Quantification of the Nucleophilic Reactivity of Nicotine

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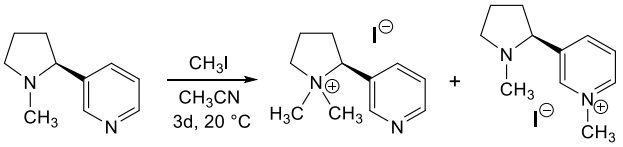
Abstract

Rate and equilibrium constants of the reactions of nicotine and structurally related compounds with benzhydrylium ions have been determined photometrically using conventional UV-Vis spectroscopy, stopped-flow, and laser-flash techniques. The pyridine nitrogen of nicotine was identified as the site of thermodynamically and kinetically controlled attack. Quantum chemical calculations showed that the introduction of a 3-pyridyl moiety into the 2-position of *N*-methylpyrrolidine (to give nicotine) reduces the Lewis basicity of the pyrrolidine ring by 24 kJ mol^{-1}, whereas the analogous introduction of a phenyl ring only decreases this quantity by only 11 kJ mol^{-1}.

Introduction

Nicotine (**1a**) is one of the most widespread drugs in our culture, and there have been countless investigations of its reactivity and physiological activity.[1] When Kekulé reported about the first alkylations of nicotine in 1853,[2] he assumed an empirical formula of $C_{10}H_7N$ or $C_{20}H_{14}N_2$ for nicotine, both incorrect, as later shown by Pinner.[3] Detailed studies on the alkylation of nicotine and related compounds were carried out in the Philip Morris Research Center.[4] Though the pyrrolidine nitrogen of nicotine (pK_{aH} in water = 7.84) is almost four orders of magnitude more basic than its pyridine nitrogen (pK_{aH} in water = 3.04),[4a] the reaction with methyl iodide gave a mixture of products arising from attack at both nucleophilic positions (Scheme 1). The fact that alkylation of **1a** at the pyridine nitrogen is competitive with alkylation of the pyrrolidine nitrogen could be a consequence of either of the following effects, as delineated by Seeman: (i) a rate decrease in pyrrolidine alkylation caused by the pyridine ring or (ii) a pyridine nitrogen alkylation rate enhancement due to the presence of the pyrrolidine ring.[4a]



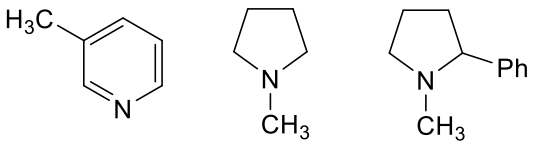
Scheme 1. Product ratio in the methylation of nicotine (**1a**) by iodomethane in MeCN solvent.[4a]

We now report on the investigation of the nucleophilic reactivity of nicotine by the benzhydrylium methodology.[5] In numerous articles we have shown that eq. (1) allows one to calculate the second-order rate constants of the reactions of electrophiles with nucleophiles at 20 °C using a solvent-independent electrophilicity parameter E and two solvent-dependent nucleophile-specific parameters N and s_N.

$$\lg k\ (20°C) = s_N(E + N) \qquad (1)$$

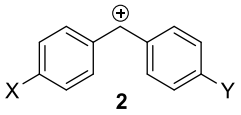
By employing *p*- and *m*-substituted benzhydrylium ions of widely differing electrophilicity as reference electrophiles, we succeeded in generating the most comprehensive nucleophilicity scale presently available.[6] In previous work, we have characterized the nucleophilic reactivities of differently substituted pyridines[7] as well as of acyclic and cyclic tertiary amines.[8] As pyridines react over considerably higher intrinsic barriers than alkylamines, they were found to react considerably slower than alkylamines of comparable pK_{aH} values.[9] For that reason, it is even more surprising that the pyrrolidine nitrogen reacts *only 2.5 times faster* with iodomethane than the pyridine nitrogen of nicotine (**1a)** (Scheme 1) despite the 7 orders of magnitude higher basicity of pyrrolidine (pK_{aH} in acetonitrile = 19.56) compared with pyridine (pK_{aH} in acetonitrile = 12.53).[10]

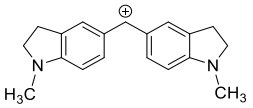
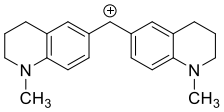
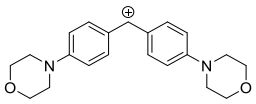
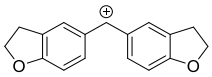
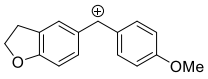
In order to elucidate the origin of this behavior we first studied the kinetics of the reactions of nicotine (**1a**) and the model compounds **1(b-d)** with the benzhydrylium ions **2(a-o)** (Table 1), which have been used as reference electrophiles in many earlier studies, before determining the corresponding equilibrium constants.



Scheme 2. Structural analogues of nicotine.

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



#	Ar_2CH^+	X	Y	*E* [a]
2a	$(ind)_2CH^+$			−8.76
2b	$(thq)_2CH^+$			−8.22
2c	$(pyr)_2CH^+$	$N(CH_2)_4$	$N(CH_2)_4$	−7.69
2d	$(dma)_2CH^+$	$N(CH_3)_2$	$N(CH_3)_2$	−7.02
2e	$(mpa)_2CH^+$	$N(Ph)CH_3$	$N(Ph)CH_3$	−5.89
2f	$(mor)_2CH^+$			−5.53
2g	$(dpa)_2CH^+$	NPh_2	NPh_2	−4.72
2h	$(mfa)_2CH^+$	$N(CH_3)CH_2CF_3$	$N(CH_3)CH_2CF_3$	−3.85
2i	$(pfa)_2CH^+$	$N(Ph)CH_2CF_3$	$N(Ph)CH_2CF_3$	−3.14
2j	$(fur)_2CH^+$			−1.36
2k	$fur(ani)CH^+$			−0.81
2l	$(ani)_2CH^+$	OCH_3	OCH_3	0.00
2m	$ani(pop)CH^+$	OCH_3	OPh	0.61
2n	$ani(tol)CH^+$	OCH_3	CH_3	1.48
2o	$ani(Ph)CH^+$	H	OCH_3	2.11
2p	$pop(Ph)CH^+$	H	CH_3	2.90
2q	$(tol)_2CH^+$	CH_3	CH_3	3.63
2r	$tol(Ph)CH^+$	H	CH_3	4.43
2s	Ph_2CH^+	H	H	5.47

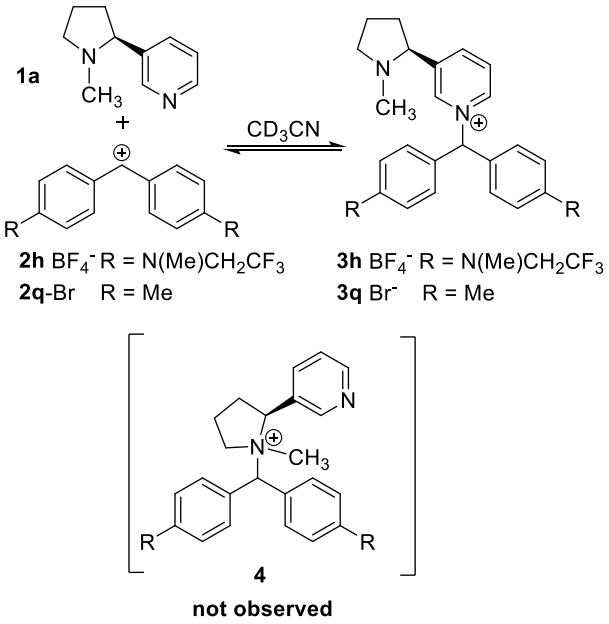
[a] See reference 6.

Results

1. Product studies

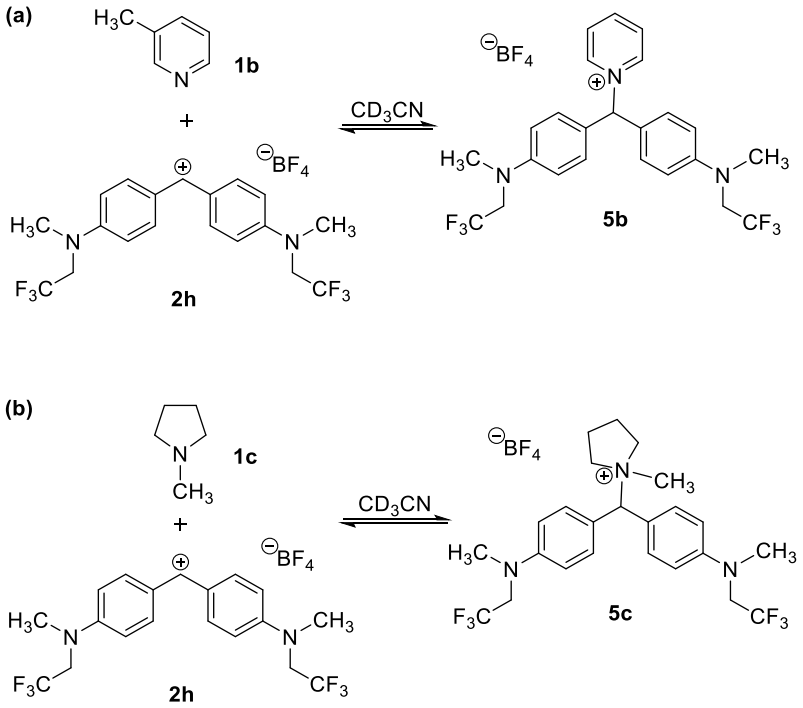
While compounds **1(a-c)** were commercially available, *N*-methyl-2-phenyl-pyrrolidine (**1d**) was synthesized according to Craig[11] by reaction of *N*-methyl-α-pyrrolidone with phenylmagnesium bromide, and subsequent reduction of the resulting crude product with magnesium turnings and hydrochloric acid.

To confirm the identity of the products formed in the reactions of these nucleophiles with benzhydrylium ions in MeCN, selected representatives of these reactions were studied by NMR in CD_3CN. The reactions of nicotine (**1a**) with $(mfa)_2CH^+$ BF_4^- (**2h**) and $(tol)_2CH$-Br (**2q**-Br) at ambient temperature occur exclusively at the pyridine nitrogen to give complete (but reversible)[12] formation of *N*-(diarylmethyl)pyridinium salts **3** (Scheme 3). No signals attributable to *N*-methylpyrrolidinium salts **4** could be observed by NMR.



Scheme 3. Reactions of nicotine (**1a**) with benzhydrylium ions **2h** and **2q** to give *N*-diarylmethylpyridinium salts (**3h** & **3q**).

The reactions in CD_3CN of $(mfa)_2CH^+$ (**2h**) with 3-methylpyridine (**1b**) and *N*-methylpyrrolidine (**1c**), respectively, resulted in the quantitative formation of Lewis acid-base adducts **5b** and **5c** (Scheme 4).



Scheme 4. Reactions of $(mfa)_2CH^+$ $^-BF_4$ (**2h**) with (a) 3-methylpyridine to give pyridinium **5b** and (b) with *N*-methylpyrrolidine (**1c**) with to give *N*-diarylmethyl-*N*-methylpyrrolidinium salt **5c**.

Kinetic investigations

As the benzhydrylium ions (Ar_2CH^+, **2**) are colored and their reactions with **1(a-d)** yield colorless adducts, the progress of the reactions can be monitored by UV-Vis spectroscopy. However, because of the low intrinsic barriers for the reactions of benzhydrylium ions **2** with pyridines and tertiary amines, reactions which lead to the formation of thermodynamically stable pyridinium and quaternary ammonium ions are very fast and cannot be followed by conventional UV-Vis spectroscopy. In some cases (underlined rate constants in Table 2) stopped-flow-techniques could be applied to determine the rate of decay of the UV-Vis absorptions of the benzhydrylium ions **2** after mixing the benzhydrylium tetrafluoroborates with an excess of the nucleophiles **1(a-d)** using pseudo-first order conditions ($[\mathbf{1}]_0 >> [\mathbf{2}]_0$).

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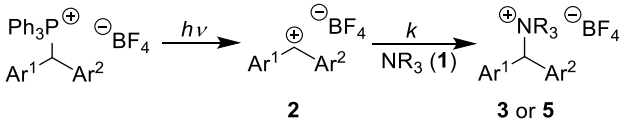
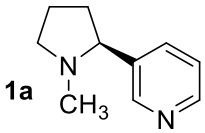
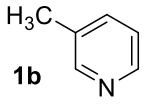
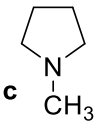
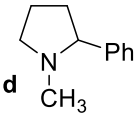


Scheme 5. Laser-flash-induced heterolytic cleavage of benzhydrylphosphonium ions yields benzhydryl cations **2**, which combine with the amines **1** to yield adducts **3** or **5**.

Table 2. Rate Constants for the Reactions of Benzhydrylium Ions **2** with Nicotine (**1a**) and Related Compounds **1**(**b-d**) at 20 °C Determined by Laser Flash and (underlined) Stopped Flow Experiments.

		 **1a**		 **1b**		 **1c**		 **1d**	
Ar_2CH^+	#	CH_3CN	CH_2Cl_2	CH_3CN	CH_2Cl_2	CH_3CN	CH_2Cl_2	CH_3CN	CH_2Cl_2
$(thq)_2CH^+$	**2b**					2.1×10^{6}			
$(pyr)_2CH^+$	**2c**					7.2×10^{6}			
$(dma)_2CH^+$	**2d**					1.2×10^{7}			
$(mpa)_2CH^+$	**2e**	1.4×10^{5}				8.6×10^{7}	5.3×10^{7}		
$(mor)_2CH^+$	**2f**	8.8×10^{4}				6.4×10^{7}	6.5×10^{7}		
		$\underline{7.7\times10^{4}}$	$\underline{1.8\times10^{5}}$	$\underline{7.6\times10^{4}}$	$\underline{1.3\times10^{5}}$				
$(dpa)_2CH^+$	**2g**		$\underline{6.2\times10^{5}}$		$\underline{4.1\times10^{5}}$	3.0×10^{8}	1.9×10^{8}		
$(mfa)_2CH^+$	**2h**	1.3×10^{6}	6.6×10^{6}	9.6×10^{5}	4.6×10^{6}	3.3×10^{8}	4.9×10^{8}	1.3×10^{6}	
		$\underline{1.1\times10^{6}}$	$\underline{3.1\times10^{6}}$	$\underline{9.2\times10^{5}}$	$\underline{1.7\times10^{6}}$				
$(pfa)_2CH^+$	**2i**	8.7×10^{6}	5.0×10^{7}	7.1×10^{6}	8.2×10^{6}	9.2×10^{8}	6.3×10^{8}	5.2×10^{6}	4.6×10^{6}
$(fur)_2CH^+$	**2j**	3.8×10^{8}	4.1×10^{8}	1.4×10^{8}	2.2×10^{8}	2.3×10^{9}	1.7×10^{9}	4.2×10^{7}	4.1×10^{7}
$fur(ani)CH^+$	**2k**	5.9×10^{8}	6.3×10^{8}	2.6×10^{8}	4.2×10^{8}			6.1×10^{7}	5.8×10^{7}
$(ani)_2CH^+$	**2l**	1.1×10^{9}	9.5×10^{8}	4.5×10^{8}	7.5×10^{8}		3.1×10^{9}	9.4×10^{7}	9.7×10^{7}
$ani(pop)CH^+$	**2m**	1.4×10^{9}	1.1×10^{9}	8.5×10^{8}	9.4×10^{8}			1.3×10^{8}	1.3×10^{8}
$ani(tol)CH^+$	**2n**	1.7×10^{9}	1.4×10^{9}	1.3×10^{9}	1.9×10^{9}			2.2×10^{8}	2.3×10^{8}
$ani(Ph)CH^+$	**2o**	2.3×10^{9}	1.7×10^{9}	1.8×10^{9}	2.4×10^{9}			3.0×10^{8}	2.7×10^{8}
$pop(Ph)CH^+$	**2p**	3.1×10^{9}	1.9×10^{9}	2.9×10^{9}	2.7×10^{9}				2.9×10^{8}
$(tol)_2CH^+$	**2q**	4.7×10^{9}	2.9×10^{9}	4.5×10^{9}	3.9×10^{9}	4.1×10^{9}	3.6×10^{9}	8.0×10^{8}	6.4×10^{8}
$tol(Ph)CH^+$	**2r**	5.5×10^{9}	2.9×10^{9}	5.0×10^{9}	3.7×10^{9}		3.7×10^{9}	1.0×10^{9}	6.3×10^{8}
$(Ph)_2CH^+$	**2s**	6.8×10^{9}		5.8×10^{9}	5.0×10^{9}	4.7×10^{9}		1.5×10^{9}	8.4×10^{8}

Most rate constants have been determined by laser-flash photolytic techniques (Scheme 5). As tertiary phosphines are known to be good photo-leaving groups,[13] benzhydryltriphenylphosphonium tetrafluoroborates were prepared as precursors by heating Ar_2CH-OH with $Ph_3PH^+BF_4^-$ or by treatment of Ar_2CH-Br with Ph_3P and subsequent anion exchange as described previously.[14] The benzhydrylium ions **2** were then generated by laser flash irradiation of the benzhydrylium precursors $Ar_2CHP(Ph)_3^+BF_4^-$ in the presence of variable concentrations of **1(a-d)**, and the decay of the benzhydrylium absorbances was measured as a function of the nucleophile concentrations. As the crystalline

benzhydryltriphenylphosphonium salts $(pfa)_2CHP(Ph)_3^+BF_4^-$ and $(mfa)_2CHP(Ph)_3^+BF_4^-$ were in equilibrium with their precursors ($Ar_2CH^+ + Ph_3P$), they reacted with **1(a-d)** within seconds to give benzhydryl- ammonium or pyridinium ions which could not be cleaved photolytically. Therefore in each measurement involving these compounds, phosphonium salt solution and nucleophile (**1(a-d)**) solution were mixed in a stopped-flow cell and irradiated immediately with a laser pulse.

Some reactions have been studied by stopped-flow as well as by Laser techniques. The agreement was usually within 10%, except for reactions with rate constants greater than 10^6 L mol^{-1} s^{-1}. In these cases, the time taken for these fast reactions to occur is comparable to or faster than the mixing time of the stopped-flow instrument, and thus a large quantity of the benzhydrylium ions decay before the reaction solution is properly mixed. As a consequence, significantly smaller rate constants were obtained by the stopped flow method, since in effect only the final portions of the decay curves can be observed and recorded.

Linear plots of lg *k* vs *E* of benzhydrylium ions have commonly been used to determine the nucleophile-specific parameters *N* and s_N of the reacting nucleophiles. However, eq. (1) only applies for rate constants below *ca*. 2 x 10^8 L mol^{-1} s^{-1}, since beyond that point the correlation lines flatten out as the reaction rates approach the diffusion limit (as can be seen in Figure 1a). The correlation line for **1d** begins to flatten out at significantly lower values of lg *k* than **1**(**a-d**) (Figure 1a). Similar behavior has previously been observed for the reactions of benzhydrylium ions with Et_3N in CH_2Cl_2 and MeCN.8 As before,8 we attribute this occurrence to the greater steric bulk in the vicinity of the nucleophilic nitrogen centre in **1d** and Et_3N compared with analogous nitrogen nucleophiles (e.g. **1c**). Since reactions of nitrogen nucleophiles with certain benzhydrylium ions (those with *E* values below a certain point) are thermodynamically unfavorable (see above), an upper bound (related to diffusion control) and a lower bound (related to thermodynamic stability of the product) apply in selecting benzhydrylium ions of suitable reactivity to employ in kinetic studies with these nucleophiles. Hence, rate constants below the diffusion limit can be determined for the reactions of only a few electrophiles (**2**) with the nucleophiles **1**(**a-d**). As a consequence, it is not possible to derive meaningful values of the reactivity parameters *N* and s_N for these nucleophiles. Approximate values for **1(a-c)** are given in Table 3, however. These were derived by least squares fitting of the linear part of each plot to Eq. (1), as shown in Figure 1b for the reactions carried out in CH_2Cl_2.[15]

Table 3. Approximate Nucleophile-Specific Reactivity Parameters for **1**(**a-d**) according to Eq. (1).[15]

#	CH_2Cl_2		CH_3CN	
	N	***s*N**	***N***	***s*N**
1a	10.4	1.04	11.6	0.81
1b	10.9	0.93	11.5	0.80
1c [a]	20.6	0.52	20.59	0.52
1d	16.8	0.49	15.7	0.54

[a] The quoted values of *N* and s_N for **1c** were reported in ref. 8.

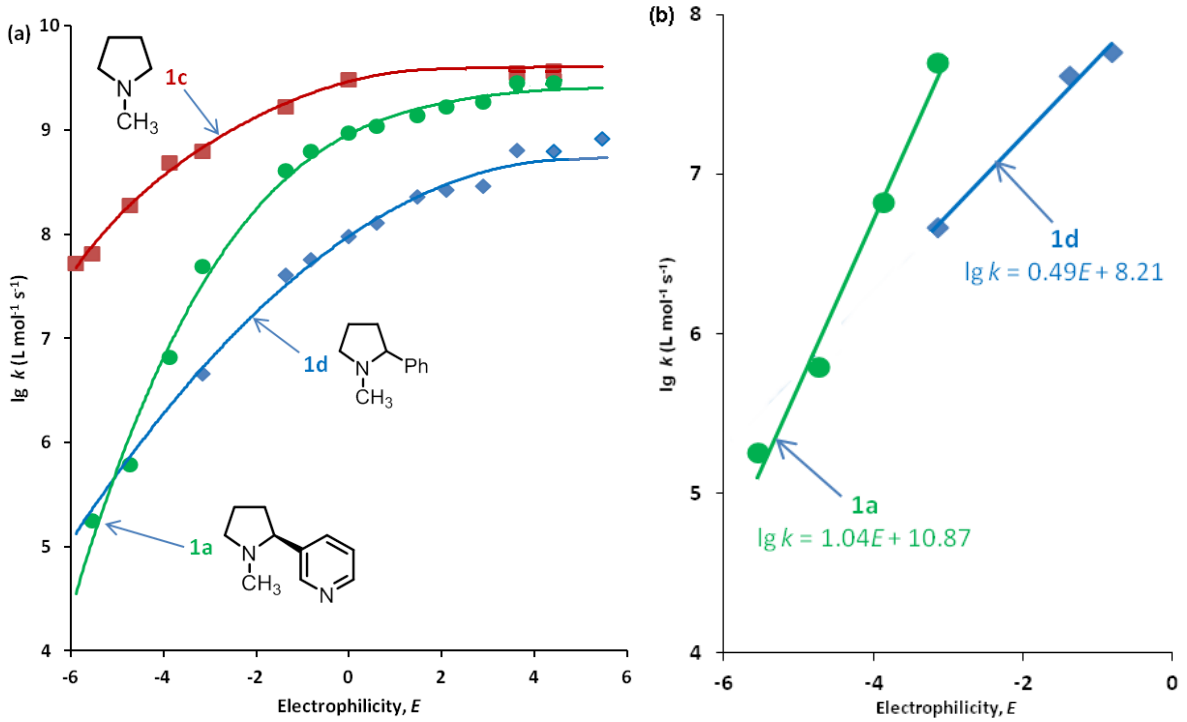


Figure 1. (a) Plot of lg *k* (second-order rate constants; L mol^{-1} s^{-1}) for the reactions of nicotine (**1a**) and structurally related compounds **1(c**,**d)** with benzhydrylium ions **2** versus the electrophilicity parameters *E* (CH_2Cl_2, 20 °C) of **2**; (b) Close-up on the linear parts of Figure 1a, which were used to determine approximate values of *N* and s_N for **1a** & **1d** (see Table 2).[15] The plot for **1b** is almost coincident with that of **1a**, and is omitted for clarity.

Table 2 as well as Figure 1 show that nicotine (**1a**) is generally less reactive than *N*-methylpyrrolidine (**1c**), and within the reactivity range studied is more reactive than *N*-methyl-2-phenyl-pyrrolidine (**1d**). Its reactivity is almost identical to that of 3-methylpyridine (**1b**), which was not included in Figure 1a for the sake of clarity since the correlation lines for nicotine (**1a**) and **1b** are almost coincident. It is thus indicated that the pyridine nitrogen is

also the site of kinetically controlled attack of benzhydrylium ions at nicotine (**1a**). In order to rationalize this behavior we have also studied equilibrium constants for these reactions.

Equilibrium studies

Equilibrium constants for the reactions of amines **1a**, **1c** and **1d** with selected benzhydrylium ions **2** were measured spectrophotometrically in dry MeCN at 20 °C under an atmosphere of nitrogen (Table 4). Addition of an aliquot of amine solution to a solution of **2** caused the absorbance to decrease from an initial constant value to a new constant value.[16] The change in the absorbance corresponds to the amount of Lewis acid-base adduct formed, and so a value of the equilibrium constant *K* for each individual titration could be calculated using the following formula:[17]

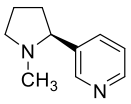
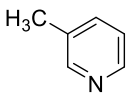
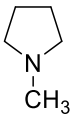
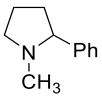
$$K = \frac{[\mathrm{Ar_2CHNR_3}^+]}{[\mathrm{Ar_2CH}^+][\mathrm{NR_3}]} = \frac{\mathrm{A}_0 - \mathrm{A}_t}{\mathrm{A}_t\left([\mathrm{NR_3}]_0 - \frac{\mathrm{A}_0 - \mathrm{A}_t}{\varepsilon l}\right)} \qquad (2)$$

where

- $[\mathrm{Ar_2CHNR_3}^+]$, $[\mathrm{Ar_2CH}^+]$, and $[\mathrm{NR_3}]$ are the equilibrium molar concentrations of Lewis acid-base adduct, of benzhydrylium ion and of Lewis base, respectively,
- $[\mathrm{NR_3}]_0$ is the initial molar concentration of Lewis base,
- A_0 is the initial absorbance of the benzhydrylium ion solution at the wavelength of measurement λ,
- A_t is the equilibrium absorbance of the reaction mixture at λ (proportional to current concentration of benzhydrylium ion),
- ε is the molar absorption coefficient (L $\mathrm{mol^{-1}}$ $\mathrm{cm^{-1}}$) of the benzhydrylium ion at λ,
- *l* is the path length (cm) through which the incident UV-visible light passes in the probe during measurement.

Several further aliquots of amine solution were added with the same result. Each reaction was repeated three or more times, and for each repeat the concentration of the amine solution added to the benzhydrylium ion solution was different. A value of *K* was calculated for every addition of amine. All of the recorded values of *K* for a given reaction were averaged to give the values reported in Table 4 (see "Experimental" columns). In some cases, after the addition of several aliquots of Lewis base, the absorbance no longer returned to a constant value. Titration steps for which a constant value of the absorbance was not reached were not used to calculate the average values of *K* shown in Table 4.

Table 4. Equilibrium constants for the reactions of **1**(**a-d**)[a] with benzhydrylium ions (**2**) at 20 °C in MeCN determined by UV-vis spectrophotometry.

#	Lewis Base	LB_{MeCN}	#	Ar_2CH^+	LA_{MeCN} [b]	Experimental [c]		Correlation	$\frac{K_{calc}}{K}$
						K (L mol^{-1})	lg K	K_{calc} (L mol^{-1})	
1a		12.46	**2c**	pyr_2CH^+	−10.83	59	1.78	43	0.72
			2d	dma_2CH^+	−9.82	357	2.55	437	1.22
			2f	mor_2CH^+	−7.52	6.9×10^4	4.84	8.71×10^4	1.26
1b		12.27[a]	**2d**	dma_2CH^+	−9.82	2.52×10^2 [a]	2.40	2.86×10^2 [a]	1.13
			2e	mpa_2CH^+	−7.87	2.71×10^4 [a]	4.43	2.54×10^4 [a]	0.94
			2f	mor_2CH^+	−7.52	6.00×10^4 [a]	4.78	5.66×10^4 [a]	0.94
1c		13.65	**2a**	ind_2CH^+	−11.46	150	2.18	155	1.03
			2b	thq_2CH^+	−11.27	253	2.40	240	0.95
1d		13.39	**2a**	ind_2CH^+	−11.46	80	1.90	85	1.06
			2b	thq_2CH^+	−11.27	150	2.18	132	0.91
			2c	pyr_2CH^+	−10.83	340	2.53	363	1.07

[a] Values of equilibrium constant K and LB parameter for compound **1b** are taken from ref. 17.

[b] Values of LA parameter taken from ref. 17.

[c] See Supporting Information for confidence intervals on the experimental values.

It has been shown[17] that the equilibrium constants K for the reactions of benzhydrylium ions (Lewis acids) with DABCO and quinuclidine,[9] pyridines,[17] phosphines,[17] thiocyanates (N-terminus),[18] isoquinoline,[17] pyrimidine,[17] imidazoles,[19] benzimidazoles,[19] and carboxylates[20] at 20 °C in MeCN, can be expressed by equation 3:

$$\lg K = LA + LB \qquad (3)$$

where LA is the Lewis acidity of the benzhydrylium ion, and LB is the Lewis basicity of the base. Plots of $\lg K$ for the reactions listed in Table 4 against the previously published LA parameters of the benzhydrylium ions are linear with slopes of 1.0 (Fig. 2) indicating that Eq. (3) and the LA values of the benzhydrylium ions reported in ref. 17 also apply for the corresponding reactions of **1**(**a-d**).[21] From these plots, the values of the LB parameters for **1a**, **1c** & **1d** have been extracted (Table 4). The observed equilibrium constants agreed very well

with those calculated from the averaged *LB* parameters and the previously reported Lewis acidity parameters *LA* of the benzhydrylium ions, as shown in the last column of Table 4.

The highest Lewis basicity is found for *N*-methylpyrrolidine (**1c**, 13.65), while *N*-methyl-2-phenylpyrrolidine (**1d**) shows a similar but slightly lower value (*LB* = 13.39). Most strikingly, the *LB* value exhibited by nicotine (**1a**, *LB* = 12.46) is one order of magnitude *lower* than that of the structurally analogous phenyl substituted pyrrolidine **1d**. The product characterization (Scheme 3) showed that nicotine (**1a**) is benzhydrylated at the pyridine nitrogen. In line with this observation, the *LB* value of **1a** is similar to that of 3-methylpyridine (**1b**, *LB* = 12.27).

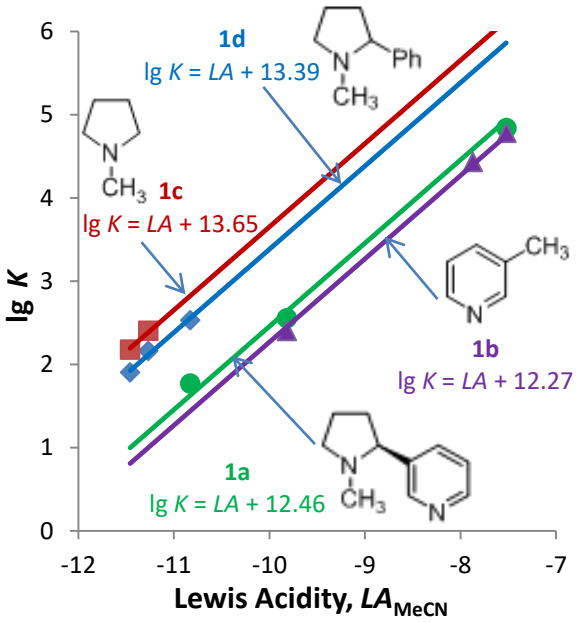
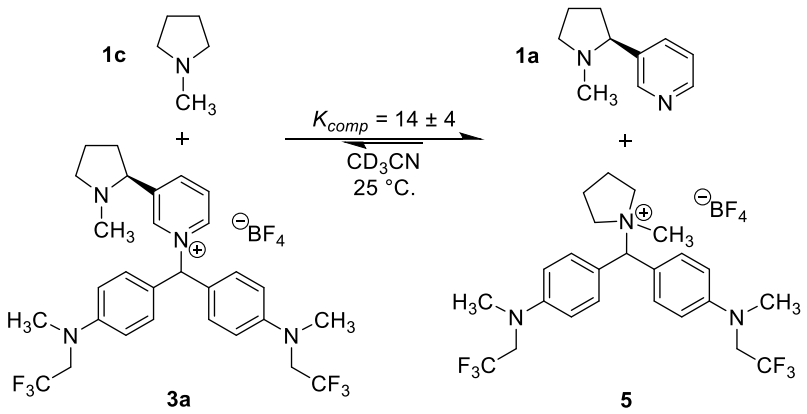


Figure 2. Plots of lg *K* for reactions of benzhydrylium ions (**2**) with amines **1** (**a**-**d**) vs. the Lewis acidity parameter *LA* in MeCN of the corresponding benzhydrylium ions.[21]

Though the equilibrium constants illustrated in Figure 2 were reproducible, the unexpected observation that the Lewis basicity of nicotine is significantly lower than that of **1c** and **1d**, prompted us to confirm this result by NMR competition experiments, i.e. by using an independent method.

For that purpose, a solution of benzhydrylium tetrafluoroborate **2h** was mixed with approximately one equivalent each of nicotine (**1a**) and *N*-methylpyrrolidine (**1c**) in CD_3CN. The blue color of **2h** disappeared, indicating quantitative consumption of the benzhydrylium ion (indeed no signals attributable to **2h** appeared in the NMR spectra of the mixture). Since

the benzhydrylium ion is completely consumed, the equilibrium in solution can be viewed as shown in Scheme 6.[22] The equilibrium constant at 25 °C for this process (K_{comp} = 14 ± 4), determined by NMR-spectroscopy, is in agreement with the low Lewis basicity of nicotine shown in Figure 2.[23]



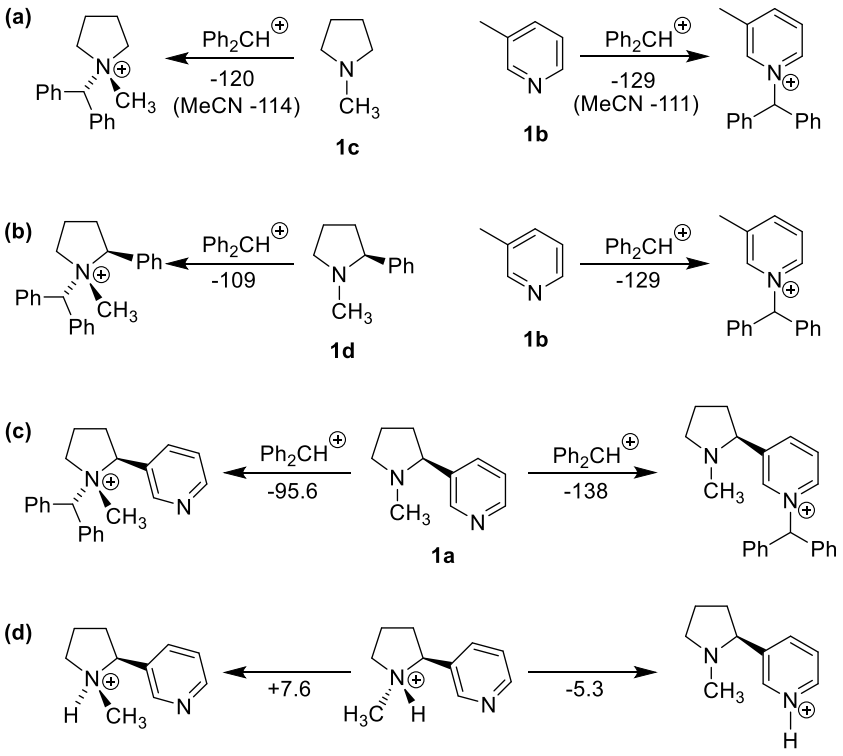
Scheme 6. Competition experiment for the determination of the relative Lewis basicities of **1a** and **1c** with respect to **2h**.[23]

An analogous competition experiment with approximately equal amounts of **2h**, **1b** and **1c** in CD_3CN gave K_{comp} = 15 ± 3 at 25 °C,[23] again in agreement with the results in Table 4 and Figure 2.

Discussion

In order to rationalize the nucleophilic reactivity of nicotine (**1a**), we synthesized *N*-methyl-2-phenylpyrrolidine (**1d**), where the pyridine ring of nicotine is replaced by a phenyl ring. According to Table 2 and Figure 1, the 2-phenyl group in **1d** indeed reduces the nucleophilic reactivity of the pyrrolidine ring by two orders of magnitude (**1c**/**1d**), which may be explained by a steric effect. However, the steric effect operates only in the transition state of the reaction, and hardly affects the relative stabilities of the products, as indicated by the similar Lewis basicities of **1c** and **1d** (Table 3, Figure 2). The observation that nicotine (**1a**) is approximately one order of magnitude more nucleophilic than **1d** (Figure 1) can then be explained by the fact that nicotine is not attacked at the pyrrolidine moiety but at the pyridine ring, in line with the observation that nicotine reacts with the same rate as 3-picoline (**1b**). The rate constants for **1a** and **1b** are so similar (Table 2) that the corresponding graphs overlap and are not shown separately in Figure 1. The NMR spectroscopic identification of adduct **3** and the similar Lewis basicities of **1a** and **1b** (Figure 2) also indicate that the pyridine nitrogen is the reactive site of nicotine.

There is a problem with this rationale, however. If one assumes that the pyridyl and the phenyl groups have similar effects on the reactivity of the *N*-methylpyrrolidine fragment in nicotine (**1a**) and in *N*-methyl-2-phenyl-pyrrolidine (**1d)**, respectively, one would expect that the pyrrolidine ring in nicotine (**1a**) would have a similar Lewis basicity to the pyrrolidine ring in **1d**. As the latter is significantly larger than the Lewis basicity of 3-methylpyridine (**1b**, Figure 2), one would expect that the pyrrolidine nitrogen of nicotine (and not the pyridine nitrogen) would be the most Lewis basic site (Lewis basicity with respect to **2**). Why is the opposite ranking observed, i. e., why is **3** and not **4** formed in the reversible reactions in Scheme 3?



Scheme 7. Calculated reaction free energies (ΔG / kJ mol^{-1}; M06-2X-D3/def2-QZVP//M06-2X-D3/6-31+G(d,p)) for the reactions of N-nucleophiles with the benzhydrylium ion Ph_2CH^+ in the gas phase (values for MeCN (IEFPCM model) in parenthesis for selected examples).

In order to resolve this paradox, we have performed quantum chemical calculations (see below for details). As shown in Scheme 7a, 3-methylpyridine (**1b**) is calculated to be 9 kJ mol^{-1} more Lewis basic than *N*-methylpyrrolidine (**1c**) in the gas phase, but 3 kJ mol^{-1} less basic in acetonitrile solution, in satisfactory agreement with the measured equilibrium constants ($\Delta\Delta G^o$ = −ln10×RT($LB_{\mathbf{1c}}$ − $LB_{\mathbf{1b}}$) = −7.9 kJ mol^{-1}, Figure 2). The stabilizing solvation of quaternary ammonium ions appears to be greater than that of pyridinium ions.

It is fair to assume that solvation affects the Lewis basicity of the pyrrolidine nitrogen in **1d** and in **1a** by the same amount. From the 13.4 kJ mol^{-1} difference of the Lewis basicities of the pyrrolidine ring of **1a** and **1d** (Scheme 7b and 7c, left part) one can calculate that the Lewis basicity of the pyrrolidine nitrogen of nicotine should be 2.4 lg *K* units lower than that of **1d**. When the correlation line for **1d** in Figure 2 is shifted downwards by this quantity (see Figure 3), one obtains a good estimate for the experimentally unobservable correlation line that would be generated for the reaction at the pyrrolidinyl nitrogen of nicotine with benzhydrylium ions (i.e., if attack of nicotine at its pyridyl nitrogen could be "switched off"). A comparison (Figure 3) of this computationally estimated correlation line for the reaction of the pyrrolidinyl nitrogen of nicotine with the experimentally measured correlation line for reaction at the pyridyl nitrogen of nicotine (**1a**) makes it clear why **3** is more stable than the regioisomer **4** (see Scheme 3).

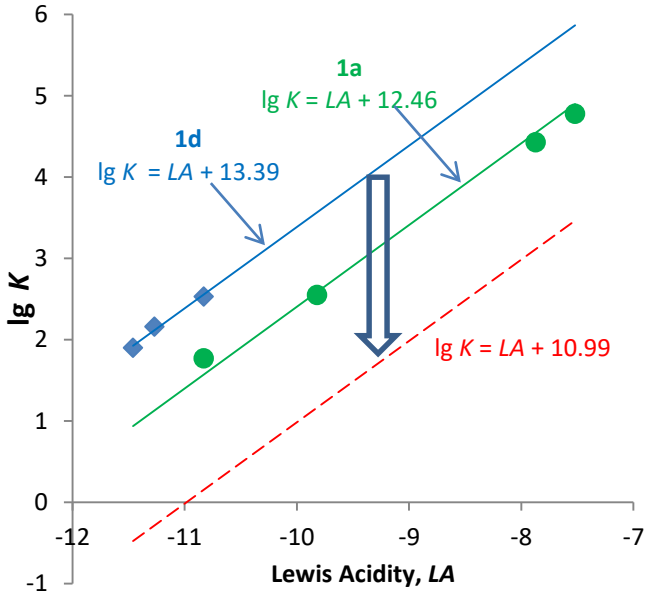
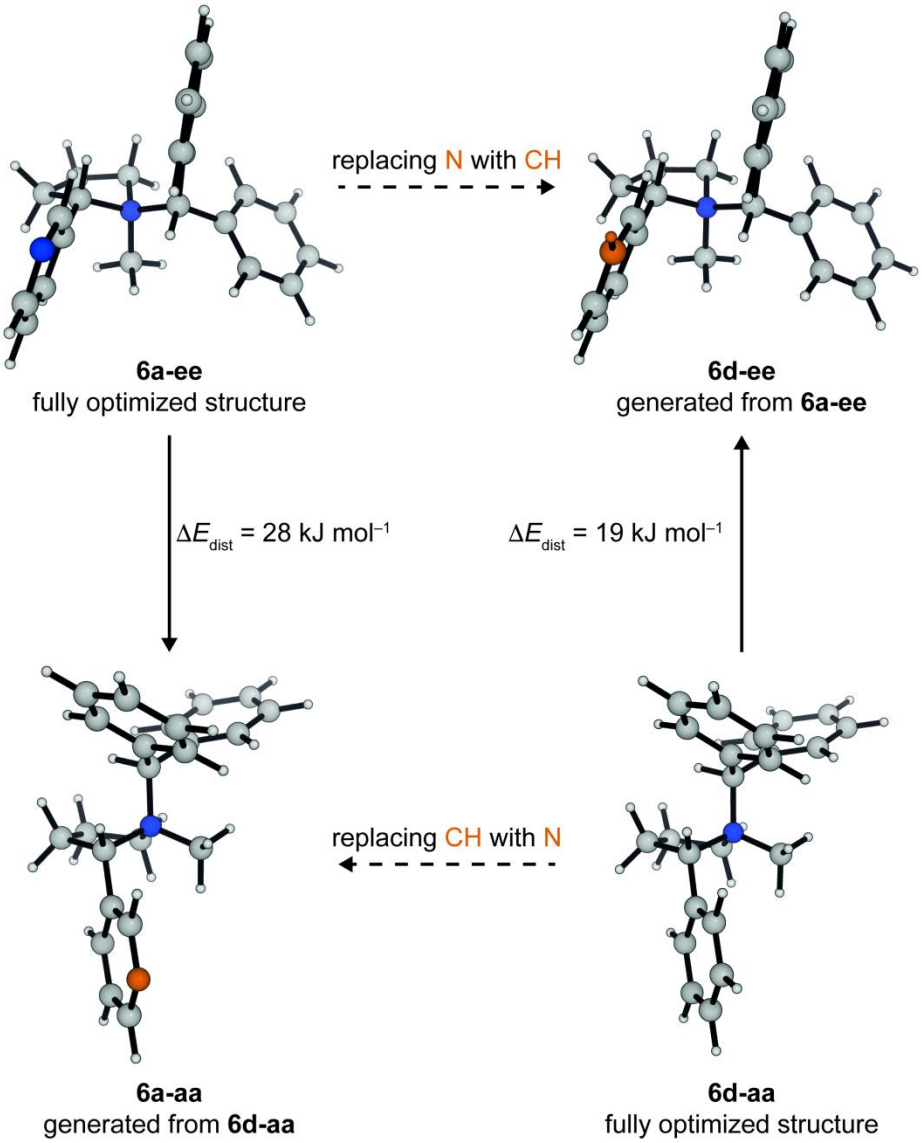


Figure 3. Moving the correlation line for **1d** down by 2.4 lg *K* units gives a good estimate for the Lewis basicity of the pyrrolidinyl nitrogen of **1a**. The estimated correlation line is indicated by the dashed red line.

Analogous phenomena appear to operate also for the Brønsted basicities. ^{13}C NMR spectra in D_2O at pD = 5.4 indicate that protonation of nicotine occurs at the pyrrolidine ring and not at the pyridine ring as calculated for the gas phase (Scheme 7d).[24] Furthermore, the Brønsted basicities (in H_2O) of **1c** (pK_{aH} = 10.18), **1a** (pK_{aH} = 7.84), and **1d** (pK_{aH} = 9.27),[4a] also indicate that the pyridine ring in **1a** lowers the basicity of the pyrrolidine ring by 1.43 p*K* units more than the phenyl ring does in **1d**. What is the reason for the different influence of the pyridyl and the phenyl group on the basicity of the pyrrolidine? Let us analyze the Lewis

basicities of **1a** and **1d** toward **2**. Quantum chemical calculations show that the pyrrolidinium ions **6a** and **6d** with a *trans* configuration of the benzhydryl and pyridyl/phenyl group, respectively (Scheme 8),[25] are 4 kJ mol^{-1} more stable than the corresponding *cis* isomers. However, whereas the pyrrolidinium ion derived from nicotine (**1a**) prefers the ee-conformation (**6a-ee**) in the lowest energy structure, **6d-aa** is the preferred conformation for the adduct derived from **1d**.



Scheme 8. Structures of the lowest-energy *N*-benzhydrylpyrrolidinium ions **6a-ee** and **6d-aa** and their isomers **6a-aa** and **6d-ee** generated from CH/N exchange of **6a-ee**/**6d-aa** (For **6a-dd** and **6d-ee**, only atoms marked in orange were allowed to relax during the optimization) [M06-2X-D3/def2-QZVP//M06-2X-D3/6-31+G(d,p)].

To rationalize these findings, we employed the model system depicted in Scheme 8, where we replaced either the pyridine nitrogen of the **1a** adduct by a CH group (**6a-ee** → **6d-ee**) or the CH group in the phenyl substituent of the **1d** adduct by a nitrogen atom (**6d-aa** → **6a-aa**), and

compared the electronic energies of both conformers. For both group exchanges, similar results have been calculated. Steric interactions between the equatorial phenyl and benzhydryl groups in **6d-ee** account for the higher stability of the bis-axial confirmer **6d-aa** (in contrast to the situation in six-membered rings, vicinal a,a is preferred over e,e in five-membered rings). When comparing the energies of the fully optimized **6a-ee** with the model **6a-aa** (left in Scheme 8), a distortion energy of 28 kJ mol^{-1} is obtained, indicating an unfavorable electronic interaction between the axial electron-withdrawing pyridyl group and the axial $Ph_2CH\text{-}N^+$ moiety. The e,e-conformer **6a-ee** can be assumed to be subject to increased steric interactions between the pyridyl and benzhydryl groups compared with the a,a conformer, like in the e,e-conformer of **6d** (**6d-ee**). However, **6a-ee** (with the five-membered ring inverted relative to **6a-aa** and the benzhydryl group and pyridyl group each in an equatorial position) avoids the unfavorable electronic interaction, and the consequent stabilization apparently more than makes up for the increase in the steric interactions in the e,e-conformer (**6a-ee**) relative to the a,a-conformer (**6a-aa**).

Conclusion

Although pyrrolidine is a significantly stronger Brønsted base than pyridine (7 pK_{aH} units in acetonitrile)[10] and alkylations of sp^3-hybridized nitrogens proceed with lower intrinsic barriers than those of sp^2-hybridized nitrogens, the pyrrolidine nitrogen of nicotine reacted only 2½ times faster with methyl iodide than the pyridine nitrogen of nicotine.[4a] The question was raised whether this small difference in reactivity was due (i) to a rate decrease in pyrrolidine alkylation caused by the pyridine ring or (ii) to a pyridine nitrogen alkylation rate enhancement due to the presence of the pyrrolidine ring.[4a] By studying rate and equilibrium constants of the reactions of nicotine with benzhydrylium ions, our reference electrophiles and reference Lewis acids, we have provided clear evidence that hypothesis (i) applies.

Benzhydrylium ions attack the pyridine nitrogen of nicotine (**1a**) with the same rate as 3-methylpyridine (**1b**). Furthermore, the equilibrium constants of the reactions of benzhydrylium ions with nicotine (**1a**) and **1b** are almost the same, showing that neither nucleophilicity (*k*) nor Lewis basicity (*K*) of the pyridine ring in nicotine are affected by the presence of the pyrrolidine ring.

On the other hand, the Lewis basicity of nicotine (which refers to the reactions of benzhydrylium ions with the pyridine nitrogen of **1a**) is approximately one order of magnitude smaller than the Lewis basicity of *N*-methyl-2-phenyl-pyrrolidine (**1d**). From the

fact that under equilibrium conditions only the benzhydrylated pyridine ring of nicotine is observable (compound **3**), one can conclude that the pyrrolidine ring of nicotine (**1a**) is more than two orders of magnitude less Lewis basic than **1d**. Quantum chemical calculations showed that the pyrrolidine nitrogen in nicotine is 24 kJ mol^{-1} less Lewis basic than *N*-methylpyrrolidine (**1c**) while **1d** is only 11 kJ mol^{-1} less Lewis basic than **1c**.

The same factors which lower the Lewis basicity of the pyrrolidine ring of **1a** toward benzhydrylium ions also account for the difference of the Brønsted basicities (in H_2O) of **1a** (pK_{aH} = 7.84) and **1d** (pK_{aH} = 9.27). Thus, experimental and computational studies agree that the low nucleophilicity and Lewis basicity of nicotine is due to the deactivating effect of the pyridyl group on the pyrrolidine ring, with the consequence that the pyrrolidinyl nitrogen is surpassed by the pyridyl nitrogen in terms of nucleophilicity and Lewis basicity.

Acknowledgments

We thank the Deutsche Forschungsgemeinschaft (SFB 749, Project B1) for financial support, the Humboldt foundation for the provision to PB of a Humboldt Research Fellowship for Postdoctoral Researchers, Nathalie Hampel for the synthesis of the reference electrophiles, and Hildegard Lipfert for help during the preparation of this manuscript.

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1 Scifinder gives 82977 hits for the key word "nicotine" (Jan. 13, 2016)

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15 See the Supporting Information for the lg *k* vs. *E* plots used to calculate the *N* and s_N values for **1a**, **1c** and **1d** in MeCN shown in Table 3, and for details of the rate constants used for the calculation of the *N* and s_N values from the lg *k* vs. *E* plots.

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21 A slope of 1 has been enforced for each line in Figure 2. The generally small deviation of the slopes of the calculated best fit lines from the lines in Figure 2, and in the precedents from reference 17, justify this method in the case of **1c**, for which only two points were experimentally accessible and the deviation from the best fit line is somewhat larger.

22 As shown in the following equation, the equilibrium constant K_{comp} (Scheme 6) is equivalent to the ratio of the individual equilibrium constants for the reactions of $(mfa)_2CH^+ BF_4^-$ (**2h**) with **1c** (K_1) and with **1a** (K_2), respectively:

$$K = \frac{[\mathbf{1c}-\mathbf{E}^+][\mathbf{1a}]}{[\mathbf{1a}-\mathbf{E}^+][\mathbf{1c}]} = \frac{\frac{[\mathbf{1c}-\mathbf{E}^+]}{[\mathbf{1c}]}}{\frac{[\mathbf{1a}-\mathbf{E}^+]}{[\mathbf{1a}]}} = \frac{\frac{[\mathbf{1c}-\mathbf{E}^+]}{[\mathbf{1c}][\mathbf{E}^+]}}{\frac{[\mathbf{1a}-\mathbf{E}^+]}{[\mathbf{1a}][\mathbf{E}^+]}} = \frac{K_1}{K_2}$$

where $[\mathbf{1c}-\mathbf{E}^+]$ & $[\mathbf{1c}-\mathbf{E}^+]$ are the concentrations of the Lewis acid-base adducts of **2h** with **1a** & **1c**, respectively, and $[\mathrm{E}^+]$ is the concentration of the Lewis acid $(mfa)_2CH^+$. The same argument applies in the competition experiment with 3-methylpyridine in place of nicotine, **2h** + **1b** + **1d**.

23 See the Supporting Information for full details on how K_{comp} was calculated using the integrals of characteristic signals of each compound in the ^{1}H NMR of the mixture.

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