Organocatalysis

DOI: 10.1002/anie.200804263

Hydride-Donor Abilities of 1,4-Dihydropyridines: A Comparison with π Nucleophiles and Borohydride Anions**

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Dedicated to Professor Ingo-Peter Lorenz on the occasion of his 65th birthday

Because of its analogy to biological reduction with NADH, hydride abstraction from various types of dihydropyridines has been studied intensively for several decades.[1] In recent years, dihydropyridines, in particular Hantzsch esters, have found numerous applications in organic synthesis, as they were found to be optimal reducing agents for organocatalytic hydrogenation.[2,3] It was our goal in this study to quantify the hydride-donating ability of 1,4-dihydropyridines and to compare the reactivity of these compounds with the reactivities of other hydride donors and of π nucleophiles that might be suitable for iminium-catalyzed reactions.

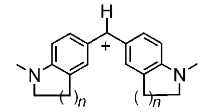
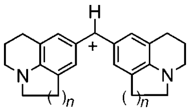
We have shown previously that benzhydrylium ions (Ar_2CH^+) and structurally related quinone methides can be employed as reference electrophiles for comparing the π nucleophilicity of alkenes, allylsilanes, and enol ethers with the σ nucleophilicity of hydride donors, such as organosilanes and organostannanes.[4] Although the same method has been employed to quantify the reactivities of strong π nucleophiles, such as pyrroles,[5] indoles,[6] and enamines,[7] we have not yet included stronger hydride donors in our comprehensive nucleophilicity scales.

We have now studied the kinetics of the reactions of dihydropyridines and borohydride anions with benzhydrylium ions **1** of known electrophilicity E to determine the nucleophilicity parameters N and s of the hydride donors **2** according to the definition in Equation (1).

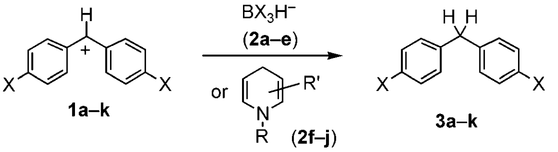
$$\log k(20\,^\circ\mathrm{C}) = s(N+E) \tag{1}$$

With this information, it should be possible to predict the rates of hydride transfer from these hydride donors to any hydride acceptor of known electrophilicity E.

Table 1: Benzhydrylium ions Ar_2CH^+ (**1**) and their electrophilicity parameters E.

Ar_2CH^+ (**1**)		E[a]
1a	$X=N(Ph)CH_2CF_3$	−3.14
1b	$X=N(CH_3)CH_2CF_3$	−3.85
1c	$X=NPh_2$	−4.72
1d	$X=N(CH_2CH_2)_2O$	−5.53
1e	$X=N(Ph)CH_3$	−5.89
1f	$X=N(CH_3)_2$	−7.02
1g	$X=N(CH_2)_4$	−7.69
1h ($n=2$) **1i** ($n=1$)		−8.22 −8.76
1j ($n=2$) **1k** ($n=1$)		−9.45 −10.04

[a] Electrophilicity parameter E as defined in Equation (1) (from Ref. [4]).



(2)

Product studies showed that the benzhydrylium tetrafluoroborates (**1a**–**k**)–BF_4 (Table 1) reacted quantitatively with the borohydrides **2a**–**e** and the dihydropyridines **2f**–**j** to give the corresponding diarylmethanes **3a**–**k** [Eq. (2)].

The conversion of the blue carbocations **1a**–**k** into the colorless diarylmethanes **3a**–**k** was monitored photometrically by using the methods described previously.[4a] All kinetic investigations were performed under first-order conditions by using the hydride donors **2a**–**j** in large excess (10–100 equivalents). In accordance with Equations (3) and (4), plots of the resulting first-order rate constants k_{obs} versus the concentrations of **2a**–**j** were linear with negligible intercepts; their slopes gave the second-order rate constants k_2 (see the Supporting Information).

$$-d[\mathbf{1}]/dt = k_2\,[\mathbf{1}]\,[\mathbf{2}] = k_{obs}\,[\mathbf{1}] \tag{3}$$

$$\text{for } [\mathbf{2}] \approx \text{const.};\ k_2 = k_{obs}/[\mathbf{2}] \tag{4}$$

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[**] We thank the Deutsche Forschungsgemeinschaft (Ma673/21-2) and the Fonds der Chemischen Industrie for financial support, Dr. Gabriele Lang and Dr. Ludwig Schappele for preliminary experiments, and Dr. Armin Ofial for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804263.

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Most electrophile–nucleophile combinations have been studied previously in dichloromethane, acetonitrile, or dimethyl sulfoxide (DMSO) as the solvent.[4–10] As several of the borohydrides studied are only slightly soluble in CH_2Cl_2 and CH_3CN, we investigated their reactivity in DMSO.

The almost identical reactivities of $NaBH_4$, KBH_4, and Bu_4NBH_4 indicate that we are observing the reactions of the free BH_4^- anions (Table 2). $B(OAc)_3H^-$ is approximately three times less reactive than BH_4^-, and BH_3CN^- is 10^3 times less reactive than BH_4^-. Smaller differences in the reactivity of these anions were observed previously for their reaction with tritylium ions in aqueous solution ($k(BH_4^-)/k(BH_3CN^-) = 12$ for malachite green, and $k(BH_4^-)/k(BH_3CN^-) = 144$ for $(4\text{-MeO-}C_6H_4)_3C^+$).[11]

Table 2: Second-order rate constants k_2 ($\text{M}^{-1}\,\text{s}^{-1}$) for the reactions of the borohydrides **2a–e** with the benzhydrylium ions **1** in DMSO at 20 °C.

Ar_2CH^+	$NaBH_4$ (**2a**)	KBH_4 (**2b**)	Bu_4NBH_4 (**2c**)	$NaB(OAc)_3H$ (**2d**)	$NaBH_3CN$ (**2e**)
1f				4.32×10^5	9.98×10^2
1g	5.24×10^5	4.87×10^5	5.11×10^5	1.61×10^5	4.37×10^2
1h	2.01×10^5	2.27×10^5	2.03×10^5	5.50×10^4	1.53×10^2
1j	1.66×10^4	1.87×10^4	1.85×10^4	5.55×10^3	
1k	7.17×10^3	9.10×10^3	7.88×10^3	2.52×10^3	

In an analogous manner, hydride abstraction from the dihydropyridines **2f–j** was measured in dichloromethane. In general, the Hantzsch ester **2f** is two to five times more reactive than *N*-benzyl-1,4-dihydronicotinamide (**2g**; Table 3). The replacement of the *N*-benzyl group in **2g** with an *N*-phenyl group (to give **2h**) decreases the reactivity by a factor of four to six. The introduction of a methyl substituent at the *para* position of the *N*-phenyl group (to give **2i**) leads to an acceleration of the hydride transfer by a factor of two, whereas a *para* methoxy group (in **2j**) activates the reaction by a factor of three to four. Zhu, Cheng, et al. observed the same trend in reactions of **2h–j** with *p*-trifluoromethylbenzylidenemalononitrile.[12]

Solvent effects were studied for the reaction of the dihydropyridine **2g** with **1f**. This reaction was four times faster in acetonitrile ($k_2 = 88.8\,\text{M}^{-1}\,\text{s}^{-1}$) than in dichloromethane (Table 3). An increase in the water content of the solution in acetonitrile accelerated the hydride transfer significantly: In 90% water/10% acetonitrile the reaction proceeded eight times faster than in 100% acetonitrile.

Plots of $\log k_2$ versus the electrophilicity parameters *E* of the benzhydrylium ions are linear (Figure 1), which indicates the applicability of Equation (1). The slopes of these correlations gave the parameters *s*, and the nucleophilicity parameters *N* (listed in Table 4) were found by changing the sign of the *x* coordinate at the position at which the lines intercepted the *x* axis.

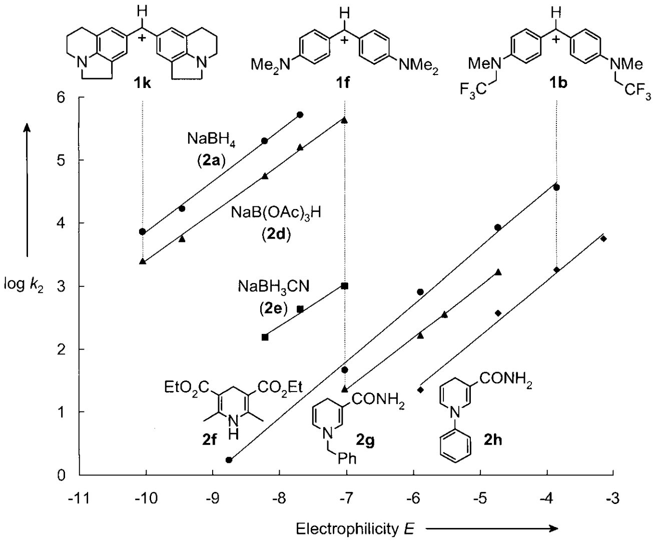
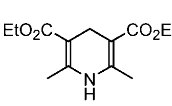
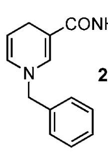
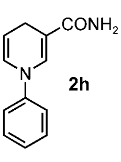
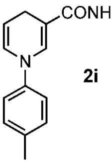
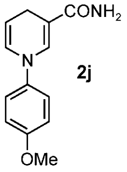


Figure 1. Correlation of $\log k_2$ with the electrophilicity parameter $E(\mathbf{1})$ for reactions of the hydride donors **2** with the benzhydrylium ions **1** at 20 °C (borohydrides in DMSO, dihydropyridines in CH_2Cl_2).

Table 3: Second-order rate constants k_2 ($\text{M}^{-1}\,\text{s}^{-1}$) for the reactions of the dihydropyridines **2f–j** with the benzhydrylium ions **1** at 20 °C.

	 **2f**	 **2g**		 **2h**	 **2i**	 **2j**
Ar_2CH^+	CH_2Cl_2	CH_2Cl_2	90W10AN[a]	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2
1a				5.48×10^3		
1b	3.56×10^4			1.82×10^3	4.85×10^3	5.60×10^3
1c	8.43×10^3	1.69×10^3		3.74×10^2	6.72×10^2	2.04×10^3
1d		3.66×10^2				2.75×10^2
1e	7.92×10^2	1.68×10^2		2.22×10^1	3.83×10^1	9.87×10^1
1f	4.68×10^1	2.28×10^1	6.93×10^{2}[b]		5.07	
1g			2.30×10^2		(1.1)[c]	2.16
1h			1.44×10^2			
1i	1.70		4.97×10^1			
1j			1.54×10^1			
1k			7.73			

[a] 90W10AN = mixture of 90% water and 10% acetonitrile (v/v). [b] Rate constants in further acetonitrile–water mixtures: $360\,\text{M}^{-1}\,\text{s}^{-1}$ in 80W20AN, $165\,\text{M}^{-1}\,\text{s}^{-1}$ in 67W33AN, $87.4\,\text{M}^{-1}\,\text{s}^{-1}$ in 50W50AN, and $88.8\,\text{M}^{-1}\,\text{s}^{-1}$ in pure acetonitrile. [c] Less-reliable k_2 value, not used for the determination of the *N* and *s* parameters of **2i**.

To examine the relevance of the *N* and *s* parameters of the hydride donors **2a–j** listed in Table 4 for reactions with other types of electrophiles, we investigated the kinetics of hydride transfer from some borohydrides and dihydropyridines to Michael acceptors and tritylium ions.

The reactions of tetrabutylammonium borohydride (**2c**) with five different Michael acceptors [for example with **4a**, Eq. (5)] were found to be 4 to 19 times faster (see the Supporting

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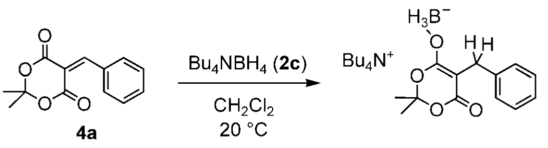


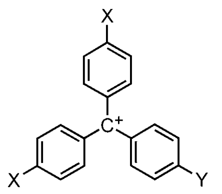
(5)

Table 4: *N* and *s* parameters for the hydride donors **2a–j**.

Hydride donor	Solvent	*N*	*s*
2a	DMSO	14.74	0.81
2b	DMSO	15.14	0.77
2c	DMSO	14.94	0.79
2d	DMSO	14.45	0.76
2e	DMSO	11.52	0.67
2f	CH_2Cl_2	9.00	0.90
2g	CH_2Cl_2	8.67	0.82
	H_2O/MeCN (9:1, v/v)	11.35	0.66
2h	CH_2Cl_2	7.53	0.87
2i	CH_2Cl_2	7.68	0.95
2j	CH_2Cl_2	8.11	0.92

Information) than calculated with Equation (1) from the *N* and *s* parameters in Table 4 and the electrophilicity parameters *E* of the Michael acceptors.[8,9] These deviations are acceptable in view of the reactivity range of 10^{40} covered by the three-parameter Equation (1) and the fact that the *E* parameters of the Michael acceptors were derived from reactions with carbanions.[8,9]

However, significant differences between expected and reported rate constants were found for the reactions of tritylium ions **5** with the dihydronicotinamide **2g** (Table 5). Whereas the calculated second-order rate constants, $k_{2,\text{calcd}}$, for the reactions of **2g** with **5a–c** agree within a factor of three with the experimental rate constants determined in this study and are in line with the rate constants determined by Bunton and co-workers at 25 °C,[11] the reported rate constant for the reaction of the parent tritylium ion **5d** with **2g** is 382 times lower than that calculated with Equation (1) (Table 5, entry 5).[13] As this rate constant was the basis for the mechanistic analysis of hydride abstraction from NADH analogues,[14] we reexamined the hydride transfer from **2g** to **5d** and found it to be much faster than reported, in agreement with the prediction based on Equation (1). Although our equipment does not enable us to follow the kinetics of this fast reaction, our measurements showed clearly that the previously published rate constant is much too small.



	X	Y
5a	NMe_2	H
5b	OMe	OMe
5c	Me	Me
5d	H	H

Table 5: Experimental ($k_{2,\text{exp}}$) and calculated ($k_{2,\text{calcd}}$) second-order rate constants ($M^{-1}s^{-1}$) for the reactions of **2g** with tritylium ions **5** in CH_2Cl_2 and water at 20 °C.

Entry		E[a]	Solvent	$k_{2,\text{calcd}}$	$k_{2,\text{exp}}$ (this study)	$k_{2,\text{exp}}$ (25 °C) (literature)
1	**5a**	−10.29	H_2O[b]	5.0	1.5×10^1	2.7×10^1[c]
2	**5b**	−4.35	CH_2Cl_2	3.5×10^3	2.4×10^3	
3			H_2O[b]	4.2×10^4	1.2×10^5	2.1×10^5[c]
4	**5c**	−1.21	CH_2Cl_2	1.3×10^6	6.1×10^5	
5	**5d**	0.51	CH_2Cl_2	3.4×10^7	$\gg10^6$	8.9×10^4[d]

[a] Electrophilicity parameter from Ref. [10]. [b] Rate constants $k_{2,\text{calcd}}$ and $k_{2,\text{exp}}$ (this study) refer to the reaction in H_2O/MeCN (9:1, v/v). [c] Data was taken from Ref. [11]; because of the low solubility in pure water, we assume that these rate constants were also determined in the presence of a small amount of a cosolvent. [d] Data from Ref. [13].

With $E = -3.72$ for the tropylium ion[4c] and the *N* and *s* parameters for the *N*-phenyl substituted dihydropyridines **2h–j** in Table 4, hydride-transfer rate constants can be calculated which deviate by less than a factor of two to four from those reported by Zhu, Cheng, et al.[15]

Let us now compare the reactivities of the borohydrides and dihydropyridines with those of previously investigated hydride donors (Figure 2). The borohydrides BH_4^- and $B(OAc)_3H^-$ are approximately five orders of magnitude more reactive than the Hantzsch ester **2f**, which is slightly more reactive than the dihydronicotinamides **2g** and **2h**. Whereas trialkylstannanes and the borane–triethylamine complex have similar reactivities to those of the dihydropyr-

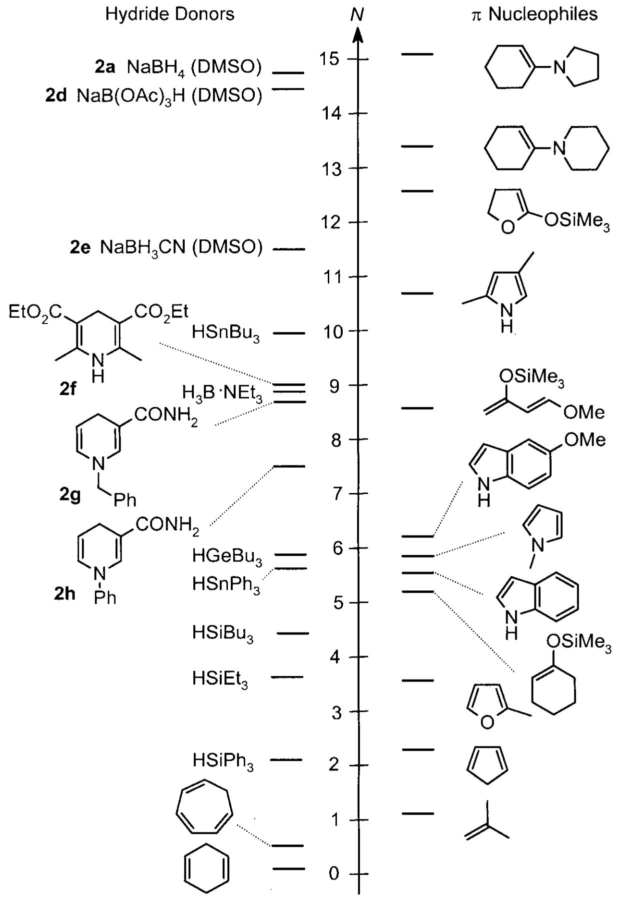


Figure 2. Comparison of the nucleophilic reactivities *N* of hydride donors and π nucleophiles; the solvent is CH_2Cl_2 unless otherwise noted (*N* parameters are from Table 4 and Refs. [4–7,19]).

idines, silanes and the CH_2 groups in cycloheptatriene and cyclohexa-1,4-diene are significantly less reactive.

In detailed mechanistic studies, in which carbocations with different counterions were used, we demonstrated previously that hydride abstractions from amine–borane complexes,[16] trialkyl- and triarylsilanes,[17] and analogous stannanes and germanes[18] do not proceed by single-electron transfer but by polar mechanisms.

What are the consequences of these data for iminium catalysis? Figure 2 shows that dihydropyridines have similar nucleophilic reactivities to those of indoles and pyrroles, which have been employed previously as nucleophiles in iminium-activated Friedel–Crafts reactions.[3a,i] The nucleophilicity parameters *N* can thus be used as a clue for the suitability of certain nucleophiles in iminium-catalyzed reactions. However, *N* is not the only criterion to be considered. Although amine–boranes and dihydropyridines have similar nucleophilicities,[4a,16] our efforts to use the former for iminium-catalyzed conjugate reductions have not been successful so far because of competing 1,2-addition reactions. On the other hand, the similar *N* values of *N*-methylpyrrole and some trialkylsilanes suggest that the latter compounds may also be suitable for iminium-catalyzed reductions if those amines are used as organocatalysts, which were previously found to catalyze Friedel–Crafts reactions with *N*-methylpyrrole.

Received: August 28, 2008
Revised: November 11, 2008
Published online: February 2, 2009

Keywords: iminium catalysis · kinetics · linear free-energy relationships · nucleophilicity · reduction

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