Nucleophilicities and Lewis basicities of imidazoles, benzimidazoles, and benzotriazoles†‡

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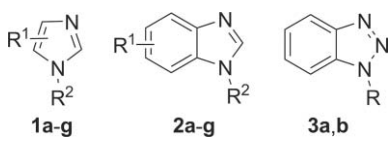
The kinetics of the reactions of some imidazoles, benzimidazoles and benzotriazoles with benzhydrylium ions (diarylcarbenium ions) have been studied photometrically in DMSO, acetonitrile, and aqueous solution at 20 °C. The resulting second-order rate constants have been used to determine the nucleophile-specific parameters N and s of these azoles according to the linear-free-energy relationship $\log k$ (20 °C) = $s(N + E)$. With $N = 11.47$ (imidazole in acetonitrile), $N = 10.50$ (benzimidazole in DMSO), and $N = 7.69$ (benzotriazole in acetonitrile) these azoles are significantly less nucleophilic than previously characterized amines, such as DMAP ($N = 14.95$ in acetonitrile) and DABCO ($N = 18.80$ in acetonitrile). For some reactions of the 1-methyl substituted azoles with benzhydrylium ions equilibrium constants have been measured, which render a comparison of the Lewis basicities of these compounds. Substitution of the rate and equilibrium constants of these reactions into the Marcus equation yields the corresponding intrinsic barriers $\Delta G_0^{\neq}$. From the ranking of $\Delta G_0^{\neq}$ (imidazoles > pyridines > 1-azabicyclooctanes) one can derive that the reorganization energies for the reactions of imidazoles with electrophiles are significantly higher than those for the other amines and that imidazoles are less nucleophilic than pyridines and 1-azabicyclooctanes of comparable basicity.

Introduction

Azoles, such as imidazoles, benzimidazoles, and benzotriazoles, are important reagents in organic synthesis.[1] They are common structural motifs in natural products, and several N-substituted azoles have become well established drugs,[1d–g] which can be synthesized by metal catalyzed N-arylation[2] and N-allylation[3] of imidazoles and benzimidazoles. Iminium catalyzed enantioselective 1,4-conjugate additions of azoles to α,β-unsaturated aldehydes have been reported by Jørgensen *et al.* and Vicario *et al.* and reviewed by Buckley and Enders.[4] A chiral [(salen)Al] complex was used as catalyst for conjugate additions of azoles to α,β-unsaturated ketones and imides by Jacobsen and Gandelman.[5] Wang and co-workers reported cinchona alkaloid-catalyzed enantioselective additions of benzotriazole to nitroolefins.[6] The nucleophilic displacement of acetoxy groups in Baylis–Hillman acetates by imidazoles and benzimidazoles under DABCO-catalysis has been demonstrated by Zhang *et al.*[7]

Since the discovery of the participation of the imidazole moiety of histidine in the active center of several enzymes,[8] imidazole and its derivatives have become a natural choice as organocatalysts for a manifold of reactions[9] in particular for acylation reactions.[10] Miller has designed imidazole containing small peptides for kinetic resolutions of alcohols.[10h] Recently Ishihara and co-workers developed artificial acylases derived from L-histidine for the kinetic resolution of mono-protected *cis*-1,2-diols and N-acylated 1,2-amino alcohols.[10j] Imidazoles have also been used to promote Baylis–Hillman and aza-Morita–Baylis–Hillman reactions[11] including reactions of nitroalkenes with carbonyl compounds and azodicarboxylates.[12] Six-membered carbocycles have been obtained by imidazole-catalyzed reactions of nitroalkenes with two equivalents of benzylidenemalononitriles.[13] Recently 1-methylimidazole was employed for transferring the thiocyanate group from acylisothiocyanates to phenacyl or benzyl bromides.[14]

Though all of these reactions have been rationalized by the nucleophilic properties of azoles,[15] quantitative studies of their reactivities are rare.[16] It was the goal of this investigation to quantify the nucleophilicities and Lewis basicities of imidazoles **1a–g**, benzimidazoles **2a–g**, and benzotriazoles **3a,b** (Scheme 1) in comparison with previously characterized nucleophilic organocatalysts. For this purpose we have performed kinetic and equilibrium studies with the title azoles by employing the benzhydrylium methodology where benzhydrylium ions (diarylcarbenium ions, Table 1) are used as reference electrophiles and reference Lewis acids.[17]



Scheme 1 Azoles investigated in this work (for precise structures see Table 3).

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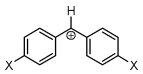
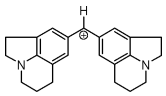
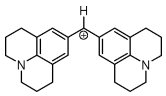
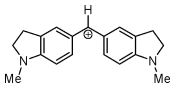
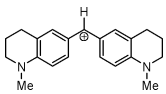
† Dedicated to Professor Christian Reichardt on the occasion of his 75th birthday.

‡ Electronic supplementary information (ESI) available: Synthetic procedures and product characterization, details of the determination of rate and equilibrium constants. See DOI: 10.1039/c000965b

Table 1 Abbreviations and electrophilicity parameters E of the benzhydrylium ions Ar_2CH^+

Ar_2CH^+		E[a]
$(lil)_2CH^+$		−10.04
$(jul)_2CH^+$		−9.45
$(ind)_2CH^+$		−8.76
$(thq)_2CH^+$		−8.22
$(pyr)_2CH^+$	X = $N(CH_2)_4$	−7.69
$(dma)_2CH^+$	X = $N(CH_3)_2$	−7.02
$(mpa)_2CH^+$	X = $N(Ph)CH_3$	−5.89
$(mor)_2CH^+$	X = $N(CH_2CH_2)_2O$	−5.53
$(mfa)_2CH^+$	X = $N(CH_3)CH_2CF_3$	−3.85
$(pfa)_2CH^+$	X = $N(Ph)CH_2CF_3$	−3.14

[a] Empirical electrophilicity parameter from ref. 17a.

Results and discussion

Product studies

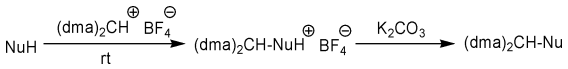
When solutions of $(dma)_2CH^+BF_4^-$ in acetonitrile were added to solutions of imidazoles in acetonitrile at room temperature, 1-benzhydryl substituted imidazoles were formed and isolated after deprotonation with K_2CO_3 (Table 2, entries 1, 2). 1-Benzhydryl substituted benzimidazoles were obtained analogously in DMSO solutions (Table 2, entries 3–5). Unsymmetrical imidazoles or benzimidazoles yield mixtures of regioisomers. While 5-methylbenzimidazole renders equal amounts of both regioisomers (entry 4), 4-methylimidazole yields a 1.0 : 0.4 mixture of 4-methyl and 5-methyl-1-benzhydrylimidazole (entry 2), the constitution of which was derived from two-dimensional ^{1}H NMR spectroscopy. This ratio may be rationalized by the repulsive steric interaction of the *ortho*-substituents in the 5-methyl-isomer. Details of individual experiments are given in the ESI.‡

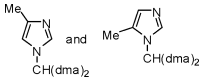
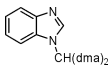
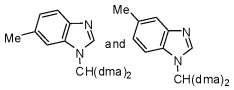
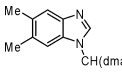
Products of the reactions of benzotriazole with highly reactive benzhydrylium ions ($E > 0$) have previously been reported.[18] We have now observed that the reactions with amino-substituted benzhydrylium ions ($E < -7$) are highly reversible. Only small amounts of carbocations were consumed even when high concentrations of benzotriazole were added, and products from the reactions of highly stabilized benzhydrylium ions with benzotriazole could not be isolated.

Kinetics

Rates of the reactions of the imidazoles **1**, benzimidazoles **2**, and benzotriazoles **3** (Table 3) with benzhydrylium ions (Table 1) were determined by monitoring the decay of the benzhydrylium

Table 2 Benzhydrylations of imidazoles and benzimidazoles



Entry	NuH		Solvent	Product	Yield/%[a]
1		**1a**	CH_3CN		87
2		**1e**	CH_3CN		82[b]
3		**2a**	DMSO		76
4		**2d**	DMSO		74[c]
5		**2f**	DMSO		84

[a] Isolated yield. [b] 1.0 : 0.4 mixture of regioisomers. [c] 1 : 1 mixture of regioisomers.

absorbances after combining the benzhydrylium tetrafluoroborates with the azoles **1–3** using stopped-flow techniques or conventional UV-Vis spectrometers equipped with fiber optics as described previously.[17] As **1–3** are generally used in high excess over the benzhydrylium ions to achieve pseudo-first-order conditions, the absorbances of the benzhydrylium ions decrease monoexponentially (Fig. 1) and the pseudo-first-order rate constants k_{obs} (s^{-1}) were obtained by fitting the decays of the absorbances to the monoexponential function $A = A_0 \exp(-k_{obs}t) + C$.

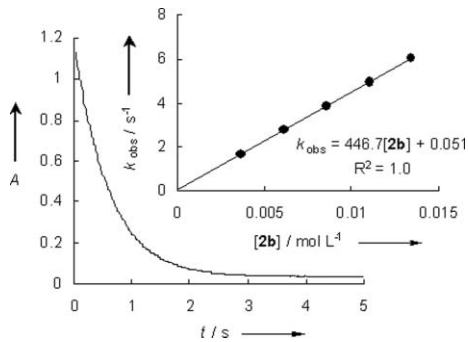


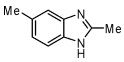
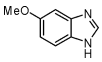
Fig. 1 Exponential decay of the absorbance A at 610 nm and linear correlation of the pseudo-first-order rate constants k_{obs} *vs.* [**2b**] for the reaction of $(dma)_2CH^+BF_4^-$ with **2b** in acetonitrile at 20 °C.

Plots of k_{obs} *versus* the concentrations of **1–3** were linear with the second-order rate constants k (M^{-1} s^{-1}) being the slopes of the correlations lines (Fig. 1, Table 3). Because most benzimidazoles **2** have low solubility in CH_3CN, and on the other side DMSO reacts with benzhydrylium ions which are more reactive than $(dma)_2CH^+$, it was not possible to perform all kinetic investigations in one of these solvents. However, kinetic studies with the parent compound **1a** show that the rate constants of its reactions with

Table 3 Second-order rate constants (k) for the reactions of azoles **1–3** with the benzhydrylium ions (Ar_2CH^+) in different solvents at 20 °C

	Azoles	solvent	N, s	Ar_2CH^+	$k/M^{-1}s^{-1}$
1a		CH_3CN	11.47, 0.79	$(ind)_2CH^+$	1.24×10^2
				$(thq)_2CH^+$	3.52×10^2
				$(pyr)_2CH^+$	1.14×10^3
				$(dma)_2CH^+$	2.74×10^3
		DMSO	11.58, 0.79	$(ind)_2CH^+$	1.37×10^2
				$(thq)_2CH^+$	4.78×10^2
				$(pyr)_2CH^+$	1.61×10^3
				$(dma)_2CH^+$	3.09×10^3
		H_2O	9.63, 0.57	$(lil)_2CH^+$	6.10×10^{-1}
				$(jul)_2CH^+$	1.23
				$(pyr)_2CH^+$	1.22×10^1
				$(dma)_2CH^+$	3.22×10^1
1b		CH_3CN	11.90, 0.73	$(lil)_2CH^+$	2.33×10^1
				$(ind)_2CH^+$	1.88×10^2
				$(thq)_2CH^+$	4.81×10^2
				$(pyr)_2CH^+$	1.44×10^3
				$(dma)_2CH^+$	3.48×10^3
		H_2O	9.91, 0.55	$(lil)_2CH^+$	9.44×10^{-1}
				$(ind)_2CH^+$	3.79
				$(thq)_2CH^+$	8.01
				$(pyr)_2CH^+$	1.63×10^1
				$(dma)_2CH^+$	4.51×10^1
1c		CH_3CN	11.31, 0.67	$(thq)_2CH^+$	9.44×10^1
				$(pyr)_2CH^+$	2.64×10^2
				$(dma)_2CH^+$	7.29×10^2
				$(mpa)_2CH^+$	6.75×10^3
				$(mor)_2CH^+$	5.21×10^3
				$(mfa)_2CH^+$	8.14×10^4
1d		CH_3CN	11.74, 0.76	$(lil)_2CH^+$	1.95×10^1
				$(jul)_2CH^+$	5.27×10^1
				$(ind)_2CH^+$	1.72×10^2
				$(thq)_2CH^+$	4.73×10^2
				$(pyr)_2CH^+$	1.47×10^3
				$(dma)_2CH^+$	3.29×10^3
		H_2O	9.45, 0.54	$(lil)_2CH^+$	5.38×10^{-1}
				$(ind)_2CH^+$	1.92
				$(thq)_2CH^+$	4.66
				$(pyr)_2CH^+$	8.72
				$(dma)_2CH^+$	2.21×10^1
1e		CH_3CN	11.79, 0.77	$(lil)_2CH^+$	2.37×10^1
				$(jul)_2CH^+$	6.41×10^1
				$(ind)_2CH^+$	1.96×10^2
				$(thq)_2CH^+$	5.23×10^2
				$(pyr)_2CH^+$	1.76×10^3
				$(dma)_2CH^+$	4.59×10^3
1f		CH_3CN	11.51, 0.84	$(jul)_2CH^+$	4.96×10^1
				$(ind)_2CH^+$	2.44×10^2
				$(thq)_2CH^+$	4.92×10^2
				$(pyr)_2CH^+$	2.06×10^3
				$(dma)_2CH^+$	5.41×10^3
1g		CH_3CN	11.43, 0.79	$(jul)_2CH^+$	3.69×10^1
				$(ind)_2CH^+$	1.20×10^2
				$(pyr)_2CH^+$	1.03×10^3
				$(dma)_2CH^+$	2.74×10^3
				$(mpa)_2CH^+$	2.34×10^4
2a		DMSO	10.50, 0.79	$(jul)_2CH^+$	6.97
				$(ind)_2CH^+$	1.96×10^1
				$(thq)_2CH^+$	6.55×10^1
				$(pyr)_2CH^+$	2.19×10^2
				$(dma)_2CH^+$	4.65×10^2
2b		CH_3CN	10.37, 0.82	$(ind)_2CH^+$	2.02×10^1
				$(thq)_2CH^+$	5.97×10^1
				$(pyr)_2CH^+$	1.60×10^2
				$(dma)_2CH^+$	4.47×10^2
				$(mpa)_2CH^+$	4.84×10^3
2c		DMSO	10.02, 0.85	$(jul)_2CH^+$	2.89
				$(ind)_2CH^+$	1.08×10^1
				$(thq)_2CH^+$	3.38×10^1
				$(pyr)_2CH^+$	1.39×10^2
				$(dma)_2CH^+$	2.75×10^2

Table 3 (*Contd.*)

	Azoles	solvent	N, s	Ar_2CH^+	$k/M^{-1}s^{-1}$
2d		DMSO	10.69, 0.79	$(jul)_2CH^+$	9.75
				$(ind)_2CH^+$	2.73×10^1
				$(thq)_2CH^+$	9.13×10^1
				$(pyr)_2CH^+$	3.19×10^2
				$(dma)_2CH^+$	6.37×10^2
2e		DMSO	10.21, 0.85	$(jul)_2CH^+$	4.53
				$(ind)_2CH^+$	1.45×10^1
				$(thq)_2CH^+$	4.75×10^1
				$(pyr)_2CH^+$	2.00×10^2
				$(dma)_2CH^+$	4.12×10^2
2f		DMSO	11.08, 0.71	$(lil)_2CH^+$	5.87
				$(jul)_2CH^+$	1.46×10^1
				$(ind)_2CH^+$	3.65×10^1
				$(thq)_2CH^+$	1.18×10^2
				$(dma)_2CH^+$	8.03×10^2
2g		DMSO	11.0, 0.71	$(lil)_2CH^+$	4.62
				$(jul)_2CH^+$	1.22×10^1
3a		CH_3CN	7.69, 0.76	$(dma)_2CH^+$	h.r.[b]
				$(mor)_2CH^+$	4.50×10^1
				$(mfa)_2CH^+$	8.64×10^2
3b		CH_3CN	7.77, (0.76)[a]	$(pyr)_2CH^+$	n.r.[c]
				$(dma)_2CH^+$	n.r.[c]
				$(mfa)_2CH^+$	9.46×10^2

[a] N was calculated from the single rate constant, see text. [b] h.r. = highly reversible. [c] n.r. = no reaction.

various benzhydrylium ions differ by less than a factor of 1.4 in DMSO and CH_3CN. For that reason one can neglect solvent effects when comparing rate constants determined in any of these two solvents.

Some rate constants for the reactions of imidazoles with benzhydrylium ions have also been determined in water. When an amine is dissolved in water, the concentration of hydroxide ions increases by protolysis. For that reason competing reactions of the carbocations with hydroxide have to be considered.[19] However, the pK_{aH} values of imidazoles **1** in H_2O are close to 7;[20] therefore, only very small amounts of hydroxide ions will be generated which are negligible when evaluating the kinetic experiments. This statement is quantified in the ESI (pp. S49–S51),‡ where the second-order rate constant for the reaction of 2-methylimidazole (**1d**) with $(ind)_2CH^+$ was calculated with and without consideration of the contribution of hydroxide ions. Both methods yielded identical second-order rate constants and because the other azoles have similar or even smaller pK_{aH} values, we have generally neglected the effect of OH^-. As the reactions of benzhydrylium ions with water[21] are also very slow compared to the corresponding reactions with imidazoles, the second-order rate constants for the reactions of azoles **1** with benzhydrylium ions in water (Table 3) were determined without considering the contribution from hydroxide ions and water, following the procedure described for the reactions in acetonitrile and DMSO.

Correlation analysis

In numerous publications we have shown that the rate constants for the reactions of carbocations with nucleophiles can be described by eqn (1) where electrophiles are characterized by the electrophilicity parameter E and nucleophiles are characterized

by the nucleophilicity parameter N and the nucleophile-specific slope parameter s. On this basis it became possible to compare the reactivities of numerous σ-, n-, and π-nucleophiles in a single scale.[17]

$$\log k(20\ ^\circ\mathrm{C}) = s(N + E) \quad (1)$$

Fig. 2 correlates second-order rate constants k (Table 3) with the previously published electrophilicity parameters E (Table 1). The linear correlations for the different reaction series demonstrate that the reactions of carbocations with the azoles **1–3** also follow eqn (1). The slopes of these correlations yield the nucleophile-specific parameters s, and the intercepts on the abscissa give the nucleophilicity parameters N listed in Table 3.

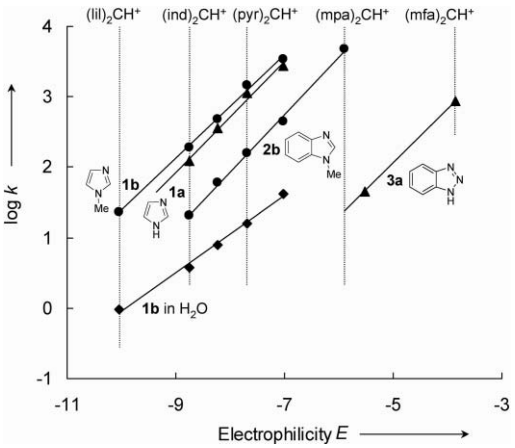


Fig. 2 Plots of log k for the reactions of **1–3** with the benzhydrylium ions *versus* the electrophilicity parameters E in acetonitrile at 20 °C (**1b** also in H_2O; for the sake of clarity only a few correlation lines are shown, for other correlations see ESI‡).

In agreement with our earlier observations,[17b] Table 3 demonstrates that structurally related nucleophiles have closely similar s values in a particular solvent. Therefore, the nucleophilicity parameter N of **3b** was derived from the rate constant for its reaction with $(mfa)_2CH^+$ in CH_3CN assuming $s = 0.76$ as for **3a**.

The almost parallel correlation lines in Fig. 2 imply that the relative reactivities of the N-heterocyclic compounds **1–3** are almost independent of the reactivities of electrophiles (Ar_2CH^+). Table 3 and Fig. 2 show that in acetonitrile imidazoles **1** are one and three orders of magnitude more nucleophilic than the benzimidazoles **2** and the benzotriazoles **3**, respectively.

Because of the paucity of pK_{aH} values for **1–3** in organic solvents, pK_{aH} values in water have been used for the Brønsted correlations shown in Fig. 3.[20,22] Though the correlation is not very good, one can see that in general the nucleophilicities increase with basicities.

Fig. 4 shows that the second-order rate constant for the reaction of the parent imidazole **1a** with $(pyr)_2CH^+BF_4^-$ decreases with increasing solvent polarity $E_T{}^N$.[23] The reactions in water are approximately two orders of magnitude slower than in CH_3CN and DMSO.

Fig. 5 compares the nucleophilicities of azoles with those of other nucleophilic organocatalysts and some compounds which have been used as nucleophilic substrates in iminium catalyzed reactions.[25,26] The N-values show that the imidazoles **1** are among the weakest nucleophiles of the commonly used catalysts in Baylis–

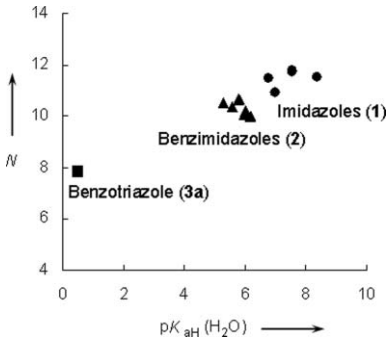


Fig. 3 Plots of nucleophilicity parameters N (in CH_3CN or DMSO) *vs.* pK_{aH} (H_2O) for the azoles **1–3**.

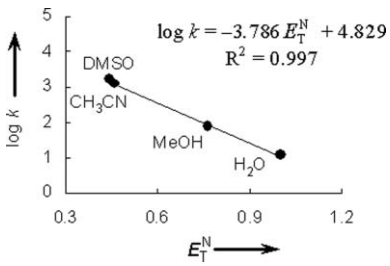


Fig. 4 Plot of rate constants log k *vs.* $E_T{}^N$ for the reactions of imidazole **1a** with $(pyr)_2CH^+$ BF_4^- in different solvents at 20 °C.[24]

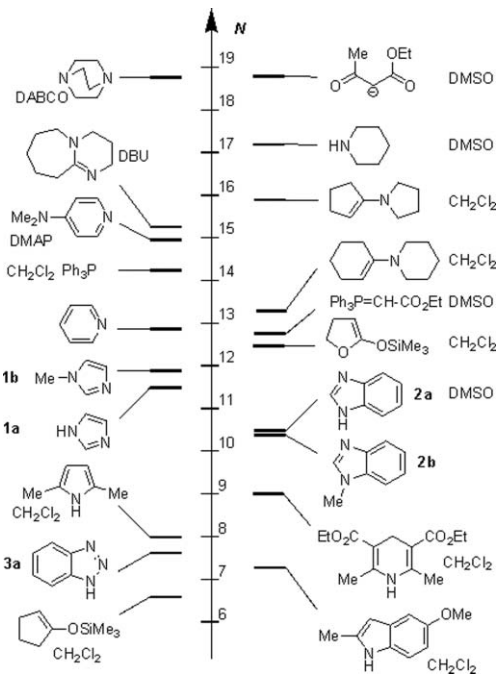


Fig. 5 Comparison of the nucleophilicities of organocatalysts and of nucleophilic substrates used in organocatalysis (solvent is CH_3CN unless otherwise mentioned, N from ref. 25, 26).

Hillman reactions. They are more than six orders of magnitude less nucleophilic than DABCO and 10^2 to 10^3 times less nucleophilic than Ph_3P, DBU, and DMAP. While the reactivities of the imidazoles are comparable to those of cyclic ketene acetals, they are considerably higher ($\Delta N \geq 2.5$) than those of Hantzsch ester,

pyrroles, indoles, and silyl enol ethers. Ordinary enamines are also more nucleophilic than imidazoles.

Lewis basicities and intrinsic barriers

In previous work we have shown that nucleophilicity is not the only factor controlling the efficiency of nucleophilic organocatalysts. Lewis basicity towards an electron deficient carbon center is an equally important issue.[25h,i] Therefore, we have also determined the equilibrium constants for the reactions of azoles with benzhydrylium ions (eqn (2)).

$$Ar_2CH^+ + NR_3 \underset{CH_3CN}{\overset{K}{\rightleftharpoons}} Ar_2CH\text{-}NR_3^+ \quad (2)$$

While most of the azoles **1–3** react quantitatively with the benzhydrylium tetrafluoroborates, some of the reactions proceed incompletely. As benzhydrylium ions are colored and the resulting adducts are colorless, the equilibrium constants can be determined by UV-Vis spectroscopy. Assuming proportionality between the absorbances and the concentrations of the benzhydrylium ions (Lambert–Beer law), the equilibrium constants K for reaction (2) can be expressed by the absorbances of the benzhydrylium ions before (A_0) and after (A) addition of the amines (eqn (3)).

$$K = \frac{[Ar_2CH\text{-}NR_3^+]}{[Ar_2CH^+][NR_3]} = \frac{A_0 - A}{A[NR_3]} \quad (3)$$

$$\text{Where } [NR_3] = [NR_3]_0 - [Ar_2CH\text{-}NR_3^+]$$

Comparison of the equilibrium constants in Table 4 shows that 1-methylimidazole **1b** is a 30 times stronger Lewis base than 1-methylbenzimidazole **2b** and a 50–60 times stronger Lewis base than 1-phenylimidazole **1c**. Though a direct comparison of the Lewis basicity of the benzotriazole **3b** with the Lewis basicities of imidazole **1b** and benzimidazole **2b** is not possible, it is obvious that 1-methylbenzotriazole **3b** is a much weaker Lewis base because it only gives adducts with less stabilized carbocations ($E > -7$).

Fig. 6 shows that the nucleophilicities (k) and Lewis basicities (K) of different organocatalysts towards a carbon center do not correlate with each other. Despite the fact that 1-methylimidazole **1b** has a higher Lewis basicity than DABCO and Ph_3P, it is less nucleophilic. DMAP is a 100 times stronger Lewis base than 1-methylimidazole **1b**. This absence of a rate-equilibrium-relationship indicates the presence of different intrinsic barriers.[27]

Table 4 Equilibrium constants (K) for the reactions of the azoles **1-3** with benzhydrylium ions in CH_3CN at 20 °C

Azoles	Ar_2CH^+	K/M^{-1}
1b	$(lil)_2CH^+$	2.44×10^2
	$(jul)_2CH^+$	2.42×10^2
	$(ind)_2CH^+$	5.56×10^3
	$(thq)_2CH^+$	8.69×10^3
1c	$(ind)_2CH^+$	9.08×10^1
	$(thq)_2CH^+$	1.83×10^2
	$(pyr)_2CH^+$	4.72×10^2
	$(dma)_2CH^+$	4.99×10^3
2b	$(ind)_2CH^+$	1.86×10^2
	$(thq)_2CH^+$	2.60×10^2
	$(pyr)_2CH^+$	9.99×10^2
	$(dma)_2CH^+$	1.11×10^4
3b	$(mfa)_2CH^+$	2.11×10^2
	$(pfa)_2CH^+$	8.54×10^3

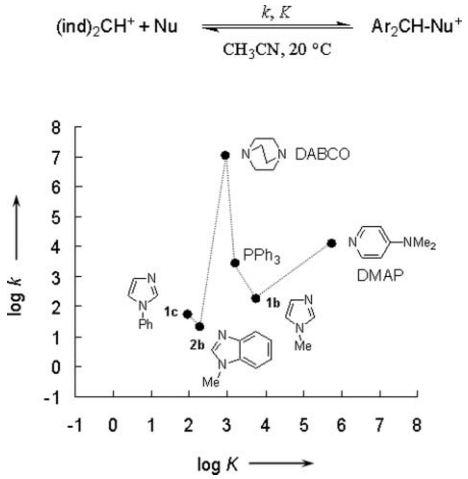


Fig. 6 Relationship between rate and equilibrium constants of the reaction of $(ind)_2CH^+$ with different Lewis bases in CH_3CN at 20 °C. Data from Tables 3 and 4 and ref. 25h and 28; log k for **1c** was calculated from N, s, and E.

From the rate (Table 3) and equilibrium constants (Table 4) one can calculate activation free energies $\Delta G^{\neq}$ (using the Eyring equation) and reaction free energies ΔG^0 ($-RT\ \ln K$) for the reactions of the azoles **1–3** with benzhydrylium ions (Ar_2CH^+). Substitution of these values into the Marcus equation (eqn (4)) yields the intrinsic barriers $\Delta G_0^{\neq}$, which are defined as the activation free energies of processes with $\Delta G^0 = 0$.[27]

$$\Delta G^{\neq} = \Delta G_0^{\neq} + 0.5\ \Delta G^0 + ((\Delta G^0)^2/16\Delta G_0^{\neq}) \quad (4)$$

In line with previous studies,[19a,25g,h,29] Table 5 shows that for reactions with a certain azole, the intrinsic barriers $\Delta G_0^{\neq}$ decrease slightly with increasing reactivity of the benzhydrylium ions, though this decrease is not steady. Comparison of the intrinsic barriers referring to reactions with the same carbocations shows that those for the reactions of the imidazoles **1b**,**c** are similar and

Table 5 Activation energies $\Delta G^{\neq}$, reaction free energies ΔG^0, intrinsic barriers $\Delta G_0^{\neq}$ (in kJ mol^{-1}) and rate constants of the reverse reactions $k_{\leftarrow}$ for the reactions of benzhydrylium ions with azoles **1–3** in CH_3CN at 20 °C

Azoles	Ar_2CH^+	$\Delta G^{\neq}$	ΔG^0	$\Delta G_0^{\neq}$	$k_{\leftarrow}$/s^{-1}
1b	$(lil)_2CH^+$	64.1	−13.4	70.6	0.10
	$(ind)_2CH^+$	59.0	−21.0	69.1	0.034
	$(thq)_2CH^+$	56.7	−22.1	67.3	0.055
1c	$(thq)_2CH^+$	60.7	−12.7	66.9	0.52
	$(pyr)_2CH^+$	58.2	−15.0	65.5	0.56
	$(dma)_2CH^+$	55.7	−20.7	65.6	0.15
2b	$(ind)_2CH^+$	64.4	−12.7	70.6	0.11
	$(thq)_2CH^+$	61.8	−13.5	68.4	0.23
	$(pyr)_2CH^+$	59.4	−16.8	67.5	0.16
	$(dma)_2CH^+$	56.9	−22.7	67.8	0.040
3b	$(mfa)_2CH^+$	55.1	−13.0	61.4	4.5
DMAP[a,b]	$(lil)_2CH^+$	53.1	−24.6	64.8	0.086
	$(ind)_2CH^+$	48.7	−32.2	63.8	0.023
	$(thq)_2CH^+$	46.4	(−33.7)	(62.1)	(3×10^{-2})
DABCO[a,b]	$(ind)_2CH^+$	32.2	(−16.2)	(39.9)	(1×10^4)
	$(thq)_2CH^+$	30.0	−17.9	38.4	1.79×10^4
	$(pyr)_2CH^+$	27.7	−20.7	37.3	1.42×10^4
Ph_3P	$(ind)_2CH^+$	52.4	−18.0	61.1	1.7

[a] $\Delta G^{\neq}$, ΔG^0, and $k_{\leftarrow}$ values for DMAP and DABCO from ref. 25h; $\Delta G_0^{\neq}$ has been recalculated. [b] Values in parentheses were estimated in ref. 25h.

1–2 kJ mol^{-1} lower than those for benzimidazole **2b**. The reactions involving **1b** have intrinsic barriers which are 5–6 kJ mol^{-1} higher than those for the corresponding reactions with DMAP because electrophilic attack at the unsubstituted nitrogen is associated with a significant structural reorganization, *i.e.* lengthening of CN-double bond and shortening of the vicinal CN-bond.[25h] This finding is in line with the principle of least motion which was used by Hine to rationalize why imidazoles abstract protons more slowly than pyridines of comparable basicity.[30] From the comparison of the reaction free energies ΔG^0, it is clear that imidazole **1b** is a significantly stronger Lewis base than DABCO ($\Delta\Delta G^0 = 5$ kJ mol^{-1}). It is the large reorganization energy for the electrophilic attack at the imidazoles, which gives rise to the high intrinsic barriers of these reactions and eventually leads to the much lower nucleophilicities of imidazoles compared with DABCO. The higher nucleophilicity of Ph_3P compared with the stronger Lewis base imidazole **1b** can analogously be assigned to the 8 kJ mol^{-1} difference of the intrinsic barriers.

Combination of the rate constants in Table 3 with the equilibrium constants in Table 4 yields the rate constants for the reverse reactions ($k_{\leftarrow}$) which reflect the leaving group abilities of these amines (last column, Table 5).[31] While the leaving group ability of 1-methylimidazole **1b** is 3–4 times smaller than that of 1-methylbenzimidazole **2b**, it is comparable to that of DMAP and 3×10^5 times smaller than that of DABCO.

Conclusion

The rate constants of the reactions of imidazoles and benzimidazoles with benzhydrylium ions follow the linear free energy relationship (eqn (1)). It is, therefore, possible to determine the nucleophilicity parameters N for these azoles and compare them with those of other amines and phosphines. The poor correlation between N and pK_{aH} shows that Brønsted basicities cannot be used for predicting relative nucleophilicities. Because pK_{aH} values refer to relative basicities towards the proton, while the nucleophilicity parameters N refer to the rates of reactions with an electrophilic carbon center, the origin of the poor Brønsted correlation has previously been not clear.

By using benzhydrylium ions of variable reactivity as reaction partners, it was possible to find systems for which rate and equilibrium constants could be determined. Substitution of these data into the Marcus equation rendered the corresponding intrinsic barriers $\Delta G_0^{\neq}$ which decreased in the order imidazoles > pyridines ≫ 1-azabicyclooctane. As a result, imidazoles are weaker nucleophiles than pyridines, and much weaker nucleophiles than 1-azabicyclooctanes of comparable Lewis and Brønsted basicity. Because rate and equilibrium constants refer to reactions with the same substrate, the low nucleophilicities of imidazoles can now unambiguously be assigned to the high reorganization energies required for their reactions with electrophiles.

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Notes and references

1 (*a*) A. F. Pozharskii, A. T. Soldatenkov and A. R. Katritzky, *Heterocycles in Life and Society*, Wiley, New York, 1997; (*b*) A. R. Katritzky and A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, 2nd ed, Pergamon, Oxford, 2000; (*c*) A. R. Katritzky, X. Lan, J. Z. Yang and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409–548; (*d*) I. L. Kruse, in *Comprehensive Medicinal Chemistry*, C. Hansch, P. G. Sammes, J. B. Taylor, Eds, Pergamon Press: Oxford, England, 1990, vol. 2, pp 123–145; (*e*) F. Corelli, V. Summa, A. Brogi, E. Monteagudo and M. Botta, *J. Org. Chem.*, 1995, **60**, 2008–2015; (*f*) M. C. Venuti, R. A. Stephenson, R. Alvarez, J. J. Bruno and A. M. Strosberg, *J. Med. Chem.*, 1988, **31**, 2136–2145; (*g*) M. Botta, F. Corelli, F. Gasparrini, F. Messina and C. Mugnaini, *J. Org. Chem.*, 2000, **65**, 4736–4739.

2 For arylation reactions see: (*a*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337–2364; (*b*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449; (*c*) R. A. Altman and S. L. Buchwald, *Org. Lett.*, 2006, **8**, 2779–2782; (*d*) R. Jitchati, A. S. Batsanov and M. R. Bryce, *Tetrahedron*, 2009, **65**, 855–861.

3 For allylation reactions see: L. M. Stanley and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 8971–8983.

4 (*a*) P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1983–1987; (*b*) U. Uria, J. L. Vicario, D. Badia and L. Carrillo, *Chem. Commun.*, 2007, 2509–2511; (*c*) B. R. Buckley, *Annu. Rep. Prog. Chem., Sect. B*, 2008, **104**, 88–105; (*d*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058–11076.

5 M. Gandelman and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 2393–2397.

6 J. Wang, H. Li, L. Zu and W. Wang, *Org. Lett.*, 2006, **8**, 1391–1394.

7 J. Li, X. Wang and Y. Zhang, *Tetrahedron Lett.*, 2005, **46**, 5233–5237.

8 F. Schneider, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 583–592 and the references therein.

9 Books: (*a*) P. I. Dalko, *Enantioselective organocatalysis*, Wiley-VCH, Weinheim, 2007; (*b*) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, 2005.

10 (*a*) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 1957, **79**, 1652–1655; (*b*) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 1959, **234**, 1272–1279; (*c*) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 1959, **234**, 1280–1285; (*d*) R. Wolfenden and W. P. Jencks, *J. Am. Chem. Soc.*, 1961, **83**, 4390–4393; (*e*) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 833–837; (*f*) K. A. Connors and N. K. Pandit, *Anal. Chem.*, 1978, **50**, 1542–1545; (*g*) R. L. Kogan and T. H. Fife, *Biochemistry*, 1984, **23**, 2983–2989; (*h*) S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601–610; (*i*) B.-K. Liu, Q. Wu, J.-M. Xu and X.-F. Lin, *Chem. Commun.*, 2007, 295–297; (*j*) K. Ishihara, Y. Kosugi and M. Akakura, *J. Am. Chem. Soc.*, 2004, **126**, 12212–12213; (*k*) K. Martinek, A. P. Osipov, A. K. Yatsimirski and I. V. Berezin, *Tetrahedron*, 1975, **31**, 709–718.

11 (*a*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811–892; (*b*) S. Luo, B. Zhang, J. He, A. Janczuk, P. G. Wang and J.-P. Cheng, *Tetrahedron Lett.*, 2002, **43**, 7369–7371; (*c*) R. Gatri and M. M. E. Gaied, *Tetrahedron Lett.*, 2002, **43**, 7835–7836; (*d*) J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2003, **5**, 3741–3743; (*e*) S. Luo, X. Mi, P. G. Wang and J.-P. Cheng, *Tetrahedron Lett.*, 2004, **45**, 5171–5174; (*f*) S. Luo, P. G. Wang and J.-P. Cheng, *J. Org. Chem.*, 2004, **69**, 555–558; (*g*) C. E. Aroyan, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2005, **7**, 3849–3851; (*h*) S.-H. Chen, B.-C. Hong, C.-F. Su and S. Sarshar, *Tetrahedron Lett.*, 2005, **46**, 8899–8903; (*i*) N. Utsumi, H. Zhang, F. Tanaka and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2007, **46**, 1878–1880.

12 (*a*) I. Deb, M. Dadwal, S. M. Mobin and I. N. N. Namboothiri, *Org. Lett.*, 2006, **8**, 1201–1204; (*b*) M. Dadwal, S. M. Mobin and I. N. N. Namboothiri, *Org. Biomol. Chem.*, 2006, **4**, 2525–2528.

13 (*a*) X.-G. Liu and M. Shi, *Eur. J. Org. Chem.*, 2008, 6168–6174; See also (*b*) M. Adib, B. Mohammadi, M. Mahdavi, A. Abbasi and M. R. Kesheh, *Synlett*, 2007, 2497–2500.

14 C. C. Palsuledesai, S. Murru, S. K. Sahoo and B. K. Patel, *Org. Lett.*, 2009, **11**, 3382–3385.

15 For more examples of nucleophilic behaviour of N-heterocycles see: (*a*) R. K. Howe, *J. Org. Chem.*, 1969, **34**, 2983–2985; (*b*) M. J. Alves, A. G. Fortes and L. F. Goncalves, *Tetrahedron Lett.*, 2003, **44**, 6277–6279; (*c*) D. Lin, J. Zhang and L. M. Sayre, *J. Org. Chem.*, 2007, **72**, 9471–9480; (*d*) W. Zhang, L. Zhu and J. Hu, *Tetrahedron*, 2007, **63**, 10569–10575; (*e*) M. D. S. Maria, R. M. Claramunt, M. A. Garcia and

J. Elguero, *Tetrahedron*, 2007, **63**, 3737–3744; (*f*) W. Zhang, F. Wang and J. Hu, *Org. Lett.*, 2009, **11**, 2109–2112; (*g*) K. F. Ansari and C. Lal, *Eur. J. Med. Chem.*, 2009, **44**, 4028–4033.
16 (*a*) C. K. M. Heo and J. W. Bunting, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2279–2290; (*b*) A. A. Matveev, A. N. Vdovichenko, A. F. Popov, L. M. Kapkan, A. Y. Chervinskii and V. N. Matvienko, *Russ. J. Org. Chem.*, 1995, **31**, 1646–1649.
17 (*a*) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov and H. Schimmel, *J. Am. Chem. Soc.*, 2001, **123**, 9500–9512; (*b*) H. Mayr, B. Kempf and A. R. Ofial, *Acc. Chem. Res.*, 2003, **36**, 66–77; (*c*) H. Mayr and A. R. Ofial, *J. Phys. Org. Chem.*, 2008, **21**, 584–595; (*d*) H. Mayr and A. R. Ofial, *Pure Appl. Chem.*, 2005, **77**, 1807–1821.
18 (*a*) A. R. Katritzky and B. Yang, *J. Heterocycl. Chem.*, 1996, **33**, 607–610; (*b*) Also see ref. 1c.
19 For the contribution of OH^- in reactions of amines in aqueous solution see: (*a*) F. Brotzel, B. Kempf, T. Singer, H. Zipse and H. Mayr, *Chem.–Eur. J.*, 2007, **13**, 336–345; (*b*) F. Brotzel, Y. C. Chu and H. Mayr, *J. Org. Chem.*, 2007, **72**, 3679–3688.
20 pK_{aH} values (*a*) For **1a** see: V. P. Vasil'ev, N. K. Grechina and G. A. Zaitseva, *Zh. Obshch. Khim.*, 1983, **53**, 199–203; (*b*) For **1b** see: M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 1957, **79**, 1656–1662; (*c*) For **1d** see: K. I. Skorey, V. Somayaji and R. S. Brown, *J. Am. Chem. Soc.*, 1989, **111**, 1445–1452; (*d*) For **1e** see: J. P. Street, K. I. Skorey, R. S. Brown and R. G. Ball, *J. Am. Chem. Soc.*, 1985, **107**, 7669–7679; (*e*) For **1f** see: Y. Nozaki, F. R. N. Gurd, R. F. Chen and J. T. Edsall, *J. Am. Chem. Soc.*, 1957, **79**, 2123–2129.
21 S. Minegishi, S. Kobayashi and H. Mayr, *J. Am. Chem. Soc.*, 2004, **126**, 5174–5181.
22 pK_{aH} values (*a*) For **2a** see: H. F. W. Taylor, *J. Chem. Soc.*, 1948, 765–766; (*b*) For **2b-g** see: T. M. Davies, P. Mamalis, V. Petrow and B. Sturgeon, *J. Pharm. Pharmacol.*, 1951, **3**, 420–430; (*c*) For **3a** see: H. Wang, C. Burda, G. Persy and J. Wirz, *J. Am. Chem. Soc.*, 2000, **122**, 5849–5855.
23 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, 2003.
24 Rate constant for the reaction of **1a** with $(pyr)_2CH^+$ in MeOH was calculated using eqn (1) with the published $N = 10.41$ and $s = 0.69$ of imidazole in MeOH containing 9 vol% CH_3CN, see: T. B. Phan, M. Breugst and H. Mayr, *Angew. Chem., Int. Ed.*, 2006, **45**, 3869–3874.
25 (*a*) For silyl enol ethers and ketene acetals see: ref. 17a; (*b*) For indoles see: S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial and H. Mayr, *J. Org. Chem.*, 2006, **71**, 9088–9095; (*c*) For pyridines see: ref. 19a; (*d*) For pyrroles see: T. A. Nigst, M. Westermaier, A. R. Ofial and H. Mayr, *Eur. J. Org. Chem.*, 2008, 2369–2374; (*e*) For carbanions see: R. Lucius, R. Loos and H. Mayr, *Angew. Chem., Int. Ed.*, 2002, **41**, 91–95; (*f*) For enamines see: B. Kempf, N. Hampel, A. R. Ofial and H. Mayr, *Chem.–Eur. J.*, 2003, **9**, 2209–2218; (*g*) For Ph_3P see: B. Kempf and H. Mayr, *Chem.–Eur. J.*, 2005, **11**, 917–927; (*h*) For DABCO see: M. Baidya, S. Kobayashi, F. Brotzel, U. Schmidhammer, E. Riedle and H. Mayr, *Angew. Chem., Int. Ed.*, 2007, **46**, 6176–6179; (*i*) For DBU see: M. Baidya and H. Mayr, *Chem. Commun.*, 2008, 1792–1794.
26 For comprehensive database of reactivity parameters *E*, *N*, and *s*: www.cup.lmu.de/oc/mayr/DBintro.html.
27 (*a*) R. A. Marcus, *J. Phys. Chem.*, 1968, **72**, 891–899; (*b*) W. J. Albery, *Annu. Rev. Phys. Chem.*, 1980, **31**, 227–263.
28 $k = 2.79 \times 10^3\ s^{-1}$ and $K = 1.60 \times 10^3\ M^{-1}s^{-1}$ for the reaction of Ph_3P with $(ind)_2CH^+$ in CH_3CN at 20 °C; M. Baidya and H. Mayr, unpublished.
29 H. F. Schaller, A. A. Tishkov, X. Feng and H. Mayr, *J. Am. Chem. Soc.*, 2008, **130**, 3012–3022.
30 J. Hine, *J. Org. Chem.*, 1966, **31**, 1236–1244.
31 Benzotriazole as a leaving group see: (*a*) J. P. Richard, R. W. Nagorski, S. Rudich, T. L. Amyes, A. R. Katritzky and A. P. Wells, *J. Org. Chem.*, 1995, **60**, 5989–5991; (*b*) A. R. Katritzky and D. Toader, *J. Org. Chem.*, 1997, **62**, 4137–4141; (*c*) A. R. Katritzky, L. Khelashvili, K. N. B. Le, P. P. Mohapatra and P. J. Steel, *J. Org. Chem.*, 2007, **72**, 5805–5808; (*d*) Also see ref. 1c.