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Nucleophilicities and Carbon Basicities of Pyridines

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Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday

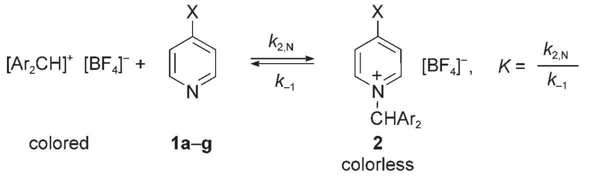
Abstract: Rate and equilibrium constants for the reactions of pyridines with donor-substituted benzhydrylium ions have been determined spectrophotometrically. The correlation equation $\log k(20\,^\circ\mathrm{C}) = s(N+E)$, in which s and N are nucleophile-specific parameters and E is an electrophile-specific parameter, has been used to determine the nucleophilicity parameters of various pyridines in CH_2Cl_2 and aqueous solution and to compare them with N of other nucleophiles. It is found that the nucleophilic organocatalyst 4-(dimethylamino)pyridine (DMAP) and tertiary phosphanes have comparable nucleophilicities and carbon basicities despite widely differing Brønsted basicities. For that reason, these reactivity parameters are suggested as guidelines for the development of novel organocatalysts. The Marcus equation is employed for the determination of the intrinsic barriers of these reactions.

Keywords: carbocations · intrinsic barriers · kinetics · organocatalysis · pyridines

Introduction

Pyridines, in particular 4-(dimethylamino)pyridine (DMAP), are important catalysts for many reactions, primarily acylations.[1] Though the mechanisms of pyridine catalysis have previously been studied,[1,2] and correlations between the catalytic activities of pyridines and their pK_{aH} values[1b] and calculated acyl cation affinities[3] have been discussed, systematic studies on the relationships between the nucleophilic reactivities of pyridines and their Lewis basicities towards carbon centers have not yet been performed.[4,5] Since such data are crucial for understanding the catalytic activities of pyridines in comparison with other organocatalysts, we set out to investigate these relationships employing benzhydrylium ions as reference substrates.

Previously, we have reported that benzhydrylium ions of different electrophilicity can be utilized for comparing the reactivities of nucleophiles of widely varying structure.[6] We will now report on the kinetics of the reactions of various benzhydrylium ions (Table 1) with several pyridines **1** in different solvents (Scheme 1). The data will then be used to determine the nucleophilicity parameters N and s of the pyridines **1a–g** according to Equation (1), which has been used for characterizing a large variety of electrophiles and nucleophiles. In Equation (1), k is the second-order rate constant [$M^{-1}s^{-1}$], s is the nucleophile-specific slope parameter, N is the nucleophilicity parameter, and E is the electrophilicity parameter.



Scheme 1.

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

Several of these reactions do not proceed to completion, which allowed us to determine the equilibrium constants of the reactions in Scheme 1 and to compare the resulting carbon basicities of pyridines (K of Scheme 1) with the corresponding Brønsted basicities (pK_{aH}).

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

Results and Discussion

Reaction products: Products $[\mathbf{2a–c}][BF_4]^-$ of the addition reactions of DMAP (**1f**) with equimolar amounts of $[(dma)_2CH]^+[BF_4]^-$, $[(jul)_2CH]^+[BF_4]^-$, and $[(lil)_2CH]^+[BF_4]^-$, respectively, in CH_2Cl_2 were characterized by ^1H and ^{13}C NMR spectroscopy (Table 2).

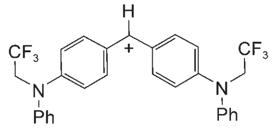
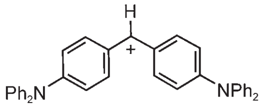
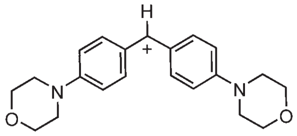
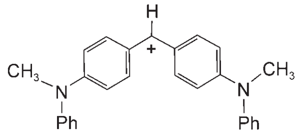
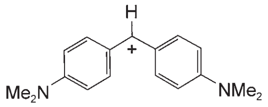
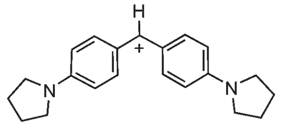
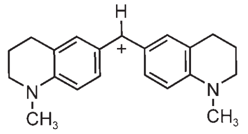
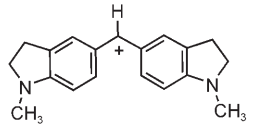
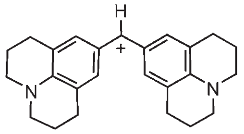
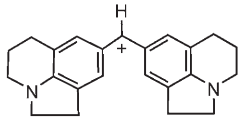
The ^1H and ^{13}C NMR shifts in Table 2 correlate loosely with the electrophilicities of the benzhydrylium ions. Combinations of highly stabilized benzhydrylium ions with pyridine derivatives of low basicity were reversible, which prevented the isolation of the reaction products.

Kinetic investigations: The rates of the reactions of the colored benzhydrylium tetrafluoroborates with pyridines were followed photometrically under pseudo-first-order conditions by using more than ten equivalents of the pyridines. Under such conditions, the concentrations of the pyridines **1a–g** were almost constant throughout the reaction and gave rise to an exponential decay of the benzhydrylium absorbances, from which the first-order rate constants $k_{1\psi}$ were derived. Because the electrolyte concentrations were generally lower than 8.5×10^{-5} M, variations of ion strengths have been neglected. The slopes of the linear plots of $k_{1\psi}$ versus [**1**] gave the second-order rate constants $k_{2,N}$, which are listed in Table 3. Instrumentation and kinetic methods have been described previously.[6] Experimental details are given in the Supporting Information.

At first glance, the choice of benzhydrylium ions, which were selected for characterizing the reactivities of the individual pyridines, looks rather arbitrary. Why have different electrophiles, sometimes only one of them, been employed for the kinetic studies? The problem of these experiments is that all reactions are reversible, and in many cases, we can only find one or two benzhydrylium ions for which the equilibrium is on the product side (*N*-benzhydrylpyridinium ions **2**, Scheme 1) and which at the same time react slowly

Abstract in German: *Geschwindigkeits- und Gleichgewichtskonstanten der Reaktionen von Pyridinen mit Donor-substituierten Benzhydrylium-Ionen wurden spektralphotometrisch bestimmt. Die Korrelationsgleichung* $\log k(20\,^\circ C) = s(N+E)$*, die mit* s *und* N *Nucleophil-spezifische und mit* E *einen Elektrophil-spezifischen Parameter enthält, wurde verwendet, um die Nucleophilie-Parameter von verschiedenen Pyridinen in* CH_2Cl_2 *und in wässrigen Lösungen zu bestimmen und um diese mit* N *anderer Nucleophile zu vergleichen. Es wurde gefunden, dass der nucleophile Organokatalysator 4-(Dimethylamino)pyridin (DMAP) und tertiäre Phosphane vergleichbare Nucleophilien und Kohlenstoffbasizitäten haben, obwohl ihre Brønsted-Basizitäten sehr unterschiedlich sind. Daher wird vorgeschlagen, die Reaktivitätsparameter als Richtgrößen zur Entwicklung neuer Organokatalysatoren heranzuziehen. Die Marcus-Gleichung wird eingesetzt, um die intrinsischen Barrieren dieser Reaktionen zu bestimmen.*

Table 1. Benzhydrylium ions employed in this work.

Electrophile		$E^{[a]}$
$[(pfa)_2CH]^+$		−3.14
$[(dpa)_2CH]^+$		−4.72
$[(mor)_2CH]^+$		−5.53
$[(mpa)_2CH]^+$		−5.89
$[(dma)_2CH]^+$		−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 reference [6].

Table 2. ^1H (and ^{13}C) NMR chemical shifts of pyridinium tetrafluoroborates $\mathbf{2}\text{-}BF_4^-$ (in CD_3CN) obtained from the reactions of DMAP (**1f**) with $[Ar_2CH]^+[BF_4]^-$ (Scheme 1).

Ar_2CH^+	Product	$[4\text{-}(CH_3)_2N\text{-}C_5H_4N\text{-}\mathit{CH}Ar_2]^+$	$[4\text{-}(\mathit{CH_3})_2N\text{-}C_5H_4N\text{-}CHAr_2]^+$
$[(dma)_2CH]^+$	**2a**	6.57[a] (73.8)[a]	3.13[a] (39.9)[a]
$[(jul)_2CH]^+$	**2b**	6.29 (75.0)	3.14[b] (40.6)
$[(lil)_2CH]^+$	**2c**	6.45 (75.6)	3.15 (40.6)

[a] Solvent: $CDCl_3$. [b] Signal is superimposed by signals of the benzhydryl substituents.

Table 3. Second-order rate constants $k_{2,N}$ and equilibrium constants K for the reactions of benzhydrylium tetrafluoroborates with the pyridines **1a**–**g** in different solvents (20 °C).

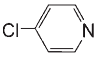
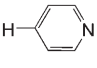
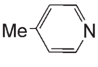
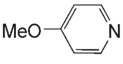
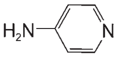
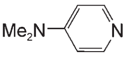
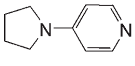
Nucleophile	N/s	$[Ar_2CH]^+$	$k_{2,N}$ [$M^{-1}s^{-1}$]	K [M^{-1}][c]
 **1a**				
1a in CH_2Cl_2	(11.7/0.67)[a]	$[(pfa)_2CH]^+$	5.17×10^5	(4.83×10^3)[b]
1a in H_2O	(10.5/0.73)[a]	$[(mor)_2CH]^+$	4.58×10^3	(3.73×10^3)[b]
 **1b**				
1b in CH_2Cl_2	(12.9/0.67)[a]	$[(dpa)_2CH]^+$	3.02×10^5	2.23×10^4 [c]
1b in H_2O	11.05/0.73	$[(mor)_2CH]^+$	1.08×10^4	
		$[(dma)_2CH]^+$	8.82×10^2	(9.04×10^1)[b]
 **1c**				
1c in CH_2Cl_2	(13.7/0.67)[a]	$[(dpa)_2CH]^+$	8.90×10^5	5.07×10^5 [c]
1c in H_2O	11.10/0.75	$[(mor)_2CH]^+$	1.53×10^4	
		$[(dma)_2CH]^+$	1.16×10^3	
 **1d**				
1d in CH_2Cl_2	(13.7/0.67)[a]	$[(dpa)_2CH]^+$	8.97×10^5	
1d in H_2O	11.44/0.68	$[(mor)_2CH]^+$	1.15×10^4	
		$[(dma)_2CH]^+$	9.50×10^2	
		$[(pyr)_2CH]^+$	3.98×10^2	(1.59×10^2)[b]
 **1e**				
1e in CH_2Cl_2	(15.2/0.67)[a]	$[(dma)_2CH]^+$	2.88×10^5	
1e in H_2O	12.19/0.66	$[(mor)_2CH]^+$	2.58×10^4	
		$[(dma)_2CH]^+$	2.23×10^3	
		$[(pyr)_2CH]^+$	8.04×10^2	
		$[(thq)_2CH]^+$	4.81×10^2	
 **1f**				
1f in CH_2Cl_2	15.80/0.66	$[(mpa)_2CH]^+$	2.72×10^6	
		$[(dma)_2CH]^+$	6.43×10^5	
		$[(thq)_2CH]^+$	1.35×10^5	2.81×10^5 [c]
		$[(ind)_2CH]^+$	4.96×10^4	1.71×10^5 [c]
		$[(jul)_2CH]^+$	9.84×10^3	5.85×10^3 [c]
			(1.01×10^4)[d]	
		$[(lil)_2CH]^+$	6.45×10^3 [e]	5.70×10^3 [c]
1f in MeCN	14.95/0.67	$[(dma)_2CH]^+$	2.31×10^5	
		$[(thq)_2CH]^+$	3.32×10^4	
		$[(ind)_2CH]^+$	1.29×10^4	

Table 3. (Continued)

Nucleophile	N/s	$[Ar_2CH]^+$	$k_{2,N}$ [$M^{-1}s^{-1}$]	K [M^{-1}][c]
		$[(jul)_2CH]^+$	5.30×10^3	
		$[(lil)_2CH]^+$	2.11×10^3	
1f in H_2O	13.19/0.56	$[(mor)_2CH]^+$	2.39×10^4	
		$[(dma)_2CH]^+$	2.66×10^3	
		$[(pyr)_2CH]^+$	9.88×10^2	
		$[(thq)_2CH]^+$	5.81×10^2	
		$[(ind)_2CH]^+$	2.41×10^2	
		$[(jul)_2CH]^+$	1.31×10^2	
		$[(lil)_2CH]^+$	7.42×10^1	
1f in MeOH[f]	(13.2/0.67)[a]	$[(dma)_2CH]^+$	1.46×10^4	
1f in DMSO	(14.8/0.67)[a]	$[(dma)_2CH]^+$	1.53×10^5	
1f in DMF	(14.9/0.67)[a]	$[(dma)_2CH]^+$	2.04×10^5	
 **1g**				
1g in CH_2Cl_2	(15.9/0.67)[a]	$[(dma)_2CH]^+$	8.76×10^5	
1g in H_2O	12.39/0.66	$[(mor)_2CH]^+$	3.49×10^4	
		$[(dma)_2CH]^+$	3.60×10^3	
		$[(pyr)_2CH]^+$	1.16×10^3	
		$[(thq)_2CH]^+$	6.17×10^2	

[a] Estimated slope parameter s, see text. [b] Determined by $K = k_{2,N}/k_{-1}$. [c] Equilibrium constants K were derived from the photometrically determined absorbances of the benzhydrylium ions and the initial concentrations of the reactants as described in the Supporting Information. [d] Counterion: PF_6^-. [e] Eyring activation parameters: $\Delta H^{\ddagger} = 37.1\ kJ\,mol^{-1}$, $\Delta S^{\ddagger} = -45.3\ J\,mol^{-1}\,K^{-1}$. [f] Cosolvent: 9 vol-% MeCN.

enough ($k_{2,N} < 10^6\,M^{-1}s^{-1}$) so that we can follow the kinetics with the stopped-flow technique. The unsubstituted pyridine **1b**, for example, has only been studied with $[(dpa)_2CH]^+$ in CH_2Cl_2. Benzhydrylium ions, which are more electrophilic than $[(dpa)_2CH]^+$, react so fast in CH_2Cl_2 that we cannot follow the kinetics, and benzhydrylium ions, which are less electrophilic than $[(dpa)_2CH]^+$, give such a low degree of conversion that we were not able to determine the combination rates. It will be discussed below that it is due to the higher intrinsic barriers of the reactions with DMAP (**1f**) that a series of rate constants could be measured with this pyridine derivative.

When CH_2Cl_2, CH_3CN, DMF, or DMSO were used as solvents, the reversibility of the reactions was the only complication in the evaluation of the kinetics. When the benzhydrylium ions were not consumed completely, plots of $k_{1\Psi}$ versus [**1**] gave straight lines with intercepts that corresponded to the rate constants k_{-1} of the reverse reactions [Eq. (2)].[7] Details of the evaluation are discussed below.

$$k_{obs} = k_{1\Psi} = k_{1\Psi,N} + k_{-1} = k_{2,N}[\mathbf{1}] + k_{-1} \tag{2}$$

When the benzhydrylium ions were combined with pyridines in water, competing reactions of the carbocations with hydroxide and water have to be considered. The observed pseudo-first-order rate constants k_{obs} reflect the sum of the reactions of the electrophile with the pyridine **1** ($k_{1\Psi,N}$), OH^- ($k_{1\Psi,OH}$), water (k_W), and the reverse reaction (k_{-1}), as described in Equation (3).

$$\begin{aligned} k_{obs} &= k_{1\Psi,N} + k_{1\Psi,OH} + k_W + k_{-1} \\ &= k_{2,N}[\mathbf{1}] + k_{2,OH}[OH^-] + k_W + k_{-1} \end{aligned} \tag{3}$$

Rearrangement of Equation (3) yields Equation (4), which defines $k_{1\Psi}$ as the overall rate constant minus the contribution by hydroxide.

$$k_{1\Psi} = k_{obs} - k_{2,OH}[OH^-] = k_{2,N}[\mathbf{1}] + k_W + k_{-1} \tag{4}$$

The concentrations of the pyridines [**1**] and of hydroxide [OH^-] are calculated from pK_{aH} as described in the Supporting Information. With the already published second-order rate constants $k_{2,OH}$[8c] and the calculated concentrations of hydroxide [OH^-], the partial pseudo-first-order rate constants $k_{1\Psi,OH}$ ($= k_{2,OH}[OH^-]$) can be calculated. The slopes of the plots of $k_{1\Psi}$ ($= k_{obs} - k_{1\Psi,OH}$) versus [**1**] correspond to the second-order rate constants $k_{2,N}$, as shown in Figure 1. The intercepts, which correspond to the sum of the reverse reac-

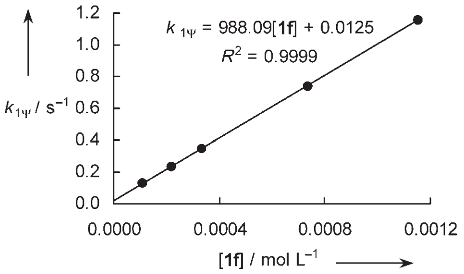


Figure 1. Determination of the second-order rate constant $k_{2,N} = 988\,M^{-1}s^{-1}$ for the reaction of $[(pyr)_2CH]^+$ with DMAP (**1f**) in water at 20 °C.

tions and the reactions of the benzhydrylium ions with water [Eq. (4)], are generally negligible when the equilibrium is far on the product side. This finding is in agreement with the previously reported rate constants for the reactions of benzhydrylium ions with water (k_W).[8c]

In the case of incomplete consumption of the benzhydrylium ions (Figure 2), the slope of the plot of $k_{1\Psi}$ versus [**1**] corresponds to the second-order rate constant for the forward reaction $k_{2,N}$,[7] while the intercept corresponds to the first-order rate constant for the backward reaction k_{-1} [Eq. (2), if CH_2Cl_2 is used as the solvent] or the sum $k_W + k_{-1}$ [Eq. (4), if water is the solvent].

As shown in Figure 3, the plot of $k_{1\Psi}$ versus [**1b**] is linear.

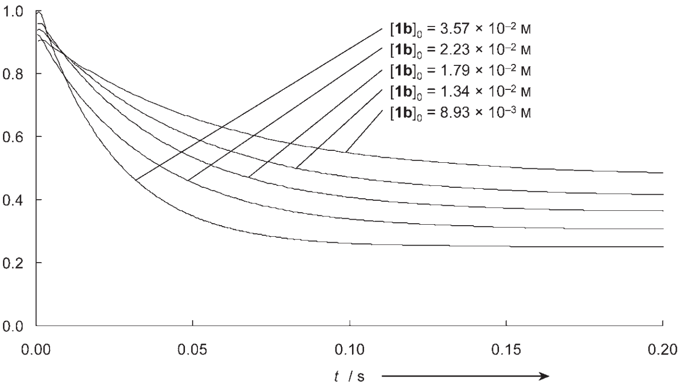


Figure 2. Plot of the absorbance at 607 nm versus t for the reactions of pyridine (**1b**) with $[(dma)_2CH]^+$ ($c_0 = 7.62\times10^{-5}\,M$) at different initial concentrations of pyridine in water (20 °C).

As we observed linear plots also for all other reaction series, we exclude the association of the pyridines in the concentration ranges investigated. Such association has been observed at higher pyridine concentrations from convex k_{obs} versus [pyridine] plots in reactions of pyridines with phosphate derivatives.[9]

Nucleophilic reactivities of pyridines: When $\log k_{2,N}$ for the reactions of the pyridines **1a–g** with benzhydrylium ions are plotted against their electrophilicity parameters E, linear correlations are obtained (Figure 4) indicating that these reactions follow Equation (1). The slopes of these correlations

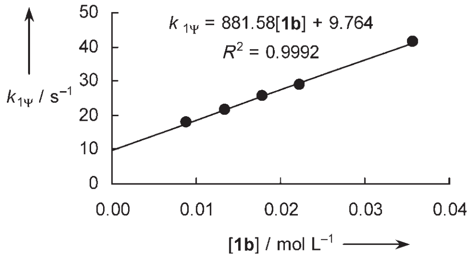


Figure 3. Determination of the forward ($k_{2,N} = 882\,M^{-1}s^{-1}$) and reverse rate constant ($k_{-1} = 9.76\,s^{-1}$) for the reaction of $[(dma)_2CH]^+$ with pyridine (**1b**) in water at 20 °C ($k_W = 2.06\times10^{-2}\,s^{-1}$ from reference [8c] can be neglected).

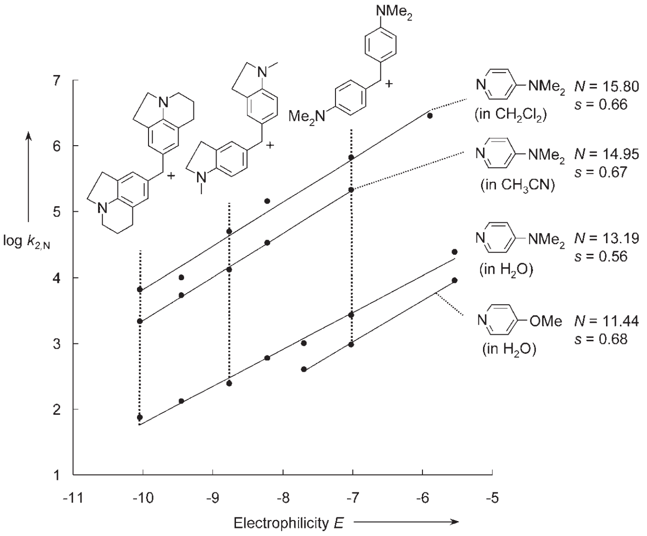


Figure 4. Plots of the rate constants $\log k_{2,N}$ for the reactions of pyridines with benzhydrylium cations (from Table 3) versus the electrophilicity parameters E of $[Ar_2CH]^+$ (from Table 1).

yield the parameters s, and the intercepts on the abscissa correspond to the negative values of the nucleophilicity parameters N.

In all cases in which rate constants with more than one electrophile have been determined, slope parameters of $s = 0.67\pm0.08$ were obtained [exception s(**1f** in H_2O) = 0.56]. Because there is no systematic dependence of s on the reactivity of the pyridine, the average value of $s = 0.67$ was adopted for calculating the nucleophilicity parameters N of such pyridines, which have only been studied with one electrophile in CH_2Cl_2, DMF, DMSO, or methanol (Table 3). For 4-chloropyridine (**1a**) in water, the same s value was assumed as for the unsubstituted pyridine **1b** in water. Figure 4, which depicts correlations with slopes from $s = 0.56$ to 0.67, illustrates that because of the small differences in s the relative nucleophilic reactivities of pyridines are almost independent of the nature of the benzhydrylium ions. Therefore, the following structure–reactivity discussions can be based on the nucleophilicity parameters N.

Figure 5 shows that pyridines are two to three orders of magnitude more nucleophilic in CH_2Cl_2 than in water. The

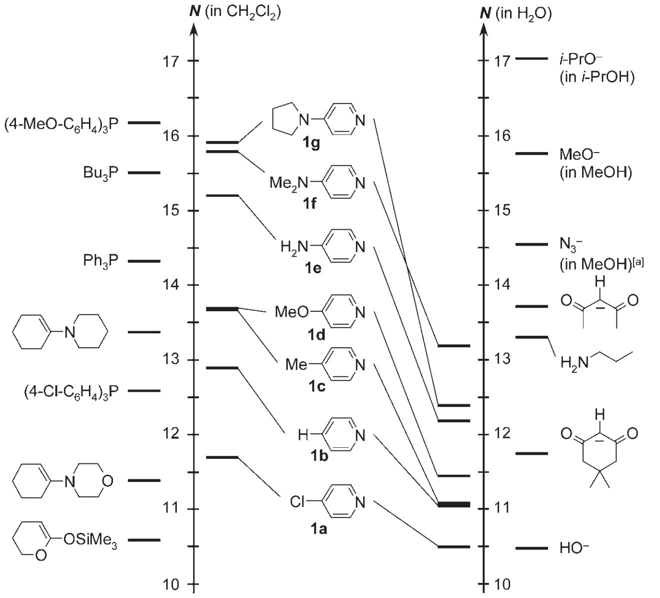


Figure 5. Comparison of the nucleophilic reactivities of pyridines with other types of nucleophiles (N parameters from reference [8]) in CH_2Cl_2 and water. Other solvents are given in parenthesis. [a] Cosolvent: 9 vol% acetonitrile.

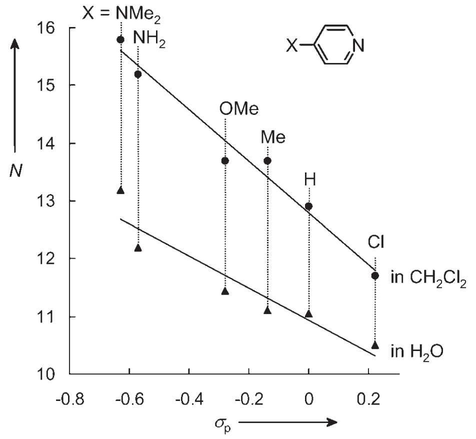


Figure 6. Correlation of N with σ_p (from reference [11]) for 4-X-substituted pyridines in CH_2Cl_2 ($N = -4.49\sigma_p + 12.8$, $R^2 = 0.9752$) and water ($N = -2.76\sigma_p + 10.9$, $R^2 = 0.8860$).

larger spread of N in CH_2Cl_2 than in water can be explained by hydrogen bonding in water, which increases with increasing basicity of the pyridines. Though 4-pyrrolidinopyridine (**1g**) is slightly more reactive than DMAP (**1f**) toward $[(dma)_2CH]^+$ in CH_2Cl_2 and toward a series of benzhydrylium ions in water, the reactivity ratio $k(\mathbf{1g})/k(\mathbf{1f})$ decreases slightly with decreasing electrophilicity of the benzhydrylium ions in water. The resulting higher slope for **1g** in H_2O is responsible for the fact that in water $N(\mathbf{1f}) > N(\mathbf{1g})$. It is particularly noteworthy that 4-methyl- (**1c**) and 4-methoxypyridine (**1d**) are three times more reactive than the parent compound (**1b**) toward $[(dpa)_2CH]^+$ in CH_2Cl_2, whereas the reactivities of **1b**, **1c**, and **1d** differ by less than a factor of 1.4 toward $[(dma)_2CH]^+$ and $[(mor)_2CH]^+$ in water, which is also revealed by the closely similar N values of these compounds in H_2O. Comparison with other classes of nucleophiles in Figure 5 shows that the reactivity of pyridines in dichloromethane is comparable to that of phosphanes, an observation that is relevant for organocatalysis.[10] In aqueous solution, pyridines are more nucleophilic than hydroxide. This fact, in combination with the higher acidity of pyridinium ions compared to water, explains why in aqueous solutions of pyridines, generally pyridines and not hydroxide are the active nucleophiles.

Figure 6 shows a moderate correlation of N with Hammett's σ_p constants.[11] The large scatter around the correlation lines can be explained by the fact that the nucleophilic site of the pyridines is the lone-pair at nitrogen, which is perpendicular to the π system. For that reason, the substituent constant that describes a combination of mesomeric and inductive effects fails to give a good correlation with N. The smaller slope of the correlation line in water, which reflects the smaller reactivity range in water (Figure 5), can again be explained by the fact that the more basic, donor-substituted pyridines experience a higher stabilization by hydrogen bonding in water.

While the correlation between pyridine nucleophilicities N in water and $pK_{aH}(H_2O)$[12] is only of moderate quality ($R^2 = 0.901$, Figure 7, top), a fairly good correlation is observed between the N parameters for pyridines in CH_2Cl_2 and their pK_{aH} constants in acetonitrile[13] ($R^2 = 0.987$, Figure 7, bottom), which can be assumed to mimic the situation in CH_2Cl_2 better than the pK_{aH} constants determined in water.

In previous work, we found that the rates of the reactions of carbocations with uncharged nucleophiles are only slightly affected by solvent polarity, since charges are neither cre-

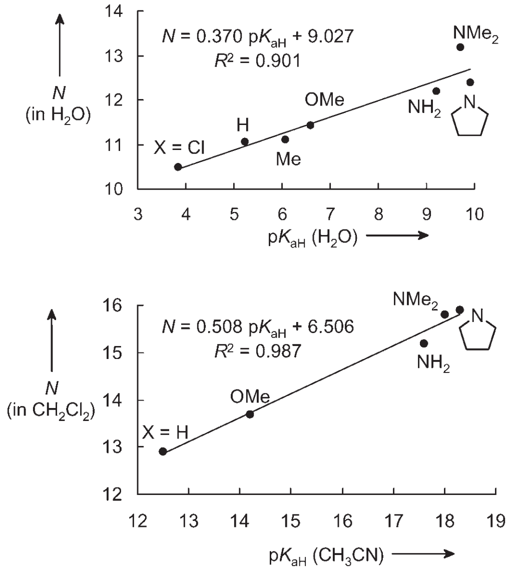


Figure 7. Top: Correlation of N (in H_2O) with pK_{aH} (in H_2O, from reference [12]) for the 4-X-substituted pyridines **1a–g**. Bottom: Correlation of N (in CH_2Cl_2) with pK_{aH} (in CH_3CN, from reference [13]) for the 4-X-substituted pyridines **1a–g**.

ated nor destroyed in reactions of benzhydrylium ions with neutral nucleophiles.[14] Figure 8 illustrates a different situation for the reactions with pyridines. While the correlation between the rate constants for the reactions of $[(dma)_2CH]^+$ with DMAP (**1f**) and Gutmann's donor numbers $DN^{[15,16]}$ is rather poor (not depicted), Figure 8 shows that the rate constants decrease slightly with increasing E_T^N values[15,17] of the solvents; the reaction of DMAP (**1f**) with $[(dma)_2CH]^+$ is 240 times slower in water than in dichloromethane.

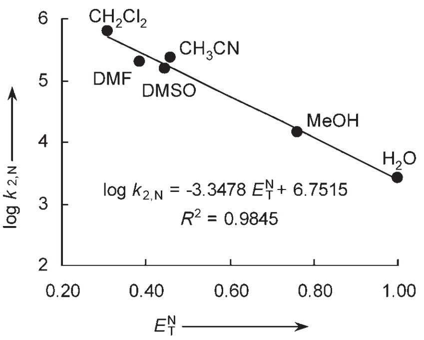
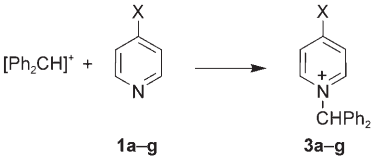


Figure 8. Plot of the rate constants $\log k_{2,N}$ versus E_T^N for the reactions of DMAP (**1f**) with $[(dma)_2CH]^+$ in different solvents at 20°C (rate constants from Table 3, E_T^N from reference [15]; MeOH contained 9 vol% MeCN as a cosolvent).

Energies for the reactions of the parent benzhydrylium ion with the pyridines **1a–g** in the gas phase (Scheme 2) have been obtained by ab initio MO calculations at the MP2(fc)/6–31G(d) level of theory (Table 4).[18] As expected from the results shown in Figure 7, the reaction energies become more negative as the basicity of the pyridines increases. The range of the reaction energies amounts to 80 ± 1 kJ mol^{-1} when using E_{tot}, E_0, or H_{298} molecular energies. Essentially the same results are obtained when using MP2(fc)/6–311++G(d,p)//MP2(fc)/6–31G(d) energies (see Supporting Information for details). The inclusion of entropy narrows the range to 73 kJ mol^{-1} in G_{298}.



Scheme 2.

Table 4. Reaction energies for the additions of the parent benzhydrylium cation $[Ph_2CH]^+$ to the 4-X-substituted pyridines **1a–g**, charge parameters and structural characteristics of the corresponding adducts **3a–g** as calculated at the MP2(fc)/6–31G(d) level of theory.

	ΔE_{tot} [kJ mol^{-1}]	ΔE_0 [kJ mol^{-1}]	ΔH_{298} [kJ mol^{-1}]	ΔG_{298} [kJ mol^{-1}]	q(Py)[a]/e	r(C–N) [pm]
1a	−182.2	−172.2	−172.8	−123.2	0.645	152.5
1b	−198.7	−187.8	−188.8	−139.2	0.648	152.6
1c	−210.5	−200.1	−200.8	−149.9	0.654	152.2
1d	−219.4	−209.1	−209.2	−158.2	0.661	151.7
1e	−236.4	−227.3	−227.3	−177.8	0.671	151.2
1f	−253.7	−244.0	−243.7	−195.1	0.679	150.8
1g	−263.2	−251.7	−252.6	−196.9	0.682	150.6

[a] Overall charges in the pyridine fragments of the adducts **3** as calculated at the MP2(fc)/6–31G(d) level of theory using the NPA scheme.

As shown in Figure 9 a good linear correlation (R^2 = 0.982) is found between the nucleophilicity parameter N determined in CH_2Cl_2 and the reaction free energies ΔG_{298}. The small negative slope of −0.0555 of this correlation indicates that only a small amount of the reaction energy differences enters into the lowering of the reaction barrier. Because multiplication of ΔN (ordinate of Figure 9) with s = 0.67 yields relative rate constants ($\Delta \log k_{2,N}$) and division of ΔG_{298} by 5.71 (= 2.303RT) yields $\Delta \log K$, one can calculate a slope of 0.21 for the $\log k_{2,N}$ versus $\log K$ correlation corresponding to the plot of Figure 9.

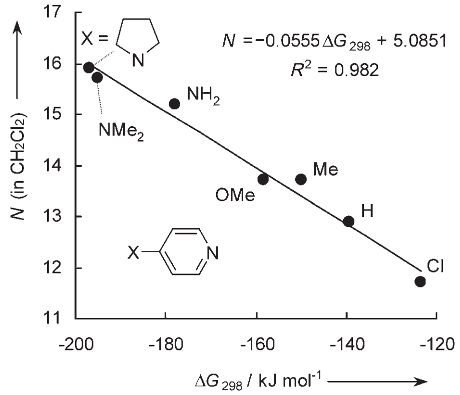


Figure 9. Plot of nucleophilicity parameters N of pyridines in CH_2Cl_2 versus ΔG_{298} (for the reaction defined in Scheme 2) at the MP2(fc)/6–31G(d)//MP2(fc)/6–31G(d) level.

As exemplified for the reaction of DMAP (**1f**) with the benzhydrylium ion $[Ph_2CH]^+$ in Figure 10, the reaction is accompanied by substantial changes in structural and electronic characteristics of the reactants. Formation of the new C–N bond transforms the formerly fully planar cationic center of the benzhydrylium ion (with d_{def} = 0.0°) into an adduct of almost ideal tetrahedral structure (with d_{def} = 58.2°).[19] Despite these structural changes, only 68% of the positive charge are transferred from the benzhydrylium cation to the pyridine moiety in the course of the reaction, leaving the former with a charge of +0.32 in the adduct **3f**. Despite the fact that the calculated degree of charge transfer depends somewhat on the particular quantum mechanical level and charge derivation scheme,[20] it remains without doubt that the Lewis structure shown in Scheme 2 does not fully reflect the charge distribution in the reaction products **3**. The overall positive charge of the pyridine moiety also depends on the substituent present in 4-position, but as shown in Table 4 the range covered from the least to the most reactive pyridine is rather small (+0.645 to +0.682). The most pro-

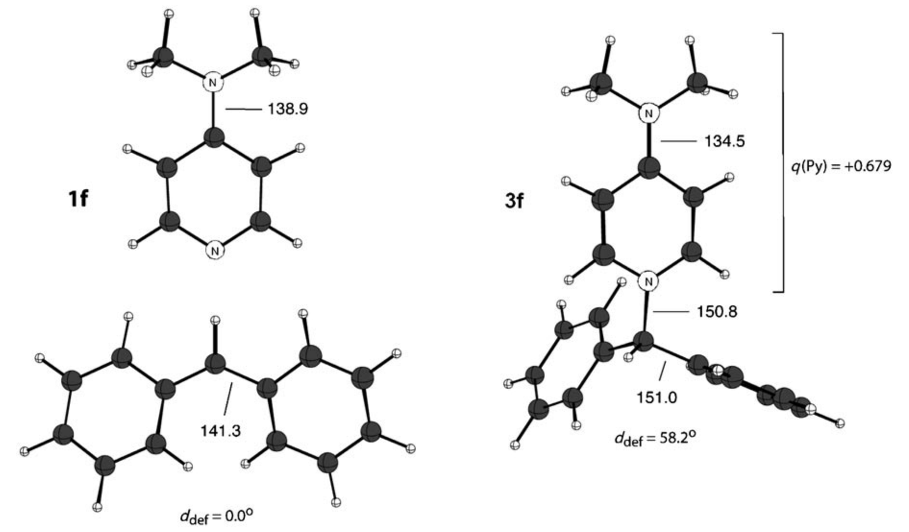


Figure 10. Structures of DMAP (**1f**), benzhydrylium cation $[Ph_2CH]^+$, and the corresponding adduct **3f** according to Scheme 2 as calculated at the MP2(fc)/6–31G(d) level of theory (distances are given in pm).

nounced stabilization is achieved through dialkylamino substituents, the electron donation of which to the pyridine ring is accompanied by substantial shortening of the C–NMe_2 bond from 138.9 pm in DMAP (**1f**) to 134.5 pm in the adduct **3f**.

Reactions of pyridines with other electrophiles: Numerous kinetic studies on the nucleophilicities of pyridines have been published,[4,5,21] supplemented by a recent theoretical work by Campodónico, Aizman, and Contreras.[22] However, only in few cases the overlap with the systems studied in this work was sufficient to perform meaningful correlations, which will be discussed later.

The potential of Equation (1) to predict absolute rate constants is convincingly demonstrated in Table 5. When the nucleophilicity parameters N and s for pyridine (**1b**) determined in this work (Table 3) are combined with previously published electrophilicity parameters for tricarbonyl–iron–dienylium complexes, Equation (1) yields rate constants which closely resemble those measured by Kane-Maguire and co-workers.[5]

Table 5. Comparison of calculated and observed second-order rate constants (20°C) for the reactions of tricarbonyl iron dienylium ions $[Fe(CO)_3R]^+$ with pyridine (**1b**).

$[Fe(CO)_3R]^+$	E[a]	k_{calc} [$M^{-1}s^{-1}$]	k_{exp} [$M^{-1}s^{-1}$]
$[Fe(CO)_3(C_6H_7)]^+$	−7.76	2.78×10^3 [b]	7.25×10^3 [c]
$[Fe(CO)_3(2\text{-}MeOC_6H_6)]^+$	−8.94	4.49×10^2 [b]	1.31×10^3 [c]
$[Fe(CO)_3(C_7H_9)]^+$	−9.21	2.97×10^2 [b]	3.24×10^2 [c]

[a] From reference [8a]. [b] Calculated by Equation (1), using the E parameters of this Table and N and s for **1b** in CH_2Cl_2 from Table 3. [c] Rate constants in acetonitrile calculated for 20°C from the Eyring activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ given in reference [5b].

Johnson and co-workers determined the rates of the ethylation reactions of various 3- and 4-substituted pyridine derivatives with iodoethane in different solvents.[4h] In numerous solvents (CH_3OH, CH_2Cl_2, CH_3CN, nitrobenzene) donor-substituted pyridines reacted considerably faster than acceptor-substituted derivatives, and approximately one third of the differences in $pK_{aH}(H_2O)$ were found in the rate constants of the nucleophilic substitutions ($\log k_2$). Figure 11 shows that the rate constants for the reactions of pyridines with iodoethane in CH_2Cl_2 [($\log k_2$)/s] correlate linearly with the nucleophilicity parameters N, but as previously reported for other S_N2 type reactions, the slope is smaller than 1, and the previously proposed Equation (5)[23] can be used to calculate $s_E = 0.73$ and an electrophilicity parameter $E = -22.3$ for iodoethane in CH_2Cl_2. In Equation (5), k, N, and E are the parameters already defined in Equation (1) s_N is the nucleophile-specific slope [$=s$ of Eq. (1)], and s_E is the electrophile-specific slope.

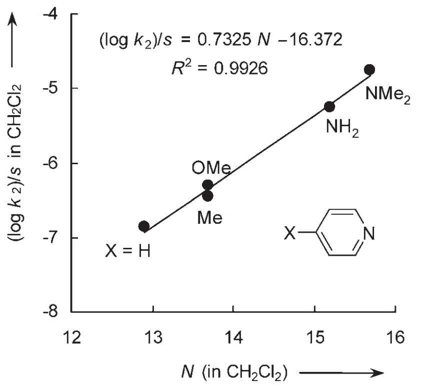
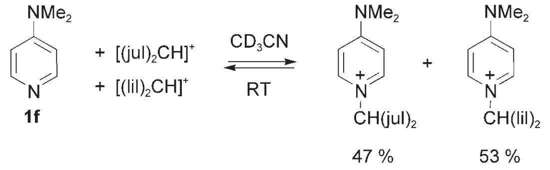


Figure 11. Correlation of $\log k_2/s$ for the reactions of iodoethane with the 4-X-pyridines **1a–f** at 25°C versus their N parameters in CH_2Cl_2 (k_2 from reference [4h]).

$$\log k = s_N s_E (E + N) \tag{5}$$

Equilibrium constants and intrinsic barriers: Because of the reversibility of these reactions, for some of them rate and equilibrium constants are available as listed in Table 3. It is remarkable that the equilibrium constant for the reaction of DMAP (**1f**) with $[(lil)_2CH]^+$ in CH_2Cl_2 was found to be slightly larger than that for the corresponding reaction with $[(jul)_2CH]^+$, though in dozens of reactions $[(jul)_2CH]^+$ has generally been found to react approximately four times faster than $[(lil)_2CH]^+$. Though a breakdown of rate-equilibrium relationships had already been observed for the reactions of these two carbocations with phosphanes[8e] and the azide ion,[8h] we wanted to exclude an error in the relative Lewis acidities of these two carbocations indicated by the equilibrium constants K of Table 3. We therefore mixed equimolar amounts of $[(\mathrm{lil})_2\mathrm{CH}]^+$, $[(\mathrm{jul})_2\mathrm{CH}]^+$, and DMAP (**1f**) in CD_3CN in an NMR tube. Comparison of the integrals over the methine signals indicated a 53:47 ratio of the two adducts (Scheme 3) in agreement with the relative reaction free energies $\Delta_rG°$ derived from K (Table 3) and listed in Table 6.



Scheme 3. Products of the reaction of equimolar amounts of **1f**, $[(\mathrm{jul})_2\mathrm{CH}]^+[\mathrm{BF}_4]^-$, and $[(\mathrm{lil})_2\mathrm{CH}]^+[\mathrm{BF}_4]^-$ (product ratio determined by ^{1}H NMR spectroscopy).

Table 6. Activation free energies $\Delta G^{\neq}$, reaction free energies $\Delta_rG°$, and intrinsic barriers $\Delta G_0^{\neq}$ for the reactions of benzhydrylium tetrafluoroborates with pyridines **1** (in CH_2Cl_2, 20 °C, energies in kJ mol^{-1}).

Pyridine	Ar_2CH^+	$\Delta G^{\neq}$	$\Delta_rG°$	$\Delta G_0^{\neq}$
pyridine (**1b**)	$[(\mathrm{dpa})_2\mathrm{CH}]^+$	41.0	−24.4	52.5
4-methylpyridine (**1c**)	$[(\mathrm{dpa})_2\mathrm{CH}]^+$	38.4	−32.0	53.2
DMAP (**1f**)	$[(\mathrm{lil})_2\mathrm{CH}]^+$	50.3	−21.1	60.4
	$[(\mathrm{jul})_2\mathrm{CH}]^+$	49.3	−21.1	59.9
	$[(\mathrm{ind})_2\mathrm{CH}]^+$	45.4	−29.4	59.2
	$[(\mathrm{thq})_2\mathrm{CH}]^+$	42.8	−30.6	57.1

As a consequence, a rather poor correlation was found between the rate and equilibrium constants of the reactions of DMAP (**1f**) with benzhydrylium ions. These deviations are reminiscent of previously reported reactions of triphenylphosphane[8e] and the azide ion[8h] with benzhydrylium ions, for which the $[(\mathrm{jul})_2\mathrm{CH}]^+$ and $[(\mathrm{thq})_2\mathrm{CH}]^+$ ions, with annelated six-membered rings, also react faster than expected from the correlation of $\log k_{2,\mathrm{N}}$ versus $\log K$ (Figure 12).

Deviations from rate equilibrium relationships reveal variable intrinsic barriers $\Delta G_0^{\neq}$, which can be calculated by substituting $\Delta_rG°$ and $\Delta G^{\neq}$ from the equilibrium and rate constants given in Table 3 into the Marcus equation [Eq. (6)], in which the work term has been omitted.

$$\Delta G^{\neq} = \Delta G_0^{\neq} + 0.5\Delta_rG° + [(\Delta_rG°)^2/16\Delta G_0^{\neq}] \qquad (6)$$

The last four entries of Table 6 show the origin of the deviations from the correlation line in Figure 12. For unknown reasons the reactions of $[(\mathrm{jul})_2\mathrm{CH}]^+$ and $[(\mathrm{thq})_2\mathrm{CH}]^+$ with nucleophiles proceed with less reorganization energy λ ($=4\Delta G_0^{\neq}$) than the reactions of the corresponding benzhydrylium ions with annelated five-membered rings, that is $[(\mathrm{lil})_2\mathrm{CH}]^+$ and $[(\mathrm{ind})_2\mathrm{CH}]^+$.

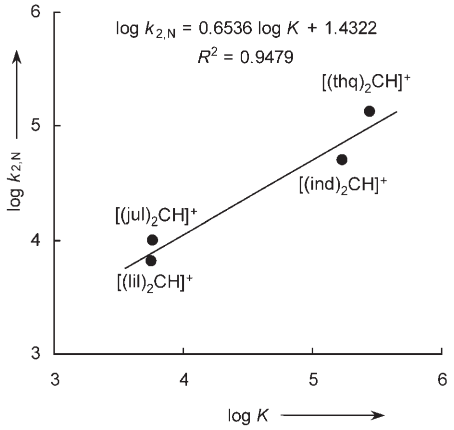
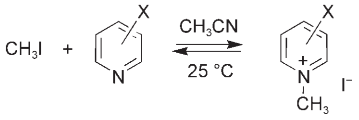


Figure 12. Plot of $\log k_{2,\mathrm{N}}$ versus $\log K$ for the reactions of DMAP (**1f**) with $[Ar_2CH]^+$ in CH_2Cl_2 at 20 °C.

Though the intrinsic barriers are thus not independent of the nature of the carbocation, Table 6 shows that the dependence of $\Delta G_0^{\neq}$ on the nature of the benzhydrylium ion is not very strong. For that reason it is concluded that the significantly lower intrinsic barriers observed for the reactions of **1b** and **1c** with $[(\mathrm{dpa})_2\mathrm{CH}]^+$ are predominantly due to variation of the pyridine.

Arnett and Reich had previously reported rate and equilibrium constants for the reactions of differently substituted pyridines with iodomethane.[4g] It is evident that the S_N2 reactions of pyridines (Scheme 4) that have comparable reaction free energies $\Delta_rG°$ (Table 7) as the reactions of pyridines with carbocations (Table 6) have considerably higher activation free energies $\Delta G^{\neq}$. The differences are caused by the higher intrinsic barriers of the reactions with iodomethane, in which the breaking of the C−I bond requires additional reorganization energy. Like in the reactions of pyridines with carbocations, also in S_N2 reactions of pyridines, the intrinsic barriers $\Delta G_0^{\neq}$ decrease with decreasing basicities of the pyridines (Table 7).



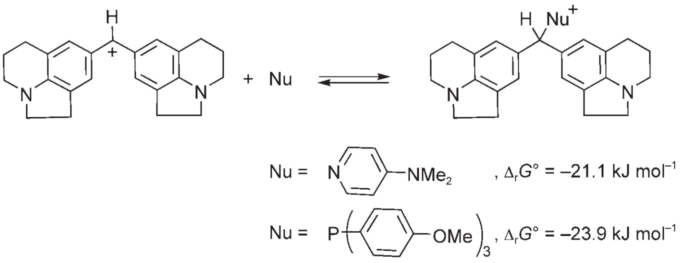
Scheme 4.

Table 7. Activation free energies $\Delta G^{\neq}$, reaction free energies $\Delta_rG°$, and intrinsic barriers $\Delta G_0^{\neq}$ for the reactions of iodomethane with pyridines (acetonitrile, 25 °C, energies in kJ mol^{-1}, data from reference [4g]).

Pyridine	$\Delta G^{\neq}$	$\Delta_rG°$	$\Delta G_0^{\neq}$
pyridine	92.6	−49.9	117.6
3-bromopyridine	97.8	−26.1	110.8
3-chloropyridine	98.0	−24.7	110.3
4-cyanopyridine	100.5	−21.3	111.2
3,5-dichloropyridine	103.3	−11.4	108.9
2-chloropyridine	103.7	−11.4	109.4

Conclusion

Organocatalytic activities of amines have often been correlated with their pK_{aH} values.[24] While such correlations hold within a narrow class of compounds, they cannot be used for the comparison of different classes of compounds. With pK_{aH} values of 7.61 (Ph_3P) and 9.96 ($MePh_2P$) tertiary phosphanes are considerably weaker Brønsted bases in acetonitrile than pyridine **1b** ($pK_{aH}=12.53$) and DMAP (**1f**; $pK_{aH}=17.95$).[13] These pK_{aH} values do not rationalize the observation that DMAP (**1f**) and phosphanes, but not the unsubstituted pyridine **1b**, are efficient catalysts for Baylis–Hillman and related reactions.[25] Our finding that the well-known organocatalyst DMAP (**1f**) and triarylphosphanes or trialkylphosphanes have comparable nucleophilicity parameters *N*, and even more important, comparable carbon basicities[26] (Scheme 5) suggests to employ these quantities for the systematic analysis of nucleophilic organocatalysts.



Scheme 5. Comparison of the carbon basicities of DMAP (**1f**, this work) and tris(4-methoxyphenyl)phosphane (from reference [8e]) in dichloromethane at 20 °C.

Acknowledgements

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