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Nucleophilicities of Primary and Secondary Amines in Water

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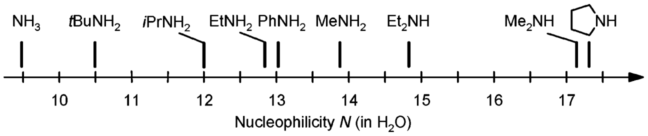

The kinetics of the reactions of 26 primary and secondary amines with benzhydrylium ions in water were investigated photometrically. Because the parallel reactions of the benzhydrylium ions with hydroxide and water are much slower, the second-order rate constants for the reactions of amines with benzhydrylium ions could be determined reliably. Reactivities of anilines were also studied in acetonitrile solution. Plots of log $k_{2,\mathrm{N}}$ for these reactions vs the electrophilicity parameters E of the benzhydrylium ions were linear, which allowed us to derive the nucleophilicity parameters N and s for amines as defined by the equation log $k(20\ °\mathrm{C}) = s(E + N)$. Because the slope parameters for the different amines are closely similar; the relative nucleophilicities are almost independent of the electrophiles and can be expressed by the nucleophilicity parameters N. The correlation between nucleophilicity N and pK_{aH} values is poor, and it is found that secondary alkyl amines and anilines are considerably more nucleophilic, while ammonia is much less nucleophilic than expected on the basis of their pK_{aH} values.

Introduction

Relationships between structure and nucleophilic reactivities of amines have been derived from kinetic investigations of nucleophilic additions[1] as well as nucleophilic substitutions[2] including nucleophilic vinylic substitutions[3] and nucleophilic aromatic substitutions.[4] Swain and Scott studied the rates of reactions of amines with CH_3Br and CH_3I in several solvents and characterized their reactivities by the parameter n, which is defined by eq 1[5]

$$\log(k/k_0) = sn \tag{1}$$

Ritchie determined the rates of the reactions of primary and secondary amines with stabilized carbocations and identified their nucleophilicities by the electrophile independent parameter N_+, which is defined by eq 2[6]

$$\log(k/k_0) = N_+ \tag{2}$$

The parameters N_+ have later been reported also to be applicable for the reactions of amines with cationic transition metal π-complexes.[7] The most comprehensive investigation of amine reactivities has so far been performed by Bunting, who reported second-order rate constants for the reactions of 72 primary and secondary amines with the 1-methyl-4-vinylpyridinium cation in aqueous solution[8] and investigated their relationship with the corresponding reactivities toward methyl 4-nitrobenzenesulfonate.[9]

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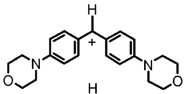
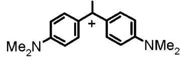
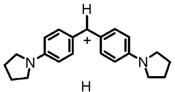
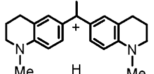
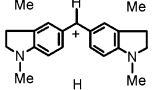
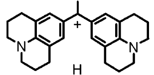
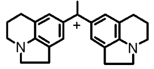
TABLE 1. Benzhydrylium Ions Ar_2CH^+ Employed in This Work

Electrophile	Ar_2CH^+	E^a
$(mor)_2CH^+$		-5.53
$(dma)_2CH^+$		-7.02
$(pyr)_2CH^+$		-7.69
$(thq)_2CH^+$		-8.22
$(ind)_2CH^+$		-8.76
$(jul)_2CH^+$		-9.45
$(lil)_2CH^+$		-10.04

[a] Electrophilicity parameters E from ref 10.

In earlier work we have reported that benzhydrylium ions can be used as reference electrophiles[10] for characterizing a large variety of π-nucleophiles (alkenes,[11] arenes,[11] enol ethers,[11] ketene acetals,[11,12] enamines,[11,13] allyl element compounds,[11,14] transition metal π-complexes,[15] diazoalkanes,[16] delocalized carbanions[17]), n-nucleophiles (amines,[18] alcohols,[19] alkoxides,[20] phosphanes,[21] inorganic anions,[22] pyridines[23]), and σ-nucleophiles (hydrides[10,24]). The rate constants have been correlated on the basis of eq 3

$$\log k_{20\,°\mathrm{C}} = s(N + E) \tag{3}$$

k = second-order rate constant in $M^{-1}\ s^{-1}$
s = nucleophile specific slope parameter
N = nucleophilicity parameter
E = electrophilicity parameter

Only few amines have so far been characterized by eq 3.[18] Because the nucleophilicity parameters N have recently been reported to hold also for S_N2-type reactions,[25] and the systematic design of organocatalytic reactions requires the comparison of the nucleophilicities of amines with those of other nucleophiles, we set out to extend our nucleophilicity scales by determining N parameters for various types of amines. We now report on the kinetics of the reactions of amines with the reference electrophiles listed in Table 1 and use these data to determine N and s of these nitrogen nucleophiles (Scheme 1).

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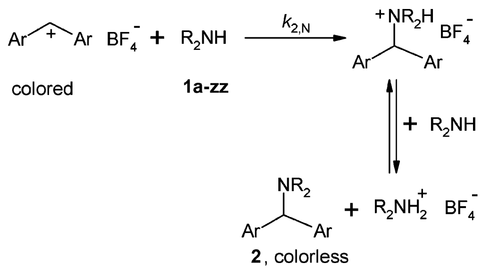
SCHEME 1



Results

Because the reactions were carried out in water, three parallel reactions may account for the consumption of the benzhydrylium ions, and the observed first-order rate constants k_{obs} reflect the sum of the reactions of the electrophile with the amine **1** ($k_{1\Psi,\mathrm{N}}$), with OH⁻ ($k_{1\Psi,\mathrm{OH}^-}$), and with water (k_{W})

$$k_{\mathrm{obs}} = k_{1\Psi,\mathrm{N}} + k_{1\Psi,\mathrm{OH}^-} + k_{\mathrm{W}}$$

$$= k_{2,\mathrm{N}}[\mathbf{1}] + k_{2,\mathrm{OH}^-}[\mathrm{OH}^-] + k_{\mathrm{W}} \qquad (4)$$

Rearrangement of eq 4 yields eq 5, which defines $k_{1\Psi}$ as the overall rate constant minus the contribution by hydroxide

$$k_{1\Psi} = k_{\mathrm{obs}} - k_{2,\mathrm{OH}^-}[\mathrm{OH}^-] = k_{2,\mathrm{N}}[\mathbf{1}] + k_{\mathrm{W}} \qquad (5)$$

The actual concentrations of the amines [**1**] and of hydroxide [OH⁻] are calculated from $[\mathbf{1}]_0$ and $\mathrm{p}K_{\mathrm{aH}}$ as described in the Supporting Information. With the previously published values[18] for k_{2,OH^-} and the calculated concentrations of hydroxide [OH⁻], the partial pseudo-first-order rate constants $k_{1\Psi,\mathrm{OH}^-}$ can be derived. The slopes of the plots of $k_{1\Psi}$ ($=k_{\mathrm{obs}} - k_{1\Psi,\mathrm{OH}^-}$) vs [**1**] correspond to the second-order rate constants $k_{2,\mathrm{N}}$, as shown in Figure 1 and in the Supporting Information. The intercepts, which correspond to the reactions of the benzhydrylium ions with water (eq 5), are generally negligible in agreement with previous work,[18] showing that water ($N = 5.11$) reacts more than 4.5 orders of magnitude slower with benzhydrylium ions than the amines investigated in this work.

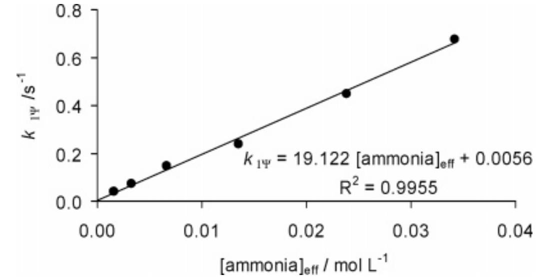


FIGURE 1. Determination of the second-order rate constant ($k_{2,\mathrm{N}} = 19.1$ M^{-1} s^{-1}) for the reaction of $(\mathrm{dma})_2\mathrm{CH}^+$ with ammonia (**1a**) in water at 20 °C.

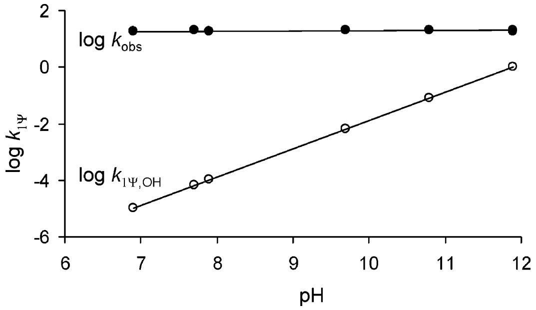


FIGURE 2. Plot of the measured rate constants log k_{obs} (●) and the calculated rate constants log $k_{1\Psi,\mathrm{OH}^-}$ (○) vs pH for the reactions of aniline ($c_0 = 9.27 \times 10^{-4}$ M) with $(\mathrm{dma})_2\mathrm{CH}^+$ ($c_0 = 3.47 \times 10^{-5}$ M) at 20 °C in aqueous phosphate buffer (cosolvent, 9 vol % $\mathrm{CH_3CN}$; $k_{1\Psi,\mathrm{OH}^-} = k_{2,\mathrm{OH}^-}[\mathrm{OH}^-]$ was calculated from the measured pH and k_{2,OH^-} from ref 18).

The linear dependence of $k_{1\Psi}$ on the concentration of amine, as depicted in Figure 1, indicates either that the attack of the amines at the benzhydrylium ions is rate-determining (Scheme 1) or that amines act as general base catalysts for the attack of water on $\mathrm{Ar_2CH^+}$. The latter explanation has been excluded by Bunton[26] by demonstrating amine formation in the reaction of the tris(*p*-methoxy)tritylium ions with ammonia and with several amines. In accordance with rate-determining attack of the amines at the benzhydrylium ions, identical rate constants were found within experimental error when the reaction of $(\mathrm{dma})_2\mathrm{CH}^+$ and aniline (**1p**) was studied at different pH (phosphate buffer) and without buffer (Figure 2). In the reactions of anilines with less electrophilic benzhydrylium ions, reversibility of the initial attack was indicated by a deviation of the disappearance of $[\mathrm{Ar_2CH^+}]$ from the single-exponential decay. In such cases, first-order decay of $[\mathrm{Ar_2CH^+}]$ was achieved by using high concentrations of the anilines or by working in buffered solutions ($\mathrm{HPO_4^{2-}/PO_4^{3-}}$) at pH 11.

Table 2 collects all second-order rate constants determined in this investigation.

Structure Nucleophilicity Relationships. As previously reported for analogous reactions of numerous other nucleophiles,

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TABLE 2. Second-Order Rate Constants for the Reactions of Benzhydrylium Tetrafluoroborates with Primary Amines 1 in Water (20 °C)

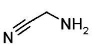
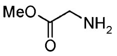
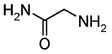
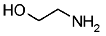
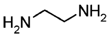
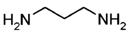
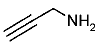
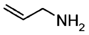
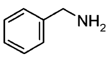
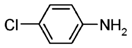
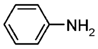
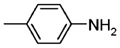
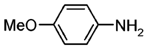
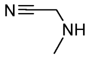
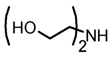
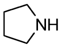
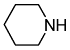
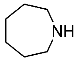
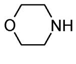
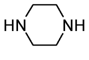
	Amine	N	s	Ar_2CH^+	$k_{2,N}$ / $M^{-1}s^{-1}$
1a	NH_3	9.48	0.59	$(mor)_2CH^+$	2.51×10^{2} [a]
				$(dma)_2CH^+$	1.91×10^{1}
				$(pyr)_2CH^+$	1.43×10^{1}
				$(thq)_2CH^+$	5.39
				$(ind)_2CH^+$	2.39
				$(jul)_2CH^+$	1.41
				$(lil)_2CH^+$	4.07×10^{-1}
1b	$MeNH_2$	13.85	0.53	$(dma)_2CH^+$	4.25×10^{3}
				$(pyr)_2CH^+$	1.72×10^{3}
				$(thq)_2CH^+$	9.21×10^{2}
				$(ind)_2CH^+$	4.24×10^{2}
				$(jul)_2CH^+$	2.03×10^{2}
				$(lil)_2CH^+$	1.11×10^{2}
1c	$EtNH_2$	12.87	0.58	$(dma)_2CH^+$	2.39×10^{3}
				$(pyr)_2CH^+$	9.70×10^{2}
				$(ind)_2CH^+$	2.36×10^{2}
1d	$i$$PrNH_2$	12.00	0.56	$(dma)_2CH^+$	6.70×10^{2}
				$(pyr)_2CH^+$	2.52×10^{2}
				$(thq)_2CH^+$	1.34×10^{2}
				$(jul)_2CH^+$	2.79×10^{1}
1e	$t$$BuNH_2$	10.48	0.65	$(mor)_2CH^+$	2.14×10^{3} [a]
				$(dma)_2CH^+$	1.60×10^{2}
				$(pyr)_2CH^+$	6.01×10^{1}
				$(thq)_2CH^+$	2.97×10^{1}
				$(ind)_2CH^+$	9.90
				$(lil)_2CH^+$	2.61
1f		10.80	0.61	$(dma)_2CH^+$	2.19×10^{2}
				$(pyr)_2CH^+$	7.74×10^{1}
				$(thq)_2CH^+$	3.91×10^{1}
				$(ind)_2CH^+$	1.79×10^{1}
				$(jul)_2CH^+$	6.08
				$(lil)_2CH^+$	3.20
1g		12.08	0.60	$(dma)_2CH^+$	1.21×10^{3}
				$(pyr)_2CH^+$	4.09×10^{2}
				$(thq)_2CH^+$	2.04×10^{2}
				$(jul)_2CH^+$	4.02×10^{1}
1h		12.29	0.58	$(mor)_2CH^+$	1.03×10^{4} [a]
				$(dma)_2CH^+$	1.05×10^{3}
				$(pyr)_2CH^+$	4.19×10^{2}
				$(thq)_2CH^+$	2.38×10^{2}
				$(ind)_2CH^+$	9.22×10^{1}
				$(jul)_2CH^+$	4.77×10^{1}
				$(lil)_2CH^+$	2.45×10^{1}
1i		12.61	0.58	$(mor)_2CH^+$	1.40×10^{4} [a]
				$(dma)_2CH^+$	1.64×10^{3}
				$(pyr)_2CH^+$	6.38×10^{2}
				$(thq)_2CH^+$	3.23×10^{2}
				$(jul)_2CH^+$	6.49×10^{1}
				$(lil)_2CH^+$	3.50×10^{1}
1j		13.28	0.58	$(mor)_2CH^+$	3.78×10^{4} [a]
				$(dma)_2CH^+$	4.19×10^{3}
				$(pyr)_2CH^+$	1.69×10^{3}
				$(thq)_2CH^+$	8.67×10^{2}
				$(ind)_2CH^+$	3.78×10^{2}
				$(jul)_2CH^+$	1.74×10^{2}
				$(lil)_2CH^+$	9.03×10^{1}
1k		14.02	0.54	$(dma)_2CH^+$	5.80×10^{3}
				$(pyr)_2CH^+$	2.28×10^{3}
				$(thq)_2CH^+$	1.30×10^{3}
				$(jul)_2CH^+$	2.73×10^{2}
				$(lil)_2CH^+$	1.38×10^{2}
1l		12.29	0.59	$(mor)_2CH^+$	1.17×10^{4} [a]
				$(dma)_2CH^+$	1.20×10^{3}
				$(pyr)_2CH^+$	4.47×10^{2}
				$(thq)_2CH^+$	2.42×10^{2}
				$(ind)_2CH^+$	1.09×10^{2}
				$(jul)_2CH^+$	4.81×10^{1}
				$(lil)_2CH^+$	2.57×10^{1}
1m		13.21	0.54	$(dma)_2CH^+$	2.35×10^{3}
				$(pyr)_2CH^+$	9.55×10^{2}
				$(thq)_2CH^+$	4.98×10^{2}
				$(jul)_2CH^+$	1.03×10^{2}
				$(lil)_2CH^+$	5.53×10^{1}
1n		13.44	0.55	$(mor)_2CH^+$	3.13×10^{4} [a]
				$(dma)_2CH^+$	3.04×10^{3}
				$(pyr)_2CH^+$	1.29×10^{3}
				$(thq)_2CH^+$	7.82×10^{2}
				$(ind)_2CH^+$	3.06×10^{2}
				$(jul)_2CH^+$	1.82×10^{2}
				$(lil)_2CH^+$	9.46×10^{1}
1o					
	Solvent: CH_3CN	12.92	0.60	$(mor)_2CH^+$	3.29×10^{4}
				$(dma)_2CH^+$	2.63×10^{3}
				$(pyr)_2CH^+$	1.85×10^{3}
1p					
	Solvent: H_2O	12.99	0.73	$(mor)_2CH^+$	4.06×10^{5} [a]
				$(dma)_2CH^+$	1.70×10^{4}
				$(pyr)_2CH^+$	4.98×10^{3}
				$(thq)_2CH^+$	3.26×10^{3}
				$(thq)_2CH^+$	3.38×10^{3} [b]
				$(ind)_2CH^+$	1.27×10^{3}
				$(jul)_2CH^+$	5.17×10^{2} [b]
	Solvent: CH_3CN	12.64	0.68	$(mor)_2CH^+$	7.02×10^{4}
				$(dma)_2CH^+$	7.16×10^{3}
				$(pyr)_2CH^+$	3.14×10^{3}
				$(thq)_2CH^+$	8.71×10^{2}
1q					
	Solvent: H_2O	13.00	0.79	$(mor)_2CH^+$	1.06×10^{6} [a]
				$(dma)_2CH^+$	3.99×10^{4}
				$(pyr)_2CH^+$	1.07×10^{4}
				$(thq)_2CH^+$	7.34×10^{3}
				$(ind)_2CH^+$	2.88×10^{3}
	Solvent: CH_3CN	13.19	0.69	$(mor)_2CH^+$	2.07×10^{5}
				$(dma)_2CH^+$	1.98×10^{4}
				$(pyr)_2CH^+$	6.21×10^{3}
				$(thq)_2CH^+$	2.90×10^{3}
1r					
	Solvent: H_2O	16.53	0.50	$(dma)_2CH^+$	6.68×10^{4}
				$(thq)_2CH^+$	1.31×10^{4}
				$(lil)_2CH^+$	1.96×10^{3}
	Solvent: CH_3CN	13.42	0.73	$(mor)_2CH^+$	6.23×10^{5}
				$(dma)_2CH^+$	4.72×10^{4}
				$(pyr)_2CH^+$	1.65×10^{4}
1s	Me_2NH	17.12	0.50	$(mor)_2CH^+$	6.10×10^{5} [a]
				$(dma)_2CH^+$	1.05×10^{5}
				$(pyr)_2CH^+$	4.89×10^{4}
				$(thq)_2CH^+$	2.87×10^{4}
				$(ind)_2CH^+$	1.20×10^{4}
				$(jul)_2CH^+$	7.06×10^{3}
				$(lil)_2CH^+$	3.52×10^{3}

TABLE 2. Continued

	Amine	N	s	Ar_2CH^+	$k_{2,N}$ / $M^{-1}s^{-1}$
1t	Et_2NH	14.68	0.53	$(mor)_2CH^+$	$7.92 \times 10^{4\,a}$
				$(dma)_2CH^+$	1.12×10^4
				$(pyr)_2CH^+$	4.88×10^3
				$(thq)_2CH^+$	2.84×10^3
				$(ind)_2CH^+$	1.16×10^3
				$(jul)_2CH^+$	6.46×10^2
				$(lil)_2CH^+$	3.16×10^2
1u		13.50	0.59	$(dma)_2CH^+$	6.47×10^3
				$(pyr)_2CH^+$	2.37×10^3
				$(thq)_2CH^+$	1.29×10^3
1v		13.00	0.61	$(dma)_2CH^+$	4.88×10^3
				$(pyr)_2CH^+$	1.70×10^3
				$(thq)_2CH^+$	9.01×10^2
1w		17.21	0.49	$(dma)_2CH^+$	1.06×10^5
				$(pyr)_2CH^+$	5.08×10^4
				$(thq)_2CH^+$	2.62×10^4
				$(ind)_2CH^+$	1.22×10^4
				$(jul)_2CH^+$	7.33×10^3
				$(lil)_2CH^+$	3.41×10^3
1x		18.13	0.44	$(dma)_2CH^+$	6.09×10^4
				$(pyr)_2CH^+$	3.68×10^4
				$(thq)_2CH^+$	2.64×10^4
				$(ind)_2CH^+$	9.01×10^3
				$(jul)_2CH^+$	6.99×10^3
				$(lil)_2CH^+$	3.05×10^3
1y		18.29	0.46	$(dma)_2CH^+$	1.60×10^5
				$(pyr)_2CH^+$	7.29×10^4
				$(thq)_2CH^+$	4.40×10^4
				$(ind)_2CH^+$	2.13×10^4
				$(jul)_2CH^+$	1.23×10^4
				$(lil)_2CH^+$	6.37×10^3
1z		15.62	0.54	$(mor)_2CH^+$	$3.16 \times 10^{5\,a}$
				$(dma)_2CH^+$	4.61×10^4
				$(pyr)_2CH^+$	1.89×10^4
				$(thq)_2CH^+$	1.08×10^4
				$(ind)_2CH^+$	4.51×10^3
				$(jul)_2CH^+$	2.36×10^3
				$(lil)_2CH^+$	1.14×10^3
1zz		17.22	0.50	$(mor)_2CH^+$	$6.10 \times 10^{5\,a}$
				$(dma)_2CH^+$	1.27×10^5
				$(pyr)_2CH^+$	5.34×10^4
				$(thq)_2CH^+$	3.04×10^4
				$(ind)_2CH^+$	1.36×10^4
				$(jul)_2CH^+$	7.50×10^3
				$(lil)_2CH^+$	3.74×10^3

[a] Cosolvent: 9 vol-% CH_3CN. [b] At pH = 11.

[a] Cosolvent 9 vol % CH_3CN. [b] At pH = 11.

linear correlations are obtained (Figure 3), when log $k_{2,N}$ for the reactions of the amines **1a**−**zz** with benzhydrylium ions are plotted against their electrophilicity parameters E, indicating that these reactions follow eq 3. The intercepts on the abscissa correspond to the negative values of the nucleophilicity parameters N, and the slopes of these correlations yield the parameters s ($=s_N$, if they are used for S_N2 reactions[25]).

The second-order rate constants $k_{2,N}$ for the reactions of the amines **1b**−**zz** with $(dma)_2CH^+$ are between 1.6×10^2 (**1e**) and 1.6×10^5 M^{-1} s^{-1} (**1y**), and only ammonia ($k_{2,N} = 19$ M^{-1} s^{-1}) reacts more slowly. Because all reactivities are thus within 4 orders of magnitude, structure reactivity relationships might be based on reactivities toward a single electrophile, e.g., toward $(dma)_2CH^+$. However, the small differences in slopes s imply that the relative nucleophilicities of the amines depend only slightly on the electrophilicity of the reaction partners (as in Ritchie-type correlations),[6,27] which allows us to base the discussion on the nucleophilicity parameters N, which reflect the negative intercepts of the correlation lines of Figure 3 on the abscissa.

Figure 4 illustrates that the nucleophilicities of primary alkyl amines decrease significantly with increasing branching from $MeNH_2$ ($N = 13.85$) to *tert*-butylamine ($N = 10.48$). The second column of Figure 4 reveals that the decrease of nucleophilicity caused by an α-cyano group is significantly stronger than the effect of an α-ester, α-amido, or β-hydroxy group. Because the N parameters refer to molecules and do not contain statistical corrections, the increase of N from aminoethane (**1c**) to 1,2-diaminoethane (**1j**) and 1,3-diaminopropane (**1k**) does not indicate increased nucleophilicities of the individual amino groups. The approximate doubling of the rate constants for the reactions of $(dma)_2CH^+$ with 1,2-diaminoethane (**1j**) (4190 $M^{-1}s^{-1}$) and 1,3-diaminopropane (**1k**, 5800 $M^{-1}s^{-1}$) relative to aminoethane (**1c**, 2390 $M^{-1}s^{-1}$) shows that there is only little interaction between the amino groups in 1,2-diaminoethane (**1j**) and 1,3-diaminopropane (**1k**) and that the individual amino groups have approximately the same reactivity in all three compounds. Closely similar reactivities of aminoethane (**1c**), benzylamine (**1n**), allyl amine (**1m**), and propargyl amine (**1l**)

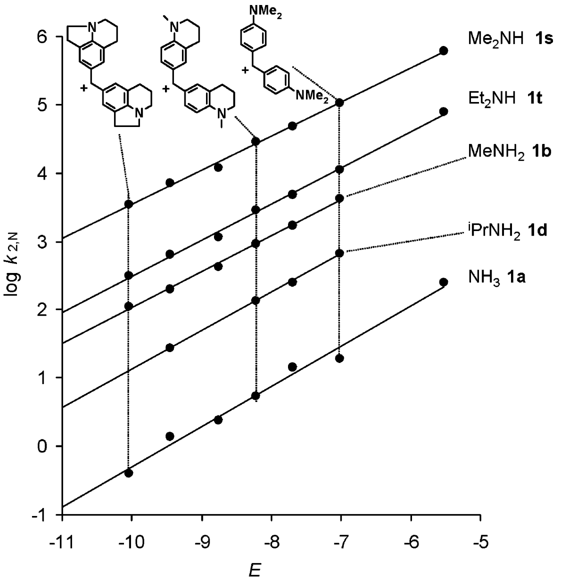


FIGURE 3. Plots of the rate constants log $k_{2,N}$ for the reactions of amines with benzhydrylium cations (from Table 2) vs the electrophilicity parameters E of Ar_2CH^+ (from Table 1).

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(27) Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239−2250.

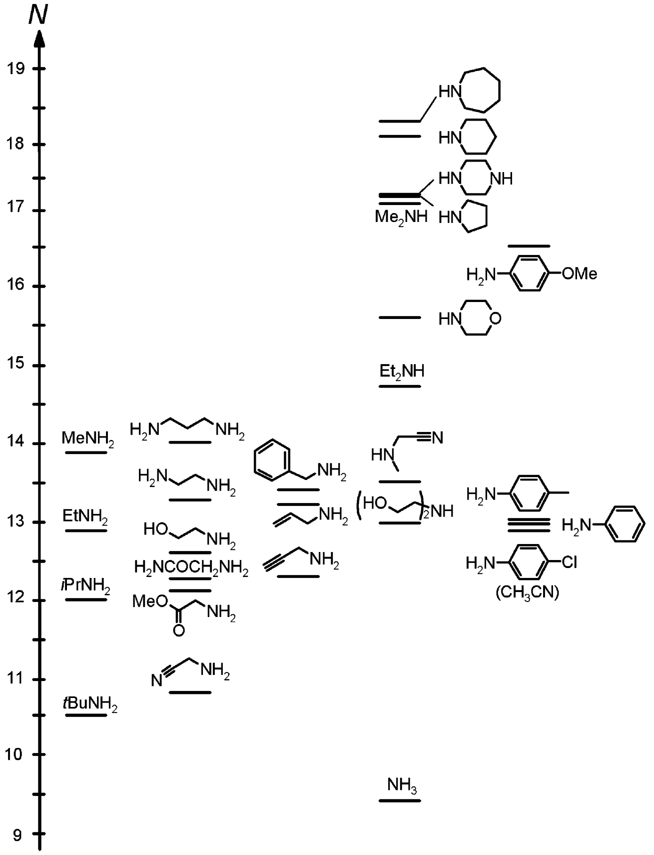

FIGURE 4. Comparison of the nucleophilic reactivities of amines in water. Other solvents are given in parentheses.

show (Column 3, Figure 4) that replacement of the methyl group in aminoethane (**1c**) by unsaturated hydrocarbon groups also has only little influence on the reactivity of the amino group.

Tremendous effects are observed, however, when the hydrogens of ammonia ($N = 9.48$) are successively replaced by one ($MeNH_2$, $N = 13.85$) and two methyl groups (Me_2NH, $N = 17.12$). While the pK_{aH} values in water show only a moderate increase in basicity from NH_3 ($pK_{aH} = 9.25$) to $MeNH_2$ ($pK_{aH} = 10.66$) and Me_2NH ($pK_{aH} = 10.73$), nucleophilicity grows steadily in this series and can be explained by the decrease of hydration energy as the hydrogen atoms of ammonia are successively replaced by methyl groups.[26] As shown by the comparison of dimethylamine (**1s**, $N = 17.12$) and diethylamine (**1t**, $N = 14.68$) steric factors play a considerably greater role for secondary amines than for primary amines ($MeNH_2$, $N = 13.85$; $EtNH_2$, $N = 12.87$).

Most remarkable in view of nucleophilicity/basicity correlations is the fact that aniline, which is less basic than ammonia by 4.7 pK_{aH} units, is a considerably stronger nucleophile than ammonia. The direct comparison of the rate constants shows that $(dma)_2CH^+$ reacts even 7 times faster with aniline (**1p**) than with ethylamine (**1c**), and it is because of the different slope parameters that aniline (**1p**) and ethylamine (**1c**) have comparable values of N. Because of the much smaller value of s for *p*-methoxyaniline (**1r**) in water in comparison with the other anilines, its N parameter turns out to be particularly high, and good Hammett correlations N/σ do not result. When the rate constants for the reactions of **1o**−**r** with $(dma)_2CH^+$ are plotted vs σ (Figure 5) linear correlations are obtained, from which ρ values of −2.1 (in H_2O) and −2.5 (in CH_3CN) result.

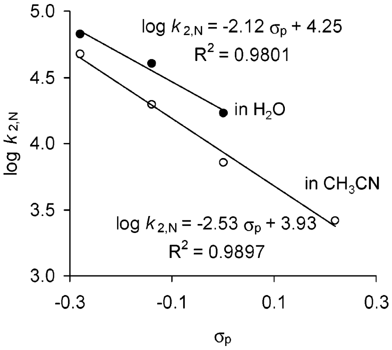

FIGURE 5. Correlation of the rate constants log $k_{2,N}$ vs σ_p for the reactions of anilines with $(dma)_2CH^+$ in H_2O and CH_3CN at 20 °C.

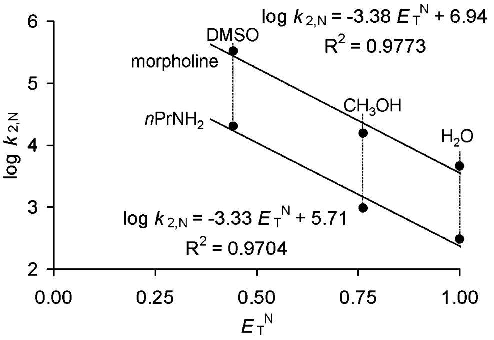

FIGURE 6. Plot of the rate constants log $k_{2,N}$ vs E_T^N for the reactions of morpholine (**1z**) and nPrNH$_2$ with $(ind)_2CH^+$ in different solvents at 20 °C (rate constants from Table 2, refs 18 and 25; E_T^N from refs 29 and 30; MeOH containing 9 vol % MeCN as a cosolvent).

The cyclic amines **1w**−**1y** show similar reactivities toward $(dma)_2CH^+$ comparable to dimethylamine, and the small differences in N are due to differences in s. The noticeably smaller N value for morpholine (**1z**, $N = 15.62$) compared to piperidine (**1x**, $N = 18.13$) is also a consequence of the different slopes (0.54 vs 0.44). While $(dma)_2CH^+$ reacts only 1.3 times faster with **1x** than with **1z**, this ratio increases to 3 for the less reactive $(jul)_2CH^+$ and is expected to grow even more as the electrophilicity of the reaction partner decreases further.

Solvent Effects. Figure 5 shows that anilines react approximately two times faster in water than in acetonitrile. Obviously, hydrogen-bond stabilization of anilines in water plays a minor role because of their low basicity. On the other hand, pyridines which have similar pK_{aH} values in water as anilines react 90 times faster with benzhydrylium ions in acetonitrile than in water.[23] For a variety of alkyl amines reactivities toward benzhydrylium ions have also been determined in methanol.[25] While the N parameters are of comparable magnitude as in water, the rate constants for the reactions with $(dma)_2CH^+$ are generally three to six times greater in methanol than in water.

In previous work we have found, that the rates of the reactions of carbocations with neutral σ- and π-nucleophiles are only slightly affected by solvent polarity, because charges are neither created nor destroyed in the rate-determining step.[28] Figure 6 shows that the situation is different for amines: the rate

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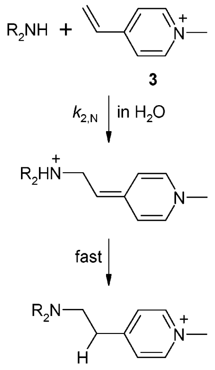
(28) (a) Mayr, H.; Schneider, R.; Schade, C.; Bartl, J.; Bederke, R. *J. Am. Chem. Soc.* **1990**, *112*, 4446−4454. (b) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954−4961. (c) Mayr, H.; Basso, N.; Hagen, G. *J. Am. Chem. Soc.* **1992**, *114*, 3060−3066.

constants decrease with increasing E_T^N values[29,30] of the solvents; the reaction of morpholine (**1z**) with $(ind)_2CH^+$ is 72 times slower in water than in DMSO. A similar behavior was found for the reaction of 4-(dimethylamino)pyridine with $(dma)_2CH^+$ in different solvents ($\log k_{2,N} = -3.35E_T^N + 6.75$).[23]

Reactions of Amines with Other Electrophiles. The most comprehensive work on amine nucleophilicities in water was previously published by Heo and Bunting[8] who investigated the reactivities of 91 amines toward the 1-methyl-4-vinylpyridinum cation **3** (Scheme 2).

SCHEME 2



It was reported[8] that the correlation between nucleophilicity and basicity of amines was rather poor (Figure 7). Although the subclasses of primary, secondary, and tertiary amines cluster together in the same regions of Figure 7, the individual treatments of these subclasses still show poor rate equilibrium relationships.

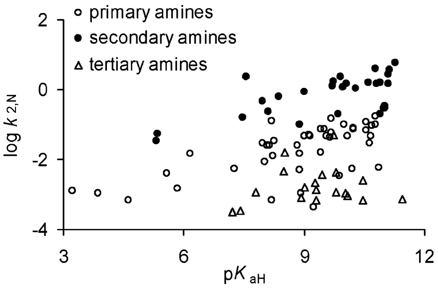


FIGURE 7. Plot of the rate constants $\log k_{2,N}$ vs pK_{aH} for the reactions of amines with 1-methyl-4-vinylpyridinium **3** in water at 25 °C (rate constants from ref 8).

Figure 8 shows a linear correlation of moderate quality between $(\log k_{2,N})/s$ and N, where $k_{2,N}$ refers to the reactions of amines with the vinylpyridinium ion **3**, and N and s are derived from the reactions of amines with benzhydrylium ions (Table 2 and ref 23). Because the slope of this correlation line (0.765) deviates from 1, the rate constants for the nucleophilic additions of amines to **3** are not properly reproduced by eq 3, and it has to be examined whether the consideration of an additional, electrophile-specific slope parameter, as previously described for S_N2 reactions,[25] is sufficient to reproduce also the rate constants for the reactions of **3** with other types of nucleophiles.

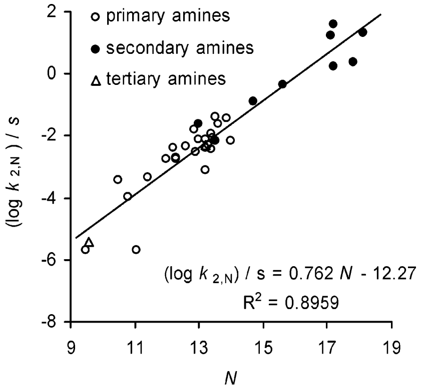


FIGURE 8. Relationship between the rate constants for the reactions of amines with 1-methyl-4-vinylpyridinium **3** in water at 25 °C with the N and s parameters of amines given in Table 2 (rate constants $k_{2,N}$ from ref 8; data for imidazole, amino acids, and peptides, which will be reported separately, have also been included).

TABLE 3. Estimates of *N* Parameters for Amines from Reactivities toward the 1-Methyl-4-vinylpyridinium Ion 3 from the Correlation Given in Figure 8

nucleophile	$k_{2,N}{}^a/M^{-1}\,s^{-1}$	model for s	s	$N_{estimated}$
$HO(CH_2)_3NH_2$	7.30×10^{-2}	$H_2N(CH_2)_3NH_2$	0.54	13.3
$C_6H_5(CH_2)_2NH_2$	9.86×10^{-2}	$C_6H_5CH_2NH_2$	0.55	13.7
$CH_3O(CH_2)_2NH_2$	4.60×10^{-2}	$HO(CH_2)_2NH_2$	0.58	13.1
$H_3N^+(CH_2)_3NH_2$	1.50×10^{-2}	$H_2N(CH_2)_3NH_2$	0.54	11.7
$H_3N^+(CH_2)_2NH_2$	5.57×10^{-3}	$H_2N(CH_2)_2NH_2$	0.58	11.0
$CF_3CH_2NH_2$	1.52×10^{-3}	$EtNH_2$	0.58	9.7
cyclohexylamine	4.80×10^{-2}	$(CH_3)_2CHNH_2$	0.56	13.0
$HOCH_2CH(CH_3)NH_2$	1.62×10^{-2}	$(CH_3)_2CHNH_2$	0.56	11.9
$HOCH_2C(CH_3)_2NH_2$	3.40×10^{-3}	$HO(CH_2)_2NH_2$	0.58	10.5
$(HOCH_2)_2C(CH_3)NH_2$	1.05×10^{-3}	$HO(CH_2)_2NH_2$	0.58	9.4
$(HOCH_2)_3CNH_2$	6.57×10^{-4}	$HO(CH_2)_2NH_2$	0.58	8.9
$H_2NCOCH(CH_3)NH_2$	8.60×10^{-3}	$(CH_3)_2CHNH_2$	0.56	11.3
CH_3ONH_2	6.70×10^{-4}	$HONH_2$	0.55	8.5
$CH_3CONHNH_2$	1.24×10^{-3}	$H_2NCONHNH_2$	0.52	8.8
$CH_3(CH_2)_3NHCH_3$	1.63	$(CH_3)_2NH$	0.50	16.7
$CH_3NH(CH_2)_3NHCH_3$	1.52	$(CH_3)_2NH$	0.50	16.6
$CH_3NH(CH_2)_2NHCH_3$	1.08	$(CH_3)_2NH$	0.50	16.2
$HO(CH_2)_2NHCH_3$	1.17	$(CH_3)_2NH$	0.50	16.3
$NC(CH_2)_2NHCH_3$	2.30×10^{-1}	$(CH_3)_2NH$	0.50	14.4
$CH_3NH_2(CH_2)_2NHCH_3$	1.55×10^{-1}	$(CH_3)_2NH$	0.50	14.0
$(CH_3)_2CHNHCH_3$	2.02×10^{-1}	$(CH_3)_2NH$	0.50	14.3
$C_6H_5CH_2NHCH_3$	1.77	$(CH_3)_2NH$	0.50	16.8
$CH_3NHNHCH_3$	2.30	$(CH_3)_2NH$	0.50	17.1
$(CH_3CH_2CH_2)_2NH$	3.00×10^{-1}	$(CH_3CH_2)_2NH$	0.53	14.8
$HO(CH_2)_2NHCH_2CH_3$	2.00×10^{-1}	$(CH_3CH_2)_2NH$	0.53	14.4
perhydroazocine	1.42	perhydroazepine	0.46	16.5
thiamorpholine	8.64×10^{-1}	morpholine	0.54	15.9
4-formylpiperidine	4.67×10^{-1}	piperidine	0.44	15.1
2-methylpiperidine	2.92×10^{-1}	piperidine	0.44	14.5
2-hydroxylmethylpiperidine	2.31	piperidine	0.44	17.2
piperazinium cation	3.54×10^{-2}	piperazine	0.50	12.3

[a] Rate constants for reaction of the amines with **3** in H_2O at 25 °C (data from ref 8).

Irrespective of the outcome of this analysis, the correlation given in Figure 8 can be used to estimate N parameters for further amines from their reactivities toward **3** which have been reported by Heo and Bunting. In order to calculate the estimated N parameters given in Table 3, the s parameters were assumed to be the same as for structurally analogous amines.

Bunting and Heo have previously reported that the rate constants for the reactions of amines with methyl 4-nitrobenzenesulfonate (Scheme 3) correlate linearly with their reactivities toward **3**.[9]

In line with this report, Figure 9 shows that the N and s parameters of amines (Table 2) can also be used to describe

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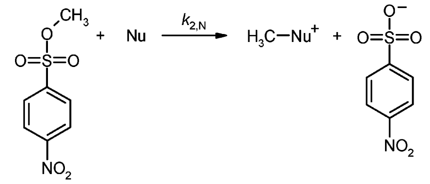
(29) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003.

(30) (a) Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlmann, F. *Liebigs Ann. Chem.* **1963**, *661*, 1−37. (b) Reichardt, C. *Liebigs Ann. Chem.* **1971**, *752*, 64−67. (c) Reichardt, C.; Harbusch-Görnert, E. *Liebigs Ann. Chem.* **1983**, 721−743.

SCHEME 3



the S_N2 reactions of amines with methyl 4-nitrobenzenesulfonate. The slope of 0.31 shows that variation of the amines affects the reactivities toward the methyl 4-nitrobenzenesulfonate by only 31% of the amount that is observed in reactions with benzhydrylium ions (slope = 1.00). Accordingly, we have previously shown that $(\log k_{2,N})/s$ vs N plots have electrophile-specific slopes <1 in the case of S_N2 reactions, which had prompted us to extend eq 3 by an electrophile-specific slope parameter s_E.[25]

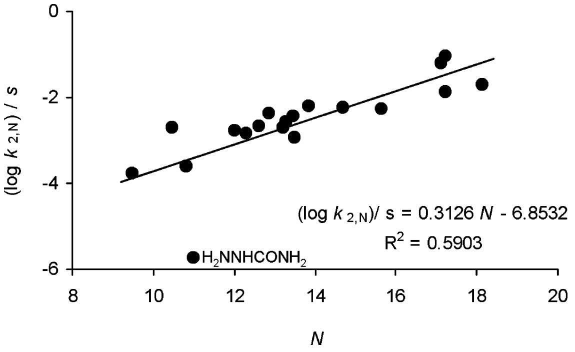


FIGURE 9. Relationship between the rate constants for the reactions of amines with methyl 4-nitrobenzenesulfonate in water at 25 °C with the N and s parameters of amines given in Table 2 (rate constants $k_{2,N}$ from ref 9; N and s parameter for semicarbazide taken from ref 18).

Freccero et al. determined the rate constants for the Michael additions of nucleophiles toward the *o*-quinone methide **4** (Scheme 4).[31] Figure 10 shows a good correlation between the reactivities of nucleophiles toward **4** and the nucleophilicity parameters N and s. The slope close to 1 derived from reactions with widely differing rate constants shows that the reactions of **4** with nucleophiles may be described by eq 3. If a slope of 1 is enforced, as required by eq 3, one can calculate an electrophilicity parameter $E(\mathbf{4}) = -2.79$. This value can be used for estimating N parameters for further nucleophiles from their reported rate constants toward **4**.

Kane-Maguire reported on the reactions of anilines with iron π-complexes in acetonitrile.[7,32] Because electrophilicity parameters for the iron π-complexes have previously been derived from the rates of their reactivities with π-nucleophiles,[11] it is now possible to analyze the reliability of eq 3 for reproducing Kane-Maguire's rate constants with the N and s parameters determined in this work. Table 4 shows that the deviation is generally smaller than a factor of 5.

Bunton investigated the reactivities of primary and secondary amines toward the tris(*p*-anisyl)methyl cation **5** (Scheme 5) in water.[26]

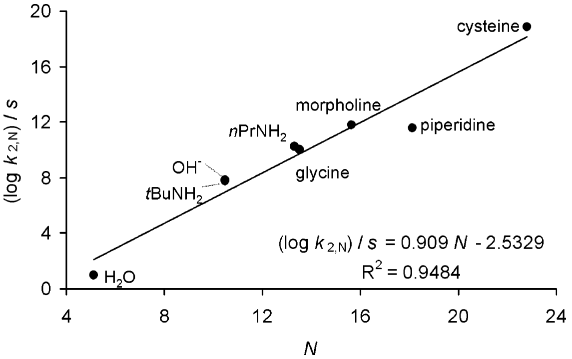


FIGURE 10. Relationship between the rate constants for the reactions of nucleophiles with *o*-quinone methide **4** in water (rate constants $k_{2,N}$ from ref 31; for H_2O determined at ionic strength $I = 0.0$; for tBuNH$_2$, nPrNH$_2$, glycine, morpholine, piperidine at pH = 12.0; for cysteine at pH = 12.2) with the N and s parameters of amines given in Table 2 (for this correlation, data from ref 18 and data from amino acids, which will be reported later, have also been included).

TABLE 4. Comparison of Calculated and Observed Second-Order Rate Constants (20 °C, CH_3CN) for the Reactions of Tricarbonyl Iron Dienylium Ions $[Fe(CO)_3R]^+$ with Anilines 1p−q

$XC_6H_4NH_2$	R	C_6H_7	2-MeOC_6H_6	C_7H_9
	E^a	−7.76	−8.94	−9.21
X = H	$k_{calc}{}^b/M^{-1}\ s^{-1}$	2.33×10^3	3.57×10^2	
	$k_{exp}{}^c/M^{-1}\ s^{-1}$	3.09×10^3	6.99×10^2	
X = CH_3	$k_{calc}{}^b/M^{-1}\ s^{-1}$	5.58×10^3	8.56×10^2	5.57×10^2
	$k_{exp}{}^c/M^{-1}\ s^{-1}$	1.43×10^4	3.93×10^3	9.06×10^2

[a] From ref 11. [b] Calculated by eq 3, using the E parameters of ref 11 and N and s for the anilines in acetonitrile from Table 2. [c] Rate constants in acetonitrile calculated for 20 °C from the Eyring activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ given in ref 32.

SCHEME 4

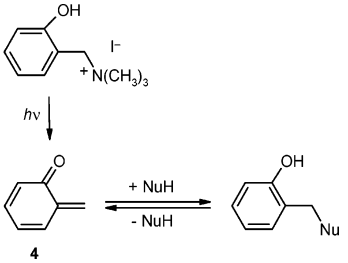


Figure 11 shows that the reactivities of amines toward the tritylium ion **5** correlate only modestly with the benzhydrylium-derived nucleophilicity parameters N, in agreement with our previous warning to apply eq 3 for reactions with tritylium ions.[11] Because tritylium reactivities are significantly controlled by steric effects, it appears likely that the small slope of the correlation in Figure 11 is due to the steric retardation of the reactions of the more nucleophilic secondary amines with the tritylium ion **5**.[11,18] The bulky tBuNH$_2$ (**1e**), which reacts 190 times more slowly with the tritylium ion **5** than predicted by eq 3, can also be explained by a steric effect.

Because of the narrow reactivity ranges investigated, meaningful correlations between the reactivities of amines with ethyleneoxide, benzoylacetylene, 5-nitrosopenicillamine, and *N*-nitrososulfonamides could not be obtained as shown in Figures 1−4 in the Supporting Information.

Correlations between Nucleophilicity and Basicity. The qualitative discussion in the section "Structure Nucleophilicity Relationships" has already shown that the nucleophilicities of

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(31) Modica, E.; Zanaletti, R.; Freccero, M.; Mella, M. *J. Org. Chem.* **2001**, *66*, 41−52.

(32) (a) Kane-Maguire, L. A. P.; Odiaka, T. I.; Turgoose, S.; Williams, P. A. *J. Organomet. Chem.* **1980**, *188*, C5−C9. (b) Kane-Maguire, L. A. P.; Odiaka, T. I.; Williams, P. A. *J. Chem. Soc., Dalton Trans.* **1981**, 200−204. c) Kane-Maguire, L. A. P.; Odiaka, T. I.; Turgoose, S.; Williams, P. A. *J. Chem. Soc., Dalton. Trans.* **1981**, 2489−2495.

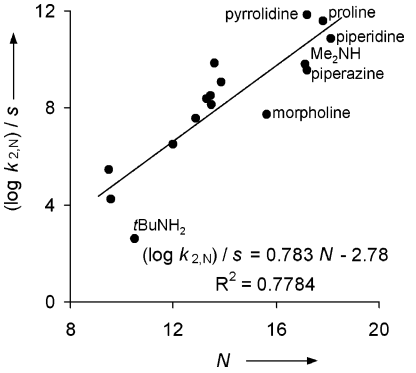
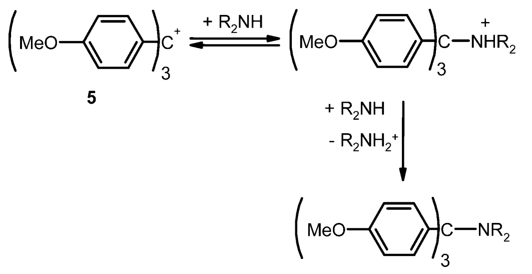


FIGURE 11. Relationship between the rate constants for the reactions of primary and secondary amines with tris(p-anisyl)methyl cation **5** in water (rate constants $k_{2,N}$ at 25 °C from ref 26) with the N and s parameters of amines given in Table 2.

SCHEME 5



some amines deviate dramatically from those expected from their basicities. Figure 12 shows that the correlation between N and pK_{aH} is indeed very poor, in line with Bunting's conclusion derived from the correlation of the reactivities of amines toward the 1-methyl-4-vinylpyridinium ion with their pK_{aH} values (Figure 7).[8]

Figure 12 shows that not only cyclic amines such as piperidine, piperazine, and pyrrolidine but also acyclic secondary amines are more nucleophilic than expected from their basicities. Particularly striking is the large difference in nucleophilicity between Me_2NH ($N = 17.12$) and $MeNH_2$ ($N = 13.85$) despite comparable Brønsted basicities (pK_{aH} = 10.66 vs 10.73). The unexpectedly high nucleophilicity of aniline, which was already mentioned above, is visualized in Figure 12: Despite its considerably lower basicity, aniline shows a nucleophilicity comparable to that of primary alkyl amines. The smaller energy of hydration, which may account for the reactivity increase from ammonia to alkyl amines is unlikely to be the only reason for the high nucleophilicity of aniline. Aniline, as well as secondary alkyl amines have lower oxidation potentials than primary alkyl amines.[33] For that reason, one can assume that in these reactions, the intrinsic barrier will be lower because of a larger contribution by inner-sphere electron transfer (favorable highest-occupied molecular orbital−lowest-unoccupied molecular orbital interactions).[34] While this explanation has to be considered tentative, it is obvious from Figure 12 that more factors, in addition to basicity, have to be considered when explaining nucleophilicity.

Conclusions

The reactions of amines with benzhydrylium ions follow the correlation eq 3, which allows us to include amines into our comprehensive nucleophilicity scales[35] and compare amine nucleophilicities with those of other nucleophiles (Figure 13). In this way it becomes possible to predict the active species in equilibrium mixtures of various nucleophiles (amines, carbanions, phenolates) in aqueous solution. For the nucleophilicity series $NH_3 < PhNH_2 \approx EtNH_2 \approx MeNH_2 < Me_2NH$, it was shown that predictions of nucleophilicities on the basis of basicities are misleading. Thus, ordinary secondary amines are considerably more nucleophilic than primary amines, and

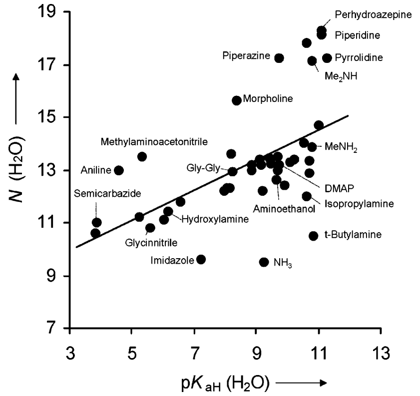


FIGURE 12. Plot of the nucleophilicity parameters N of amines vs pK_{aH} in water.

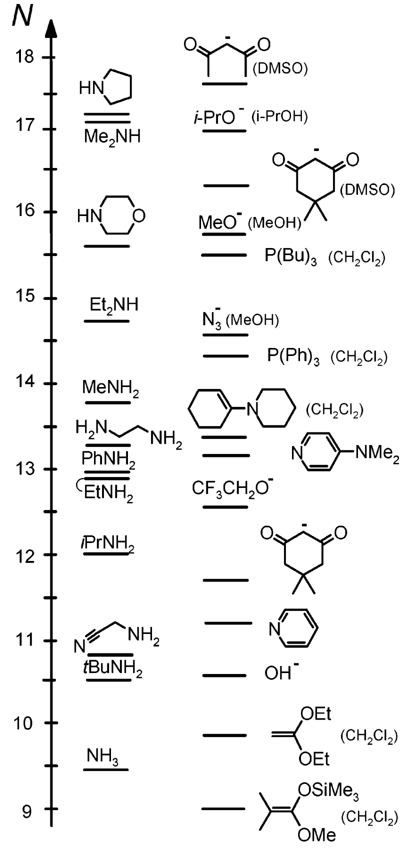


FIGURE 13. Comparison of the nucleophilic reactivities of amines with other types of nucleophiles in water.[35] Other solvents are given in parentheses.

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[33] Fu, Y.; Liu, L.; Yu, H.-Z.; Wang, Y.-M.; Guo, Q.-X. *J. Am. Chem. Soc.* **2005**, *127*, 7227−7234.

[34] Ofial, A. R.; Ohkubo, K.; Fukuzumi, S.; Lucius, R.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 10906−10912.

[35] For a comprehensive listing of nucleophilicity parameters N and electrophilicity parameters E, see http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html.

ammonia is much less reactive than primary alkyl amines, aniline, and pyridine. Because of the poor correlation between nucleophilic reactivities and pK_{aH} values of amines on one side and the demonstrated ability of the N and s parameters to properly predict nucleophilic reactivities with a variety of structurally diverse electrophiles, we recommend to replace pK_{aH} as a tool for forecasting nucleophilic reactivity by N and s.

Experimental Section

Materials. The benzhydrylium ions used in this work were synthesized according to literature procedures.[10] Potassium hydroxide was purchased as an aqueous standard solution. All amines **1a**−**1zz** were from commercial sources. They were purified, as appropriate, by recrystallization or distillation prior to use. The amines **1a**,**b**,**f**,**h**,**l**,**u** were purchased as hydrochloride salts, and the free base was liberated with potassium hydroxide. Water was distilled and passed through a Milli-Q water purification system. Acetonitrile was distilled over diphenylketene.

Kinetics. The reaction of benzhydrylium ions with amines were studied in aqueous solution or in acetonitrile. All amines were used as free bases.

As the reactions of the colored benzhydrylium ions with amines gave rise to colorless products, the reactions could be followed by employing UV−vis spectroscopy. The rates of slow reactions ($\tau_{1/2} > 10$ s) were determined by using 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 fiberoptic cables and standard SMA connectors. The temperature of solutions during all kinetic studies was kept constant (usually 20.0 ± 0.2 °C) by using a circulating bath thermostat and monitored with a thermocouple probe that was inserted into the reaction mixture.

Hi-Tech SF-61DX2 stopped-flow spectrophotometer systems (controlled by Hi-Tech KinetAsyst2 software) were used for the investigation of rapid reactions of benzhydrylium ions with amines ($\tau_{1/2} < 10$ s at 20 °C). The kinetic runs were initiated by mixing solutions of the amine and the benzhydrylium salt in a 1:1 or 10:1 ratio. Amine concentrations at least 10 times higher than the benzhydrylium ions concentrations were usually employed, resulting in pseudo-first-order kinetics with an exponential decay of the Ar_2CH^+ concentration. First-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the absorbance data (averaged from at least five kinetic runs at each amine concentration) to the single-exponential $A_t = A_0 \exp(-k_{obs}t) + C$. The most electrophilic benzhydrylium ion used in this work, $(mor)_2CH^+$, cannot be stored in aqueous solution ($k_W = 0.331$ s^{-1} at 20 °C). For that reason, solutions of $(mor)_2CH^+$ BF_4^- were prepared in dry CH_3CN and combined with the 10-fold volume of aqueous solutions of amines in the stopped-flow instrument.

Acknowledgment. Dedicated to Professor Wolfgang Beck on the occasion of his 75th birthday. We are grateful to the Deutsche Akademische Austauschdienst for a scholarship to Y.C.C. (RICh) and the Deutsche Forschungsgemeinschaft (Ma 673/21) and the Fonds der Chemischen Industrie for financial support. Help of Dr. A. R. Ofial during the preparation of the manuscript is gratefully acknowledged.

Supporting Information Available: Details of the evaluation of the kinetic data. Rate constant determinations for the reactions of amines **1a**−**zz** with benzhydrylium ions. This material is available free of charge via the Internet at http://pubs.acs.org.

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