Structure – Nucleophilicity Relationships for Enamines

Bernhard Kempf, Nathalie Hampel, Armin R. Ofial, and Herbert Mayr*[a]

Dedicated to Professor Richard Kreher on the occasion of his 70th birthday

Abstract: The kinetics of the reactions of benzhydryl cations with 22 enamines, three pyrroles, and three indoles were investigated photometrically in dichloromethane. The nucleophilicity parameters N and slope parameters s of these electron-rich π-systems were derived from equation $\log k(20\,^{\circ}\mathrm{C}) = s(E+N)$ and compared with the nucleophilicities of other π-systems (silyl enol ethers, silyl ketene acetals) and carbanions. It is shown that the nucleophilic reactivities of enamines cover more than ten orders of magnitude, comparable to enol ethers on the low reactivity end and to carbanions on the high reactivity end. Since the products of N-attack are thermodynamically less stable than the reactants, the observed rate constants refer to the formation of the carbon–carbon bonds. In some cases, equilibrium constants for the formation of iminium ions were measured, which allow one to determine the intrinsic rate constants of these reactions.

Keywords: carbocations · C–C coupling · intrinsic barriers · kinetics · structure – reactivity relationship

Introduction

Nine years before Mannich published the first general synthesis of enamines,[1] the term "enamine" was coined in 1927 by Wittig to emphasize the analogy of this class of compounds with enols.[2] While first examples of enamine chemistry date back to 1884,[3] the synthetic potential of the reactions of enamines with electrophiles was not realized until 1954 when the pioneering work of Stork[4] demonstrated their use for α-alkylations and α-acylations of carbonyl compounds.[5] In these reactions, enamines combine with electrophiles to give iminium ions which are subsequently hydrolyzed to yield α-alkylated carbonyl or 1,3-dicarbonyl compounds, respectively.

The chemistry of enamines has extensively been reviewed.[5] Their strong nucleophilic character is revealed by their reactivity towards Michael acceptors,[6] acceptor-activated aryl halides,[7] and electron-deficient dienes which act as $_{\pi}4$-cycloaddition partners.[8]

Enamines had a unique status as noncharged enolate equivalents until the early 1970s, which they have been sharing with silylated enol ethers since then.[9] In accord with the lower electronegativity of nitrogen compared with oxygen, enamines are more nucleophilic than enol ethers and, therefore, cannot be replaced by the latter in reactions with weak electrophiles, for example allylpalladium complexes.[10]

Though structure – reactivity relationships have repeatedly been reported for small groups of enamines,[11–15] there has not been an attempt to compare reactivities of enamines of widely differing structures. It was the goal of this investigation to quantify the nucleophilic reactivities of enamines and to compare them with the reactivities of silyl enol ethers and related electron-rich arenes. This information can then be used to define their potential for a systematic use in synthesis.

Reactions of carbocations and related electrophiles with n-, π-, and σ-nucleophiles can be described by Equation (1), where E represents the electrophilicity of the carbocations, while nucleophiles are characterized by two parameters, the nucleophilicity parameter N and the slope parameter s, the latter of which can be neglected for qualitative considerations ($s \approx 1$).[16]

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

Recently, we have proposed a series of benzhydryl cations as reference electrophiles and recommended to derive nucleophilicity parameters for n-, π-, and σ-nucleophiles from the kinetics of their reactions with these carbocations.[17–20] It has been shown that the nucleophilicity order thus derived also holds for reactions of these nucleophiles with noncharged electrophiles such as quinone methides.[21] In this work we have employed the benzhydrylium ions depicted in Table 1 for characterizing the nucleophilic reactivities of enamines,

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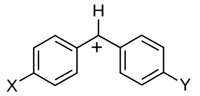
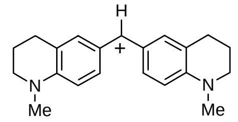
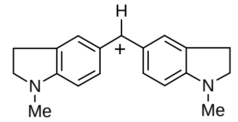
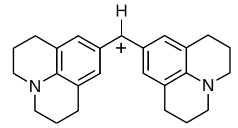
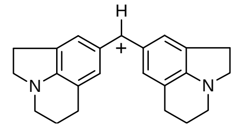
Procedures and characterized products of reactions of enamines with benzhydryl cations, and tables containing the concentrations and rate constants for the individual runs of the kinetic experiments are available as Supporting Information.

DOI: 10.1002/chem.200204666

Table 1. Abbreviations and electrophilicity parameters E of the employed reference electrophiles for determining the nucleophilicities of enamines.



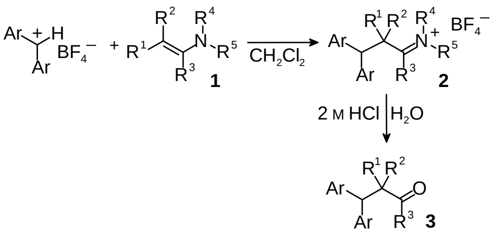
Ar_2CH^+	X	Y	E[a]
$(pfa)_2CH^+$	$N(Ph)CH_2CF_3$	$N(Ph)CH_2CF_3$	−3.14
$(mfa)_2CH^+$	$N(CH_3)CH_2CF_3$	$N(CH_3)CH_2CF_3$	−3.85
$(dpa)_2CH^+$	NPh_2	NPh_2	−4.72
$(mpa)_2CH^+$	$N(Ph)CH_3$	$N(Ph)CH_3$	−5.89
$(dma)_2CH^+$	$N(CH_3)_2$	$N(CH_3)_2$	−7.02
$(pyr)_2CH^+$	$N(CH_2)_4$	$N(CH_2)_4$	−7.69
$(thq)_2CH^+$			−8.22
$(ind)_2CH^+$			−8.76
$(jul)_2CH^+$			−9.45
$(lil)_2CH^+$			−10.04

[a] From ref. [17].

and provide the first quantitative comparison of enamines of widely differing reactivity with each other as well as with other types of nucleophiles.

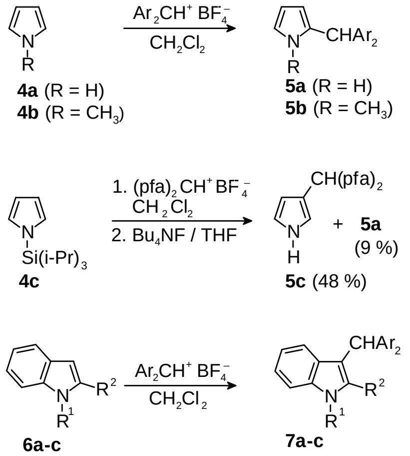
Results

The reactions of the enamines **1** with the benzhydrylium salts $Ar_2CH^+BF_4^-$ produce the iminium tetrafluoroborates **2**, usually in high yield. These were either isolated and characterized or hydrolyzed to the corresponding ketones or aldehydes **3** by treatment with dilute hydrochloric acid (Scheme 1). Some combinations of enamines with benzhydryl cations are reversible which impedes the isolation of iminium salts (see Table 2).[22–24]



Scheme 1. Reactions of enamines with benzhydryl cations.

The NMR analysis of the products **5a** and **5b**[24] showed that pyrrole **4a** (R = H) and its N-methylated analogue **4b** (R = CH_3) are alkylated by benzhydrylium salts $Ar_2CH^+BF_4^-$ at position 2 (Scheme 2, for yields see Table 2), as generally found for electrophilic substitutions of pyrroles.[25] In accord with the reports by Muchowski and co-workers,[26] the *N*-triisopropylsilylated pyrrole **4c** is mainly attacked at the 3-position (Scheme 2). Since the substituted products **5** are more nucleophilic than **4a–c**, they were found only as the predominant products when the pyrroles were used in large excess (10 equiv) over the benzhydrylium salts.[24] Alkylation of the indoles **6a–c** occurs at position 3 with formation of compounds **7a–c**, in analogy to previously reported electrophilic substitutions of indoles.[27, 28]



Scheme 2. Reactions of substituted pyrroles and indoles with benzhydryl cations.

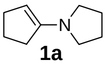
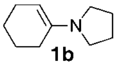
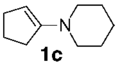
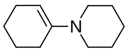
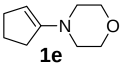
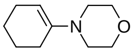
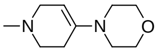
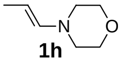
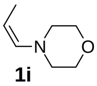
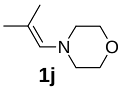
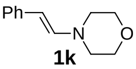
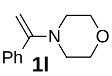
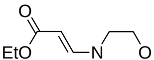
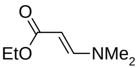
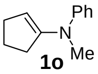
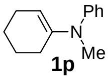
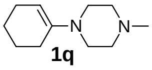
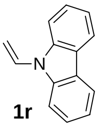
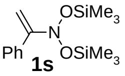
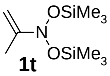
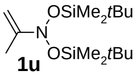
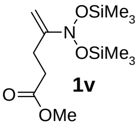
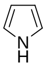
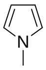
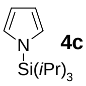
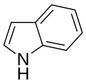
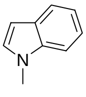
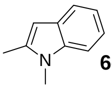
The rates of the reactions of the benzhydryl cations with the enamines **1**, pyrroles **4**, and indoles **6** were followed by UV/Vis spectroscopy. Solutions of the tetrafluoroborates of Ar_2CH^+ in dichloromethane were combined with an excess of the nucleophiles, and the decay of the carbenium absorbance at $\lambda_{\mathrm{max}} = 590–680$ nm was monitored as a function of time (Figure 1).

Nucleophile concentrations considerably higher than the benzhydryl cation concentrations were usually employed (10 to 100 equivalents), resulting in pseudo-first order kinetics with an exponential decay of the benzhydryl cation concentration. For slow reactions ($\tau_{1/2} > 10$ s) with complete consumption of the benzhydryl cations, the decrease of the absorbances of Ar_2CH^+ was followed and evaluated as described before[23, 29] to obtain the second-order rate constants k_2 ($\mathrm{M}^{-1}\mathrm{s}^{-1}$). For reversible reactions with incomplete consumption of the colored benzhydryl cations, the pseudo-first order rate constants k_{eff} (s^{-1}) were obtained from the slopes of plots of $\ln(A_t - A_{\mathrm{end}})$ versus t according to Equation (2), where A_t is the absorption of Ar_2CH^+ at the time t.

$$k_{\mathrm{eff}}t = \ln(A_0 - A_{\mathrm{end}}) - \ln(A_t - A_{\mathrm{end}}) \qquad (2)$$

Variation of the nucleophile concentrations $[\mathrm{Nuc}]_0$ allows one to derive the rate constants for the forward (k_2) and backward

Table 2. Second-order rate constants for the reactions of enamines, pyrroles and indoles with benzhydryl cations in CH$_2$Cl$_2$ at 20 °C.

Enamine	N	s[a]	Ar$_2$CH$^+$	$k_2/\mathrm{M^{-1}\,s^{-1}}$	Products
 **1a**	15.91	0.86	(lil)$_2$CH$^+$	1.26×10^5	
			(jul)$_2$CH$^+$	3.32×10^5	**2a** (62 %)
			(thq)$_2$CH$^+$	4.48×10^6	**3a** (39 %)
 **1b**	14.91	0.86	(lil)$_2$CH$^+$	1.48×10^{4}[b]	
			(jul)$_2$CH$^+$	4.59×10^4	
			(thq)$_2$CH$^+$	7.30×10^5	
			(dma)$_2$CH$^+$	5.33×10^6	**3b** (65 %)
 **1c**	15.06	0.82	(lil)$_2$CH$^+$	1.15×10^{4}[b]	
			(jul)$_2$CH$^+$	4.57×10^{4}[b]	**2c** (89 %)
			(thq)$_2$CH$^+$	4.44×10^5	
			(dma)$_2$CH$^+$	3.68×10^6	**3c** (49 %)
 **1d**	13.36[c]	0.81[c]	(lil)$_2$CH$^+$	5.06×10^{2}[c]	see ref. [17]
			(jul)$_2$CH$^+$	1.41×10^{3}[c]	see ref. [17]
			(pyr)$_2$CH$^+$	3.95×10^{4}[b,c]	
 **1e**	13.41	0.82	(lil)$_2$CH$^+$	4.70×10^{2}[b]	**3e**
			(jul)$_2$CH$^+$	1.76×10^{3}[b]	
			(thq)$_2$CH$^+$	1.71×10^{4}[b]	
			(dma)$_2$CH$^+$	2.44×10^5	**2e** (90 %)
			(mpa)$_2$CH$^+$	9.71×10^5	
 **1f**	11.40[c]	0.83[c]	(lil)$_2$CH$^+$	1.58×10^{1}[c]	see ref. [17]
			(jul)$_2$CH$^+$	3.35×10^{1}[c]	see ref. [17]
			(ind)$_2$CH$^+$	1.51×10^{2}[b,c]	see ref. [17]
			(thq)$_2$CH$^+$	3.97×10^{2}[b,c]	see ref. [17]
			(pyr)$_2$CH$^+$	1.36×10^{3}[b,c]	see ref. [17]
			(dma)$_2$CH$^+$	4.69×10^{3}[b,c]	see ref. [17]
			(dpa)$_2$CH$^+$	3.38×10^{5}[c]	
 **1g**	12.03	(0.80)	(dma)$_2$CH$^+$	1.01×10^{4}[b]	**3g** (76 %)
 **1h**	12.06	(0.80)	(dpa)$_2$CH$^+$	7.44×10^5	
 **1i**	12.26	(0.80)	(dpa)$_2$CH$^+$	1.07×10^{6}[d]	
 **1j**	10.04	0.82	(dma)$_2$CH$^+$	2.53×10^{2}[b,e]	**3j** (52 %)
			(mpa)$_2$CH$^+$	3.33×10^{3}[e]	
			(dpa)$_2$CH$^+$	2.41×10^4	
			(mfa)$_2$CH$^+$	1.28×10^5	
			(pfa)$_2$CH$^+$	4.24×10^5	**2j**
 **1k**	10.76	0.87	(mpa)$_2$CH$^+$	1.49×10^4	
			(dpa)$_2$CH$^+$	2.21×10^5	**3k** (70 %)
			(mfa)$_2$CH$^+$	1.07×10^6	
			(pfa)$_2$CH$^+$	3.72×10^6	
 **1l**	9.96	0.79	(thq)$_2$CH$^+$	2.34×10^1	
			(dma)$_2$CH$^+$	2.11×10^{2}[b]	
			(mpa)$_2$CH$^+$	1.68×10^3	
			(dpa)$_2$CH$^+$	1.36×10^4	**3l** (46 %)
			(mfa)$_2$CH$^+$	6.68×10^4	
			(pfa)$_2$CH$^+$	2.49×10^5	**2l** (83 %)
 **1m**	8.52	(0.80)	(pfa)$_2$CH$^+$	2.02×10^{4}[e]	
 **1n**	9.43	(0.80)	(pfa)$_2$CH$^+$	1.07×10^5	
 **1o**	12.90	0.79	(lil)$_2$CH$^+$	2.02×10^{2}[b]	
			(jul)$_2$CH$^+$	4.31×10^2	
			(thq)$_2$CH$^+$	5.01×10^3	
			(dma)$_2$CH$^+$	4.96×10^4	**2o** (92 %)
			(mpa)$_2$CH$^+$	3.21×10^5	
			(dpa)$_2$CH$^+$	2.76×10^6	
 **1p**	10.73	0.81	(thq)$_2$CH$^+$	1.04×10^2	
			(dma)$_2$CH$^+$	1.05×10^{3}[e]	
			(mpa)$_2$CH$^+$	8.43×10^3	
			(dpa)$_2$CH$^+$	8.64×10^4	**3p** (35 %)
			(mfa)$_2$CH$^+$	3.40×10^5	
 **1q**	12.51	(0.80)	(dma)$_2$CH$^+$	2.45×10^{4}[b]	**2q** (93 %), **3q** (59 %)
 **1r**	5.02[f]	0.94[f]	(dma)$_2$CH$^+$	1.35×10^{-2}[f]	see ref. [22]
			(dpa)$_2$CH$^+$	1.93[f]	
 **1s**	4.80[g]	(0.86)[g]	various	see ref. [23]	
 **1t**	4.76[g]	0.86[g]	various	see ref. [23]	
 **1u**	4.23[g]	0.93[g]	various	see ref. [23]	
 **1v**	3.84[g]	0.87[g]	various	see ref. [23]	
 **4a**	4.63	(1.00)	(pfa)$_2$CH$^+$	3.12×10^1	**5a** (32 %)
 **4b**	5.85[c]	1.03[c]	various	see ref. [24]	
 **4c**	3.12	0.93	(dpa)$_2$CH$^+$	4.26×10^{-2}	
			(mfa)$_2$CH$^+$	1.19×10^{-1}	
			(pfa)$_2$CH$^+$	1.33	**5c** (48 %)[h]
 **6a**	5.80	(0.80)	(pfa)$_2$CH$^+$	1.34×10^2	**7a** (70 %)
 **6b**	6.93	(0.80)	(pfa)$_2$CH$^+$	1.09×10^3	**7b** (22 %)
 **6c**	7.81	(0.80)	(pfa)$_2$CH$^+$	5.47×10^3	**7c** (34 %)

[a] Values in parentheses are estimates. [b] Eyring activation parameters are given in Table 3. [c] From ref. [17]. [d] Mixture **1i**/**1h** 89:11. [e] Reversible reaction, for equilibrium constant see Table 4. [f] From ref. [22]. [g] From ref. [23]. [h] The crude product contains also isomer **5a** (9 %) as revealed by NMR spectroscopy.

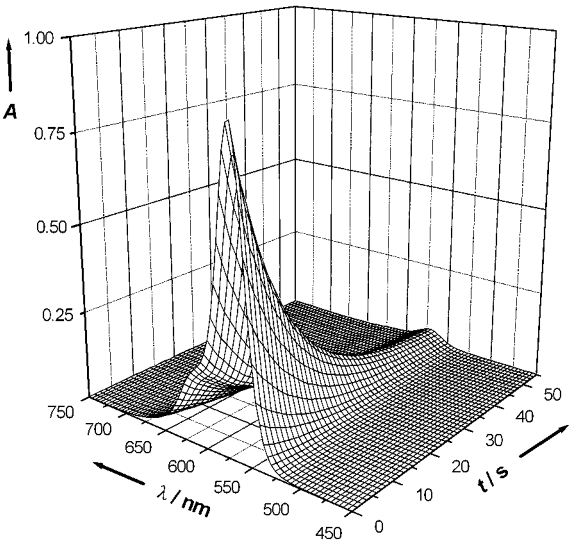


Figure 1. UV/Vis spectra during the reaction of the benzhydryl cation $(thq)_2CH^+$ with the enamine **1p** in CH_2Cl_2 at 20 °C.

(k_{-2}) reactions from the relation $k_{eff} = k_2[Nuc]_0 + k_{-2}$.[30] Equilibrium constants K (M^{-1}) were calculated from the ratios k_2/k_{-2}.

Rapid reactions ($\tau_{1/2} < 10$ s at 20 °C) were investigated with a stopped-flow spectrophotometer system, and pseudo-first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the single exponential $A_t = A_0 \exp(-k_{obs}t) + C$ to the absorbance data (averaged from at least four kinetic runs at each nucleophile concentration). Because k_{obs} was found to be proportional to the concentrations of the nucleophiles, one can conclude that the reactions follow second-order kinetics, first order with respect to the electrophile and first order with respect to the nucleophile. Second-order rate constants k_2 ($M^{-1}s^{-1}$) were calculated from $k_{obs} = k_2[Nuc]_0$.

All rate constants (20 °C) for the reactions of enamines and related compounds with benzhydrylium ions determined in this work are collected in Table 2 and are supplemented by some rate constants determined previously.

The last column of Table 2 contains the products of the reactions of benzhydryl cations with nucleophiles which were characterized as iminium salts **2**, carbonyl compounds **3**, or as the results of electrophilic aromatic substitutions (**5** or **7**).

In cases where the temperature dependence of the rate constants has been determined, the k_2 values given in Table 2 are those derived from the Eyring parameters listed in Table 3. The temperature variations show that the observed differences in reactivity are predominantly due to enthalpic effects, since $\Delta S^{\ddagger}$ is always around $-100\ J\,mol^{-1}K^{-1}$, as in previously studied reactions of carbocations with π-nucleophiles.[17, 22, 23, 31]

Discussion

Enamines are ambident nucleophiles, and the second-order rate constants k_2 in Table 2, which are derived from the disappearence of the benzhydryl cation absorptions, may either be due to direct formation of the isolated iminium ions or to the initial formation of eneammonium ions which rearrange to the observed products in a successive reaction. Electrophilic attack at nitrogen has previously been reported for reactions of enamines with protons[14, 32–34] and with alkyl halides.[35] It was shown that protonation at nitrogen initially yields eneammonium ions which successively rearrange to the more stable iminium ions[14, 33, 34] (Figure 2).

Table 3. Eyring activation parameters[a] for the reactions of benzhydryl cations with enamines in CH_2Cl_2.

Enamine	Ar_2CH^+	$\Delta H^{\ddagger}$/ kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1}K^{-1}
1b	$(lil)_2CH^+$	16.43 ± 0.70	-108.90 ± 3.34
1c	$(lil)_2CH^+$	17.13 ± 0.40	-108.65 ± 1.86
1c	$(jul)_2CH^+$	17.97 ± 0.56	-94.28 ± 2.71
1d	$(pyr)_2CH^+$	14.33 ± 0.84[b]	-107.88 ± 4.05[b]
1e	$(lil)_2CH^+$	24.10 ± 0.15	-111.41 ± 0.66
1e	$(jul)_2CH^+$	22.29 ± 0.38	-106.62 ± 1.68
1e	$(thq)_2CH^+$	17.55 ± 0.65	-103.91 ± 2.90
1f	$(ind)_2CH^+$	26.20 ± 0.43[b]	-113.71 ± 1.75[b]
1f	$(thq)_2CH^+$	24.28 ± 0.42[b]	-112.21 ± 1.83[b]
1f	$(pyr)_2CH^+$	23.33 ± 0.58[b]	-105.20 ± 2.51[b]
1f	$(dma)_2CH^+$	20.46 ± 0.94[b]	-104.71 ± 4.15[b]
1g	$(dma)_2CH^+$	25.39 ± 1.68	-81.51 ± 7.55
1j	$(dma)_2CH^+$	22.75 ± 0.28	-121.18 ± 1.28
1l	$(dma)_2CH^+$	35.20 ± 0.41	-80.20 ± 1.71
1o	$(lil)_2CH^+$	34.17 ± 0.79	-84.11 ± 3.25
1q	$(dma)_2CH^+$	17.97 ± 0.50	-99.43 ± 2.34

[a] As indicated by the error limits in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, the large number of decimals is per se meaningless, but is needed for reproducing the rate constants in Table 2. [b] From ref. [17].

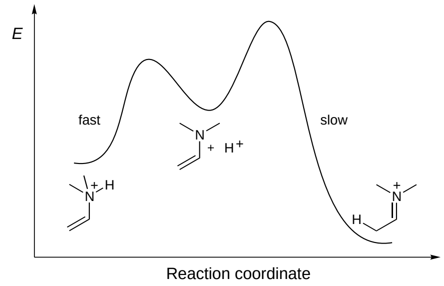
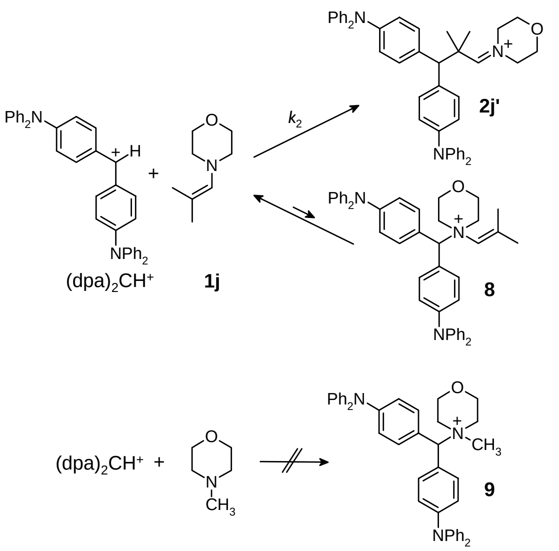


Figure 2. Protonation of enamines.

To determine the preferred site of electrophilic attack for the combinations listed in Table 2, we have investigated the reactions of benzhydrylium ions with the enamine **1j** in detail. Because of the steric shielding of the β-carbon in compound **1j** by two methyl groups, in this system the electrophilic attack at nitrogen should be particularly favorable over attack at the β-carbon.

When enamine **1j** was treated with $(dpa)_2CH^+BF_4^-$ at 20 °C, the consumption of the benzhydrylium ion was complete within 1 s (UV detection) with a second-order rate constant of $2.41 \times 10^4\ M^{-1}s^{-1}$ (Table 2). The ^1H NMR spectrum taken after 30 s indicated the exclusive formation of the iminium ion **2j′** (Scheme 3).

How can one exclude that the UV/Vis spectroscopically observed reaction (≈ 1 s) is due to the formation of **8** while the NMR spectrum shows the structure of the rearranged product **2j′**?



Scheme 3. Reactions of $(dpa)_2CH^+$ with the enamine **1j** and *N*-methylmorpholine.

Under the conditions of the UV/Vis experiment just described, *N*-methylmorpholine does not react with $(dpa)_2CH^+$ to form the ammonium ion **9** (Scheme 3), indicating an equilibrium for *N*-attack which is far on the side of the reactants.[36]

Since saturated tertiary amines are 10^2 times more basic than the corresponding enamines,[34b,c] we must conclude that the equilibrium concentration of **8** must even be smaller than the (nonobservable) equilibrium concentration of the quaternary morpholinium ion **9**. As a consequence, only a negligible concentration of the eneammonium ion **8** can be produced from $(dpa)_2CH^+$ and **1j**. Despite a potentially high rate constant for the formation of **8**, the unfavorable equilibrium constant rules out that the UV/Vis spectroscopically observed reaction is due to *N*-attack.

The ratio *C*- versus *N*-attack should even be higher with the other enamines of Table 2, and one can, therefore, generalize that all rate constants in Table 2 refer to the attack of the carbocations Ar_2CH^+ at the β-carbon atom of enamines. Since the initial formation of small equilibrium concentrations of eneammonium ions does not have any influence on the rates of consumption of the benzhydrylium ions Ar_2CH^+ by β-carbon attack of the enamines, we will disregard this reversible side reaction in the following discussion.

When the rate constants (log*k*) determined for the reactions of the enamines **1** and the pyrrole derivatives **4b**, **c** with Ar_2CH^+ (Table 2) are plotted against the *E* parameters of the benzhydryl cations (from Table 1), linear correlations are obtained, from which *s* and *N* according to Equation (1) can be determined (Figure 3). Since the slopes *s* do not differ widely ($0.79 < s < 1.03$), estimated values of *s* can be used to derive *N* parameters for those compounds which have only been studied with respect to a single benzhydryl cation[37] (see Table 2).

As indicated in the footnotes of Table 2, not all reactions of benzhydrylium ions with enamines proceed quantitatively, and in four cases, equilibrium constants have been determined. While **1j** reacts quantitatively with $(dpa)_2CH^+$ and with more electrophilic benzhydrylium ions, equilibrium constants of $3.7 \times 10^4\,M^{-1}$ and $4.3 \times 10^2\,M^{-1}$ have been measured for the combinations of **1j** with $(mpa)_2CH^+$ and $(dma)_2CH^+$, respectively, in dichloromethane at 20 °C.

From the linear correlations between rate and equilibrium constants of the reactions of benzhydrylium ions with nucleophiles,[38] one can extrapolate that log*K* should be 0 for a benzhydrylium ion with $E = -8.55$ (Figure 4). Since no far-ranging extrapolation is needed, the calculated intercept

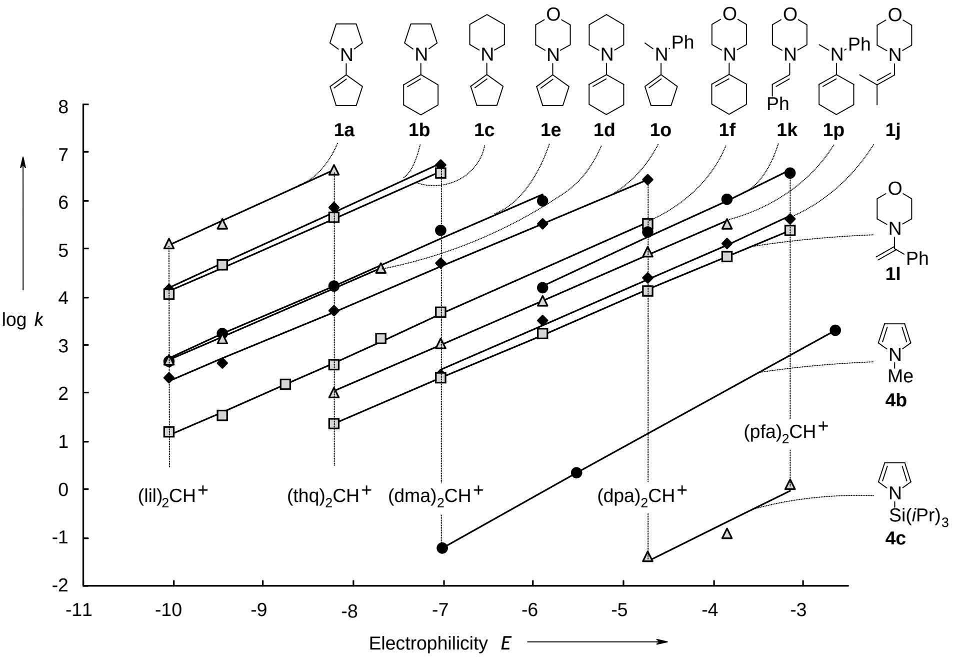


Figure 3. Correlations of the rate constants (log*k*, 20 °C, CH_2Cl_2) for the reactions of enamines **1** and pyrroles **4b**, **c** with benzhydryl cations Ar_2CH^+ versus their electrophilic reactivities *E*.

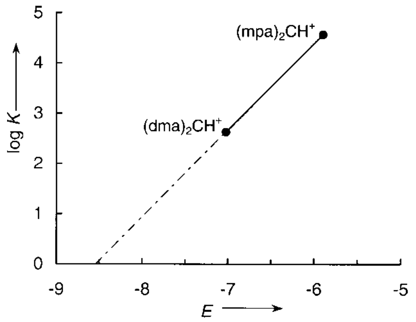


Figure 4. Correlation of log*K* versus *E* for the reactions of benzhydryl cations Ar_2CH^+ with **1j** in dichloromethane at 20 °C ($\log K = 1.72\,E + 14.67$, $n = 2$).

on the abscissa of Figure 4 is rather reliable though it is based on only two experimental equilibrium constants.

In Marcus theory,[39] the intrinsic rate constant is defined as the rate constant of a reaction that does not have a thermodynamic driving force ($\Delta_r G^\circ = 0$). Thus, the rate constant of the reaction of **1j** with the hypothetical benzhydrylium ion of $E = -8.55$ ($\approx$(ind)$_2$CH$^+$) which can be calculated as $k_2(20\,^\circ\text{C}) = 16.7\,\text{M}^{-1}\text{s}^{-1}$ by Equation (1) equals the intrinsic rate constant. The Eyring equation then allows to derive the intrinsic barrier of this reaction as $\Delta G_0^{\ddagger} = 64.9\,\text{kJ}\,\text{mol}^{-1}$ at 20 °C. Intrinsic barriers of 58 to 67 kJ mol^{-1} are calculated by the Marcus equation:

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\,\Delta_r G^\circ + \frac{(\Delta_r G^\circ)^2}{16\,\Delta G_0^{\ddagger}} \tag{3}$$

for the other reactions of benzhydryl cations with enamines for which equilibrium constants have been determined (Table 4). As discussed previously,[38] the work term in the Marcus Equation (3) can be neglected in ion-molecule reactions.

Table 4. Calculation of the intrinsic barriers $\Delta G_0^{\ddagger}$ from the reaction and activation free enthalpies of the reactions of benzhydrylium ions with enamines in CH_2Cl_2 at 20 °C.

Enamine	Ar_2CH^+	K/ M^{-1}	$\Delta_r G^\circ$/ kJ mol^{-1}	$\Delta G^{\ddagger}$/ kJ mol^{-1}	$\Delta G_0^{\ddagger}$/ kJ mol^{-1}
1j	(dma)$_2$CH$^+$	4.26×10^2	−14.76	58.27	65.44
1j	(mpa)$_2$CH$^+$	3.72×10^4	−25.65	51.99	64.17
1m	(pfa)$_2$CH$^+$	1.08×10^4	−22.63	47.60	58.37
1p	(dma)$_2$CH$^+$	3.66×10^4	−25.61	54.80	66.99

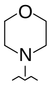
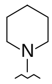
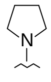
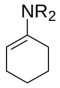
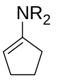
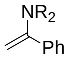
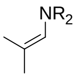
The intrinsic barriers ($\Delta G_0^{\ddagger}$) in Table 4 closely resemble those previously estimated for the reactions of benzhydrylium ions with 2-methyl-1-pentene,[29] and are larger than those observed for the reactions with phosphanes and amines.[40]

The almost parallel lines in Figure 3, numerically expressed by the closely similar *s*-parameters in Table 2, imply that the relative reactivities of these enamines are almost independent of the nature of the benzhydrylium ions Ar_2CH^+ (constant-selectivity relationship). For that reason, discussions of structure – reactivity correlations can be based on the magnitude of *N* or on relative reactivities towards any specific benzhydrylium ion. We will employ both quantities in the following discussion.

As shown in Table 5, the relative reactivities of different types of enamines towards various electrophiles generally decrease in the order pyrrolidine > piperidine > morpholine.

The higher reactivity of pyrrolidine compounds compared to piperidine analogues can be explained by the higher p-character of the nitrogen lone-pair in a five-membered ring compared with a six-membered ring which is revealed by a lower first vertical ionization potential (IP$_1$)[5a, 41] of pyrrolidino compared to piperidino compounds (Figure 5). Replacement of the 4-CH$_2$ group in piperidine by the more electronegative oxygen further increases the ionization potential and consequently reduces nucleophilicity. The increasing degree of pyramidalization of nitrogen from pyrrolidino to piperidino and morpholino has also been confirmed by X-ray crystallography of derivatives of these compounds.[42]

Table 5. Comparison of relative rate constants k_{rel} for the reactions of enamines with various electrophiles.

	Reactions	Relative reactivities k_{rel} of enamines		
	NR$_2$ =			
	+ (lil)$_2$CH$^+$ (CH_2Cl_2, 20 °C)	1	32	937
	+ (jul)$_2$CH$^+$ (CH_2Cl_2, 20 °C)	1	42	1370
	+ (lil)$_2$CH$^+$ (CH_2Cl_2, 20 °C)	1	24	268
	+ (jul)$_2$CH$^+$ (CH_2Cl_2, 20 °C)	1	26	189
	+ (thq)$_2$CH$^+$ (CH_2Cl_2, 20 °C)	1	26	262
	+ PhN$_3$ (C_6H_6, 25 °C)[a]	1	–	45
	+ PhN$_3$ ($CHCl_3$, 44.8 °C)[b]	1	5	155
	+ Ph$_2$C=C=O (PhCN, 40.3 °C)[c]	1	–	1420
	+ H$_3$O$^+$ (H_2O, 25 °C)[d]	1	452	27100

[a] From ref. [11]. [b] From ref. [12]. [c] From ref. [13]. [d] From ref. [14].

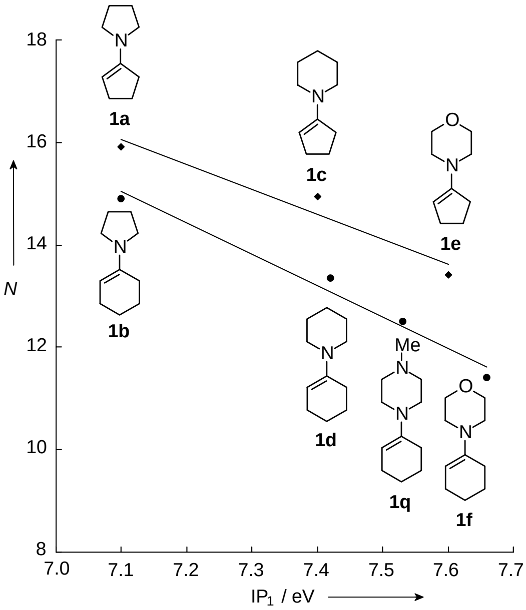
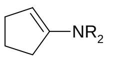
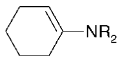
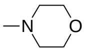
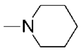
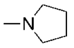


Figure 5. Correlation of the nucleophilic reactivities *N* with the first vertical ionization potentials IP$_1$ for cyclic enamines[41] (cyclopentenes: $N = -4.86\,\text{IP}_1 + 50.54$, $n = 3$, $r^2 = 0.9397$; cyclohexenes: $N = -6.11\,\text{IP}_1 + 58.44$, $n = 4$, $r^2 = 0.9772$).

Comparison of compounds **1e** with **1o** or of **1f** with **1p** (Table 2) indicates that enamines with a methylphenylamino group are three to five times less nucleophilic than analogous structures with morpholino moieties. From the comparison of **1m** with **1n** (Table 2) one can derive that a dimethylamino group activates the double bond five times better than an *N*-morpholino group.

Cyclopentanone-derived enamines in general show higher reactivities than compounds derived from cyclohexanone (Table 6), and the ratio decreases in the series morpholino > piperidino > pyrrolidino compounds.

Table 6. Comparison of relative rate constants k_{rel} for the reactions of enamines from cyclopentanone and cyclohexanone with electrophiles.

Electrophile (reaction conditions)	Relative reactivities k_{rel} of enamines		
	-NR_2		
			
$(lil)_2CH^+$ (CH_2Cl_2, 20 °C)		30	1
$(jul)_2CH^+$ (CH_2Cl_2, 20 °C)		53	1
$(thq)_2CH^+$ (CH_2Cl_2, 20 °C)		43	1
$(dma)_2CH^+$ (CH_2Cl_2, 20 °C)		52	1
			
$(lil)_2CH^+$ (CH_2Cl_2, 20 °C)		23	1
$(jul)_2CH^+$ (CH_2Cl_2, 20 °C)		32	1
			
$(lil)_2CH^+$ (CH_2Cl_2, 20 °C)		8.5	1
$(jul)_2CH^+$ (CH_2Cl_2, 20 °C)		7.2	1
$(thq)_2CH^+$ (CH_2Cl_2, 20 °C)		6.1	1
PhN_3 (C_6H_6, 25 °C)[a]		12	1

[a] From ref. [11].

As shown in Figure 6, analogous dependencies of the nucleophilic reactivities on the ring size are also found for the corresponding 1-(trimethylsiloxy)cycloalkenes[17, 43] and 1-methylcycloalkenes.[17] The linear correlation between N and σ^+ of the substituent R[44] corresponds to that previously reported for proton additions to substituted C=C double bonds.[45]

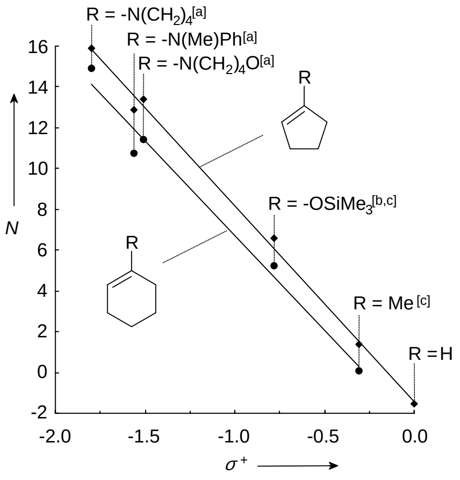


Figure 6. Correlation of N with σ^+ for cyclic enamines, silyl enol ethers, and alkenes (cyclopentenes: $N = -9.60\sigma^+ - 1.43$, $n = 6$, $r^2 = 0.9967$; cyclohexenes: $N = -9.28\sigma^+ - 2.60$, $n = 5$, $r^2 = 0.9829$). [a] σ^+ from ref. [17]. [b] The σ^+ value of -OMe was used. [c] σ^+ from ref. [44].

Substituents at the β-carbon atom (site of electrophilic attack) also have a noticeable influence on the reactivity of enamines. Replacement of substituents with electron donating properties like methyl (compound **1h**) by electron-withdrawing substituents such as ethoxycarbonyl (compound **1m**) reduces the reactivity of $_{\beta}$C-substituted morpholinoethenes by a factor of about 700 (calculated for $(pfa)_2CH^+$, CH_2Cl_2, 20 °C). The corresponding phenyl-substituted enamine **1k** is in between. A plot of the N parameters (from Table 2) versus the σ_p values[44] of the β-substituents of these enamines shows a linear correlation (Figure 7). Since the variable substituent is at a position which does not adopt a formal positive charge in the product, the slope of this correlation is considerably smaller than that in Figure 6.

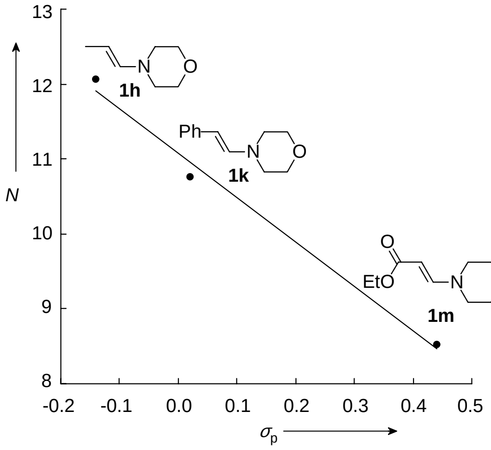
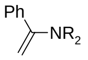
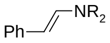
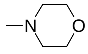
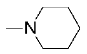
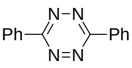


Figure 7. Correlation of N with σ_p[44] for $_{\beta}$C-substituted (E)-morpholinoethenes ($N = -5.95\sigma_p + 11.08$, $n = 3$, $r^2 = 0.9898$).

Comparison of compounds **1h** and **1i** (Table 2) shows that E,Z-isomeric enamines differ little in reactivity. An additional methyl group at the β-carbon atom (**1j**) reduces the reactivity by a factor of 30 – 40 because of steric shielding.

In contrast to intuition, β-(N-morpholino)styrene (**1k**) reacts 15 times faster with benzhydrylium ions than α-(N-morpholino)styrene (**1l**) (Table 7). Obviously, the delocalization of the positive charge by the morpholino group is so efficient that the presence of an additional phenyl group at the new carbocation center is not helpful. In the transition state, the destabilization due to disturbing the amino resonance is more effective than the stabilization by the +M-effect of the phenyl group. Similar reactivity ratios were found for α- and β-aminostyrenes in 1,3-dipolar cycloadditions of phenyl azide[12] and Diels – Alder reactions with 3,6-diphenyl-1,2,4,5-tetrazine[15] (Table 7).

Table 7. Relative rate constants for the reactions of $_{\alpha}$C- and $_{\beta}$C-phenyl-substituted enamines with various electrophiles.

Electrophile (reaction conditions)	Relative reactivities k_{rel} of enamines		
	-NR_2		
			
$(mpa)_2CH^+$ (CH_2Cl_2, 20 °C)		1	8.9
$(dpa)_2CH^+$ (CH_2Cl_2, 20 °C)		1	16
$(mfa)_2CH^+$ (CH_2Cl_2, 20 °C)		1	16
$(pfa)_2CH^+$ (CH_2Cl_2, 20 °C)		1	15
PhN_3 ($CHCl_3$, 30 °C)[a]		1	13
 (dioxane, 20 °C)[b]	-NMe_2	1	8

[a] From ref. [12]. [b] From ref. [15].

According to Figure 8, increasing basicity of the indoles, as expressed by the pK_a values of their conjugate acids,[46] is associated with increasing nucleophilicity. The slope of the correlation line (0.50) indicates that roughly 50% of the changes in $\Delta_r G^\circ$ are found in $\Delta G^{\ddagger}$.

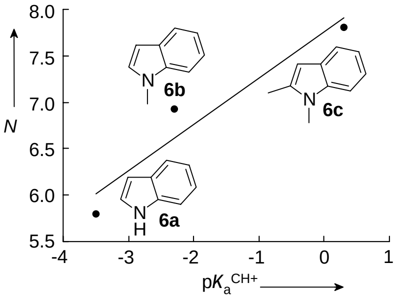


Figure 8. Plot of N versus pK_a^{CH+} (H_2O, 25°C)[46] for indoles ($N = 0.50$ p$K_a^{CH+} + 7.76$, $n = 3$, $r^2 = 0.923$).

Comparison of **4a–c** indicates that N-methylation of pyrrole increases the nucleophilicity by a factor of 20 while N-triisopropylsilylation reduces the nucleophilicity by a factor of 23 (calculated for $(pfa)_2CH^+$, CH_2Cl_2, 20°C).

Conclusion

As outlined in the Introduction, enamines have long been known as strong nucleophiles. With our method of using reference electrophiles[17, 18] it is now possible to compare nucleophilicities of enamines with widely varying reactivity. As shown in Figure 9, enamines cover a wide range of nucleophilicity from $N \approx 4$ such as typical enol ethers[17] to $N \approx 16$ such as stabilized carbanions in DMSO.[21] For a typical s value of 0.85, this range corresponds to roughly ten orders of magnitude in rate constants or relative reaction times of one minute for **1a** versus 20000 years for **1v**. The benefit of this scale in synthesis design is obvious.

Experimental Section

Chemicals: The benzhydrylium salts $Ar_2CH^+BF_4^-$ (see Table 1) were prepared as described in ref. [17]. Details will be published separately. Compounds **1n**, **4a–c**, **6a–c**, and N-methylmorpholine have been purchased and purified by distillation or recrystallization prior to use.

Enamines **1a–g**, **1j–l**, and **1o-q** were prepared by condensation of the ketone or aldehyde with the corresponding secondary amine.[47] Enamine **1i** was obtained by base-catalyzed (KO*t*Bu/DMSO) isomerization of 4-allylmorpholine.[48] The resulting 11:89 mixture of **1h** and **1i** underwent a benzoic acid-catalyzed isomerization to give pure **1h**.[48] For the preparation of **1m**, morpholine was added to ethyl propiolate.[49]

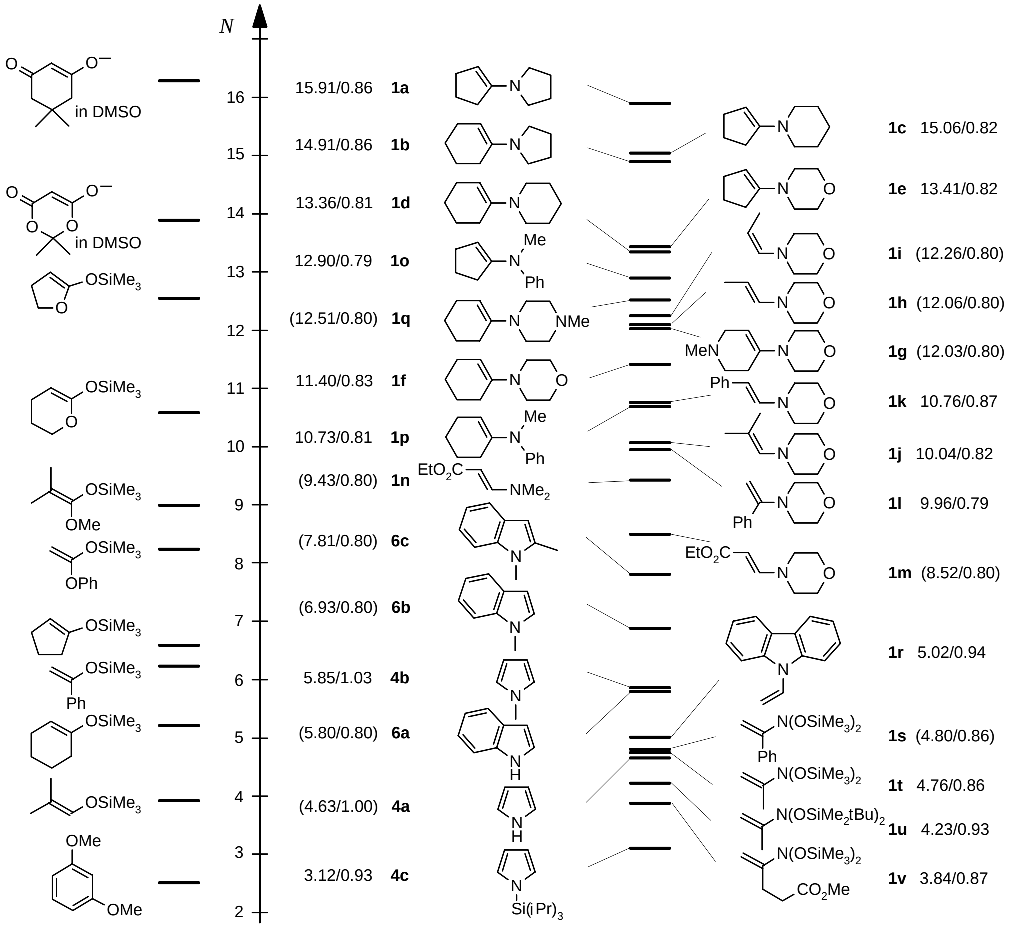


Figure 9. Nucleophilicity and slope parameters N/s of enamines, pyrroles and indoles from Table 2 compared with other π-systems and carbanions (parentheses indicate estimated values of s). While the N parameters of neutral π-nucleophiles depend little on solvent, nucleophilicity parameters of carbanions refer to the specified solvent.[21]

Reactions: The products of the reactions of enamines **1** with the benzhydrylium salts Ar$_2$CH$^+$ BF$_4^-$ were synthesized by adding the enamine to a stirred solution of the benzhydrylium salts in dry CH$_2$Cl$_2$ at room temperature. After the blue color of the reaction mixture faded, the solvent was removed in vacuo. The residue was then washed with dry Et$_2$O and either dried in vacuo to obtain the iminium products **2** or hydrolyzed with dilute HCl to give the corresponding ketones or aldehydes **3** which were purified by crystallization or column chromatography.

The substituted pyrroles **5** and indoles **7** were obtained by dropwise addition of dichloromethane solutions of Ar$_2$CH$^+$ BF$_4^-$ (25 mL) to solutions of freshly distilled or recrystallized pyrroles **4** (10 equiv) or indoles **6** (10 equiv), respectively, in CH$_2$Cl$_2$ (25 mL). After fading of the color, the solvent was evaporated in vacuo to yield the crude products which were purified by column chromatography.

For details and characterization of the products see the Supporting Information.

Kinetics: The kinetics of the reactions of the benzhydryl cations with enamines, pyrroles, or indoles were followed by UV/Vis spectroscopy by using working stations similar to those previously described.[29]

For slow reactions ($\tau_{1/2} > 10$ s) the UV/Vis spectra were collected at different times either by using a Schölly KGS III photometer with fiber optics and band-pass filters by Corion or a J&M TIDAS diode array spectrophotometer that was connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) through fiber optic cables with standard SMA connectors. All kinetic measurements were made in Schlenk glassware under exclusion of moisture. The temperature of the solutions during the kinetic studies was maintained to within ±0.2 °C by using circulating bath cryostats and monitored with thermo-couple probes that were inserted into the reaction mixture.

Stopped-flow spectrophotometer systems (Hi-Tech SF-61DX2 controlled by Hi-Tech KinetAsyst2 software) were used for the investigation of rapid reactions of benzhydrylium ions with nucleophiles ($\tau_{1/2} < 10$ s). The kinetic runs were inititated by mixing equal volumes of dichloromethane solutions of the nucleophile and the benzhydrylium salt. Concentrations and rate constants for the individual kinetic experiments for the reactions of enamines, pyrroles, and indoles with benzhydryl cations are given in the Supporting Information.

Eyring activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of the electrophile – nucleophile combinations were calculated from second-order rate constants that were measured at different temperatures ($\Delta T > 30$ K).

Acknowledgement

We thank Konrad Koszinowski for performing the experiments with **1e** and (jul)$_2$CH$^+$ BF$_4^-$. Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

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Received: December 12, 2002 [F4666]