4** were unsuccessful, we have determined the methyl cation affinity (MCA) as defined in Scheme 3 of differently substituted carbenes at the MP2/6-31+G(2d,p)//B98/6-31G(d) level of theory using Gaussian 09.<sup>[13]</sup> This method has previously been shown to offer a practicable and reliable approach to methyl cation affinities for various organic bases.<sup>[14]</sup>

The two nonbonding electrons of carbenes can either reside in the same orbital with anti-parallel spins (singlet) or in two different orbitals with parallel spins (triplets).<sup>[2h,15]</sup> In line with previous investigations<sup>[2h,16]</sup> the singlet structures of



**Scheme 3.** Definition of the methyl cation affinity (MCA) of **1**.

the NHCs **1–3** were found to be much more stable than the corresponding triplets (290–360  $\text{kJ mol}^{-1}$ ).

As specified in the Supporting Information, the calculated bond lengths and angles (Table 3) of the cyclic framework deviate by less than 0.04 Å or 0.7°, respectively, from the experimental values obtained by X-ray crystallography.<sup>[16,17]</sup> The five-membered ring is planar for most NHCs, and only the carbene derived from di-*tert*-butyl imidazole (**2b**) adopts a twist conformation with an N-C-C interplanar angle of 18°. While the phenyl groups in **1c–3c** are coplanar with the five-membered ring or only slightly distorted out of plane (interplanar angle 25° for **1c** and 27° for **3c**), the mesityl substituents in **1d–3d** are almost perpendicular to the plane of the heterocyclic ring (interplanar angle 77–78° in **1d**, **2d**, and **3d**). In contrast, all phenyl and mesityl groups are almost perpendicular to the heterocyclic ring in the azolium ions obtained by methylation of the carbenes **1c–3c** and **1d–3d**, which can be explained by the steric interaction of the aryl groups with the methyl group at the former carbene center.

The calculated  $H_{298}$  values for the carbenes **1–3** and the corresponding  $H_{298}$  values for the methylated azolium ions (Tables 34/35 of the Supporting Information) have been combined with  $H_{298}$  of the methyl cation to give the MCAs as defined in Scheme 3 (Table 3).

**Table 3:** MCAs (in  $\text{kJ mol}^{-1}$ ) [MP2/6-31+G(2d,p)//B98/6-31G(d)] and NCN angles of the carbenes **1–3**.

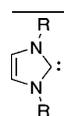
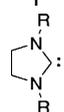
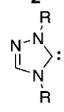
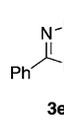
		<b>1a</b>	<b>1b</b>	<b>1c</b>	<b>1d</b>
	R = $\text{CH}_3$	718.0	714.3	742.4	767.2
	MCA	101.4°	102.6°	101.8°	101.3°
	R = $\text{CH}_3$	719.3	699.4	722.9	768.9
	MCA	105.1°	106.6°	105.7°	105.4°
	R = $\text{CH}_3$	674.4	676.8	694.4	728.4
	MCA	99.8°	100.7°	100.3°	100.0°
				<b>3e</b>	
	MCA			712.2	103.7°

Table 3 shows that the methyl-substituted imidazole- and imidazoline-derived carbenes **1a** and **2a** have the same MCAs indicating that the extra double bond in **1a** does not affect its Lewis basicity. Analogously, the mesityl-substituted carbenes **1d** and **2d** have approximately the same MCAs. Though the mesityl groups are almost perpendicular to the heterocyclic rings in the carbenes **1d** and **2d** and, therefore, cannot operate through mesomeric electron donation, the MCAs of

**1d** and **2d** are almost 50 kJ mol<sup>-1</sup> higher than those of the methyl analogues **1a** and **2a**.

Both phenyl-substituted carbenes **1c** and **2c** are weaker Lewis bases than their mesityl analogues **1d** and **2d** because the phenyl groups can stabilize the carbenes **1c** and **2c** by  $\pi$ -conjugation, but not the resulting amidinium ions, in which the phenyl group is distorted out of the plane by the methyl group. As the mesomeric stabilization of the ground state is more efficient in **2c** (interplanar angle 0°; phenyl staggered with the CH<sub>2</sub> group) than in **1c** (interplanar angle 25°; interaction between phenyl and the vinylic CH), **2c** is a weaker Lewis base than **1c**.

While **1a**, **1b**, and **2a** have similar MCAs, the MCA of the *tert*-butyl-substituted carbene **2b** is smaller by 15 to 20 kJ mol<sup>-1</sup> because methylation of **2b** forces the twist conformation of the CH<sub>2</sub>-CH<sub>2</sub> bridge in **2b** into a strained planar ring conformation.

The substituent effects on the triazole-derived carbenes **3a-d** are similar as in the isoelectronic series **1a-d**. The electron-withdrawing effect of the additional nitrogen in **3a-d** accounts for the fact that their methyl cation affinities are 38 to 48 kJ mol<sup>-1</sup> smaller than those of the analogously substituted carbenes **1a-d**. The 18 kJ mol<sup>-1</sup> increase of the MCA from **3c** to **3e** can, finally, be assigned to the mesomeric effect of the additional phenyl group.

Table 4 shows that the MCAs of the NHCs **2d**, **1d**, and **3e** are more than 100 kJ mol<sup>-1</sup> greater than those of PPh<sub>3</sub> (**6**) and of the N-nucleophiles **7-9**, in accord with our observation that the weakly Lewis acidic quinone methides **4g,h** react quantitatively with these three NHCs but not with PPh<sub>3</sub> (**6**), DMAP (**7**), and DABCO (**9**).

The similar MCAs of **1d** and **2d** are reflected by their similar nucleophilicities, expressed by the relative reactivities of these two carbenes towards **4h** (Table 4). The extra

nitrogen atom in **3e** reduces the MCA by 55 kJ mol<sup>-1</sup> and the nucleophilicity by a factor of 10<sup>3</sup> [ $k_{\text{rel}}$ (**4h**)].

The lower part of Table 4 shows that the MCAs of **3e** and **6-9** do not correlate with the corresponding nucleophilicities. DABCO (**9**), the compound with the lowest MCA, has by far the highest nucleophilicity. The Enders carbene **3e** is a slightly weaker nucleophile than DBU (**8**) and DMAP (**7**) [ $k_{\text{rel}}$ (**4d**)] despite its much higher MCA.

In previous work we had derived relative Lewis basicities of **7-9** from equilibrium constants of their reactions with benzhydrylium ions and structurally related Michael acceptors. The ordering **8** > **7** > **9** was the same as for the MCAs in Table 4.<sup>[6d,9d]</sup> The fact that DABCO (**9**) is a much stronger nucleophile and at the same time a much weaker Lewis base than DMAP (**7**), as well as the observation that DBU (**8**) has a similar nucleophilicity as DMAP (**7**) yet a much higher Lewis basicity was explained by widely differing Marcus intrinsic barriers in the order **8** > **7** > **9**.<sup>[6d,9d]</sup>

Since compounds **7** and **8** have similar nucleophilic reactivities as the Enders carbene **3e**, while their MCAs are more than 100 kJ mol<sup>-1</sup> lower, one has to conclude that NHCs must react via much higher intrinsic barriers than compounds **6-9**.<sup>[18]</sup>

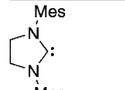
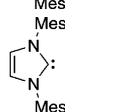
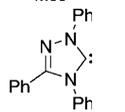
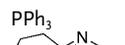
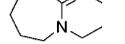
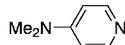
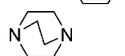
The ability of NHCs to act as umpolung reagents<sup>[19]</sup> has been explained by the high acidity of the former aldehyde proton in the initially formed adduct, which gives rise to the formation of the Breslow intermediate.<sup>[20]</sup> A further specialty is their extraordinarily high Lewis basicity quantified in this work, which explains that they do not catalyze Baylis-Hillman reactions of  $\alpha,\beta$ -unsaturated aldehydes but instead induce their homoenolate chemistry through umpolung.<sup>[4d,21]</sup> As discussed elsewhere,<sup>[18]</sup> nucleophiles generally attack at the carbonyl group of  $\alpha,\beta$ -unsaturated aldehydes under conditions of kinetic control. With tertiary amines and phosphanes, this attack is reversible, and the subsequent conjugate addition gives rise to the Baylis-Hillman reactions. Because of the high Lewis basicity of NHCs, the kinetically preferred attack at the carbonyl group has a lower degree of reversibility and therefore, enables their use as umpolung reagents also of  $\alpha,\beta$ -unsaturated aldehydes.

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**Table 4:** MCAs (in kJ mol<sup>-1</sup>) [MP2/6-31+G(2d,p)//B98/6-31G(d)] and relative rate constants for the reactions of **4h** and **4d** with different organocatalysts.

Organocatalysts	MCA	$k_{\text{rel}}$ ( <b>4h</b> )	$k_{\text{rel}}$ ( <b>4d</b> )
	<b>2d</b>	768.9	$2.5 \times 10^3$
	<b>1d</b>	767.2	$1.1 \times 10^3$
	<b>3e</b>	712.2	1.0
	<b>6</b>	618.4 <sup>[a]</sup>	$6.8 \times 10^{-2}$
	<b>8</b>	609.6 <sup>[b]</sup>	3.9
	<b>7</b>	581.2 <sup>[b]</sup>	2.1
	<b>9</b>	562.2 <sup>[c]</sup>	$5.3 \times 10^{2[d]}$

[a] From ref. [14c]. [b] From ref. [14a]. [c] From ref. [14b]. [d] In MeCN at 20 °C:  $k_2 = 1.10 \times 10^7$  L mol<sup>-1</sup> s<sup>-1</sup>, from ref. [6d].

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## Nucleophilic Reactivities of Primary and Secondary Amines in Acetonitrile

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The kinetics of the reactions of primary and secondary amines with benzhydrylium ions and quinone methides in acetonitrile have been studied under pseudo-first-order conditions (high excess of amines) by UV/Vis spectrophotometry. Generally, the plots of  $k_{\text{obs}}$  versus amine concentration were linear, in line with a second-order rate law. However, for some reactions of secondary amines with quinone methides, the plots of  $k_{\text{obs}}$  versus amine concentration showed an upward curvature, which indicates rate-limiting deprotonation of the initially formed adduct by a second molecule of amine.

From the second-order rate constants  $k_2$  for the attack on the electrophiles by the amines, the nucleophilicity parameters  $N$  and  $s$  for the amines were determined from the linear free energy relationship  $\log k_2 (20^\circ\text{C}) = s(N + E)$ . The rates of the reactions of the amines with benzhydrylium ions are strongly affected by solvent polarity, in sharp contrast to the analogous reactions of other neutral nucleophiles.

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## Introduction

Amines are amongst the most important reagents in organic synthesis and numerous kinetic investigations have been performed to determine their nucleophilic reactivities in various types of reactions.<sup>[1]</sup> They have been characterized on the Swain–Scott  $n$  scale as well as on the Ritchie  $N_+$  scale.<sup>[1d,2]</sup>

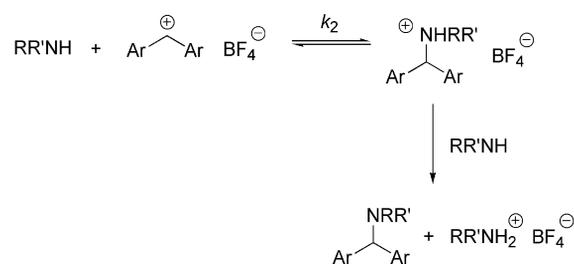
Recently, we employed Equation (1), which characterizes nucleophiles by the parameters  $N$  and  $s$ , and electrophiles by the parameter  $E$ ,<sup>[3]</sup> for determining  $N$  and  $s$  for a variety of amines in aqueous solution.<sup>[4]</sup> In this way it became possible to add amines to our comprehensive nucleophilicity scale, which includes  $n$ ,  $\pi$ , and  $\sigma$  nucleophiles.<sup>[5]</sup> Comparison with the few available data in DMSO<sup>[4a,6]</sup> and methanol<sup>[7]</sup> showed that amine nucleophilicities are strongly dependent on the solvent, in contrast to the nucleophilicities of most neutral  $\pi$  and  $\sigma$  nucleophiles.

$$\log k_2(20^\circ\text{C}) = s(N + E) \quad (1)$$

Systematic investigations of the nucleophilic reactivities of amines in acetonitrile have so far not been reported. Such data are of eminent importance for two reasons. (a) Acetonitrile is an ideal solvent for exploring the combat

zone of nucleophilic aliphatic substitutions, that is, the zone in which the change from the  $S_N1$  to  $S_N2$  mechanism occurs.<sup>[6,8]</sup> (b) Acetonitrile is the solvent of choice for the photolytic cleavage of carbocation precursors.<sup>[9]</sup> By using nanosecond laser pulses it is possible to generate carbocations in acetonitrile in the presence of various nucleophiles and to determine the rates of reactions along the borderline between activation and diffusion control, typically second-order rate constants from  $10^8$  to  $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ .<sup>[10]</sup>

Knowledge of rate constants along this borderline is crucial for the understanding of structure–reactivity relationships, for example, correlations between reactivity and selectivity as well as the breakdown of linear free-energy relationships.<sup>[11]</sup> Because many of these investigations involve reactions with amines in acetonitrile,<sup>[9a,9b]</sup> we have now determined the  $N$  and  $s$  parameters of primary and secondary amines using benzhydryl cations (Table 1) as reference electrophiles, as described previously (Scheme 1).<sup>[5a]</sup>



Scheme 1. Reactions of amines with benzhydrylium ions.

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Table 1. List of electrophiles used in this study.

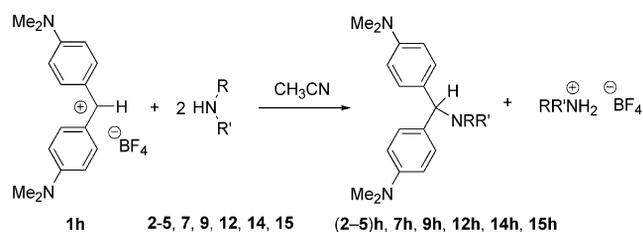
Reference electrophile <sup>[a]</sup>	$E^{[b]}$
ani( <i>t</i> Bu) <sub>2</sub> QM ( <b>1a</b> )	-16.11
tol( <i>t</i> Bu) <sub>2</sub> QM ( <b>1b</b> )	-15.83
ani(Ph) <sub>2</sub> QM ( <b>1c</b> )	-12.18
(lil) <sub>2</sub> CH <sup>+</sup> ( <b>1d</b> )	-10.04
(jul) <sub>2</sub> CH <sup>+</sup> ( <b>1e</b> )	-9.45
(ind) <sub>2</sub> CH <sup>+</sup> ( <b>1f</b> )	-8.76
(pyr) <sub>2</sub> CH <sup>+</sup> ( <b>1g</b> )	-7.69
(dma) <sub>2</sub> CH <sup>+</sup> ( <b>1h</b> )	-7.02
(mpa) <sub>2</sub> CH <sup>+</sup> ( <b>1i</b> )	-5.89
(mfa) <sub>2</sub> CH <sup>+</sup> ( <b>1j</b> )	-3.85
(ani) <sub>2</sub> CH <sup>+</sup> ( <b>1k</b> )	0.00
(ani)(tol)CH <sup>+</sup> ( <b>1l</b> )	1.48
(tol) <sub>2</sub> CH <sup>+</sup> ( <b>1m</b> )	3.63
Ph(tol)CH <sup>+</sup> ( <b>1n</b> )	4.59
Ph <sub>2</sub> CH <sup>+</sup> ( <b>1o</b> )	5.90

[a] Counterion of the benzhydryl cations: BF<sub>4</sub><sup>-</sup>. [b] Electrophilicity parameters  $E$  are from ref.<sup>[5a,b]</sup>.

## Results and Discussion

### Product Characterization

A combination of the benzhydrylium salt **1h**BF<sub>4</sub> with 2–3 equiv. of the amines **2–5**, **7**, **9**, **12**, **14**, and **15** in acetonitrile gave the corresponding benzhydrylamines **2h–5h**, **7h**, **9h**, **12h**, **14h**, and **15h**, respectively (Scheme 2). The chemical shifts of the Ar<sub>2</sub>CH protons and the isolated yields are listed in Table 2.



Scheme 2. Reactions of amines with 4,4'-bis(dimethylamino)benzhydrylium tetrafluoroborate **1h**BF<sub>4</sub>.

Table 2. <sup>1</sup>H NMR chemical shifts of the Ar<sub>2</sub>CH group of the products of the reactions of **1h** with **2–5**, **7**, **9**, **12**, **14**, and **15** and yields of the isolated products.

Amine	Product	$\delta_{\text{H}}$ [ppm]	Yield [%]
2,2,2-Trifluoroethylamine ( <b>2</b> )	<b>2h</b>	4.80	85
<i>tert</i> -Butylamine ( <b>3</b> )	<b>3h</b>	4.88	98
Isopropylamine ( <b>4</b> )	<b>4h</b>	4.81	90
Ethanolamine ( <b>5</b> )	<b>5h</b>	4.69	98
Allylamine ( <b>7</b> )	<b>7h</b>	4.70	97
<i>n</i> -Butylamine ( <b>9</b> )	<b>9h</b>	4.65	95
Diethylamine ( <b>12</b> )	<b>12h</b>	4.50	45
Piperidine ( <b>14</b> )	<b>14h</b>	3.99	71
Pyrrolidine ( <b>15</b> )	<b>15h</b>	3.97	67

### Kinetics of the Reactions of the Amines **2–15** with the Reference Electrophiles **1**

The rates of the reactions of the amines with the reference electrophiles **1a–j** were determined spectrophotometrically in CH<sub>3</sub>CN at 20 °C. For the kinetic studies, the amines **2–15** were used in large excess (>10 equiv.) over the electrophiles **1** to ensure first-order conditions. Details are given in the Supporting Information. The first-order rate constants  $k_{\text{obs}}$  were obtained from the exponential decays of the absorbances of the electrophiles (Figure 1).

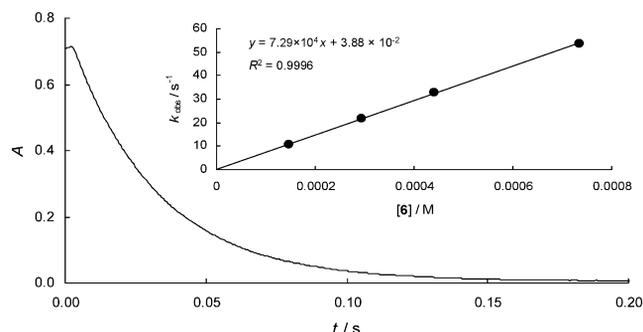


Figure 1. Exponential decay of the absorbance at 613 nm during the reaction of **1h** with benzylamine ( $[6] = 4.42 \times 10^{-4}$  M;  $k_{\text{obs}} = 32.7$  s<sup>-1</sup>). Insert: determination of the second-order rate constant  $k_2$  ( $7.31 \times 10^4$  M<sup>-1</sup>s<sup>-1</sup>) as the slope of the first-order rate constants  $k_{\text{obs}}$  versus the concentration of the amine **6**.

Plots of  $k_{\text{obs}}$  versus amine concentration were linear for the reactions of the primary and secondary amines **2–15** with the benzhydrylium ions **1d–o** (insert of Figure 1) and for the reactions of the primary amines **2–9** with the quinone methides **1a–c**. In these reactions the attack of the

amines on the electrophiles is rate-limiting and the slopes of these plots give the second-order rate constants  $k_2$  [Equation (2)], which are listed in Table 3.

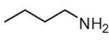
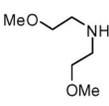
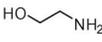
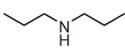
$$k_{\text{obs}} = k_2[\text{amine}] \quad (2)$$

In the case of trifluoroethylamine (**2**) and *N,N*-bis(2-methoxyethyl)amine (**10**) the reactions with benzhydrylium

ions of low reactivity become reversible, which is reflected by the positive intercepts in the plots of  $k_{\text{obs}}$  versus amine concentration.

For the reactions of the secondary amines **10–12** with the quinone methide **1c** (**1a** and **1b** were not studied), of morpholine (**13**) with the quinone methides **1b** and **1c**, and of piperidine (**14**) with the quinone methides **1a** and **1b**,

Table 3. Second-order rate constants for the reactions of the reference electrophiles **1** with the amines **2–15** in acetonitrile at 20 °C.

Amine	<i>N</i>	<i>s</i>	Electrophile	$k_2 / \text{M}^{-1}\text{s}^{-1}$	Amine	<i>N</i>	<i>s</i>	Electrophile	$k_2 / \text{M}^{-1}\text{s}^{-1}$										
	<b>2</b>	10.13	0.75	<b>1h</b>	$1.43 \times 10^2$		<b>8</b>	<b>1h</b>	$1.43 \times 10^5$										
				<b>1i</b>	$2.53 \times 10^3$			<b>1k</b>	$1.00 \times 10^9$ <sup>[a,b]</sup>										
				<b>1j</b>	$4.03 \times 10^4$			<b>1l</b>	$2.30 \times 10^9$ <sup>[a,b]</sup>										
				<b>1k</b>	$3.50 \times 10^7$ <sup>[a]</sup>			<b>1m</b>	$4.10 \times 10^9$ <sup>[a,b]</sup>										
				<b>1l</b>	$1.50 \times 10^8$ <sup>[a,b]</sup>			<b>1n</b>	$4.40 \times 10^9$ <sup>[a,b]</sup>										
				<b>1m</b>	$8.50 \times 10^8$ <sup>[a,b]</sup>			<b>1o</b>	$4.50 \times 10^9$ <sup>[a,b]</sup>										
				<b>1n</b>	$1.70 \times 10^9$ <sup>[a,b]</sup>														
	<b>3</b>	12.35	0.72	<b>1c</b>	1.52		<b>9</b>	15.27	0.63	<b>1a</b>	$3.41 \times 10^{-1}$								
				<b>1d</b>	$4.15 \times 10^1$					<b>1c</b>	$7.49 \times 10^1$								
				<b>1f</b>	$3.34 \times 10^2$					<b>1f</b>	$1.03 \times 10^4$								
				<b>1i</b>	$5.13 \times 10^4$					<b>1h</b>	$2.12 \times 10^5$								
					<b>4</b>					13.77	0.70	<b>1c</b>	$1.56 \times 10^1$		<b>10</b>	13.24	0.93	<b>1c</b>	7.89 <sup>[b,c]</sup>
												<b>1d</b>	$2.97 \times 10^2$					<b>1d</b>	$1.12 \times 10^3$
												<b>1f</b>	$2.43 \times 10^3$					<b>1e</b>	$4.47 \times 10^3$
<b>1g</b>	$2.13 \times 10^4$	<b>1f</b>	$1.25 \times 10^4$																
	<b>5</b>	14.11	0.71	<b>1h</b>	$5.24 \times 10^4$		<b>11</b>	14.51	0.80	<b>1c</b>	$6.74 \times 10^{11}$ <sup>[c]</sup>								
				<b>1c</b>	$2.71 \times 10^1$					<b>1d</b>	$3.95 \times 10^3$								
				<b>1d</b>	$5.85 \times 10^2$					<b>1e</b>	$1.38 \times 10^4$								
				<b>1f</b>	$4.94 \times 10^3$					<b>1f</b>	$3.17 \times 10^4$								
	<b>6</b>	14.29	0.67	<b>1g</b>	$4.24 \times 10^4$		<b>12</b>	15.10	0.73	<b>1c</b>	$1.51 \times 10^{2[c]}$								
				<b>1h</b>	$1.02 \times 10^5$					<b>1d</b>	$4.62 \times 10^3$								
				<b>1b</b>	$1.10 \times 10^{-1}$					<b>1e</b>	$1.29 \times 10^4$								
				<b>1c</b>	$2.06 \times 10^1$					<b>1f</b>	$3.49 \times 10^4$								
	<b>7</b>	14.37	0.66	<b>1d</b>	$6.53 \times 10^2$		<b>13</b>	15.65	0.74	<b>1b</b>	$2.03 \times 10^{-1}$ <sup>[b,c]</sup>								
				<b>1f</b>	$4.61 \times 10^3$					<b>1c</b>	$3.85 \times 10^{2[c]}$								
				<b>1g</b>	$3.48 \times 10^4$					<b>1d</b>	$1.15 \times 10^4$								
				<b>1h</b>	$7.29 \times 10^4$					<b>1e</b>	$4.11 \times 10^4$								
	<b>8</b>	15.11	0.63	<b>1b</b>	$1.25 \times 10^{-1}$		<b>14</b>	17.35	0.68	<b>1f</b>	$1.04 \times 10^5$								
				<b>1d</b>	$5.09 \times 10^2$					<b>1g</b>	$8.03 \times 10^5$								
				<b>1f</b>	$4.32 \times 10^3$					<b>1a</b>	6.04 <sup>[c]</sup>								
				<b>1g</b>	$3.64 \times 10^4$					<b>1b</b>	$1.23 \times 10^{11}$ <sup>[c]</sup>								
	<b>8</b>	15.11	0.63	<b>1h</b>	$8.61 \times 10^4$		<b>15</b>	18.64	0.60	<b>1c</b>	$3.52 \times 10^3$								
				<b>1a</b>	$2.64 \times 10^{-1}$					<b>1d</b>	$7.85 \times 10^4$								
				<b>1b</b>	$3.82 \times 10^{-1}$					<b>1e</b>	$2.69 \times 10^5$								
				<b>1c</b>	$5.46 \times 10^1$					<b>1a</b>	$3.25 \times 10^1$								
				<b>1d</b>	$1.38 \times 10^3$					<b>1b</b>	$4.82 \times 10^1$								
<b>1e</b>	$3.87 \times 10^3$	<b>1d</b>	$1.18 \times 10^5$																
<b>1f</b>	$7.54 \times 10^3$	<b>1e</b>	$3.50 \times 10^5$																
<b>1g</b>	$6.77 \times 10^4$																		

[a] Second-order rate constants  $k_2$  from ref.<sup>[9b]</sup>. [b] Not included in the determination of the *N* and *s* parameters. [c]  $k_2$  was derived from Equation (7) and is less precise.

the plots of  $k_{\text{obs}}$  versus amine concentration are not linear (Figure 2). The upward curvature in the plots of  $k_{\text{obs}}$  versus amine concentration indicate that a second molecule of the amine is involved in the reaction as a base catalyst (Scheme 3).

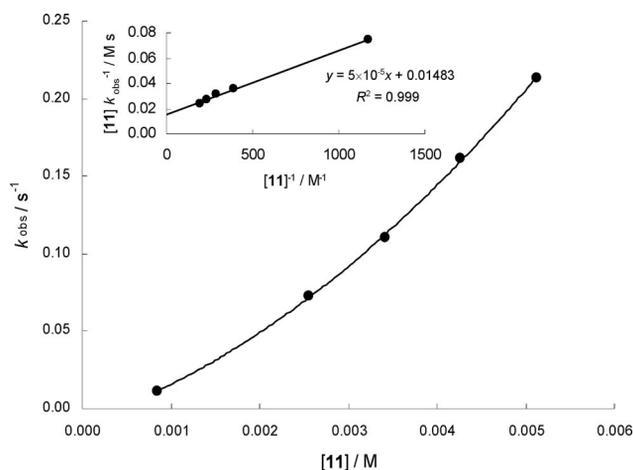
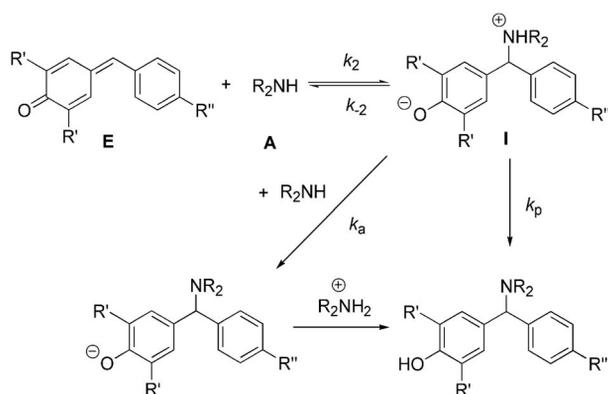


Figure 2. Plots of  $k_{\text{obs}}$  versus  $[11]$  and  $[11]/k_{\text{obs}}$  versus  $1/[11]$  (inset) for the reaction of **11** with the quinone methide **1c**. The  $k_2$  value for the reaction is  $1/(0.0148 \text{ M s}) = 67.4 \text{ M}^{-1} \text{ s}^{-1}$ .



Scheme 3. Reactions of secondary amines with quinone methides.

Analogous behavior has been reported for the reactions of secondary amines with thiocarbonates,<sup>[12]</sup> thionobenzoates,<sup>[13]</sup> and activated esters of indole-3-acetic acid.<sup>[14]</sup> The change in the concentration of the zwitterionic intermediate **I** can be expressed by Equation (3).

$$d[\text{I}]/dt = k_2[\text{E}][\text{A}] - k_{-2}[\text{I}] - k_a[\text{I}][\text{A}] - k_p[\text{I}] \quad (3)$$

By assuming a steady-state concentration for the intermediate **I**, the rate law can be expressed by Equations (4) and (5).

$$-d[\text{E}]/dt = k_2[\text{E}][\text{A}](k_a[\text{A}] + k_p)/(k_{-2} + k_a[\text{A}] + k_p) \quad (4)$$

$$k_{\text{obs}} = k_2[\text{A}](k_a[\text{A}] + k_p)/(k_{-2} + k_a[\text{A}] + k_p) \quad (5)$$

Let us first neglect the direct proton-transfer from  $\text{NH}^+$  to  $\text{O}^-$  in the zwitterionic intermediate **I**. Equation (5) is then

reduced to Equation (6), which can be transformed into Equation (7).

$$k_{\text{obs}} = k_2[\text{A}]^2 k_a / (k_{-2} + k_a[\text{A}]) \quad (6)$$

$$[\text{A}]/k_{\text{obs}} = 1/k_2 + k_{-2}/(k_2[\text{A}]k_a) \quad (7)$$

The linear plot of  $[\text{A}]/k_{\text{obs}}$  against  $1/[\text{A}]$ , as depicted in the insert of Figure 2, shows that this formalism holds for a wide range of concentrations. As shown in the Supporting Information, deviations from these linear plots occur only at very low amine concentrations and are explained by the operation of  $k_p$ . If the  $k_{\text{obs}}$  values at very low amine concentrations are neglected, the  $k_2$  values can be obtained from the intercepts ( $1/k_2$ ) of the linear correlations [see insert of Figure 2 and Equation (7)]. If  $k_{-2} \ll k_a[\text{A}]$ , Equation (6) is transformed into Equation (2), that is, a second-order reaction with rate-determining formation of the CN bond. Although this situation holds for all reactions with benzhydrylium ions, linearity between  $k_{\text{obs}}$  and  $[\text{amine}]$  was never reached for reactions of the quinone methide **1a** with **14**, **1b** with **13**, and **1c** with **10–14**, even when very high amine concentrations were used. The second-order rate constants  $k_2$  are listed in Table 3.

When the logarithms of the second-order rate constants are plotted against the previously reported electrophilicity parameters  $E$  of the reference systems, linear correlations are obtained (Figure 3), which yield the nucleophile-specific parameters  $N$  and  $s$  that are listed in Table 3. The rate constants for the reactions of trifluoroethylamine (**2**) with **11–o** and for the reactions of *n*-propylamine (**8**) with **1k–o**<sup>[9b]</sup> were not included in the determination of the nucleophilicity parameters because these reactions are close to diffusion-controlled. As the  $s$  parameters of the amines differ only slightly, their relative nucleophilicities are almost independent of the nature of the electrophiles and the reactivities of the amines can be compared by only regarding their  $N$  parameters, which cover the reactivity range of  $10 < N < 19$ . The less reactive amines react with similar rates as silyl ketene acetals, trialkyl-substituted pyrroles, and pyridines, whereas the more reactive amines show a similar nucleophilicity to stabilized carbanions (Figure 4).

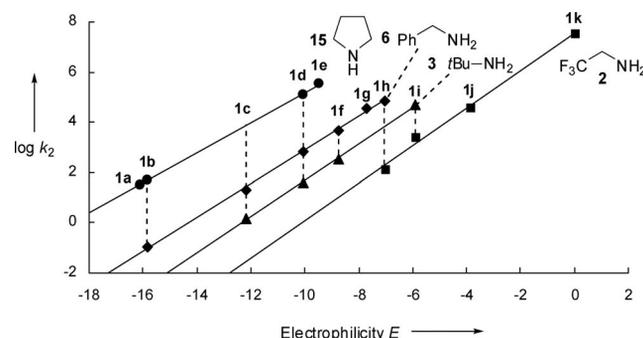


Figure 3. Plots of the second-order rate constants  $\log k_2(20 \text{ }^\circ\text{C})$  in  $\text{CH}_3\text{CN}$  against the  $E$  parameters of the reference electrophiles for the reactions of **2**, **3**, **6**, and **15** with benzhydrylium ions and quinone methides.

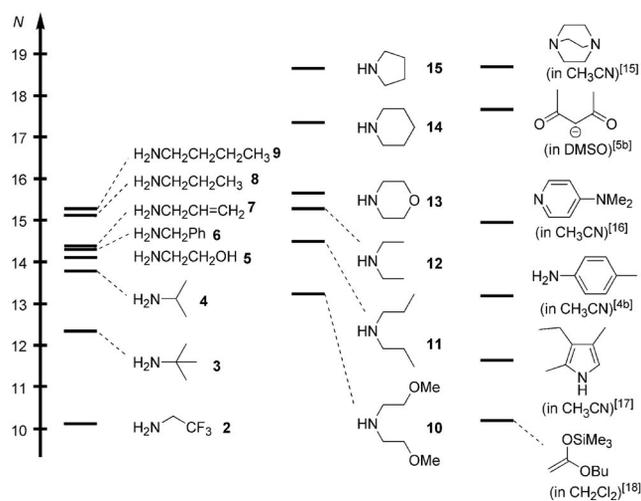


Figure 4. Comparison of the nucleophilic reactivities of amines in acetonitrile with other nucleophiles.

Figure 5 shows that the nucleophilic reactivities of the amines correlate only poorly with the corresponding  $pK_{aH}$  values in acetonitrile.<sup>[19]</sup> As previously reported for the reactions of amines in water,<sup>[4b]</sup> it is thus not possible to predict the nucleophilic reactivities of amines in  $CH_3CN$  on the basis of their  $pK_{aH}$  values.

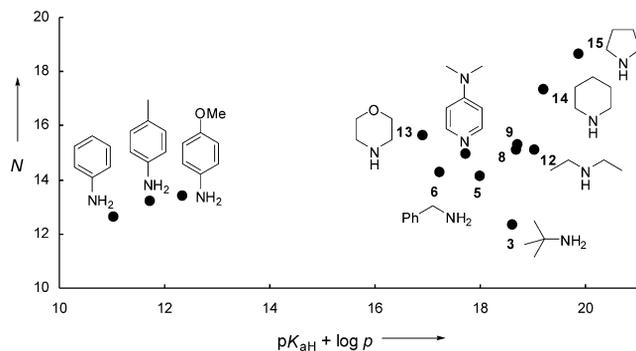


Figure 5. Plot of the  $N$  parameters of amines in acetonitrile versus the statistically corrected basicities in acetonitrile ( $p$  = numbers of protons of the conjugated acid).<sup>[4b,19]</sup>

In previous work we reported that aniline is approximately five times more nucleophilic in water than propylamine,<sup>[4b]</sup> despite the considerably higher basicity ( $pK_{aH}$ ) of the aliphatic amine. We now find that in  $CH_3CN$  the order of reactivity is reversed and that primary and secondary alkylamines are more nucleophilic than aniline ( $N = 12.64$ ,  $s = 0.68$ ).<sup>[4b]</sup>

This reversal of the relative reactivities is due to the different effects of solvent on the reactivities of aromatic and aliphatic amines. Whereas aniline and *p*-toluidine have similar nucleophilicities in water and acetonitrile (for aniline + **1h**:  $k_{CH_3CN}/k_{H_2O} = 0.42$ ), alkylamines are typically one to two orders of magnitude more reactive in acetonitrile than in water (for propylamine + **1h**:  $k_{CH_3CN}/k_{H_2O} = 46$ ).

Thus, although the nucleophilicity order alkylamines > aniline in acetonitrile is the same as that of the relative basicities ( $pK_{aH}$ ), the correlation in Figure 5 shows that

anilines in acetonitrile are considerably more reactive than expected on the basis of their basicities. In other words, the previously reported surprisingly high nucleophilicities of anilines are not a water-specific phenomenon.

In previous work we mentioned that the reliability of Equation (1) to predict rate constants for the addition of amines to various Michael acceptors is limited because of variable stabilizing interactions between the NH protons and the different basic sites in the Michael acceptors.<sup>[20]</sup> Although Figure 3 demonstrates that the reactivities of amines towards benzhydrylium ions and quinone methides correlate excellently with their electrophilicity parameters  $E$ , which have been derived from their reactivities towards C nucleophiles, significant deviations are found by applying Equation (1) to the addition of amines to other types of Michael acceptors in  $CH_3CN$ . Table 1.16 on page S57 of the Supporting Information shows that in several cases the calculated rate constants deviate by more than a factor of  $10^2$  [the common confidence limit of Equation (1)] from the experimental values. It is presently not clear whether these unusually high deviations are due to variable interactions of the NH protons with the basic sites of the Michael acceptors or whether these reactions require a specific treatment of solvent effects.

## Conclusions

The reactions of primary and secondary amines with benzhydrylium ions **1d–o** and of primary amines with quinone methides **1a–c** in acetonitrile follow a second-order rate law, which indicates rate-determining attack of the amines on the electrophiles. In contrast, for most of the reactions of the secondary amines **10–15** with the quinone methides **1a–c** the initial electrophile–nucleophile combination step is reversible and the more complicated rate law Equation (6) has to be employed to derive the rate constants  $k_2$  for the attack of the amines on the electrophiles. From the linear correlations of  $\log k_2$  with the electrophilicity parameters  $E$  of the benzhydrylium ions, the nucleophile-specific parameters  $N$  and  $s$  for amines in  $CH_3CN$  have been derived. The poor correlation between  $N$  and  $pK_{aH}$  shows that also in acetonitrile, relative basicities cannot be used to predict relative nucleophilicities. Solvent polarity affects the reactivities of alkylamines and anilines quite differently: Whereas anilines react approximately two times faster with benzhydrylium ions in water than in acetonitrile, primary alkylamines react at least 10 times faster in acetonitrile than in water. The opposite solvent effect on these closely related reactions demonstrates the limitation of the Hughes–Ingold rules<sup>[21]</sup> to predict solvent effects on polar organic reactions on the basis of the relative charge dispersal in the ground and transition states.

## Experimental Section

**General:** The benzhydrylium tetrafluoroborates **1BF<sub>4</sub>**<sup>[5a]</sup> and quinone methides<sup>[22]</sup> (see Table 1) were synthesized by literature pro-

cedures. 2,2,2-Trifluoroethylamine (**2**), *tert*-butylamine (**3**), isopropylamine (**4**), ethanolamine (**5**), benzylamine (**6**), allylamine (**7**), *n*-propylamine (**8**), *n*-butylamine (**9**), bis(2-methoxyethyl)amine (**10**), di-*n*-propylamine (**11**), diethylamine (**12**), morpholine (**13**), piperidine (**14**), and pyrrolidine (**15**) were purchased and purified by distillation prior to use. <sup>1</sup>H (300 or 400 MHz), <sup>13</sup>C (75.5 or 100 MHz), and <sup>19</sup>F NMR (282 MHz) spectra were recorded a Bruker ARX 300 or Varian Inova 400 instrument. Mass spectra were recorded with a MAT 95 Q instrument.

**Reactions:** The product of the reaction of trifluoroethylamine (**2**) with the benzhydrylium salt **1h**BF<sub>4</sub> was synthesized by the addition of **2** (70 μL, 0.88 mmol) to a mixture of **1h**BF<sub>4</sub> (0.15 g, 0.44 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.6 g, 4 mmol) in acetonitrile (8 mL) at 20 °C. Diethyl ether was added and the solution was washed with 2 M NaOH, dried, filtered, and the solvents evaporated in vacuo. The products of the reactions of the amines **3–9** with the benzhydrylium salt **1h**BF<sub>4</sub> were synthesized by the addition of the amines (0.60 mmol) to stirred solutions of the benzhydrylium salt (0.10 g, 0.30 mmol) in acetonitrile (8 mL) at 20 °C. Diethyl ether was added and the solutions were washed with 2 M NaOH, dried, filtered, and the solvents evaporated in vacuo. The products of the reactions of the amines **12–15** with the benzhydrylium salt **1h**BF<sub>4</sub> were synthesized by dropwise addition of acetonitrile solutions (3 mL) of the amines (ca. 0.7 mmol) to stirred solutions of the benzhydrylium salt (ca. 0.07 g, 0.2 mmol) in acetonitrile (10 mL) at 20 °C. The solvent was removed under reduced pressure, the remaining solid was extracted with diethyl ether, and the solvent was evaporated in vacuo. For details and characterization of the products see the Supporting Information.

**Kinetics:** The kinetics of the reactions of the benzhydrylium ions with the amines were followed by UV/Vis spectrophotometry by using work-stations similar to those described previously.<sup>[5a,23]</sup> For slow reactions ( $\tau_{1/2} > 10$  s) the UV/Vis spectra were collected at different times by using a J&M TIDAS diode array spectrophotometer connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) by fiber optic cables with standard SMA connectors. All the kinetic measurements were carried out in Schlenk glassware with the exclusion of moisture. The temperature of the solutions during the kinetic studies was maintained to within  $\pm 0.1$  °C by using circulating bath cryostats and monitored with thermocouple probes that were inserted into the reaction mixture. Stopped-flow spectrophotometer systems (Applied Photophysics SX.18MV-R or Hi-Tech SF-61DX2) were used to investigate fast reactions of benzhydrylium ions with nucleophiles (10 ms  $< \tau_{1/2} < 10$  s). The kinetic runs were initiated by mixing equal volumes of acetonitrile solutions of the amines and the benzhydrylium salts. Concentrations and rate constants for the individual kinetic experiments are given in the Supporting Information.

**Supporting Information** (see also the the footnote on the first page of this article): Preparative procedures, product characterization and details of the individual runs of the kinetic experiments are available.

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