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Nucleophilic reactivities of tertiary alkylamines[†]

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and Herbert Mayr[a]*

The kinetics of the reactions of tertiary amines, triethylamine (1a), *N*-methylpyrrolidine (1b), *N*-methylpiperidine (1c), and *N*-methylmorpholine (1d) with benzhydrylium ions (Ar_2CH^+) have been studied in acetonitrile and dichloromethane. The benzhydryl cations were generated by laser flash photolysis of quaternary phosphonium and ammonium tetrafluoroborates. For most reactions, exponential decays of the absorbances of the benzhydryl cations were observed because the carbocations were generated in the presence of a high excess of the amines (pseudo-first-order conditions). From the linear plots of k_{obs} *versus* the amine concentrations, the second-order rate constants k were obtained, which allowed us to calculate N and s for these amines in CH_3CN and CH_2Cl_2. The linear free energy relationship $\log k = s(N + E)$ was thus used to integrate 1a–d into our comprehensive nucleophilicity scales. Copyright © 2010 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper.

Keywords: amines; carbocations; kinetics; linear free energy relationships; organocatalysis

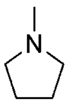
INTRODUCTION

Tertiary alkylamines are generally used as Brønsted bases in organic synthesis.[1–2] On the other hand, many reactions are known, where tertiary amines act as nucleophilic catalysts.[3–32] 1,4-Diazabicyclo[2.2.2]octane (DABCO, **1e**) and quinuclidine (**1f**), for example, are common catalysts in Baylis–Hillman reactions[7] and in cyclopropanations of Michael acceptors.[8] *N*-Methylpiperidine (**1c**) and *N*-methylmorpholine (**1d**) have been reported to function as nucleophilic catalysts in Baylis–Hillman reactions,[9,10] and *N*-methylmorpholine (**1d**) served as a catalyst for the aziridination of α,β-unsaturated carbonyl compounds.[11–13] Though acylations are commonly catalyzed by pyridines, in particular 4-dimethylaminopyridine (DMAP),[14–18] triethylamine (**1a**),[19–27] and the cyclic amines **1b**[27] and **1c**[23] have also been employed as acylation catalysts. Analogously, the hydrolyses of esters, imides, and amides are catalyzed by tertiary amines, including **1d**,[28] through a nucleophilic mechanism.[28–30] Nucleophilic substitution reactions of aromatic heterocycles have also been catalyzed by tertiary amines, including **1a** and **1c**.[31,32]

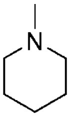
Because the nucleophilic activities of amines are known to correlate only poorly with their Brønsted basicities (pK_{aH}),[33–35] we now set out to include the tertiary amines **1(a–d)** in our comprehensive nucleophilicity scales[36–40] by studying the rates of their reactions with benzhydrylium ions.[36]

NEt_3

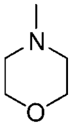
1a



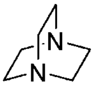
1b



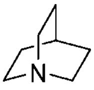
1c



1d



1e



1f

Numerous kinetic investigations have shown that the rate constants for the reactions of n-, π-, and σ-nucleophiles with carbocations can be described by Eqn (1),[36–40]

$$\log k = s(N + E) \tag{1}$$

where nucleophiles are characterized by two parameters (N, s) and electrophiles are characterized by one parameter (E). By employing benzhydrylium ions (**2**, Table 1)[36] and structurally related quinone methides[40] as reference electrophiles, it became possible to compare reactivities of a large number of nucleophiles in a single scale.[36–40] With this methodology, we have previously quantified the nucleophilicities of numerous n-, π-, and σ-nucleophiles,[41] including primary and secondary amines,[42] pyridines,[43] amidines,[44] cinchona alkaloids,[45] as well as the tertiary alkylamines **1e,f**.[46] In this work, we will report on the nucleophilic reactivities of amines **1a–d**.

RESULTS AND DISCUSSION

As the benzhydrylium ions (Ar_2CH^+, **2**) are colored and their reactions with the amines **1a–d** yield colorless adducts, the progress of the reactions can be monitored by UV–Vis spectroscopy. However, formation of quaternary ammonium salts from **1a–d** and the more stabilized benzhydrylium ions

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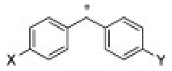
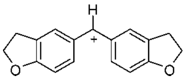
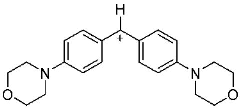
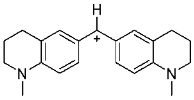
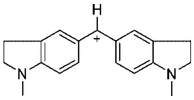
Table 1. Abbreviations and electrophilicity parameters (*E*) of the reference electrophiles employed in this work.

	 **2**		
Ar_2CH^+	X	Y	E^a
Ph_2CH^+	H	H	5.90
$(Ph)(tol)CH^+$	H	CH_3	4.59
$(tol)_2CH^+$	CH_3	CH_3	3.63
$(Ph)(ani)CH^+$	H	OCH_3	2.11
$(ani)_2CH^+$	OCH_3	OCH_3	0.00
$(fur)_2CH^+$			−1.36
$(pfa)_2CH^+$	$N(Ph)CH_2CF_3$	$N(Ph)CH_2CF_3$	−3.14
$(mfa)_2CH^+$	$N(CH_3)CH_2CF_3$	$N(CH_3)CH_2CF_3$	−3.85
$(dpa)_2CH^+$	NPh_2	NPh_2	−4.72
$(mor)_2CH^+$			−5.53
$(mpa)_2CH^+$	$N(Ph)CH_3$	$N(Ph)CH_3$	−5.89
$(dma)_2CH^+$	$N(CH_3)_2$	$N(CH_3)_2$	−7.02
$(pyr)_2CH^+$	$N(CH_2)_4$	$N(CH_2)_4$	−7.69
$(thq)_2CH^+$			−8.22
$(ind)_2CH^+$			−8.76

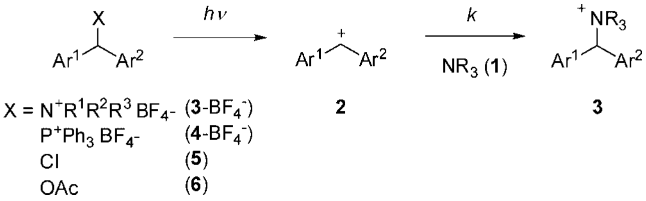
[a] From Reference [36].

($E < -9$ to -4) is thermodynamically unfavorable. Similar to previous observations for **1e,f**,[46] those benzhydryl cations, which do combine with the tertiary amines **1a–d**, react very rapidly ($k > 5 \times 10^5\ M^{-1}\ s^{-1}$ at 20 °C). Conventional UV–Vis spectroscopy, even in combination with stopped-flow techniques, was thus not suitable for following the rates of these reactions because they are completed during the mixing time of the stopped-flow instrument. For this reason, we have studied the reactions of **1a–d** with Ar_2CH^+ in CH_3CN and CH_2Cl_2 by laser-flash photolytic techniques (Scheme 1).

Laser-flash-photolytic generation of benzhydryl cations

In acetonitrile

In polar solvents like acetonitrile, numerous photo-leaving groups can be employed to generate benzhydryl cations **2** by photoheterolysis of the respective precursors.[77–79] If the corresponding benzhydrylium ion is available as a stable tetrafluoroborate[36] and the nucleophile to be studied can act as a photo-leaving group, the corresponding benzhydrylium precursor can be generated in solution by combining $Ar_2CH^+BF_4^-$ with the corresponding nucleophile. We have previously applied this approach to study the nucleophilicities of thiocyanate,[47] halide,[48] nitrite,[49] and cyanate[50] ions, as well as the tertiary amines **1e,f**.[46] In this work, we will use it to determine the nucleophilic reactivities of the tertiary amines **1a–d**. This procedure is simple because the quaternary ammonium salts **3**-BF_4^- which serve as precursors for laser flash photolysis can be prepared in solution by adding a high excess (>10 equivalents) of the tertiary amine which is required for the kinetic experiment to



Scheme 1. Laser-flash-induced heterolytic cleavage of suitable precursors yields benzhydryl cations **2** which combine with the amines **1** to yield ammonium ions **3**

a 10^{-5}–10^{-4} M solution of the benzhydrylium tetrafluoroborate **2**-BF_4^-. Due to the low concentration of **2**-BF_4^-, the concentration of the tertiary amine remains virtually unchanged. This method has the further advantage that photoheterolysis of the resulting precursors only regenerates the benzhydrylium ion and the tertiary amine.

The choice of photo-leaving group becomes more critical for less stabilized benzhydryl cations because photoheterolysis gets less favorable with decreasing cation stability. For the generation of benzhydryl cations with $E > -2$, which cannot readily be isolated as stable salts, we usually use precursors which are known to have a high efficiency of photoheterolysis, such as chlorides (**5**),[51–53] acetates (**6**),[54–58] and phosphonium salts (**4**).[59–63] The concentrations of Cl^-, AcO^-, and R_3P generated by photolysis, which can be calculated from the absorbances and known extinction coefficients[51] of the benzhydrylium ions, are so small that the rate of external return with the photo-leaving group is usually negligible.

In dichloromethane

Phosphonium tetrafluoroborates (**4**-BF_4^-) are particularly interesting precursors for laser flash photolysis, because they allow us to generate reactive carbocations efficiently in low polarity solvents such as dichloromethane.[63] Photolyses of neutral precursors, for example chlorides (**5**) or acetates (**6**), on the other hand, yield only radicals in dichloromethane if the aryl rests have *p*-MeO or less electron-donating substituents.[51] An important reason for the high efficiency of phosphonium salts **4**-BF_4^- as precursors in apolar solvents is the fact that they already bear a positive charge and no net charge is generated during the separation of the carbocation and the neutral phosphine. A similar argument could be made for quaternary ammonium salts, and therefore we were also interested in the laser flash photolysis of the ammonium salts **3**-BF_4^- in dichloromethane. As far as we are aware of, the photoheterolysis of quaternary ammonium salts[64–66,80] has only been described in more polar solvents.

Photolysis of the quaternary ammonium bromide **3e**-Br^- with $Ar^1{=}Ar^2{=}Ph$[67] in CH_2Cl_2 did not give rise to any absorbance of the benzhydryl cation (Ph_2CH^+). This is not surprising because the Br^- anion undergoes a diffusion-controlled reaction with Ph_2CH^+,[48] and in CH_2Cl_2, the Br^- anion would presumably form contact ion pairs with the ammonium ions, i.e., it can intercept the carbocation within the geminate solvent cage. We then prepared the corresponding ammonium tetrafluoroborate **3e**-BF_4^- ($Ar^1{=}Ar^2{=}Ph$) from the bromide by salt exchange with $AgBF_4$ in CH_3CN. When we photolyzed **3e**-BF_4^- ($Ar^1{=}Ar^2{=}Ph$) in CH_2Cl_2, we could indeed observe the benzhydryl cation Ph_2CH^+ and identify it by its spectrum.

Thermodynamics of the combination reactions

As mentioned above, combinations of the tertiary amines **1a–d** with the highly stabilized benzhydryl cations are thermodynamically unfavorable and their solutions remain colored even when a high excess of the amines is added. In some cases, partial combinations occur, and we have previously reported on photometric determinations of equilibrium constants for the combination reactions of benzhydrylium ions with the tertiary amines **1e,f** in acetonitrile[46] as well as for tertiary phosphines in dichloromethane.[68] Attempts to determine equilibrium constants for the combinations of **1a–d** with Ar_2CH^+ in this work were unsuccessful because the fast combination of benzhydrylium ions with the amines was followed by an unknown subsequent reaction so that the end absorptions were not constant.

Qualitatively, the thermodynamic stabilities of the quaternary ammonium salts in CH_3CN decrease for a given benzhydrylium ion in the order DMAP $\gg$ quinuclidine $>$ DABCO $\approx$ *N*-methylpyrrolidine $>$ *N*-methylpiperidine $>$ *N*-methylmorpholine $>$ NEt_3. In CH_2Cl_2, the formation of ammonium salts from benzyhydrylium ions and tertiary amines is thermodynamically less favorable than in CH_3CN.

Kinetics of the reactions of tertiary amines with benzhydryl cations

The benzhydryl cations were generated by laser flash photolysis (7 ns pulse, 266 nm, 40–60 mJ/pulse) of suitable precursors (see above and footnotes in Table 2) in the presence of a high excess of the amines **1a–d** in CH_3CN or CH_2Cl_2 (Scheme 1). The kinetics of the reactions of the benzhydrylium ions **2** with the tertiary amines **1a–d** were then followed by monitoring the decrease of the absorbance of Ar_2CH^+ at λ_{max}. Unlike primary and secondary amines, tertiary amines react only very slowly with dichloromethane,[69] which allowed us to study their reactivity also in CH_2Cl_2 solution.

In some cases, where the amines **1a–d** form only moderately stable adducts with the benzhydryl cations, we did not observe the expected pseudo-first-order kinetics due to an unidentified side or subsequent reaction on a similar timescale.

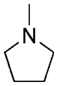
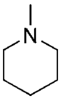
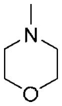
In cases, where the combination reactions of the benzhydrylium ions with the tertiary amines are fast, the absorbances of the benzhydrylium ions decrease mono-exponentially (Fig. 1) and the pseudo-first-order rate constants k_{obs} were obtained by fitting the decays of the absorbances to the mono-exponential functions $A_t = A_0 e^{-k_{obs}t} + C$. Plots of k_{obs} *versus* [amine] are linear and the second-order rate constants k (Table 2) were derived from the slopes of such plots (Fig. 1).

Figure 2 and the data in Table 2 show that the rate constants of the reactions of the benzhydrylium ions with the amines increase with increasing electrophilicity parameter E until the diffusion limit is reached, i.e., $(3–5) \times 10^9\ M^{-1}\ s^{-1}$ for **1b–d** in acetonitrile. The fact that the diffusion-controlled rate constants for the reactions of NEt_3 (**1a**) are 2–3 times smaller than for the cyclic amines **1b–d** can be rationalized by the greater steric demand of NEt_3.

Typically, plots of log k *versus* E show linear correlations from which the nucleophile-specific parameters N and s can be obtained (Eqn (1)). However, Eqn (1) is only valid for rate constants up to $\sim 2 \times 10^8\ M^{-1}\ s^{-1}$,[36] because then the correlation lines start to flatten as the rate constants approach the diffusion limit, which is also evident from Fig. 2. As a consequence, the suitable reactivity range to determine N and s parameters for **1a–d** is very narrow, limited by thermodynamic stability of the combination products on the lower end, and limited by diffusion control on the upper end. For that reason, only few rate constants can be used for the determination of N and s for triethylamine (**1a**) and *N*-methylmorpholine (**1d**) in acetonitrile, as well as for **1a–d** in dichloromethane (Table 2).

Moreover, in acetonitrile, combination reactions of *N*-phenyl substituted benzhydrylium ions, particularly $(dpa)_2CH^+$ and $(mpa)_2CH^+$, with nucleophiles are usually faster than one would predict based on their E parameters.[70] Reactions of **1b–d** with these cations in CH_3CN have similar or even higher rate constants

Table 2. Second-order rate constants for the reactions of **1a–d** with benzhydrylium ions (Ar_2CH^+, **2**) in CH_3CN and CH_2Cl_2 at 20 °C[a].

	k/M^{-1} s^{-1}							
	NEt_3							
	1a		**1b**		**1c**		**1d**	
2	CH_3CN	CH_2Cl_2	CH_3CN	CH_2Cl_2	CH_3CN	CH_2Cl_2	CH_3CN	CH_2Cl_2
Ph_2CH^{+b}	1.45×10^9		4.65×10^9		3.71×10^9		2.56×10^9	
$(Ph)(tol)CH^{+b}$				3.66×10^9				
$(tol)_2CH^{+b}$	1.64×10^9		4.06×10^9	3.55×10^9	2.97×10^9	2.00×10^9	2.66×10^9	
$(Ph)(ani)CH^{+b}$	7.31×10^8							
$(ani)_2CH^{+b}$	4.66×10^8			3.05×10^9	1.68×10^9	1.27×10^9	8.38×10^8	
$(fur)_2CH^{+b}$	1.91×10^8	1.96×10^8	2.31×10^9	1.65×10^9	8.32×10^8	5.96×10^8	2.71×10^8	7.10×10^7
$(pfa)_2CH^+$	$(1.4 \times 10^7)^c$		9.24×10^8	6.31×10^8	1.53×10^8	1.45×10^8	1.63×10^7	
$(mfa)_2CH^+$	d		3.28×10^8	4.86×10^8	4.00×10^7	7.79×10^7	4.36×10^6	
$(dpa)_2CH^+$			3.04×10^8	1.87×10^8	4.07×10^7	$(3 \times 10^7)^c$	5.06×10^6	
$(mor)_2CH^+$			6.39×10^7	6.53×10^7	5.08×10^6		6.73×10^5	
$(mpa)_2CH^+$			8.55×10^7	5.29×10^7	6.61×10^6		d	
$(dma)_2CH^+$			1.22×10^7		$(1.4 \times 10^6)^c$			
$(pyr)_2CH^+$			7.19×10^6					
$(thq)_2CH^+$			2.08×10^6					
$(ind)_2CH^+$			d					

[a] Generated from the corresponding ammonium salts **3**-BF_4^-, if not mentioned otherwise.

[b] Generated from **5**, **6**, or **4**-BF_4^- in CH_3CN, and from **4**-BF_4^- in CH_2Cl_2; for details see Supporting Information.

[c] Fits of the time-dependent absorbances of the benzhydryl cations to an exponential curve are not very good, and these rate constants have to be considered approximate.

[d] Reactions do occur when higher concentrations of amines are used, but the reactions are not of pseudo-first order.

than cations with somewhat higher E values (Table 2 and Fig. 2). This deviation indicates small differential solvent effects on the reactivities of these electrophiles with the consequence that the E-parameters of benzhydrylium ions which were derived from rate constants determined in dichloromethane[36] are not applicable in CH_3CN. Therefore, we did not consider rate constants measured with $(dpa)_2CH^+$ and $(mpa)_2CH^+$ in CH_3CN for the determination of the N and s parameters.

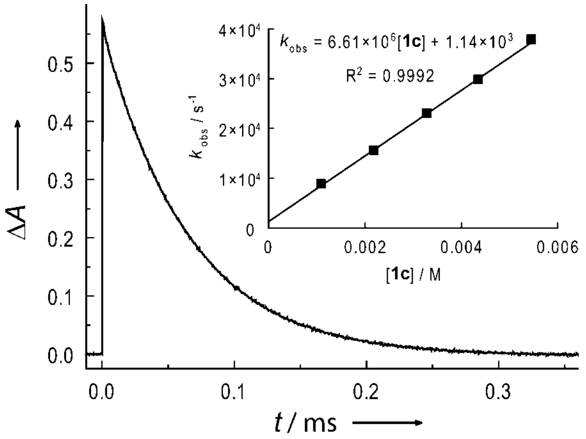


Figure 1. Exponential decay of the absorbance ΔA at 613 nm and linear correlation of the pseudo-first-order rate constants k_{obs} *versus* [**1c**] for the reaction of $(mpa)_2CH^+$ with **1c** in CH_3CN at 20 °C

Due to these limitations, only two series in Table 2 contain enough data points to derive the nucleophilicity parameters from Eqn (1), yielding $N = 20.59$, $s = 0.52$ for **1b** and $N = 18.72$, $s = 0.52$ for **1c** (Table 3). Assuming that the slope $s = 0.52$ also holds for the other reaction series, nucleophilicity parameters for **1a,d** in CH_3CN and **1a–d** in CH_2Cl_2 have been estimated from 1 to 3 reliable rate constants in the supposedly linear range of the correlations. From the N parameters in Table 3, and from the rate constants in Table 2, it can be seen that the tertiary amines **1a–d** have almost equal nucleophilicities in CH_2Cl_2 and in CH_3CN. The nucleophilicity of DMAP also differs by less than one order of magnitude in these solvents.[43] However, due to the paucity of data, the N and s parameters published in this work have to be considered approximate.

We can now compare the nucleophilic reactivities of **1a–d** with those of other N- and P-nucleophiles. Because reactions of the tertiary alkylamines **1a–f** with electrophiles which would react with second-order rate constants of $k = 1\ M^{-1} s^{-1}$ are thermodynamically unfavorable, N values (which reflect the relative reactivities toward such electrophiles) are less suitable for comparing these nucleophiles than relative reactivities toward an electrophile which does combine with these compounds. Therefore, we have plotted log k of the combination reactions with $(dma)_2CH^+$ in Fig. 3.

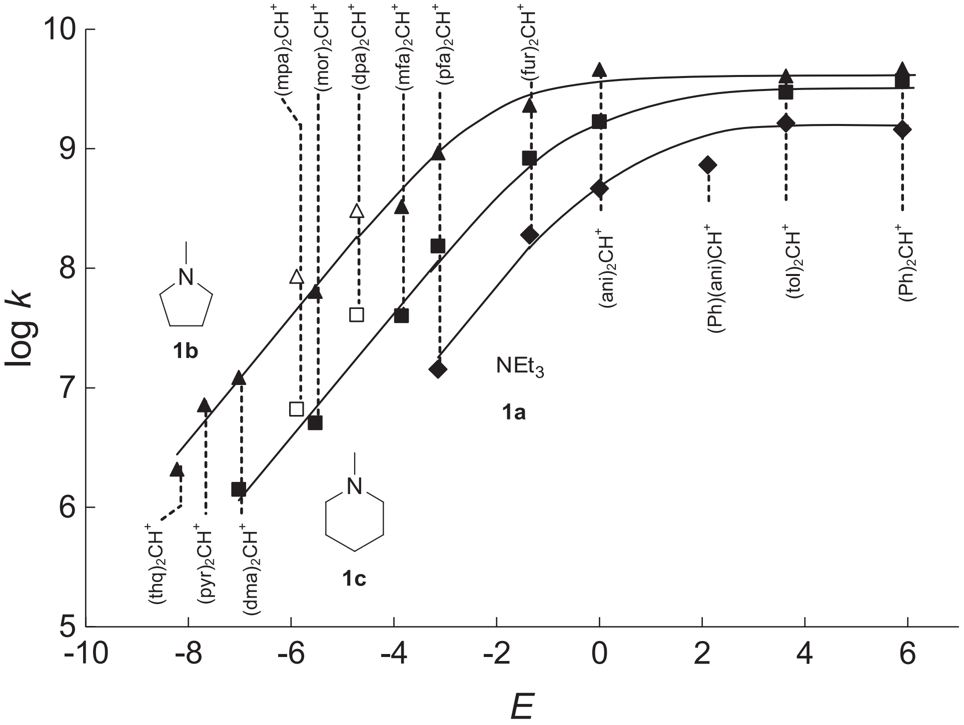


Figure 2. Correlation of log k for the reactions of triethylamine (**1a**, ◆), *N*-methylpyrrolidine (**1b**, ▲), and *N*-methylpiperidine (**1c**, ■) with benzhydrylium ions in CH_3CN at 20 °C with electrophilicity parameters E—rate constants for $(mpa)_2CH^+$ and $(dpa)_2CH^+$ (open symbols) were not used for the determination of the N and s parameters. *N*-Methylmorpholine (**1d**) is not shown because the data points overlap with the line for **1a**

As discussed previously,[46] the higher reactivity of DABCO (**1e**) compared with quinuclidine (**1f**) is due to the fact that both rate constants are close to diffusion control, and attack at the diazacompound **1e** is favored statistically. The monocyclic compounds **1b** and **1c** are one (**1b**) and two orders of magnitude less reactive. Remarkably, the five-membered ring compound **1b** is almost one order of magnitude more reactive than **1c**, while the corresponding secondary amines pyrrolidine and piperidine show very similar reactivities toward $(dma)_2CH^+$ in acetonitrile (Fig. 3) as well as in methanol and water.[42,71,72] The increase of steric hindrance, which may explain the reduction of reactivity from the bicyclic compounds **1e,f** to the monocyclic compounds **1b,c** may also account for the further reduction of nucleophilicity from **1b,c** to triethylamine (**1a**) which is so severe that the rate constant for the reaction of NEt_3 with $(dma)_2CH^+$ had to be calculated by Eqn (1) because this reaction is highly reversible and cannot be directly measured. An analogous effect was found in the series of secondary amines, as shown by the comparison of piperidine, pyrrolidine, and diethylamine on the left side of Fig. 3. Introduction of an oxygen in *N*-methylpiperidine also reduces the nucleophilicity, and *N*-methylmorpholine (**1d**) is calculated to react one order of magnitude more slowly than **1c**; again, the rate constant for the reaction $(dma)_2CH^+ + \mathbf{1d}$ could not be measured

Table 3. Reactivity parameters N of amines **1a–d** in CH_3CN and CH_2Cl_2 (with $s = 0.52$)

Amines	N (CH_3CN)	N (CH_2Cl_2)
1a	17.1[a]	17.3[a]
1b	20.59	20.6[a]
1c	18.72	18.9[a]
1d	16.8[a]	16.5[a]

[a] Estimated using $s = 0.52$.

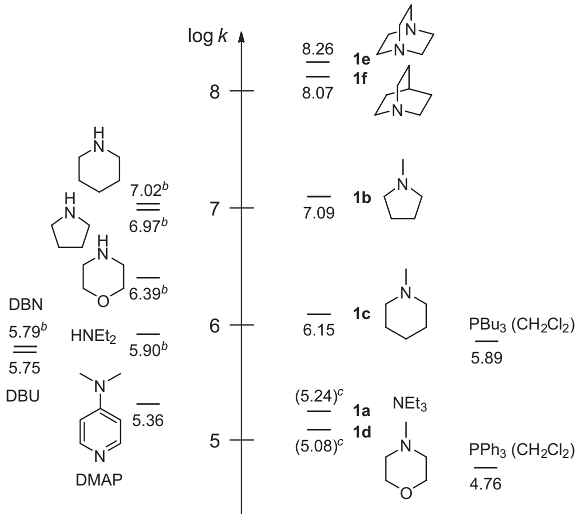


Figure 3. log k for reactions of $(dma)_2CH^+$ ($E = -7.02$) with different N and P nucleophiles in $CH_3CN^{a,b,c}$. [a]Rate constants for **1e,f**,[46] DMAP,[43] DBU,[44] and the phosphines[68] were reported previously; rate constants for **1b,c** from this work.[b]Rate constants of reactions of secondary amines and DBN with $(dma)_2CH^+$ have not been measured and were calculated from Eqn (1) using N and s parameters from References [42,44].[c]**1a** and **1d** do not react with $(dma)_2CH^+$, and rate constants for these reactions were calculated from Eqn (1)

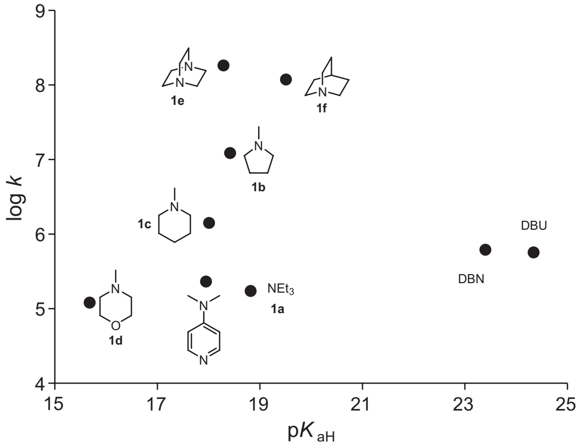


Figure 4. Correlation of log *k* for reactions of $(dma)_2CH^+$ ($E = -7.02$) in CH_3CN with different N-nucleophiles and their pK_{aH} values in CH_3CN[73–76]

directly because the equilibrium does not favor the formation of the quaternary ammonium ion.

We have repeatedly commented that the relative nucleophilicities of amines cannot be determined from the corresponding basicities (pK_{aH}). Figure 4 shows that the newly determined nucleophilic reactivities of **1a–d** support this statement. Triethylamine ($pK_{aH} = 18.82$ in CH_3CN),[73] though being a slightly stronger base than *N*-methylpyrrolidine (**1b**) and *N*-methylpiperidine (**1c**),[74] is the weakest nucleophile of the three. In subsequent work, it will be shown how the *N* and *s* parameters reported in this work can be used to rationalize the efficiency of these compounds in organocatalytic reactions.

SUPPORTING INFORMATION

Detailed kinetic data for reactions of **1a–d** with benzhydrylium ions are available with the online version of the paper.

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