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Nucleophilicities and carbon basicities of DBU and DBN†‡

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Received (in Cambridge, UK) 7th February 2008, Accepted 19th February 2008
First published as an Advance Article on the web 13th March 2008
DOI: 10.1039/b801811a

The nucleophilicity and Lewis basicity of DBU and DBN toward C_{sp^2} centers have been measured: nucleophilicities increase in the series DMAP < DBU < DBN < DABCO while Lewis basicities are DABCO < DMAP < DBU < DBN.

Bicyclic amidines, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene), are useful reagents for dehydrohalogenation reactions and have been termed ‘nonnucleophilic strong bases’.[1] On the other hand, numerous examples have been reported which demonstrate that DBU and DBN can also act as nucleophiles.[2,3] Aggarwal even claimed that DBU is the optimum catalyst for Baylis–Hillman reactions, providing adducts at much faster rates than using DABCO (1,4-diazabicyclo[2.2.2]octane).[4] The great interest in the use of DBU and DBN as organocatalysts prompted us to investigate the nucleophilicity of these amidines quantitatively.

Because much of the controversy about the properties of the title compounds arises from the synonymous use of the terms ‘nucleophilicity’ and ‘Lewis basicity towards carbon centers’, we want to recall that, according to IUPAC, ‘nucleophilicity of a Lewis base is measured by relative rate constants of different nucleophilic reagents towards a common substrate, most commonly involving formation of a bond to carbon’ (eqn (1)).[5]

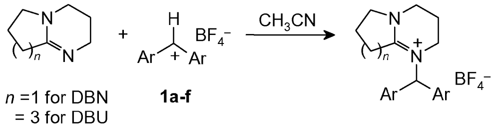
$$\mathrm{B:} + \mathrm{A} \overset{k,\,K}{\rightleftarrows} {}^{+}\mathrm{B}{-}\mathrm{A}^{-} \qquad (1)$$

The kinetic term ‘nucleophilicity’ has to be differentiated from the thermodynamic term ‘Lewis basicity’ which compares the equilibrium constants for Lewis adduct formation for a series of Lewis bases with a common reference Lewis acid (eqn (1)).[5] Hine introduced the term ‘carbon basicity’ to express relative Lewis basicities with respect to a carbon centered Lewis acid.[6] Relative nucleophilicities as well as relative Lewis basicities depend on the choice of the reference Lewis acid.

The most comprehensive nucleophilicity scales presently available have been developed with respect to benzhydrylium ions (diarylcarbenium ions) as reference electrophiles. We have shown that the rates of the reactions of σ-, n-, and π-nucleophiles with benzhydrylium ions can be described by eqn (2), where k (L mol^{-1} s^{-1}) is the second-order rate constant, E is the electrophilicity parameter, N is the nucleophilicity parameter, and s is a nucleophile specific slope parameter.[7]

$$\log k_{20\,^{\circ}\mathrm{C}} = s(N + E) \qquad (2)$$

We will now describe the determination of the nucleophilicity parameters of the title compounds and demonstrate that with these parameters rate constants for the reactions of DBU and DBN with ordinary Michael acceptors can be predicted.



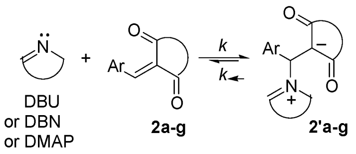
(3)

Addition of DBU to the blue solutions of the benzhydrylium tetrafluoroborates **1–BF$_4^-$** in acetonitrile leads to decolorization due to formation of adducts (eqn (3)), which have been characterized by NMR spectroscopy (see ESI‡).

The reactions, which were monitored photometrically by using the stopped-flow technique described previously,[7] followed second-order kinetics. Details are given in the ESI.‡ Table 1 shows that DBU generally reacts 2 to 3 times faster than DMAP (4-dimethylaminopyridine, Steglich's base), whereas DBN is 6 to 7 times more reactive than DMAP.

When the second-order rate constants are plotted against the electrophilicity parameters E, linear correlations are obtained (Fig. 1), as required by eqn (2), from which the nucleophile specific parameters $N = 15.29$, $s = 0.70$ for DBU and $N = 16.28$, $s = 0.67$ for DBN were obtained.

Comparison with the nucleophilicities of other tertiary amines and phosphanes (Scheme 1) shows that DBN and DBU are somewhat more nucleophilic than DMAP and considerably less nucleophilic than DABCO and quinuclidine.[8,9] The rate constants of the reactions of DBU, DBN, and DMAP with the colored Michael acceptors **2a–g** (eqn (4)) have been determined analogously, and Table 2 shows that the experimental rate constants generally deviate by less than a factor of 10 from those calculated by eqn (2); only **2b** reacts 14 times more slowly, and **2c** reacts 10–24 times faster than calculated.



(4)

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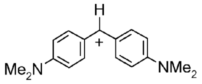
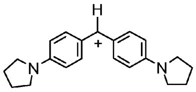
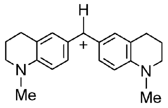
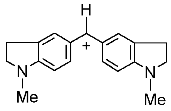
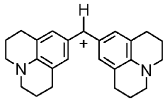
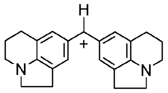
† Dedicated to Professor Wolfgang Steglich on the occasion of his 75th birthday.

‡ Electronic supplementary information (ESI) available: Details of the kinetic and thermodynamic experiments, NMR spectroscopic characterization of products. See DOI: 10.1039/b801811a

Table 1 Second-order rate constants for the reactions of DBU, DBN and DMAP with the benzhydrylium ions **1a–f** (CH_3CN, 20 °C)

Ar_2CH^+		E^a	k/L mol^{-1} s^{-1}		
			DBU	DBN	DMAP^b
1a		−7.02	5.67×10^5	—^{c}	2.31×10^5
1b		−7.69	2.33×10^5	—^{c}	
1c		−8.22	8.43×10^4	2.43×10^5	3.32×10^4
1d		−8.76	3.17×10^4	9.44×10^4	1.29×10^4
1e		−9.45	1.36×10^4	3.98×10^4	5.30×10^3
1f		−10.04	4.46×10^3	1.38×10^4	2.11×10^3

[a] Electrophilicity parameters from ref. 7. [b] Second-order rate constants for the reactions of DMAP are from ref. 8*a*. [c] Reactions of DBN with **1a** and **1b** were too fast to be measured with the stopped-flow technique.

This agreement in a reactivity scale covering more than 30 orders of magnitude is impressive, considering the fact that the N and s parameters for DBU, DBN, and DMAP have been derived from the rates of their reactions with benzhydrylium ions in CH_3CN, and the E parameters for the Michael acceptors **2** have been calculated from the rates of their reactions with carbanions in DMSO.[10] It is thus demonstrated that the N and s parameters of DBU, DBN, and DMAP can be used to roughly predict the rates of the initial steps of Baylis–Hillman and related reactions.

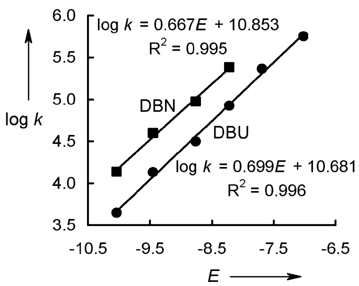
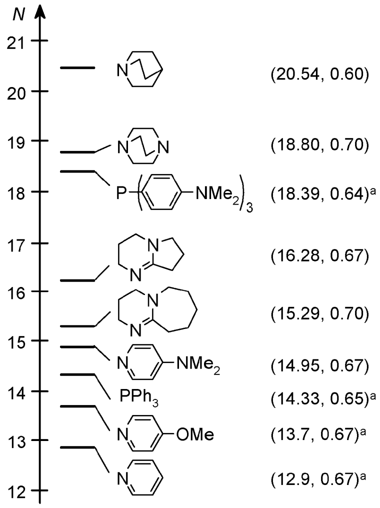


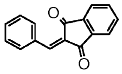
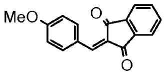
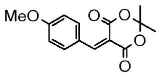
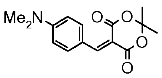
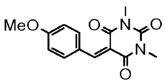
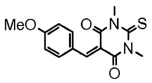
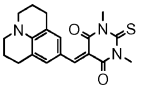
Fig. 1 Plots of log k *versus* E parameters for the reactions of DBU (●) and DBN (■) with benzhydrylium ions Ar_2CH^+ (CH_3CN, 20 °C).



Scheme 1 Comparison of the nucleophile specific reactivity parameters (N, s) for different organocatalysts in acetonitrile. [a]N parameters refer to CH_2Cl_2.

However, in previous work,[8] we have discussed that nucleophilicity, *i.e.*, the rate of a reaction with a certain electrophile, is not the only factor controlling the efficiency of nucleophilic organocatalysts. Of even greater importance is the Lewis basicity towards an electron deficient carbon center, *i.e.*,

Table 2 Comparison of experimental and calculated (eqn (1)) second-order rate constants k for the reactions of various Michael acceptors **2** with DBU, DBN, and DMAP in acetonitrile at 20 °C

Michael acceptor		E^a	k^b/L mol^{-1} s^{-1}		
			DBU	DBN	DMAP
2a		−10.11	7.39×10^3 *4.23×10^3*	2.31×10^4 *1.36×10^4*	
2b		−11.32	4.42×10^1 *6.01×10^2*		
2c		−10.28	3.26×10^4 *3.21×10^3*	1.28×10^5 *1.05×10^4*	3.20×10^4 *1.35×10^3*
2d		−12.76	8.65×10^1 *5.90×10^1*		
2e		−10.37	1.62×10^4 *2.78×10^3*	4.43×10^4 *9.11×10^3*	1.09×10^4 *1.17×10^3*
2f			1.28×10^5		8.80×10^4 5.92×10^{4c}
2g		−11.89	2.61×10^{2c} *2.40×10^2*		

[a] Electrophilicity parameters from ref. 10. [b] Calculated values in italics. [c] Rate constants in CH_2Cl_2.

Table 3 Equilibrium constants (K) and intrinsic barriers ($\Delta G_0^{\ddagger}$) for the reactions of DBU, DBN and DMAP with some Michael acceptors **2** in acetonitrile at 20 °C

	K/M^{-1}			$\Delta G_0^{\ddagger}$/kJ mol^{-1}
	DBU	DBN	DMAP	DMAP
2a	(2–20) × 10^3	(1–2) × 10^5	Small	
2c	(1–7) × 10^4	Large	1.96 × 10^2	52.7
2e	(2–8) × 10^4	Large	2.41 × 10^2	55.6
2f	Large	Large	7.58 × 10^4	56.8

carbon basicity (for definition see above). By comparing equilibrium constants for the reactions of DABCO and DMAP with benzhydrylium ions we have found that DMAP possesses a 650-fold higher carbon basicity despite its 10^3-fold lower nucleophilicity.[8] Attempts to employ benzhydrylium ions also for determining the carbon basicity of DBU and DBN were unsuccessful, however, because even the least electrophilic benzhydrylium ions **1e** and **1f** reacted quantitatively with DBU and DBN.

Therefore, we tried to determine the equilibrium constants K of eqn (4) for comparing the carbon basicities of DBU, DBN, and DMAP. While DBU and DBN showed a much higher Lewis basicity than DMAP towards the Michael acceptors **2** (Table 3), only the reactions of DMAP with **2** could accurately be described by the simple Lewis acid–Lewis base coordination shown in eqn (4). With DBU and DBN as Lewis bases, the equilibrium 'constants' calculated as K = [**2′**]/([**2**]-[amine]) were found to depend on the concentrations of the reactants. Because we were not able to formulate an alternative relationship which yields concentration-independent equilibrium constants, approximate values of K according to eqn (4) are given in Table 3.

Because rate and equilibrium constants could be determined for the reactions of DMAP with **2c**, **2e** and **2f**, it was possible to calculate the intrinsic barriers $\Delta G_0^{\ddagger}$ (Table 3) for these reactions by substituting $\Delta G^{\ddagger}$ and $\Delta_r G^0 = -RT \ln K$ into the Marcus eqn (5), where the work term has been neglected.[11]

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\Delta_r G^0 + (\Delta_r G^0)^2/16\Delta G_0^{\ddagger} \qquad (5)$$

One can see that the intrinsic barriers, *i.e.*, the barriers in the absence of a thermodynamic driving force, are approximately 10 kJ mol^{-1} smaller for the reactions of DMAP with these Michael acceptors than with the benzhydrylium ions **1d–f** in the same solvent (CH_3CN).[8] None of the Michael acceptors **2a–f** yields measurable amounts of adducts with the considerably stronger nucleophiles quinuclidine and DABCO (Scheme 1), in accordance with our previous conclusion that these bicyclic amines are much weaker carbon bases than DMAP. In line with this observation, an equilibrium constant K = 35 M^{-1} (25 °C, CH_3CN) has been reported for the reaction of quinuclidine with the unsubstituted benzylidene-*N*,*N′*-dimethylbarbituric acid which must be a stronger Lewis acid than its *p*-methoxy-derivative **2e**.[12] Despite our failure to derive accurate equilibrium constants for the reactions of DBU and DBN with carbon centered Lewis acids, the semiquantitative order of carbon basicities DABCO < DMAP < DBU < DBN is unambiguous.

Aggarwal's observation that DBU is a superior catalyst in Baylis–Hillman reactions[4] can, therefore, be explained by its superior carbon basicity combined with a nucleophilicity comparable to that of DMAP. It cannot be the low nucleophilicity of DBU and DBN which limits their use as organocatalysts in Baylis–Hillman reactions, but rather their low nucleofugality, which is responsible for the formation of products which include DBU or DBN as building blocks.[3] Another limitation of the use of these amidines as nucleophilic catalysts is their high Brønsted basicity,[13] which triggers reactions *via* initial deprotonation of the substrates.[14]

Support by the Deutsche Forschungsgemeinschaft (Ma673/21-2) and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Dr A. R. Ofial for performing the correlation analysis.

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