

Nucleophilic Reactivities of Primary and Secondary Amines in Acetonitrile

Tanja Kanzian,^[a] Tobias A. Nigst,^[a] Andreas Maier,^[a] Stefan Pichl,^[a] and Herbert Mayr*^[a]*Dedicated to Professor Rolf W. Saalfrank on the occasion of his 70th birthday***Keywords:** Kinetics / Linear free energy relationships / Solvent effects / Nucleophilicity / Amines

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_{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_{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 °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.^[1] They have been characterized on the Swain–Scott n scale as well as on the Ritchie N_+ scale.^[1d,2]

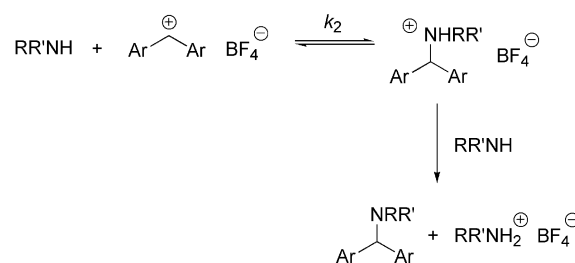
Recently, we employed Equation (1), which characterizes nucleophiles by the parameters N and s , and electrophiles by the parameter E ,^[3] for determining N and s for a variety of amines in aqueous solution.^[4] In this way it became possible to add amines to our comprehensive nucleophilicity scale,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

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

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.^[6,8] (b) Acetonitrile is the solvent of choice for the photolytic cleavage of carbocation precursors.^[9] 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 $10^{10}\text{ M}^{-1}\text{ s}^{-1}$.^[10]

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.^[11] Because many of these investigations involve reactions with amines in acetonitrile,^[9a,9b] 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).^[5a]



Scheme 1. Reactions of amines with benzhydrylium ions.

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Table 1. List of electrophiles used in this study.

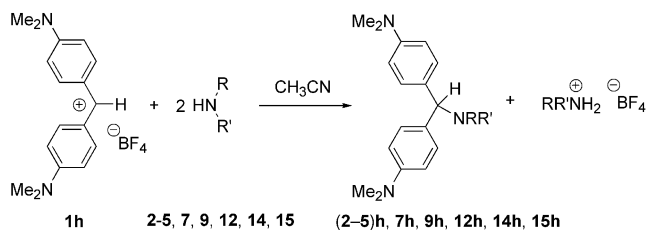
Reference electrophile ^[a]		<i>E</i> ^[b]
	ani(<i>t</i> Bu) ₂ QM (1a)	−16.11
	tol(<i>t</i> Bu) ₂ QM (1b)	−15.83
	ani(Ph) ₂ QM (1c)	−12.18
	(lil) ₂ CH ⁺ (1d)	−10.04
	(jul) ₂ CH ⁺ (1e)	−9.45
	(ind) ₂ CH ⁺ (1f)	−8.76
	(pyr) ₂ CH ⁺ (1g)	−7.69
	(dma) ₂ CH ⁺ (1h)	−7.02
	(mpa) ₂ CH ⁺ (1i)	−5.89
	(mfa) ₂ CH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

[a] Counterion of the benzhydryl cations: BF₄[−]. [b] Electrophilicity parameters *E* are from ref.^[5a,b].

Results and Discussion

Product Characterization

A combination of the benzhydrylium salt **1h**BF₄ 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 Ar₂CH protons and the isolated yields are listed in Table 2.



Scheme 2. Reactions of amines with 4,4'-bis(dimethylamino)benzhydrylium tetrafluoroborate **1h**BF₄.

Table 2. ¹H NMR chemical shifts of the Ar₂CH 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	δ_{H} [ppm]	Yield [%]
2,2,2-Trifluoroethylamine (2)	2h	4.80	85
<i>tert</i> -Butylamine (3)	3h	4.88	98
Isopropylamine (4)	4h	4.81	90
Ethanolamine (5)	5h	4.69	98
Allylamine (7)	7h	4.70	97
<i>n</i> -Butylamine (9)	9h	4.65	95
Diethylamine (12)	12h	4.50	45
Piperidine (14)	14h	3.99	71
Pyrrolidine (15)	15h	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 CH₃CN 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*_{obs} were obtained from the exponential decays of the absorbances of the electrophiles (Figure 1).

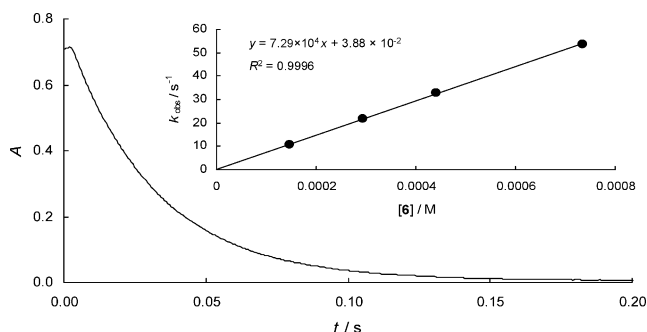


Figure 1. Exponential decay of the absorbance at 613 nm during the reaction of **1h** with benzylamine ($[6] = 4.42 \times 10^{-4}$ M; $k_{\text{obs}} = 32.7$ s^{−1}). Insert: determination of the second-order rate constant k_2 (7.31×10^4 M^{−1} s^{−1}) as the slope of the first-order rate constants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

Plots of k_{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.

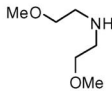
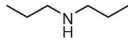
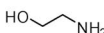
$$k_{\text{obs}} = k_2[\text{amine}] \quad (2)$$

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_{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	<i>k</i> ₂ / M ^{−1} s ^{−1}	Amine	<i>N</i>	<i>s</i>	Electrophile	<i>k</i> ₂ / M ^{−1} s ^{−1}		
	2	10.13	0.75	1h	1.43×10^2		8	1h	1.43×10^5		
				1i	2.53×10^3				1k	1.00×10^9 [a,b]	
				1j	4.03×10^4				1l	2.30×10^9 [a,b]	
				1k	3.50×10^7 [a]				1m	4.10×10^9 [a,b]	
				1l	1.50×10^8 [a,b]				1n	4.40×10^9 [a,b]	
				1m	8.50×10^8 [a,b]				1o	4.50×10^9 [a,b]	
				1n	1.70×10^9 [a,b]				1a	3.41×10^{-1}	
				1o	2.00×10^9 [a,b]					1c	7.49×10^1
	3	12.35	0.72	1c	1.52		10	13.24	0.93	1h	2.12×10^5
				1d	4.15×10^1					1c	7.89 [b,c]
				1f	3.34×10^2					1d	1.12×10^3
				1i	5.13×10^4					1e	4.47×10^3
				1f	2.43×10^3					1f	1.25×10^4
	4	13.77	0.70	1g	2.13×10^4		11	14.51	0.80	1g	1.17×10^5
				1h	5.24×10^4					1c	$6.74 \times 10^{1[c]}$
				1c	2.71×10^1					1d	3.95×10^3
				1d	5.85×10^2					1e	1.38×10^4
				1f	4.94×10^3					1f	3.17×10^4
	5	14.11	0.71	1g	4.24×10^4		12	15.10	0.73	1g	2.77×10^5
				1h	1.02×10^5					1c	$1.51 \times 10^{2[c]}$
				1b	1.10×10^{-1}					1d	4.62×10^3
				1c	2.06×10^1					1e	1.29×10^4
	6	14.29	0.67	1d	6.53×10^2		13	15.65	0.74	1f	3.49×10^4
				1f	4.61×10^3					1g	3.24×10^5
				1g	3.48×10^4					1b	$2.03 \times 10^{-1[b,c]}$
				1h	7.29×10^4					1c	$3.85 \times 10^{2[c]}$
				1b	1.25×10^{-1}					1d	1.15×10^4
	7	14.37	0.66	1d	5.09×10^2		14	17.35	0.68	1e	4.11×10^4
				1f	4.32×10^3					1f	1.04×10^5
				1g	3.64×10^4					1g	8.03×10^5
				1h	8.61×10^4					1a	$6.04^{[c]}$
	8	15.11	0.63	1a	2.64×10^{-1}		15	18.64	0.60	1b	$1.23 \times 10^{1[c]}$
				1b	3.82×10^{-1}					1c	3.52×10^3
				1c	5.46×10^1					1d	7.85×10^4
				1d	1.38×10^3					1e	2.69×10^5
				1e	3.87×10^3					1a	3.25×10^1
				1f	7.54×10^3					1b	4.82×10^1
				1g	6.77×10^4					1d	1.18×10^5
									1e	3.50×10^5	

[a] Second-order rate constants k_2 from ref.^[9b], [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_{obs} versus amine concentration are not linear (Figure 2). The upward curvature in the plots of k_{obs} versus amine concentration indicate that a second molecule of the amine is involved in the reaction as a base catalyst (Scheme 3).

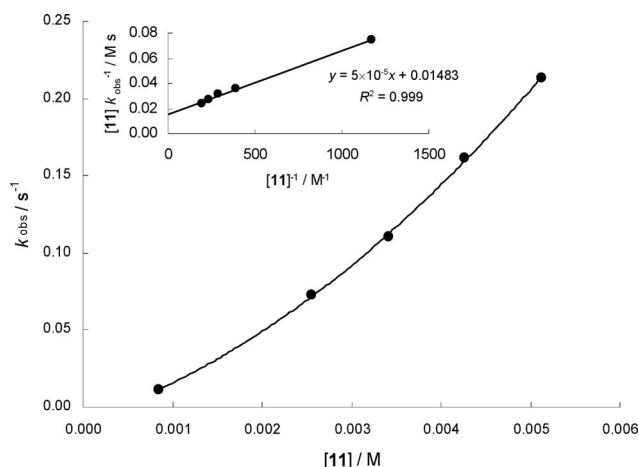
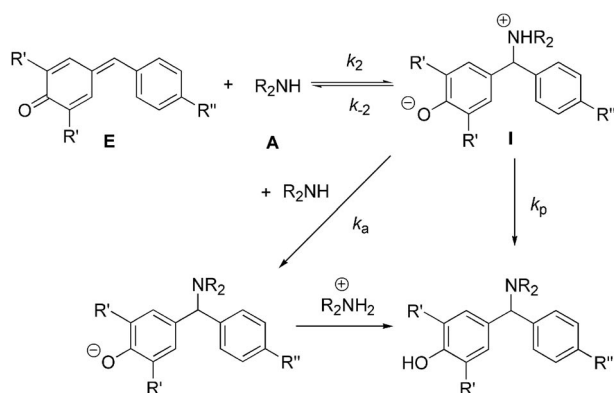


Figure 2. Plots of k_{obs} versus $[11]$ and $[11]/k_{\text{obs}}$ versus $1/[11]$ (inset) for the reaction of **11** with the quinone methide **1c**. The k_2 value for the reaction is $1/(0.0148 \text{ ms}) = 67.4 \text{ M}^{-1} \text{ s}^{-1}$.



Scheme 3. Reactions of secondary amines with quinone methides.

Analogous behavior has been reported for the reactions of secondary amines with thiocarbonates,^[12] thionobenzoates,^[13] and activated esters of indole-3-acetic acid.^[14] 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 NH^+ to 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_{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_{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**^[9b] 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).

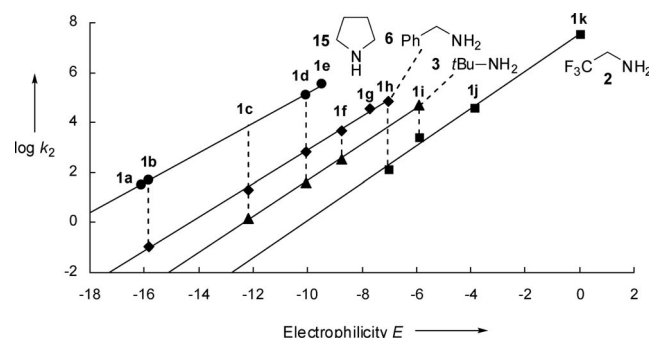


Figure 3. Plots of the second-order rate constants $\log k_2$ (20 °C) in CH_3CN against the E parameters of the reference electrophiles for the reactions of **2**, **3**, **6**, and **15** with benzhydrylium ions and quinone methides.

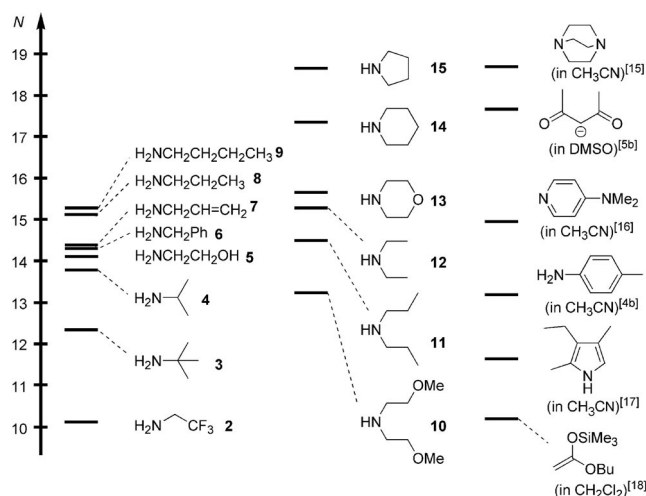


Figure 4. Comparison of the nucleophilic reactivities of amines in acetonitrile with other nucleophiles.

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

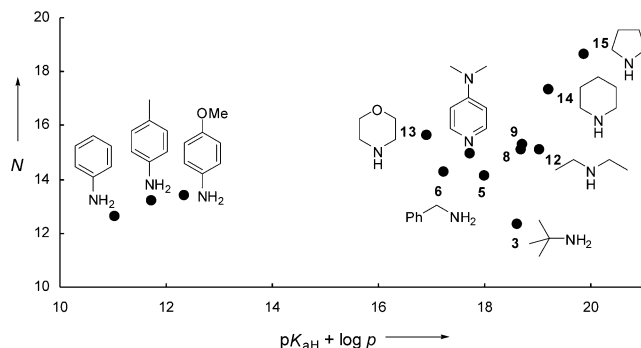


Figure 5. Plot of the N parameters of amines in acetonitrile versus the statistically corrected basicities in acetonitrile (p = numbers of protons of the conjugated acid).^[4b,19]

In previous work we reported that aniline is approximately five times more nucleophilic in water than propylamine,^[4b] 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 ($N = 12.64$, $s = 0.68$).^[4b]

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.^[20] 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^[21] 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 **1BF₄**^[5a] and quinone methides^[22] (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. ^1H (300 or 400 MHz), ^{13}C (75.5 or 100 MHz), and ^{19}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 **1hBF₄** was synthesized by the addition of **2** (70 μL , 0.88 mmol) to a mixture of **1hBF₄** (0.15 g, 0.44 mmol) and K_2CO_3 (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 **1hBF₄** 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 **1hBF₄** 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.^[5a,23] 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 ± 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 ($10\text{ ms} < \tau_{1/2} < 10$ 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 footnote on the first page of this article): Preparative procedures, product characterization and details of the individual runs of the kinetic experiments are available.

Acknowledgments

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