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Quantification of the nucleophilic reactivity of nicotine

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Rate and equilibrium constants of the reactions of nicotine and structurally related compounds with benzhydrylium ions have been determined UV-Vis spectroscopically using 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 pyrid-3-yl 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 decreases this quantity by only 11 kJ mol^{-1}. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: equilibrium constants; nucleophilicity; Lewis basicity; kinetics; N-Heterocycles

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] Although 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 because of the presence of the pyrrolidine ring.[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 Eqn 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.

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

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 with considerably higher intrinsic barriers than alkylamines, they were found to be considerably weaker nucleophiles 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)** (Scheme 2) 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.

RESULTS

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** BF_4^-) and $(tol)_2CH$-Br (**2q**-Br) at ambient

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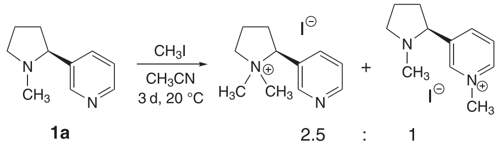
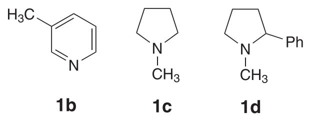


Scheme 1. Product ratio in the methylation of nicotine (**1a**) by iodomethane in MeCN solvent[4a]

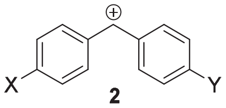


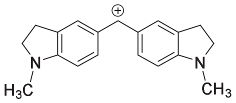
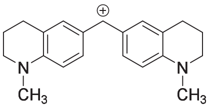
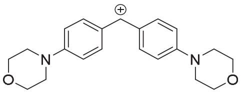
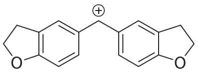
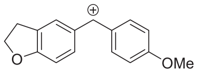
Scheme 2. Structural analogues of nicotine

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.

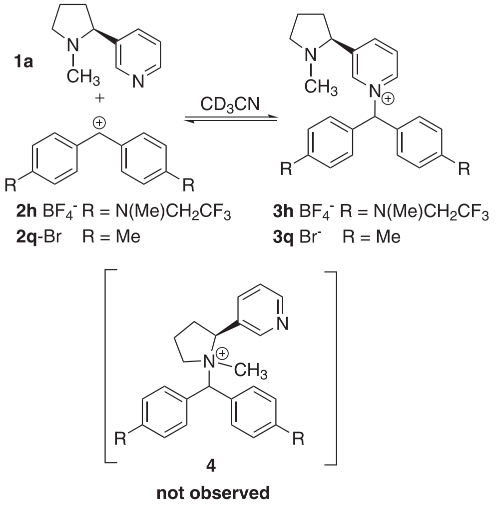
The reactions of $(mfa)_2CH^+$ (**2h**) with 3-methylpyridine (**1b**) and *N*-methylpyrrolidine (**1c**), respectively in CD_3CN, resulted in the quantitative formation of Lewis acid–base adducts **5b** and **5c** (Scheme 4).

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

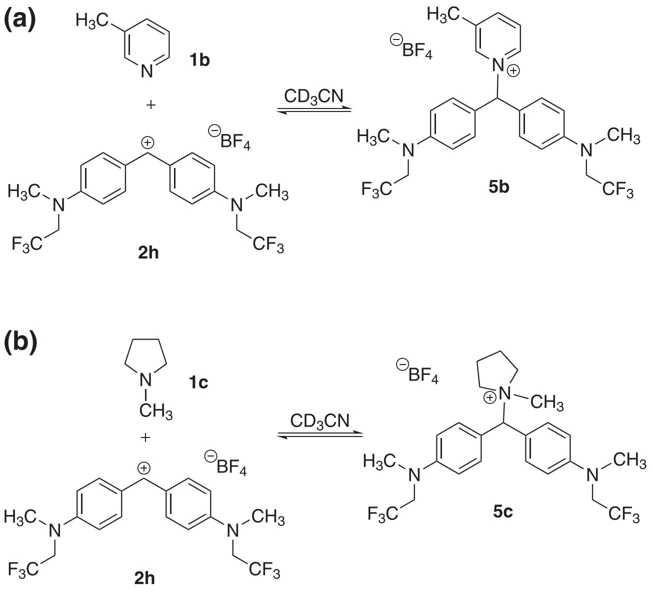


#	Ar_2CH^+	X	Y	E^a
2a	$(ind)_2CH^+$			−8.76
2b	$(thq)_2CH^+$			−8.22
2c	$(pyr)_2CH^+$	$N(CH_2)_4$	$N(CH_2)_4$	−7.69
2d	$(dma)_2CH^+$	$N(CH_3)_2$	$N(CH_3)_2$	−7.02
2e	$(mpa)_2CH^+$	$N(Ph)CH_3$	$N(Ph)CH_3$	−5.89
2f	$(mor)_2CH^+$			−5.53
2g	$(dpa)_2CH^+$	NPh_2	NPh_2	−4.72
2h	$(mfa)_2CH^+$	$N(CH_3)CH_2CF_3$	$N(CH_3)CH_2CF_3$	−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.



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



Scheme 4. Reactions of $(\text{mfa})_2\text{CH}^+\ {}^-\text{BF}_4$ **(2h)** with (a) 3-methylpyridine **(1b)** to give pyridinium **5b** and (b) *N*-methylpyrrolidine **(1c)** 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 ($[\mathbf{1}]_0 >> [\mathbf{2}]_0$).

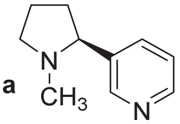
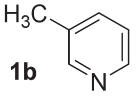
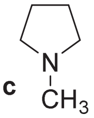
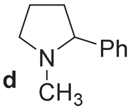
Most rate constants were determined by laser-flash photolytic techniques (Scheme 5). As tertiary phosphines are known to be good photo-leaving groups,[13] benzhydryltriphenylphosphonium tetrafluoroborates were prepared as precursors by heating $Ar_2CH\text{-}OH$ with $Ph_3PH^+BF_4^-$ or by treatment of $Ar_2CH\text{-}Br$ 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 $(\text{pfa})_2\text{CHP}(\text{Ph})_3^+\text{BF}_4^-$ and $(\text{mfa})_2\text{CHP}(\text{Ph})_3^+\text{BF}_4^-$ 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.

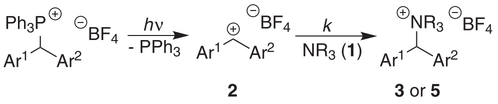
Some reactions have been studied by stopped-flow as well as by laser-flash techniques. The agreement was usually within 10%, except for reactions with rate constants greater than $10^6\ \text{L mol}^{-1}\ \text{s}^{-1}$. In these cases, the reaction time for these fast reactions is comparable to or faster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

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, Eqn 1 only applies for rate constants below ca $2 \times 10^8\ \text{L mol}^{-1}\ \text{s}^{-1}$, because beyond that point the correlation lines flatten out as the reaction rates approach the diffusion limit (as can be seen in Fig. 1a). The correlation line for **1d** begins to flatten out at significantly lower values of lg *k* than those for **1**(**a–c**) (Fig. 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 center in **1d** and Et_3N compared with other nitrogen nucleophiles (e.g. **1c** or pyridines). Because reactions of nitrogen nucleophiles with certain benzhydrylium ions (those with *E* values below a certain point) are thermodynamically unfavorable, 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 Eqn 1, as shown in Fig. 1b for the reactions carried out in CH_2Cl_2.[15]

Table 2 as well as Fig. 1 shows that nicotine (**1a**) is generally less reactive than *N*-methylpyrrolidine (**1c**), and within the reactivity range studied is more reactive than *N*-methyl-2-phenylpyrrolidine (**1d**). Its reactivity is almost identical to that of 3-methylpyridine (**1b**), which was not included in Fig. 1a for

Table 2. Rate constants (Lmol^{-1}s^{-1}) 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	
		$\underline{1.1\times10^6}$	$\underline{3.1\times10^6}$	$\underline{9.2\times10^5}$	$\underline{1.7\times10^5}$				
$(pfa)_2CH^+$	**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



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**

the sake of clarity because 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 Eqn 2[17]

$$K = \frac{[Ar_2CHNR_3{}^+]}{[Ar_2CH^+][NR_3]} = \frac{A_0 - A_t}{A_t\left([NR_3]_0 - \frac{A_0 - A_t}{\varepsilon l}\right)} \qquad (2)$$

where

- $[Ar_2CHNR_3^+]$, $[Ar_2CH^+]$, and $[NR_3]$ are the equilibrium molar concentrations of Lewis acid–base adduct, of benzhydrylium ion and of Lewis base, respectively,
- $[NR_3]_0$ 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 mol^{-1} 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 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 arrived at 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.

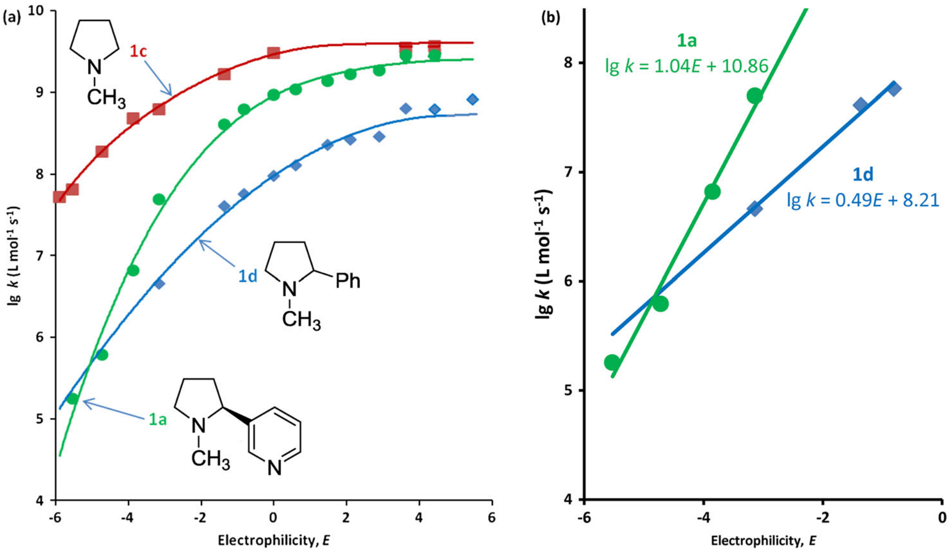


Figure 1. (a) Plots of lg *k* (second-order rate constants; L mol^{-1} s^{-1}) for the reactions of nicotine **(1a)** and structurally related compounds **1(c,d)** with benzhydrylium ions **2** versus the electrophilicity parameters *E* (CH_2Cl_2, 20°C) of **2**; (b) Close-up on the linear parts of Fig. 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 3. Approximate nucleophile-specific reactivity parameters for **1**(**a–d**) according to Eqn 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.

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 Eqn 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 Eqn 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**, and **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).

Although the equilibrium constants illustrated in Fig. 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.

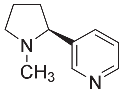
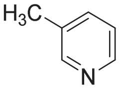
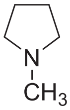
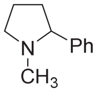
For that purpose, a solution of benzhydrylium tetrafluoroborate **2h** was mixed with approximately one equivalent each of nicotine (**1a**) and *N*-methylpyrrolidine (**1c**) in CD_3CN. The blue color of **2h** disappeared, indicating quantitative consumption of the benzhydrylium ion (indeed no signals attributable to **2h** appeared in the NMR spectra of the mixture). Because 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 ($K_{comp} = 14 \pm 4$), determined by NMR-spectroscopy, is in agreement with the low Lewis basicity of nicotine shown in Fig. 2.[23]

An analogous competition experiment with approximately equal amounts of **2h**, **1b**, and **1c** in CD_3CN gave $K_{comp} = 15 \pm 3$ at 25°C,[23] again in agreement with the results in Table 4 and Fig. 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 Fig. 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 4, Fig. 2). The observation that nicotine (**1a**) is

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	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 parameters taken from ref. 17.
[c] See Supporting Information for confidence intervals on the experimental values.

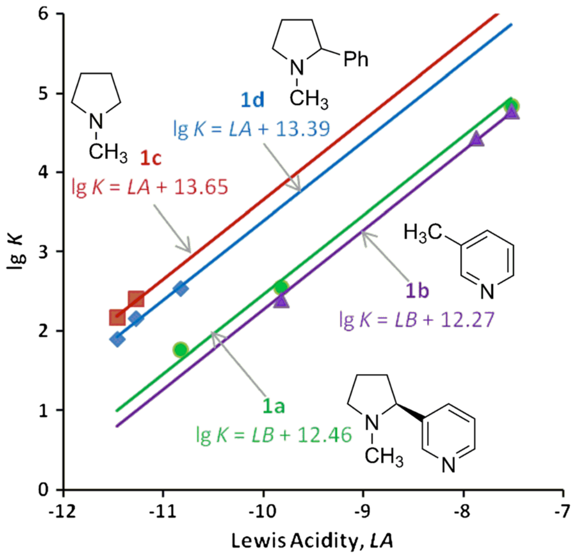
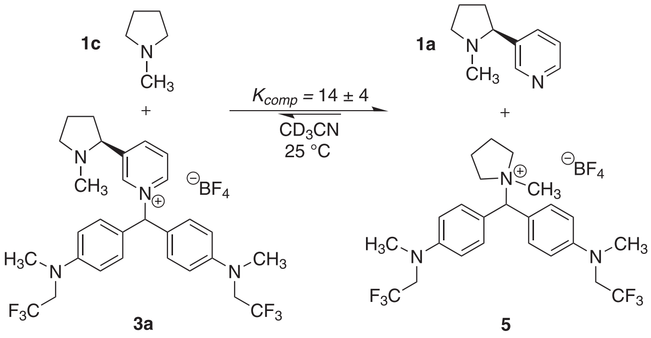


Figure 2. Plots of lg K for reactions of benzhydrylium ions **(2)** with amines **1(a–d)** vs. the Lewis acidity parameter LA in MeCN of the corresponding benzhydrylium ions[21]



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

approximately one order of magnitude more nucleophilic than **1d** (Fig. 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 Fig. 1. The NMR spectroscopic identification of adduct **3** and the similar Lewis basicities of **1a** and **1b** (Fig. 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 Lewis basicity similar to the pyrrolidine ring in **1d**. As the latter is significantly larger than the Lewis basicity of 3-methylpyridine (**1b**, Fig. 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?

In order to resolve this paradox, we have performed quantum chemical calculations (see below for details). As shown in

Scheme 7a, 3-methylpyridine (**1b**) was 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 ($\Delta\Delta G^{o} = -\ln 10 \times RT(LB_{\mathbf{1c}} - LB_{\mathbf{1b}}) = -7.9\ \mathrm{kJ\ mol^{-1}}$, Fig. 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 Fig. 2 is shifted downwards by this quantity (see Fig. 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 (Fig. 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).

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?

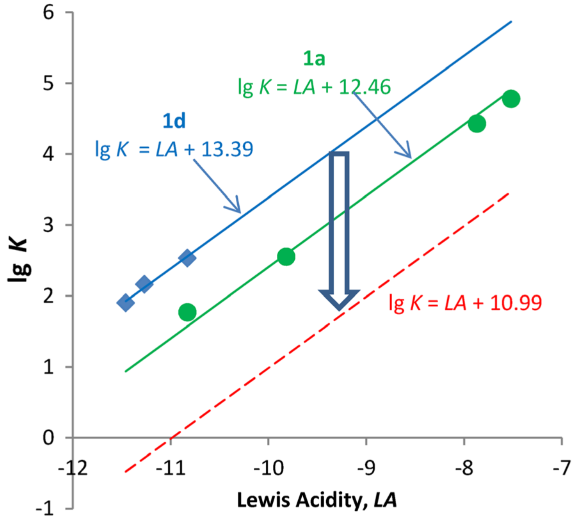
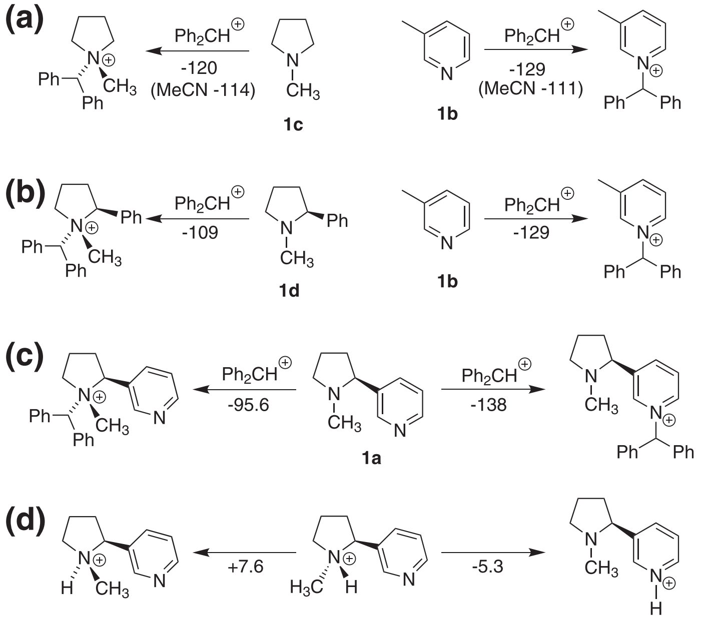


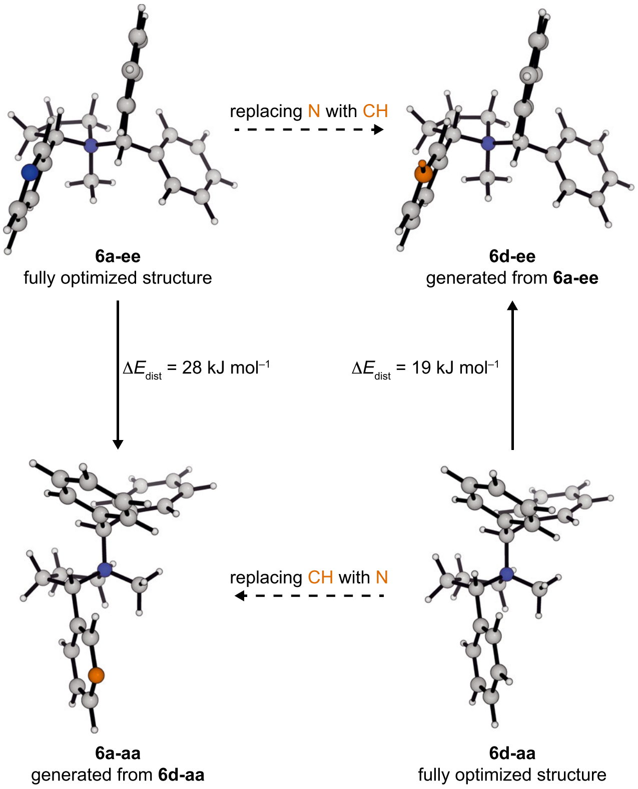
Figure 3. Moving the correlation line for **1d** down by 2.4 lg *K* units gives a good estimate for the Lewis basicity of the pyrrolidinyl nitrogen of **1a** in acetonitrile. The estimated correlation line is indicated by the dashed red line

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* arrangement of the benzhydryl and pyridyl/phenyl group, as depicted in Scheme 8, are 4 kJ mol^{-1} more stable than the corresponding *cis* isomers.[25] However, whereas the pyrrolidinium ion derived from nicotine (**1a**) prefers the conformation **6a-ee** in which pyridyl and benzhydryl are both in an equatorial position in the lowest energy structure, the axial–axial conformation **6d-aa** with phenyl and benzhydryl *trans* to each other is the preferred conformation for the adduct derived from **1d**.

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



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)



Scheme 8. Structures of the lowest-energy *N*-benzhydrylpyrrolidinium ions **6a-ee** and **6d-aa** and their isomers **6a-aa** and **6d-ee** generated by CH/N exchange from **6a-ee** and **6d-aa**, respectively (For **6a-aa** 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)]

nitrogen atom (**6d-aa** → **6a-aa**), and compared the electronic energies of both structures. Steric interactions between the equatorial phenyl and benzhydryl groups in **6d-ee** account for the higher stability of the bis-axial conformer **6d-aa**. Although the conformational preferences in substituted cyclopentanes are more complex than in cyclohexanes,[26] small preferences of the axial–axial conformers (*ca* 1.7 – 3.8 kJ mol^{-1}) were determined experimentally for 1,2-dihalocyclopentanes at 25°C in acetonitrile.[27]

The calculated energy minimum structure for **6a** is the bis-equatorial conformer **6a-ee** (in stark contrast to what is observed for **6d**). Conformer **6a-ee** can be assumed to suffer from destabilizing steric interactions comparable to those that exist in **6d-ee**. However, 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. This indicates that some destabilizing effect must exist in **6a-aa** (one which does not affect **6d-aa**) whose magnitude exceeds that of the expected stabilizing effect brought about by reduced steric interactions in **6a-aa** (vs. **6a-ee**). The origin of this destabilizing effect is not clear, but we suggest that it may arise as a consequence of an unfavorable electronic interaction between the axial electron-withdrawing pyridyl group and the $Ph_2CH\text{-}N^+$ moiety (with the benzhydryl group in an axial position).

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 because of 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 that of 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 are because of 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.

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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.

[16] Note that if even slightly wet MeCN (*ca.* 50 ppm) was used, addition of a single aliquot of amine solution would cause the absorbance to decrease indefinitely, and never return to a constant value.

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[21] A slope of 1 has been enforced for each line in Fig. 2. The generally small deviation of the slopes of the calculated best fit lines from the lines in Fig. 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 $(\text{mfa})_2\text{CH}^+\ \text{BF}_4^-$ (**2h**) with **1c** (K_1) and with **1a** (K_2), respectively: $K = \frac{[\mathbf{1c}\text{–}\mathbf{E}^+][\mathbf{1a}]}{[\mathbf{1a}\text{–}\mathbf{E}^+][\mathbf{1c}]} = \frac{\frac{[\mathbf{1c}\text{–}\mathbf{E}^+]}{[\mathbf{1c}]}}{\frac{[\mathbf{1a}\text{–}\mathbf{E}^+]}{[\mathbf{1a}]}} = \frac{\frac{[\mathbf{1c}\text{–}\mathbf{E}^+]}{[\mathbf{1c}][\mathbf{E}^+]}}{\frac{[\mathbf{1a}\text{–}\mathbf{E}^+]}{[\mathbf{1a}][\mathbf{E}^+]}} = \frac{K_1}{K_2}$ where [**1a**–**E**$^+$] & [**1c**–**E**$^+$] are the concentrations of the Lewis acid–base adducts of **2h** with **1a** & **1c**, respectively, and [**E**$^+$] is the concentration of the Lewis acid $(\text{mfa})_2\text{CH}^+$. 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 spectrum of the mixture.

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