

Nucleophilic Reactivities of Schiff Bases

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Dedicated to Professor Heinrich Nöth on the occasion of his 85th birthday

The nucleophile-specific parameters N and s_N , as defined by the linear free energy relationship $\log k = s_N(N + E)$ (*J. Am. Chem. Soc.* **2001**, 123, 9500–9512), were determined for five imines **1a–e** by studying the kinetics of their reactions with benzhydrylium ions in dichloromethane solution at 20 °C. These parameters allowed us to include representative Schiff bases into our comprehensive nucleophilicity scale and compare their reactivities with those of other N -nucleophiles.

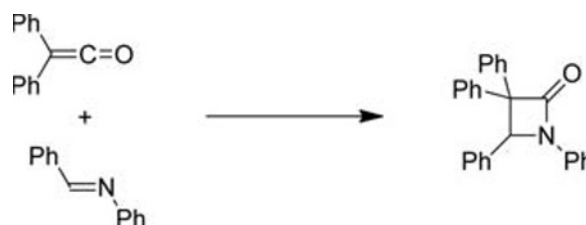
Key words: Kinetics, Linear Free Energy Relationship, Imine, Azomethine, Carbenium Ions

Introduction

Schiff bases (imines, **1**), first prepared by Hugo (Ugo) Schiff one and a half century ago [1, 2], are among the most widely used reagents and intermediates in organic synthesis, and are important ligands in coordination chemistry [3–10]. Already in 1907, Hermann Staudinger discovered their [2 + 2] cycloadditions with ketenes to give β -lactams (Scheme 1) [11]. In 1950 Corey *et al.* utilized this cycloaddition reaction for the first laboratory synthesis of penicillin [12].

Despite the use of Schiff bases in numerous reactions, their nucleophilic reactivities have so far not been quantified. Since the nucleophilic reactivities of various nucleophiles toward electrophiles correlate only poorly with the corresponding Brønsted basicities [13–16], we have previously introduced the benzhydrylium methodology for the construction of a comprehensive nucleophilicity scale [17–24]. In this approach, benzhydrylium ions with variable *p*- and *m*-substituents (**2**, some of them are depicted in Table 1), which cover a broad range of reactivity while the steric shielding of the reaction center is kept constant, were used as reference electrophiles to compare reactivities of various classes of nucleophiles [17–24].

In numerous publications it was demonstrated that the rates of the reactions ($\log k$) of n -, π -, and σ -nucleophiles toward carbocations and Michael accep-



Scheme 1. Staudinger β -lactam synthesis.

tors can be described by the linear-free energy relationship (Eq. 1) [17–24], where electrophiles are characterized by one solvent-independent electrophilicity parameter E , and nucleophiles are characterized by two solvent-dependent nucleophile-specific parameters N and s_N . As explained previously in detail [22], the uncommon shape of Eq. 1 avoids far-reaching extrapolations by defining nucleophilicity N as the negative intercept on the abscissa in $\log k$ versus E plots. Based on this equation it was possible to construct the most comprehensive nucleophilicity scale presently available, which currently covers 40 orders of magnitude and includes 923 nucleophiles [24].

$$\log k = s_N(N + E) \quad (1)$$

In this work we have employed Eq. 1 for the determination of nucleophilicity parameters of the imines **1a–e**

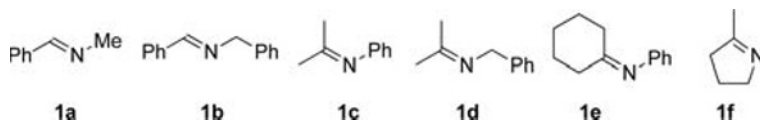
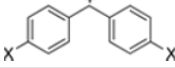
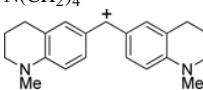
Scheme 2. Imines **1a–f** studied in this work.

Table 1. Electrophilicity parameters for the benzhydrylium ions used for this work.

				
X	Abbreviation	E^a	λ_{\max} (nm)	
OMe	2a (ani) ₂ CH ⁺	0	516	
N(Ph)CH ₂ CF ₃	2b (pfa) ₂ CH ⁺	−3.14	601	
N(CH ₃)CH ₂ CF ₃	2c (mfa) ₂ CH ⁺	−3.85	593	
NPh ₂	2d (dpa) ₂ CH ⁺	−4.72	672	
N(CH ₂ CH ₂) ₂ O	2e (mor) ₂ CH ⁺	−5.53	620	
N(Ph)CH ₃	2f (mpa) ₂ CH ⁺	−5.89	622	
N(CH ₃) ₂	2g (dma) ₂ CH ⁺	−7.02	613	
N(CH ₂) ₄	2h (pyr) ₂ CH ⁺	−7.69	620	
	2i (thq) ₂ CH ⁺	−8.22	628	

^a Electrophilicity parameters E for benzhydrylium ions from ref. [18].

listed in Scheme 2 which are then compared with other classes of nucleophiles [24–28].

Results and Discussion

Reactions of imines with benzhydrylium ions

As the reactions of the imines **1** with the amino-substituted benzhydrylium ions **2b–i**, which were used for the kinetic studies, were highly reversible, we have employed the more Lewis-acidic bis(4-methoxyphenyl)methylium ion **2a** for the product studies. When acetonitrile solutions of the imines **1a, b**

were treated with bis(methoxy)benzhydryl chloride **2a-Cl** in the presence of an equimolar amount of silver triflate, the benzhydryl-substituted iminium triflates **3a, b** were formed (Scheme 3), which were characterized by NMR spectroscopy as specified in the Experimental Section. From the fact that we see only a single stereoisomer in the NMR spectra we conclude that the *E*-configuration of the imines **1a, b** has been retained in the products **3a, b**.

Kinetics of the reactions of the imines **1** with the benzhydrylium ions **2** were performed in dichloromethane solution at 20 °C by monitoring the decays of the absorbances of the colored benzhydrylium ions at or close to their absorption maxima. In order to simplify the kinetics, the imines were used in high excess (> 10 equivalents). Thus their concentrations remain almost constant throughout the reactions, and pseudo-first-order conditions were achieved. In many cases complete conversions of the benzhydrylium ions were not observed because of the high reversibilities of the reactions, but attempted photometric determinations of the equilibrium constants for these reactions were unsuccessful, since the fast initial combinations of the benzhydrylium ions with the imines were followed by unknown subsequent reactions. The first-order rate constants k_{obs} (s^{−1}) were obtained by fitting the absorbances of the benzhydrylium ions to the mono-exponential function $A = A_0 e^{-k_{\text{obs}} t} + C$. Plots of k_{obs} against the concentrations of the nucleophiles were linear, and the slopes of these plots gave the second-order rate constants k (M^{−1}s^{−1}), which are listed in Table 2. Table 3

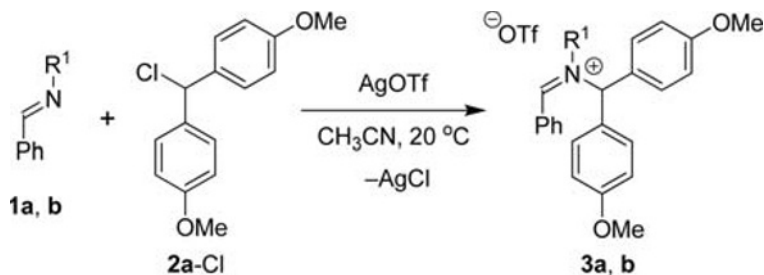
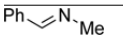
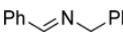
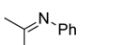



Scheme 3. Products of the reactions of the imines **1a, b** with **2a-Cl**/AgOTf.

Table 2. Second-order rate constants for the reactions of the imines **1a–f** with the benzhydrylium tetrafluoroborates **2**-BF₄ in CH₂Cl₂ at 20 °C.

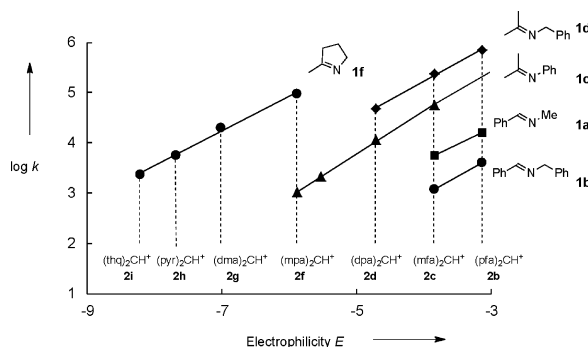
Imine		N , s_N^a	Ar_2CH^+	k (M ⁻¹ s ⁻¹)
	1a	8.60, 0.77	(pfa) ₂ CH ⁺	1.60×10^4
			(mfa) ₂ CH ⁺	4.56×10^3
			(dpa) ₂ CH ⁺	— ^b
	1b	7.9, 0.76 ^c	(pfa) ₂ CH ⁺	4.1×10^3 ^c
			(mfa) ₂ CH ⁺	1.2×10^3 ^c
			(dpa) ₂ CH ⁺	— ^b
	1c	9.53, 0.85	(mfa) ₂ CH ⁺	5.61×10^4
			(dpa) ₂ CH ⁺	1.13×10^4
			(mor) ₂ CH ⁺	2.11×10^3
			(mpa) ₂ CH ⁺	1.04×10^3
	1d	11.13, 0.73	(pfa) ₂ CH ⁺	6.93×10^5
			(mfa) ₂ CH ⁺	2.41×10^5
			(dpa) ₂ CH ⁺	4.84×10^4
	1e	8.80, 1.00	(mfa) ₂ CH ⁺	9.70×10^4
			(dpa) ₂ CH ⁺	1.14×10^4
			(mor) ₂ CH ⁺	2.01×10^3
	1f	13.12, 0.69 ^d	(mpa) ₂ CH ⁺	9.53×10^4 ^d
			(dma) ₂ CH ⁺	2.02×10^4 ^d
			(pyr) ₂ CH ⁺	5.57×10^3 ^d
			(thq) ₂ CH ⁺	2.37×10^3 ^d

^a N and s_N parameters as defined by Eq. 1; ^b highly reversible;^c smaller degree of conversion leading to rate constants of lower precision; ^d data for **1f** from ref. [28].

in the Experimental Section collects all concentrations of the reactants and the individual rate constants.

Correlation analysis

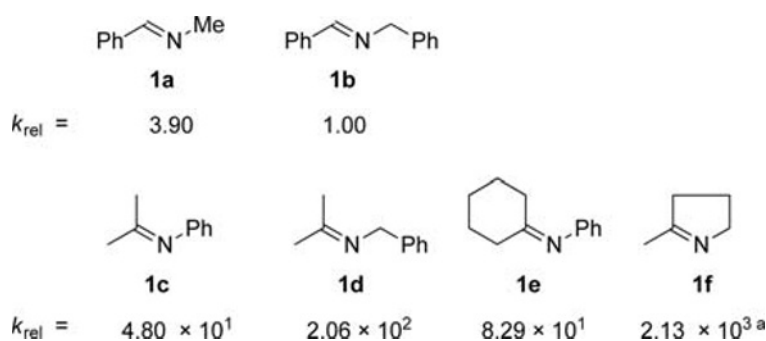
Plots of $\log k$ for the reactions of the imines **1** with the benzhydrylium ions **2** against the previously published electrophilicity parameters E of the benzhydrylium ions were linear as shown for some sys-

Fig. 1. Plots of $\log k$ for the reactions of the imines **1** with benzhydrylium ions *versus* their electrophilicity parameters E in CH₂Cl₂ at 20 °C. For the sake of clarity, the data for **1e** are not shown. Data for **1f** from ref. [28].

tems in Fig. 1, indicating the applicability of Eq. 1 for these reactions [17–24]. From the slopes of these linear correlations the nucleophile-specific sensitivity parameters s_N were derived, and the negative intercepts on the abscissa ($\log k = 0$) give the nucleophilicity parameters N , which are also listed in Table 2.

Relationships between structure and nucleophilicity

Table 2 and Scheme 4 show that the aldimine **1b** is approximately 200 times less nucleophilic than the ketimine **1d** ($k_{1d}/k_{1b} = 206$). Replacement of the benzyl group in **1b** by the better electron-donating methyl group (**1b** → **1a**) increases the nucleophilicity by a factor of 4 ($k_{1a}/k_{1b} = 3.9$) whereas replacement of the benzyl group in **1d** by a phenyl group (**1d** → **1c**) reduces the nucleophilicity by a factor of 4 ($k_{1d}/k_{1c} = 4.3$). Scheme 4 also demonstrates that *N*-cyclohexylideneaniline **1e** has a similar nucleophilicity

Scheme 4. Relative nucleophilic reactivities of the imines **1a–f** toward (mfa)₂CH⁺ (**2c**) in CH₂Cl₂. ^a k [(mfa)₂CH⁺] was calculated by using Eq. 1 and N and s_N values from Table 2 and E from Table 1.

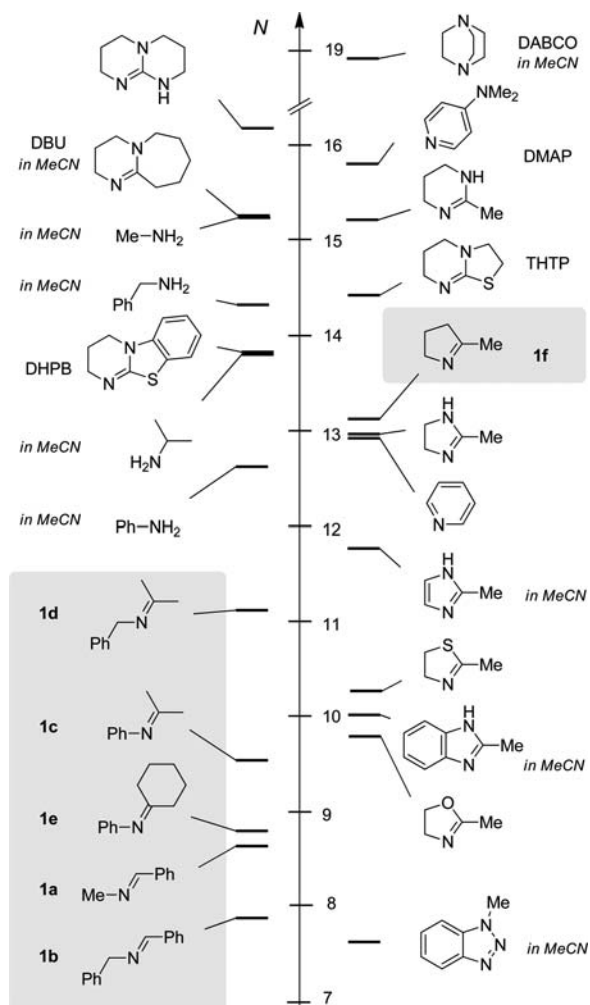


Fig. 2. Comparison of the nucleophilicities N of the imines **1a–f** with other N -centered nucleophiles (the solvent is CH_2Cl_2 unless otherwise stated, N from Table 2 and refs. [24–28]).

ty as N -(propan-2-ylidene)aniline **1c** ($k_{1e}/k_{1c} = 1.7$). Due to different sensitivities s_N , the ratio k_{1e}/k_{1c} decreases with decreasing electrophilicity of the reaction partner (Table 2). The cyclic imine **1f** is about 10 times more nucleophilic than its acyclic analog (**1d**) and is the most nucleophilic imine in this series.

Conclusion

As the rate constants for the reactions of the imines **1a–f** with benzhydrylium ions **2** have been found to follow the Eq. 1, it was possible to derive their re-

activity parameters N and s_N and to include these nucleophiles into our comprehensive nucleophilicity scale. The N values in Fig. 2 show that imines **1** are among the less reactive N -nucleophiles. While the aldimines **1a, b** have similar nucleophilicities as 1-methylbenzotriazole, and the ketimines **1c–e** have similar nucleophilicities as 2-methyl-oxazoline, 2-methyl-thiazolines and benzimidazole, all of them are 10^3 to 10^8 times less nucleophilic than commonly used nucleophilic organocatalysts like DHPB, DBU, DMAP or DABCO.

Experimental Section

General

CH_2Cl_2 was freshly distilled over CaH_2 prior to use. Benzhydrylium tetrafluoroborates **2b–i** [18] were prepared as described before. Compounds **1a** (Aldrich), and **1b** (Aldrich) were purchased and used without further purification. **1c** [29], **1d** [30], and **1e** [31] were synthesized according to the procedures described in quoted references.

Reactions of the imines **1a, b** with **2a–Cl** / AgOTf

To a 2-mL vial charged with a CD_3CN solution (0.5 mL) of **2a–Cl** (26.7 mg, 0.100 mmol) a CD_3CN solution (0.5 mL) of corresponding imine (1 equivalent) was added. After addition of AgOTf (25.9 mg, 0.100 mmol) under argon atmosphere and shaking the vial for 2–3 min, the formed precipitate was allowed to settle. The solution was decanted, and the NMR was recorded. Attempted purification by crystallization led to decomposition of the product and formation of non-identified side products.

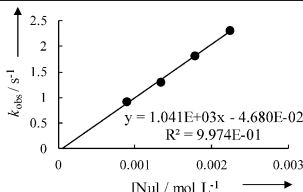
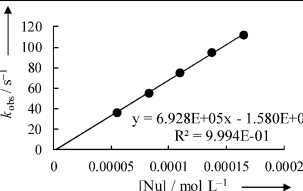
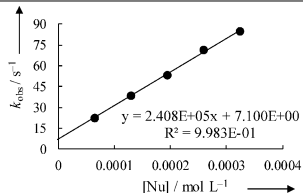
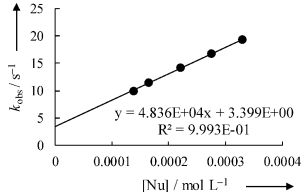
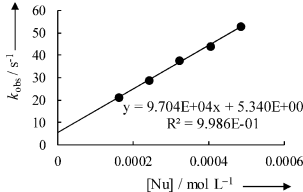
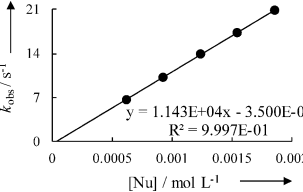
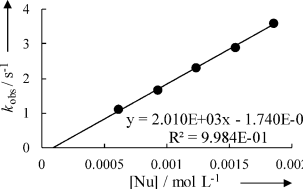
3a: ^1H NMR (CD_3CN , 400 MHz): $\delta = 3.77$ (s, 3 H, N^+CH_3), 3.83 (s, 6 H, OCH_3), 6.52 (s, 1 H, Ar_2CH), 7.06 (d, $J = 8.8$ Hz, 4 H, Ar), 7.34 (d, $J = 8.8$ Hz, 4 H, Ar), 7.67–7.71 (m, 2 H, Ar), 7.82–7.86 (m, 1 H, Ar), 7.89–7.91 (m, 2 H, Ar), 8.64 (s, 1 H, $\text{CH}=\text{N}^+$) ppm. – ^{13}C NMR (CD_3CN , 100 MHz): $\delta = 44.2$ (q, N^+CH_3), 56.3 (q, OCH_3), 80.2 (d, Ar_2CH^+), 115.9 (d, Ar), 126.6 (s, Ar), 128.1 (s, Ar), 130.7 (d, Ar), 131.9 (d, Ar), 134.5 (d, Ar), 137.5 (d, Ar), 161.8 (s, Ar), 172.1 (d, $\text{CH}=\text{N}^+$) ppm.

3b: ^1H NMR (CD_3CN , 400 MHz): $\delta = 3.82$ (s, 6 H, OCH_3), 5.41 (s, 2 H, CH_2), 6.41 (s, Ar_2CH), 7.03 (d, $J = 8.7$ Hz, 4 H, Ar), 7.22 (d, $J = 8.7$ Hz, 4 H, Ar), 7.23–7.28 (m, 2 H, Ar), 7.45–7.49 (m, 3 H, Ar), 7.63–7.68 (m, 2 H, Ar), 7.81–7.89 (m, 3 H, Ar), 8.88 (s, $\text{CH}=\text{N}^+$) ppm. – ^{13}C NMR (CD_3CN , 100 MHz): $\delta = 56.3$ (q, OCH_3), 58.9 (t, CH_2), 77.4 (d, Ar_2CH), 116.0 (d, Ar), 126.4 (s, Ar), 127.7 (s, Ar), 129.1 (d, Ar), 130.5 (d, Ar), 130.6 (d, Ar), 130.9 (d, Ar), 131.8 (s, Ar), 131.9 (d, Ar), 134.1 (d, Ar), 138.0 (d, Ar), 161.9 (s, Ar), 174.0 (d, $\text{CH}=\text{N}^+$) ppm.

Table 3. Kinetics of the reactions of the imines **1a–e** with $(\text{Ar})_2\text{CH}^+$ in CH_2Cl_2 at 20 °C.

Imine	Ar ₂ CH ⁺	[Ar ₂ CH ⁺] (M)	[Nu] (M)	k _{obs} (s ⁻¹)	k (M ⁻¹ s ⁻¹)	
1a	(pfa) ₂ CH ⁺	1.40 × 10 ⁻⁵	4.11 × 10 ⁻⁴	12.7	 y = 1.604E+04x + 5.992E+00 R ² = 9.988E-01	1.60 × 10 ⁴
			8.22 × 10 ⁻⁴	18.7		
			1.23 × 10 ⁻³	26.4		
			2.06 × 10 ⁻³	38.5		
			2.47 × 10 ⁻³	45.8		
1a	(mfa) ₂ CH ⁺	1.40 × 10 ⁻⁵	8.22 × 10 ⁻⁴	16.7	 y = 4.557E+03x + 1.296E+01 R ² = 9.968E-01	4.56 × 10 ³
			1.23 × 10 ⁻³	18.7		
			1.64 × 10 ⁻³	20.0		
			2.06 × 10 ⁻³	22.4		
			2.47 × 10 ⁻³	24.7		
1b	(pfa) ₂ CH ⁺	1.40 × 10 ⁻⁵	3.16 × 10 ⁻³	35.2	 y = 4.073E+03x + 2.202E+01 R ² = 9.990E-01	4.07 × 10 ³
			4.74 × 10 ⁻³	40.8		
			6.33 × 10 ⁻³	47.9		
			7.91 × 10 ⁻³	54.4		
			9.49 × 10 ⁻³	60.6		
1b	(mfa) ₂ CH ⁺	1.81 × 10 ⁻⁵	3.16 × 10 ⁻³	35.7	 y = 1.167E+03x + 3.235E+01 R ² = 9.982E-01	1.17 × 10 ³
			6.33 × 10 ⁻³	39.9		
			9.49 × 10 ⁻³	43.9		
			1.27 × 10 ⁻²	46.9		
			1.58 × 10 ⁻²	50.8		
1c	(mfa) ₂ CH ⁺	1.81 × 10 ⁻⁵	2.22 × 10 ⁻⁴	14.8	 y = 5.611E+04x + 2.930E+00 R ² = 9.981E-01	5.61 × 10 ⁴
			4.44 × 10 ⁻⁴	27.7		
			6.67 × 10 ⁻⁴	41.8		
			8.89 × 10 ⁻⁴	52.8		
			1.11 × 10 ⁻³	64.6		
1c	(dpa) ₂ CH ⁺	1.40 × 10 ⁻⁵	5.48 × 10 ⁻⁴	6.48	 y = 1.125E+04x + 5.240E-01 R ² = 9.991E-01	1.13 × 10 ⁴
			1.10 × 10 ⁻³	13.0		
			1.64 × 10 ⁻³	19.0		
			2.19 × 10 ⁻³	25.6		
			2.74 × 10 ⁻³	31.0		
1c	(mor) ₂ CH ⁺	1.70 × 10 ⁻⁵	5.48 × 10 ⁻⁴	1.20	 y = 2.109E+03x - 5.000E-03 R ² = 9.988E-01	2.11 × 10 ³
			1.10 × 10 ⁻³	2.24		
			1.64 × 10 ⁻³	3.45		
			2.19 × 10 ⁻³	4.65		

Table 3. Continued.

Imine	Ar ₂ CH ⁺	[Ar ₂ CH ⁺] (M)	[Nu] (M)	k _{obs} (s ⁻¹)	k (M ⁻¹ s ⁻¹)
1c	(mpa) ₂ CH ⁺	1.78 × 10 ⁻⁵	8.95 × 10 ⁻⁴	0.914	1.04 × 10 ³
			1.34 × 10 ⁻³	1.31	
			1.79 × 10 ⁻³	1.81	
			2.24 × 10 ⁻³	2.30	
					
1d	(pfa) ₂ CH ⁺	7.50 × 10 ⁻⁶	5.50 × 10 ⁻⁵	36.5	6.93 × 10 ⁵
			8.25 × 10 ⁻⁵	55.3	
			1.10 × 10 ⁻⁴	74.6	
			1.38 × 10 ⁻⁴	94.9	
			1.65 × 10 ⁻⁴	112	
					
1d	(mfa) ₂ CH ⁺	6.72 × 10 ⁻⁶	6.49 × 10 ⁻⁵	22.6	2.41 × 10 ⁵
			1.30 × 10 ⁻⁴	38.7	
			1.95 × 10 ⁻⁴	52.9	
			2.60 × 10 ⁻⁴	71.1	
			3.24 × 10 ⁻⁴	84.5	
					
1d	(dpa) ₂ CH ⁺	1.31 × 10 ⁻⁵	1.38 × 10 ⁻⁴	9.97	4.84 × 10 ⁴
			1.65 × 10 ⁻⁴	11.4	
			2.20 × 10 ⁻⁴	14.2	
			2.75 × 10 ⁻⁴	16.7	
			3.30 × 10 ⁻⁴	19.3	
					
1e	(mfa) ₂ CH ⁺	1.10 × 10 ⁻⁵	1.62 × 10 ⁻⁴	21.0	9.70 × 10 ⁴
			2.43 × 10 ⁻⁴	28.9	
			3.24 × 10 ⁻⁴	37.0	
			4.06 × 10 ⁻⁴	44.0	
			4.87 × 10 ⁻⁴	52.8	
					
1e	(dpa) ₂ CH ⁺	1.00 × 10 ⁻⁵	6.20 × 10 ⁻⁴	6.73	1.14 × 10 ⁴
			9.30 × 10 ⁻⁴	10.2	
			1.24 × 10 ⁻³	14.0	
			1.55 × 10 ⁻³	17.3	
			1.86 × 10 ⁻³	20.9	
					
1e	(mor) ₂ CH ⁺	1.70 × 10 ⁻⁵	6.20 × 10 ⁻⁴	1.11	2.01 × 10 ³
			9.30 × 10 ⁻⁴	1.67	
			1.24 × 10 ⁻³	2.30	
			1.55 × 10 ⁻³	2.90	
			1.86 × 10 ⁻³	3.61	
					

Kinetics of the reaction of the imines 1a–e with benzhydrylium ions

The reactions of the imines **1a–e** with the benzhydrylium ions **2** were followed photometrically at or close to the absorption maxima of Ar_2CH^+ by stopped-flow UV/Vis spectroscopy. A circulating bath thermostat was used to keep the temperature of the solutions constant at $20.0 \pm 0.1^\circ\text{C}$ during all kinetic experiments. The pseudo-first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fit-

ting of the absorbances to the monoexponential function $A_t = A_0 \exp(-k_{\text{obs}}t) + C$. The second-order rate constants k ($\text{M}^{-1} \text{s}^{-1}$) were obtained from the slopes of the linear plots of k_{obs} against the nucleophile concentrations.

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