Organocatalysis

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N-Heterocyclic Carbenes: Organocatalysts with Moderate Nucleophilicity but Extraordinarily High Lewis Basicity**

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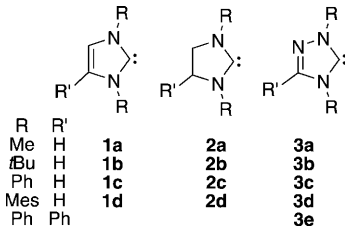
Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

Since the first isolation and characterization of stable N-heterocyclic carbenes (NHCs) by Arduengo and co-workers in 1991,[1] these compounds have attracted great interest in various fields of chemistry. As molecules with divalent carbon atoms, NHCs (e.g., **1**–**3**, Scheme 1) are not only of theoretical interest[2] but also of practical relevance as ligands in metal complexes[3] and as nucleophilic organocatalysts.[4]



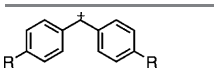
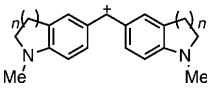
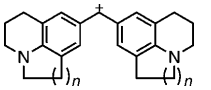
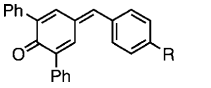
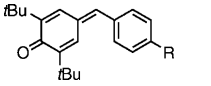
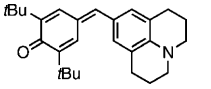
Scheme 1. Important N-heterocyclic carbenes (NHCs).

Despite the extensive use of NHCs as organocatalysts, quantitative investigations of their catalytic activities are rare.[5] Since the relative reactivities of different nucleophiles towards electrophiles correlate only poorly[6] with the corresponding Brønsted basicities (pK_{aH}),[7] we have recently employed benzhydrylium ions and structurally related quinone methides **4** (Table 1) with widely varying reactivities as reference compounds[8] to compare the nucleophilicities and Lewis basicities of various organocatalysts.[9]

It was demonstrated that the rates of the reactions of carbocations and Michael acceptors with n-, π-, and σ-nucleophiles can be described by the linear free-energy relationship in Equation (1), where electrophiles are characterized by one solvent-independent electrophilicity parameter E, and nucleophiles are characterized by two solvent-dependent parameters, the nucleophilicity parameter N, and a nucleophile-specific sensitivity parameter s_N.[8]

$$\lg k_2 = s_N(N + E) \quad (1)$$

Table 1: Benzhydrylium ions **4a–f** (BF_4^- salts) and quinone methides **4g–l** employed as reference electrophiles in this work.

Electrophile			E[a]	λ_{max}[b] [nm]
	R = NMe_2	**4a**	−7.02	611
	R = $N(CH_2)_4$	**4b**	−7.69	618
	*n* = 2	**4c**	−8.22	626
	n = 1	**4d**	−8.76	622
	*n* = 2	**4e**	−9.45	637
	n = 1	**4f**	−10.04	635
	R = OMe	**4g**	−12.18	411
	R = NMe_2	**4h**	−13.39	499
	R = Me	**4i**	−15.83	362
	R = OMe	**4j**	−16.11	384
	R = NMe_2	**4k**	−17.29	460
		**4l**	−17.90	492

[a] Electrophilicity parameters E for **4a–f** from ref. [8c], for **4g–l** from ref. [8d]. [b] In THF.

We now report on the use of the benzhydrylium methodology for characterizing the nucleophilicities of three representative NHCs (**1d**, **2d**, and **3e**) and for comparing them with other nucleophilic organocatalysts.

Representative combinations of the carbenes **1d**, **2d**, and **3e** with the reference electrophiles **4a** or **4i** showed the course of the reactions (Scheme 2). The products formed from **1d** and **2d** and the quinone methide **4i** in THF were subsequently treated with one equivalent of HBF_4 to generate the salts **5a**,**b**, which were isolated and characterized as described in the Supporting Information. Addition of the Enders carbene **3e** to the blue solution of the benzhydrylium tetrafluoroborate **4a**-BF_4 in THF at ambient temperature led to decolorization and formation of the adduct **5c**, which has been isolated and characterized by X-ray crystallography.[10]

The kinetic investigations were performed in THF at 20 °C by photometrically monitoring the disappearance of the colored electrophiles **4** (Table 1, Figure 1).[11] The NHCs were used in high excess to achieve pseudo-first-order conditions. Because of the strong overlap of the UV bands of **4i** with those of its adducts with **1d**, **2d**, and **3e**, we were

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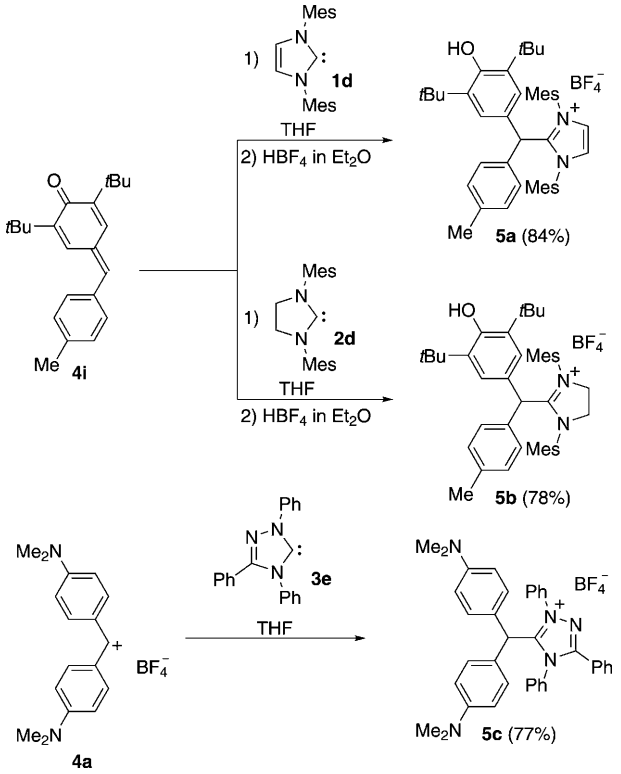


Scheme 2. Products of the reactions of the NHCs **1d**, **2d**, and **3e** with reference electrophiles in THF.

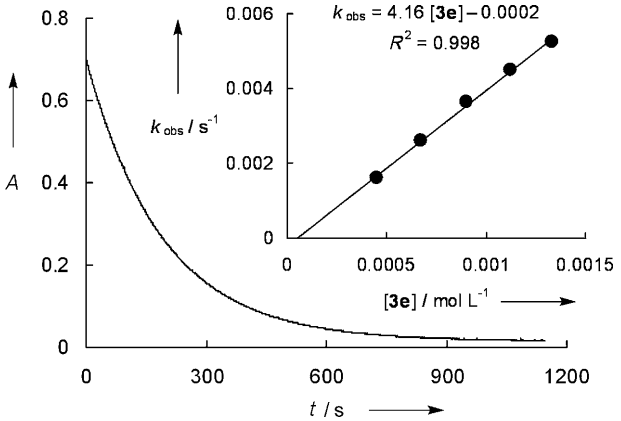


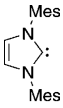
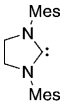
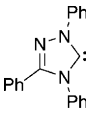
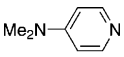
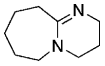
Figure 1. Exponential decay of the absorbance at 499 nm during the reaction of **3e** (1.33×10^{-3} mol L^{-1}) with **4h** (3.98×10^{-5} mol L^{-1}) at 20 °C in THF ($k_{obs}=5.26\times10^{-3}$ s^{-1}). Insert: Determination of the second-order rate constant $k_2=4.16$ L mol^{-1} s^{-1} from the dependence of k_{obs} on the concentration of **3e**.

unable to determine the kinetics of these reactions. The first-order rate constants k_{obs} (s^{-1}) were obtained by fitting the mono-exponential function $A=A_0\exp(-k_{obs}t)+C$ to the experimentally observed decay of the absorbances. The plots of k_{obs} against the concentrations of **1–3** were linear with negligible intercepts (Figure 1, insert) indicating a second-order rate law [Eq. (2)].

$$-\mathrm{d}[\mathbf{4}]/\mathrm{d}t = k_2[\mathrm{carbene}][\mathbf{4}] \qquad (2)$$

The slopes of these linear plots give the second-order rate constants k_2 which are listed in Table 2. As the nucleophilicities of triphenylphosphane (**6**), 4-(dimethylamino)pyridine (DMAP, **7**), and diazabicyclo[5.4.0]undecene (DBU, **8**) have previously only been determined in other solvents,[9] their reactivities towards the reference electrophiles **4** have now also been measured in THF solution (Table 2) to allow a comparison of the corresponding rate constants under the same conditions.[11]

Table 2: Second-order rate constants for the reactions of the NHCs **1d**, **2d**, and **3e** as well as of PPh_3 (**6**), DMAP (**7**), and DBU (**8**) with the reference electrophiles **4** in THF at 20 °C.

Nucleophile	N, s_N	Electrophile	k_2 [L mol^{-1} s^{-1}]
 **1d**	21.72, 0.45	**4g**	2.27×10^4
		4h	4.64×10^3
		4j	3.45×10^2
		4k	7.03×10^1
		4l	7.03×10^1
 **2d**	23.35, 0.40	**4h**	1.04×10^4
		4k	2.53×10^2
		4l	1.69×10^2
 **3e**	14.07, 0.84	**4c**	4.96×10^4
		4d	2.08×10^4
		4e	1.28×10^4
		4f	4.91×10^3
		4g	2.11×10^1
		4h	4.16
Ph_3P **6**	13.59, 0.66[a]	**4a**	1.93×10^4
		4b	7.80×10^3
		4d	1.42×10^3
 **7**	15.90, 0.66[a]	**4a**	7.14×10^5
		4b	3.63×10^5
		4c	1.18×10^5
		4d	4.32×10^4
		4e	2.21×10^4
		4f	7.62×10^3
 **8**	16.12, 0.67[a]	**4c**	2.13×10^5
		4d	8.12×10^4
		4e	3.01×10^4
		4f	1.24×10^4

[a] The N and s_N values of these nucleophiles in CH_2Cl_2 and CH_3CN are slightly different: ref. [12].

Figure 2 shows linear plots of $\lg k_2$ for the reactions of the NHCs **1d**, **2d**, and **3e** with the reference electrophiles **4** versus the previously published electrophilicity parameters E of **4a–l** (Table 1), from which the nucleophile-specific parameters N and s_N [Eq. (1)], listed in Table 2, have been derived. Small, but systematic deviations of the reactivities of **3e** from these correlations are noticed and are commented on page S16 of the Supporting Information.

Though the relative reactivities of the NHCs depend slightly on the nature of the reference electrophile, one can see in Figure 2 that the carbenes derived from imidazolium (**1d**) and imidazolinium (**2d**) salts are roughly 10^3 times more

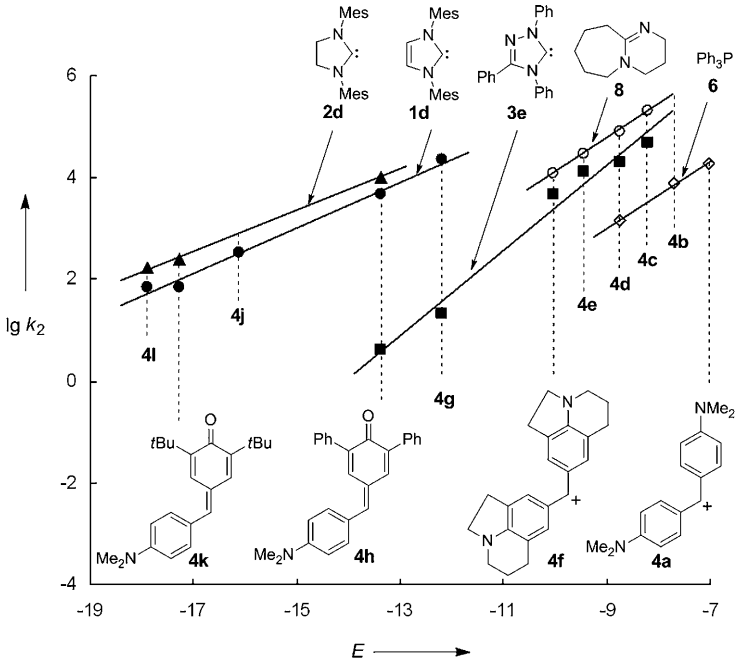


Figure 2. Plot of $\lg k_2$ for the reactions of NHCs **1d**, **2d**, and **3e**, PPh_3 (**6**), and DBU (**8**) with the reference electrophiles **4** in THF at 20 °C versus their electrophilicity parameters.

nucleophilic than the Enders carbene **3e**, which in turn has a similar nucleophilicity as DMAP (**7**) and DBU (**8**).

This gradation of the rate constants differs significantly from that of the Lewis basicities of these compounds. While **3e** combines quantitatively with **4g** and **4h**, PPh_3 (**6**) and DMAP (**7**) do not react at all with these two quinone methides, though Equation (1) predicts relatively high rate constants for these reactions. The corresponding reactions of DBU (**8**) with **4g** and **4h** proceed incompletely. The Arduengo carbenes **1d** and **2d** are so strong Lewis bases that they react quantitatively even with **4k** and **4l**, the weakest electrophiles of this series.

As all attempts to measure the equilibrium constants for the reactions of these NHCs with **4** were unsuccessful, we have determined the methyl cation affinity (MCA) as defined in Scheme 3 of differently substituted carbenes at the MP2/6-31 + G(2d,p)//B98/6-31G(d) level of theory using Gaussian 09.[13] This method has previously been shown to offer a practicable and reliable approach to methyl cation affinities for various organic bases.[14]

The two nonbonding electrons of carbenes can either reside in the same orbital with anti-parallel spins (singlet) or in two different orbitals with parallel spins (triplets).[2h,15] In line with previous investigations[2h,16] the singlet structures of the NHCs **1–3** were found to be much more stable than the corresponding triplets (290–360 kJ mol^{-1}).

As specified in the Supporting Information, the calculated bond lengths and angles (Table 3) of the cyclic framework deviate by less than 0.04 Å or 0.7°, respectively, from the experimental values obtained by X-ray crystallography.[16,17] The five-membered ring is planar for most NHCs, and only the carbene derived from di-*tert*-butyl imidazoline (**2b**) adopts a twist conformation with an N-C-C-N interplanar angle of 18°. While the phenyl groups in **1c–3c** are coplanar with the five-membered ring or only slightly distorted out of plane (interplanar angle 25° for **1c** and 27° for **3c**), the mesityl substituents in **1d–3d** are almost perpendicular to the plane of the heterocyclic ring (interplanar angle 77–78° in **1d**, **2d**, and **3d**). In contrast, all phenyl and mesityl groups are almost perpendicular to the heterocyclic ring in the azolium ions obtained by methylation of the carbenes **1c–3c** and **1d–3d**, which can be explained by the steric interaction of the aryl groups with the methyl group at the former carbene center.

The calculated H_{298} values for the carbenes **1–3** and the corresponding H_{298} values for the methylated azolium ions (Tables 34/35 of the Supporting Information) have been combined with H_{298} of the methyl cation to give the MCAs as defined in Scheme 3 (Table 3).

Table 3: MCAs (in kJ mol^{-1}) [MP2/6-31 + G(2d,p)//B98/6-31G(d)] and NCN angles of the carbenes **1–3**.

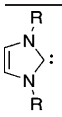
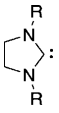
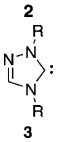
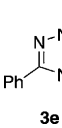
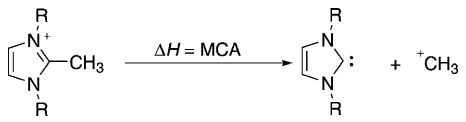
 **1**		**1a**	**1b**	**1c**	**1d**
		R = CH_3	R = *t*Bu	R = Ph	R = Mes
	MCA	718.0	714.3	742.4	767.2
	∡NCN	101.4°	102.6°	101.8°	101.3°
 **2**		**2a**	**2b**	**2c**	**2d**
		R = CH_3	R = *t*Bu	R = Ph	R = Mes
	MCA	719.3	699.4	722.9	768.9
	∡NCN	105.1°	106.6°	105.7°	105.4°
 **3**		**3a**	**3b**	**3c**	**3d**
		R = CH_3	R = *t*Bu	R = Ph	R = Mes
	MCA	674.4	676.8	694.4	728.4
	∡NCN	99.8°	100.7°	100.3°	100.0°
 **3e**				**3e**	
	MCA			712.2	
	∡NCN			103.7°	

Table 3 shows that the methyl-substituted imidazole- and imidazoline-derived carbenes **1a** and **2a** have the same MCAs indicating that the extra double bond in **1a** does not affect its Lewis basicity. Analogously, the mesityl-substituted carbenes **1d** and **2d** have approximately the same MCAs. Though the mesityl groups are almost perpendicular to the heterocyclic rings in the carbenes **1d** and **2d** and, therefore, cannot operate through mesomeric electron donation, the MCAs of



Scheme 3. Definition of the methyl cation affinity (MCA) of **1**.

1d and **2d** are almost 50 kJ mol^{-1} higher than those of the methyl analogues **1a** and **2a**.

Both phenyl-substituted carbenes **1c** and **2c** are weaker Lewis bases than their mesityl analogues **1d** and **2d** because the phenyl groups can stabilize the carbenes **1c** and **2c** by π-conjugation, but not the resulting amidinium ions, in which the phenyl group is distorted out of the plane by the methyl group. As the mesomeric stabilization of the ground state is more efficient in **2c** (interplanar angle 0°; phenyl staggered with the CH_2 group) than in **1c** (interplanar angle 25°; interaction between phenyl and the vinylic CH), **2c** is a weaker Lewis base than **1c**.

While **1a**, **1b**, and **2a** have similar MCAs, the MCA of the *tert*-butyl-substituted carbene **2b** is smaller by 15 to 20 kJ mol^{-1} because methylation of **2b** forces the twist conformation of the CH_2-CH_2 bridge in **2b** into a strained planar ring conformation.

The substituent effects on the triazole-derived carbenes **3a–d** are similar as in the isoelectronic series **1a–d**. The electron-withdrawing effect of the additional nitrogen in **3a–d** accounts for the fact that their methyl cation affinities are 38 to 48 kJ mol^{-1} smaller than those of the analogously substituted carbenes **1a–d**. The 18 kJ mol^{-1} increase of the MCA from **3c** to **3e** can, finally, be assigned to the mesomeric effect of the additional phenyl group.

Table 4 shows that the MCAs of the NHCs **2d**, **1d**, and **3e** are more than 100 kJ mol^{-1} greater than those of PPh_3 (**6**) and of the N-nucleophiles **7–9**, in accord with our observation that the weakly Lewis acidic quinone methides **4g,h** react quantitatively with these three NHCs but not with PPh_3 (**6**), DMAP (**7**), and DABCO (**9**).

The similar MCAs of **1d** and **2d** are reflected by their similar nucleophilicities, expressed by the relative reactivities of these two carbenes towards **4h** (Table 4). The extra nitrogen atom in **3e** reduces the MCA by 55 kJ mol^{-1} and the nucleophilicity by a factor of 10^3 [k_{rel}(**4h**)].

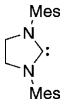
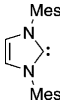
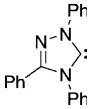
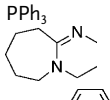
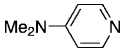
The lower part of Table 4 shows that the MCAs of **3e** and **6–9** do not correlate with the corresponding nucleophilicities. DABCO (**9**), the compound with the lowest MCA, has by far the highest nucleophilicity. The Enders carbene **3e** is a slightly weaker nucleophile than DBU (**8**) and DMAP (**7**) [k_{rel}(**4d**)] despite its much higher MCA.

In previous work we had derived relative Lewis basicities of **7–9** from equilibrium constants of their reactions with benzhydrylium ions and structurally related Michael acceptors. The ordering **8** > **7** > **9** was the same as for the MCAs in Table 4.[6d,9d] The fact that DABCO (**9**) is a much stronger nucleophile and at the same time a much weaker Lewis base than DMAP (**7**), as well as the observation that DBU (**8**) has a similar nucleophilicity as DMAP (**7**) yet a much higher Lewis basicity was explained by widely differing Marcus intrinsic barriers in the order **8** > **7** > **9**.[6d,9d]

Since compounds **7** and **8** have similar nucleophilic reactivities as the Enders carbene **3e**, while their MCAs are more than 100 kJ mol^{-1} lower, one has to conclude that NHCs must react via much higher intrinsic barriers than compounds **6–9**.[18]

The ability of NHCs to act as umpolung reagents[19] has been explained by the high acidity of the former aldehyde proton in the initially formed adduct, which gives rise to the formation of the Breslow intermediate.[20] A further specialty is their extraordinarily high Lewis basicity quantified in this work, which explains that they do not catalyze Baylis–Hillman reactions of α,β-unsaturated aldehydes but instead induce their homoenolate chemistry through umpolung.[4d,21] As discussed elsewhere,[18] nucleophiles generally attack at the carbonyl group of α,β-unsaturated aldehydes under conditions of kinetic control. With tertiary amines and phosphanes, this attack is reversible, and the subsequent conjugate addition gives rise to the Baylis–Hillman reactions. Because of the high Lewis basicity of NHCs, the kinetically preferred attack at the carbonyl group has a lower degree of reversibility and therefore, enables their use as umpolung reagents also of α,β-unsaturated aldehydes.

Table 4: MCAs (in kJ mol^{-1}) [MP2/6-31 + G(2d,p)//B98/6-31G(d)] and relative rate constants for the reactions of **4h** and **4d** with different organocatalysts.

Organocatalysts		MCA	k_{rel}(**4h**)	k_{rel}(**4d**)
	**2d**	768.9	2.5×10^3	
	**1d**	767.2	1.1×10^3	
	**3e**	712.2	1.0	1.0
PPh_3	**6**	618.4[a]		6.8×10^{-2}
	**8**	609.6[b]		3.9
	**7**	581.2[b]		2.1
	**9**	562.2[c]		5.3×10^2[d]

[a] From ref. [14c]. [b] From ref. [14a]. [c] From ref. [14b]. [d] In MeCN at 20 °C: $k_2 = 1.10\times10^7$ L mol^{-1} s^{-1}, from ref. [6d].

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