Organocatalysis

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DABCO and DMAP—Why Are They Different in Organocatalysis?**

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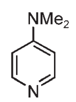
Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

1,4-Diazabicyclo[2.2.2]octane (DABCO, **1**), quinuclidine (**2**), and 4-(dimethylamino)pyridine (DMAP, Steglich's base, **3**)

DABCO (**1**)

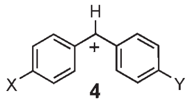
Quinuclidine (**2**)



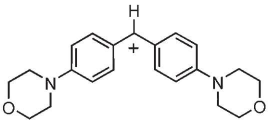
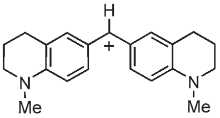
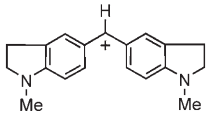
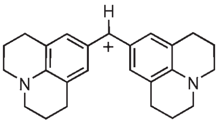
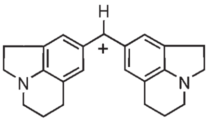
DMAP (**3**)

are important catalysts for a large variety of organic reactions.[1] Attempts have been made to correlate the efficiency of organocatalysts with their Brønsted basicities.[2] Because the relative reactivities of different nucleophiles towards electrophiles correlate only poorly with the corresponding pK_{Ha} values,[3] we recently employed the benzhydrylium ion method[4] to compare the nucleophilicities and carbon basicities of pyridines[5a] and tertiary phosphanes.[5b] By studying rates and equilibria of the reactions of these nucleophiles with a series of benzhydrylium ions **4** we showed that despite widely differing Brønsted basicities, triarylphosphanes and donor-substituted pyridines show similar basicities (K) and nucleophilicities (k) toward carbon electrophiles. Our attempts to use the same spectrophotometric method to also determine the nucleophilicities of trialkylamines, for example, the well-known organocatalysts **1** and **2**, were unsuccessful.

Table 1: Benzhydrylium ions Ar_2CH^+ (**4**) and their electrophilicity parameters E (from Ref. [4b]).



4

Ar_2CH^+	X	Y	E
Ph_2CH^+	H	H	5.90
$(tol)_2CH^+$	CH_3	CH_3	3.63
$(ani)_2CH^+$	OCH_3	OCH_3	0.00
$(pfa)_2CH^+$	$N(Ph)CH_2CF_3$	$N(Ph)CH_2CF_3$	−3.14
$(mfa)_2CH^+$	$N(CH_3)CH_2CF_3$	$N(CH_3)CH_2CF_3$	−3.85
$(dpa)_2CH^+$	NPh_2	NPh_2	−4.72
$(mor)_2CH^+$			−5.53
$(mpa)_2CH^+$	$N(Ph)CH_3$	$N(Ph)CH_3$	−5.89
$(dma)_2CH^+$	$N(CH_3)_2$	$N(CH_3)_2$	−7.02
$(pyr)_2CH^+$	$N(CH_2)_4$	$N(CH_2)_4$	−7.69
$(thq)_2CH^+$			−8.22
$(ind)_2CH^+$			−8.76
$(jul)_2CH^+$			−9.45
$(lil)_2CH^+$			−10.04

When benzhydrylium ions **4** (Table 1) of high reactivity ($E > -9$) were combined with **1** or **2**, the reactions were too fast ($k > 10^6\,\mathrm{M}^{-1}\mathrm{s}^{-1}$ at 20°C) to be followed by conventional stopped-flow methods. Less electrophilic benzhydrylium ions ($E < -9$), on the other hand, did not react with **1** or **2**. Only when high concentrations of **1** or **2** were added to solutions of $(jul)_2CH^+$ or $(lil)_2CH^+$ was a small amount of the carbocations consumed. In these cases, the quaternary ammonium ions **5** are apparently thermodynamically less favorable than the corresponding reactants.

We now report on the use of laser flash techniques[6,7] for the determination of the nucleophilicities of the tertiary

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[**] We thank the Deutsche Forschungsgemeinschaft (Ma673/21-2) and the Fonds der Chemischen Industrie for support of this work and Dr. A. Ofial for assistance in preparation of this manuscript. DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-(dimethylamino)pyridine.

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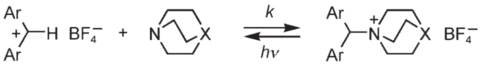
amines **1** and **2**. We will then compare the nucleophilicities[3c] and the corresponding carbon basicities[8] (derived from equilibrium constants) of **1** and **2** with those of other organocatalysts and discuss the implications.

When the tertiary amines **1** or **2** (1 mM) were added to the colored solutions of **4**-BF_4 ($-3 > E > -9$, $c_0 \approx 10^{-5}$ M) in acetonitrile, immediate decolorization was observed, indicating the formation of the colorless ammonium salts **5**-BF_4 (Scheme 1). Irradiation of the resulting solutions ([**5**] $\approx 10^{-5}$ M) with 7-ns laser pulses (266 nm, 40–60 mJ) resulted in the heterolytic cleavage of **5** with regeneration of the benzhydrylium ions **4**, which were detected by their UV/Vis spectra.[7] The benzhydrylium ions Ph_2CH^+ and $(tol)_2CH^+$ were obtained by irradiation of the corresponding diarylchloromethanes, and $(ani)_2CH^+$ was generated by irradiation of $(p\text{-}MeOC_6H_4)_2CHOAc$.



4-BF_4 **1** (X = N) **2** (X = CH) **5**-BF_4

Scheme 1. Formation of ammonium salts **5**-BF_4 from benzhydrylium tetrafluoroborates **4**-BF_4 and bicyclic amines (**1** or **2**) and laser-flash-induced heterolytic cleavage of **5**-BF_4 to give the starting materials.

Because of the high concentrations of the amines **1** and **2** relative to the benzhydrylium ions, the reactions followed first-order rate laws (exponential decay of the absorbances of **4**). Figure 1 shows that the first-order rate constants k_{obs} increased linearly with the concentration of amine, and the second-order rate constants derived from the slopes of such plots[9] are listed in Table 2. It can be seen that $(ind)_2CH^+$, the least electrophilic benzhydrylium ion that combines with **1** and **2** to give the ammonium ion **5**, reacts at almost equal rates with both amines. Considering the statistical factor, the reactivity per nitrogen is half as high for DABCO (**1**), which can be explained by the electron-withdrawing inductive effect of the second nitrogen. When reactions with more electrophilic benzhydrylium ions are considered and diffusion control[10,11] is approached, DABCO becomes slightly more reactive than quinuclidine (**2**; Figure 2).

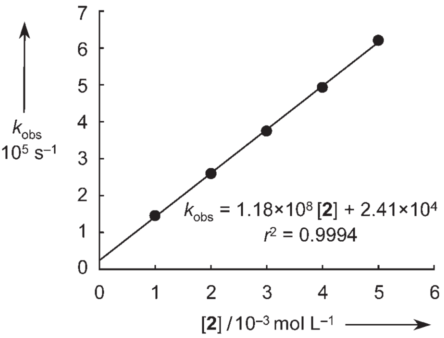


Figure 1. Plot of the first-order rate constants k_{obs} for the reaction of $(dma)_2CH^+$ with amine **2** versus the amine concentration.

Table 2: Second-order rate constants (k) for the reactions of benzhydrylium ions Ar_2CH^+ with the amines **1**–**3** in acetonitrile at 20 °C.

Ar_2CH^+	k [$M^{-1}s^{-1}$]		
	DABCO (**1**)	Quinuclidine (**2**)	DMAP (**3**)[a]
$(lil)_2CH^+$	n.r.[b]	n.r.[b]	2.11×10^3
$(jul)_2CH^+$	n.r.[b]	n.r.[b]	5.30×10^3
$(ind)_2CH^+$	1.10×10^7	1.08×10^7	1.29×10^4
$(thq)_2CH^+$	2.79×10^7	2.41×10^7	3.32×10^4
$(pyr)_2CH^+$	6.95×10^7	5.22×10^7	
$(dma)_2CH^+$	1.82×10^8	1.18×10^8	2.31×10^5
$(mpa)_2CH^+$	5.77×10^8	2.97×10^8	
$(mor)_2CH^+$	6.16×10^8	3.34×10^8	
$(dpa)_2CH^+$	1.57×10^9	9.70×10^8	
$(mfa)_2CH^+$	1.82×10^9	9.97×10^8	
$(pfa)_2CH^+$	2.50×10^9	1.59×10^9	
$(ani)_2CH^+$	4.55×10^9	2.49×10^9	
$(tol)_2CH^+$	6.33×10^9	5.25×10^9	
Ph_2CH^+	6.71×10^9	5.44×10^9	

[a] Second-order rate constants for DMAP (**3**) from Ref. [5a]. [b] No reaction.

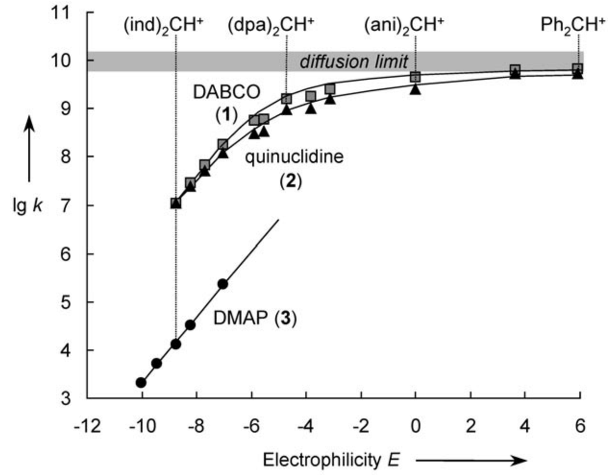


Figure 2. Plot of lg$k$ versus the electrophilicity parameters E for the reactions of the bicyclic amines DABCO (**1**) and quinuclidine (**2**) and of DMAP (**3**) with benzhydrylium ions in acetonitrile at 20 °C.

Because the linear sections of the correlations for DABCO (**1**) and quinuclidine (**2**) in Figure 2 are very short, the nucleophile-specific reactivity parameters for **1** ($N = 18.80$, $s = 0.70$) and **2** ($N = 20.54$, $s = 0.60$), as defined by the correlation equation (1) (k: second-order rate constant

$$\lg k_{20\,^\circ C} = s(N + E) \tag{1}$$

($L\,mol^{-1}\,s^{-1}$), N: nucleophilicity parameter, E: electrophilicity parameter, s: nucleophile-specific slope parameter)[4] are not very accurate.[12] Figure 2 shows clearly, however, that the bicyclic amines **1** and **2** are three orders of magnitude more nucleophilic than DMAP (**3**).

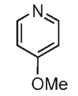
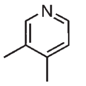
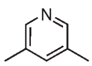
In contrast, the thermodynamic stabilities of the ammonium ions **5** obtained from **1** and **2** appear to be much smaller than those of the corresponding DMAP-derived ammonium ions, because **1** and **2** do not react with $(lil)_2CH^+$ and $(jul)_2CH^+$ despite the expected high reaction rates. In order to quantify the thermodynamic effects, the carbon basicities[8] of **1**–**3** were determined by measuring the equilibrium constants for some of the reactions described in Scheme 1.

Table 3: Equilibrium constants (K) for the reactions of amines **1**–**3** with some benzhydrylium cations Ar_2CH^+ in acetonitrile at 20 °C.[a]

Ar_2CH^+	K [M^{-1}]		
	DABCO (**1**)	Quinuclidine (**2**)	DMAP (**3**)[a]
$(lil)_2CH^+$	(4×10^{1})	(4×10^{2})	2.44×10^{4}
$(jul)_2CH^+$	(4×10^{1})	(4×10^{2})	2.60×10^{4}
$(ind)_2CH^+$	(8.7×10^{2})	(9.3×10^{3})	5.60×10^{5}
$(thq)_2CH^+$	1.56×10^{3}	1.68×10^{4}	(1×10^{6})
$(pyr)_2CH^+$	4.89×10^{3}	4.49×10^{4}	(3×10^{6})

[a] For the determination of the equilibrium constants in parentheses, see text.

Table 4: Comparison of equilibrium constants (K) for the reactions of benzhydrylium ions Ar_2CH^+ with differently substituted pyridines in acetonitrile at 20 °C.

Ar_2CH^+	K [M^{-1}]		
			
$(ind)_2CH^+$	7.02×10^{1}	4.68×10^{1}	
$(thq)_2CH^+$	1.31×10^{2}	8.04×10^{1}	3.02×10^{1}
$(pyr)_2CH^+$	3.70×10^{2}		9.52×10^{1}

While the amines **1**–**3** react quantitatively with benzhydrylium ions of $E > -7$, their reactions with less reactive benzhydrylium ions proceed incompletely. As benzhydrylium ions are colored and the resulting adducts **5** are colorless, the equilibrium constants (Table 3) can be determined by UV/Vis spectroscopy. Assuming a proportionality between the absorbances and concentrations of the benzhydrylium ions, the equilibrium constants for reaction (2) can be expressed by the absorbances of the benzhydrylium ions before (A_0) and after (A) addition of the amine [Eq. (3)].

$$Ar_2CH^+ + NR_3 \overset{K}{\rightleftarrows} Ar_2CH{-}NR_3^+ \tag{2}$$

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

where $[NR_3] = [NR_3]_0 - [Ar_2CH{-}NR_3^+]$

Only the equilibrium constants given without parentheses in Table 3 could be determined directly by this procedure. High concentrations of **1** and **2** were required to observe at least partial consumption of the least electrophilic benzhydrylium ions $(lil)_2CH^+$ and $(jul)_2CH^+$. However, the absorbances did not remain constant under such conditions, indicating a slow consecutive reaction which has not been identified so far. Also, in the reaction of $(ind)_2CH^+$ with **1** and **2**, the composition of the rapidly formed equilibrium mixture [Eq. (2)] was not constant, and $(ind)_2CH^+$ was consumed by a slow, unidentified consecutive reaction. The direct determination of the equilibrium constants for the reactions of $(thq)_2CH^+$ and $(pyr)_2CH^+$ with DMAP (**3**) failed because of the high value of K.

For this reason, an indirect method was used for estimating the equilibrium constants shown in parentheses in Table 3. Equilibrium constants for the reactions of benzhydrylium ions with other pyridines which have been determined as described above [Eqs. (2) and (3)] are given in Table 4. A comparison of Tables 3 and 4 shows that the directly measured equilibrium constants for $(pyr)_2CH^+$ are 2.67- to 3.15-times higher than those for $(thq)_2CH^+$, almost independent of the nature of the amine. Because the first two lines of Table 4 show that the reactions of $(ind)_2CH^+$ with pyridines have K values (1.80 ± 0.08) times lower than the corresponding values for $(thq)_2CH^+$, this value was used for estimating the equilibrium constants for the combinations of $(ind)_2CH^+$ with **1** and **2** in Table 3. With the assumption that the same ratios also hold for DMAP (**3**), the missing equilibrium constants in Table 3 have been calculated.

The availability of rate and equilibrium constants now allows us to calculate the intrinsic barriers $\Delta G_0^{\ddagger}$ for these reactions (i.e. the barriers of the corresponding reactions with $\Delta_r G^0 = 0$) by substituting $\Delta G^{\ddagger}$ and $\Delta_r G^0$ into the Marcus Equation (4),[13] where the work term has been omitted

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\,\Delta_r G^0 + [(\Delta_r G^0)^2/16\Delta G_0^{\ddagger}] \tag{4}$$

(Table 5). To avoid ambiguity, data derived from estimated equilibrium constants are identified by the "≈" sign in Table 5.

Table 5 shows a significant difference in the intrinsic barriers for the reactions of DABCO (**1**) and quinuclidine (**2**) on one hand and DMAP (**3**) on the other. While the $\Delta G_0^{\ddagger}$ values for the bicyclic amines are around 40 kJ mol^{-1}, those for DMAP (**3**) are greater than 60 kJ mol^{-1}. Considerably more reorganization energy appears to be needed for the reactions with the pyridine **3** than for the reactions with **1** and **2**.

From the rate constants given in Table 2 and the equilibrium constants in Table 3 one can also calculate the rate constants of the reverse reactions, which are listed in the last column of Table 5. As a consequence of the similar nucleophilicities of **1** and **2**, but the 10-times higher equilibrium constants for quinuclidine (**2**), the nucleofugality of DABCO (**1**) is estimated to be about 10 times higher than that of quinuclidine (**2**).

A more profound difference is found for DMAP (**3**), however: Its considerably lower nucleophilicity and higher carbon basicity (compared with that of **1** and **2**) implies that

Table 5: Activation energies $\Delta G^{\ddagger}$, reaction free energies $\Delta_r G^0$, and intrinsic barriers $\Delta G_0^{\ddagger}$ (in kJ mol^{-1}) for the reactions of benzhydrylium tetrafluoroborates $Ar_2CH^+BF_4^-$ with amines **1**–**3** as well as rate constants $k_{\leftarrow}$ for the back reactions (CH_3CN, 20 °C).

Amine	Ar_2CH^+	$\Delta G^{\ddagger}$	$\Delta_r G^0$	$\Delta G_0^{\ddagger}$	$k_{\leftarrow}$ [s^{-1}]
1	$(ind)_2CH^+$	≈32.2	≈−16.2	≈40.3	$\approx1\times10^{4}$
	$(thq)_2CH^+$	30.0	−17.9	38.9	1.79×10^{4}
	$(pyr)_2CH^+$	27.7	−20.7	38.1	1.42×10^{4}
2	$(ind)_2CH^+$	≈32.3	≈−22.0	≈43.3	$\approx1\times10^{3}$
	$(thq)_2CH^+$	30.3	−23.9	42.2	1.43×10^{3}
	$(pyr)_2CH^+$	28.4	−26.1	41.5	1.16×10^{3}
3	$(lil)_2CH^+$	53.1	−24.6	65.4[a]	8.65×10^{-2}
	$(jul)_2CH^+$	50.8	−24.8	63.2[a]	2.04×10^{-1}
	$(ind)_2CH^+$	48.7	−32.2	64.8[a]	2.30×10^{-2}
	$(thq)_2CH^+$	≈46.4	≈−33.7	≈63.2[a]	$\approx3\times10^{-2}$

[a] $\Delta G_0^{\ddagger}$ (in CH_2Cl_2) = 60.4, 59.9, 59.2, 57.1 kJ mol^{-1}, respectively; from Ref. [5a].

the leaving-group ability of **3** is 10^5 to 10^6 times lower than that of the bicyclic amines **1** and **2**.

In summary, we can conclude that DABCO (**1**) and quinuclidine (**2**) are significantly better nucleophiles than DMAP (**3**) (by a factor of 10^3) but at the same time significantly better nucleofuges (by a factor of 10^6 and 10^5, respectively). What is the impact of these findings for organocatalysis? It has been shown previously that the relative reactivities of nucleophiles towards typical Michael acceptors closely resemble those toward benzhydrylium ions.[14] For that reason, the different properties of **1**–**3** described in Tables 2 and 3 can be expected to reflect their efficiency in Baylis–Hillman reactions. Because of the higher carbon basicity of DMAP (**3**), it will generally be superior to DABCO (**1**) and quinuclidine (**2**), if reactivity is controlled by the concentration of the intermediate ammonium ions produced by the reactions of the amines with the electrophiles.[1,15,16] If, however, reactivity is controlled by the rate of the nucleophilic attack of the organocatalyst or by the release of the amine component in the final stage of the reaction, DABCO (**1**) and quinuclidine (**2**) will be superior.[1,15,16]

The fact that Baylis–Hillman reactions with cycloalkenones and acrylates are better catalyzed by DMAP (**3**) than by the standard catalyst DABCO (**1**)[17] possibly reflects the need for higher concentrations of the zwitterionic intermediates in these cases. The relevance of the kinetic and thermodynamic data determined in this work for acylation reactions is not yet known.

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Keywords: kinetics · linear free energy relationships · nucleofugality · nucleophilicity · organocatalysis

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[12] Based on the nucleophilicity parameters we would expect the reactions of **1** and **2** with 2,4-dinitrobenzofuroxan ($E = -5.06$, from Ref. [12a]) to be very fast (perhaps reversible), with $k > 10^9\,\text{M}^{-1}\text{s}^{-1}$ at 20 °C , in contrast to a literature report (Ref. [12b]) which gives second-order rate constants of 0.78 and $0.21\,\text{M}^{-1}\text{s}^{-1}$ (in THF), respectively. We, therefore, agree with Crampton's criticism of this work (Ref. [12c]): a) S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088–9095; b) C. Boga, L. Forlani, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1408–1413; c) B. H. M. Asghar, M. R. Crampton, *Org. Biomol. Chem.* **2005**, *3*, 3971–3978.

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