

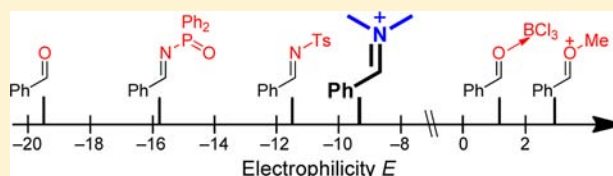
Electrophilicities of Benzaldehyde-Derived Iminium Ions: Quantification of the Electrophilic Activation of Aldehydes by Iminium Formation

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S Supporting Information

ABSTRACT: Rate constants for the reactions of benzaldehyde-derived iminium ions with C-nucleophiles (enamines, silylated ketene acetals, and enol ethers) have been determined photochemically in CH₃CN solution and used to determine the electrophilicity parameters *E* of the cations defined by the correlation $\log k_{20^\circ\text{C}} = s_N(E + N)$ (Mayr, H.; et al. *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512). With electrophilicity parameters from *E* = −10.69 (Ar = *p*-MeOC₆H₄) to *E* = −8.34 (Ar = *p*-CF₃), the iminium ions Ar–CH=NMe₂⁺ have almost the same reactivities as analogously substituted arylidenemalononitriles Ar–CH=C(CN)₂ and are 10 orders of magnitude more reactive than the corresponding aldehydes. The rate constants for the reactions of iminium ions with amines and water in acetonitrile are 10³–10⁵ times faster than predicted by the quoted correlation, which is explained by the transition states which already experience the anomeric stabilization of the resulting N,N- and O,N-acetals.



INTRODUCTION

Aminoalkylations of arenes and CH-acidic compounds (Mannich reaction),^{1,2} and iminium-activation of unsaturated carbonyl compounds in organocatalytic asymmetric transformations,³ are the most prominent examples for the use of iminium ions in organic synthesis (Scheme 1). In both types of reactions, the transformation of the carbonyl compound into an

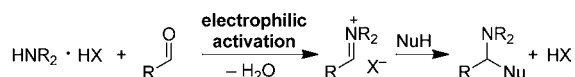
iminium species increases the electrophilicity of the carbonyl compound for the subsequent attack of nucleophiles. Related are Brønsted acid-catalyzed transformations of imines,⁴ though in these cases the protonation of the imine may be incomplete, and the effective electrophile may be either an iminium ion pair or a hydrogen-bond-activated imine.⁵

In recent years, we have shown that the rates of the reactions of carbocations and Michael acceptors with *n*-, π -, and σ -nucleophiles can be described by eq 1, where $k_{20^\circ\text{C}}$ is the

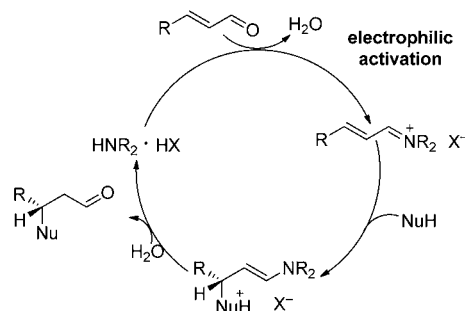
$$\log k_{20^\circ\text{C}} = s_N(N + E) \quad (1)$$

Scheme 1. Electrophilic Activation of Carbonyl Compounds in Aminoalkylations¹ and Iminium-Activated Nucleophilic Additions to α,β -Unsaturated Aldehydes³

Aminoalkylation:



Iminium Activation of Unsaturated Carbonyl Compounds:

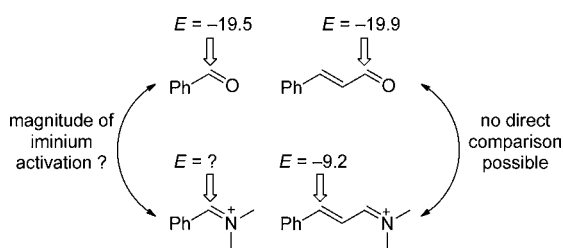


second-order rate constant in $\text{M}^{-1} \text{s}^{-1}$, s_N is a nucleophile-specific sensitivity parameter, N is a nucleophilicity parameter, and E is an electrophilicity parameter.

On the basis of this linear free-energy relationship, we have developed the most comprehensive nucleophilicity and electrophilicity scales presently available.⁶ Recently, the electrophilicity parameters for several aldehydes have been derived from the rates of their reactions with sulfur ylides in DMSO solution.⁷ Furthermore, α,β -unsaturated iminium ions derived from cinnamaldehyde have been integrated into our electrophilicity scales by studying the rates of their conjugate addition reactions with silyl enol ethers, pyrroles, amines, and phosphanes.⁸ Though the *E*-parameters of formaldehyde-derived iminium ions have previously been estimated,⁹ a direct comparison of the electrophilicities of iminium ions with their carbonyl analogues has so far not been achieved (Scheme 2).

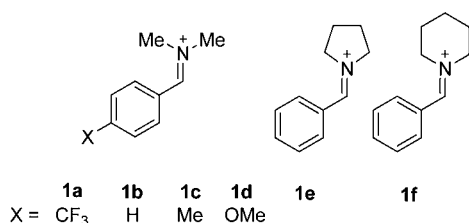
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Scheme 2. Electrophilic Reactivities of Aldehydes and Iminium Ions^{7,8a}

We now report on the kinetics of the reactions of several iminium ions, derived from different benzaldehydes (Scheme 3), with enamines, silylated ketene acetals, and silyl enol ethers

Scheme 3. Iminium Ions 1a–f Investigated in This Work



(Table 1) which are used as reference nucleophiles. Comparison of these data with previously reported carbonyl reactivities will provide a quantification of the iminium activation of aldehydes.

RESULTS AND DISCUSSION

Product Analysis. In order to establish the course of the reactions, which were investigated kinetically, we have studied the products of representative combinations of the iminium ions **1** with the nucleophiles **2**. The reactions of enamines (such as **2a,b**) with preformed iminium salts in various solvents have previously been reported to give β -amino ketones after aqueous workup.¹³

As shown in Table 2, the reactions of the silyl ketene acetals **2d,f–j** and of **2k** with the iminium triflates (**1a–c**)·OTf yielded the β -amino esters **3a,d–h** or the β -amino acids **3b,c** after aqueous workup. The silyl ketene acetal **2d** yielded only one of the two conceivable diastereomers. A moderate degree of diastereoselectivity was also observed in the reactions of **2f** with (**1a,c**)·OTf, which yielded **3b,c** with *anti:syn* ratios of 4:1 to 5:1 (NMR). The preferential formation of the *anti*-diastereomer, which has been confirmed by X-ray analysis¹⁴ (p S10 of the Supporting Information), can be explained with Zimmerman–Traxler-like transition states as depicted in Scheme 4.

The product from Danishefsky's diene **2k** and the iminium triflate **1b**·OTf could not be isolated due to its very low stability. For this reason, the reaction was performed in CDCl₃ in an NMR tube; the NMR spectra taken after addition of a trace amount of KOH in D₂O (0.1 M in D₂O) showed exclusive formation of the β -aminoketone **4**. Detailed descriptions of the experimental procedures and the characterizations of the isolated compounds are given in the Supporting Information.

When the reactions of the cyclic silyl ketene acetals **2c,e** and of the silyl enol ether **2l** with iminium triflates were performed analogously (Scheme 5), mixtures of diastereomers were obtained. As these mixtures could neither be separated nor

Table 1. Reference Nucleophiles Used in This Work and Their Nucleophilicity Parameters *N* and *s_N* in CH₂Cl₂ and CH₃CN

Nucleophile	<i>N</i> (<i>s_N</i>) ^a in CH ₂ Cl ₂	<i>N</i> (<i>s_N</i>) in CH ₃ CN
2a <i>n</i> = 1	14.91 (0.86)	16.42 (0.70) ^b
2b <i>n</i> = 2	13.36 (0.81)	14.02 (0.76) ^c
2c <i>n</i> = 1, R = H	12.56 (0.70)	12.34 (0.72) ^c
2d <i>n</i> = 1, R = Me	11.50 (0.91)	
2e <i>n</i> = 2, R = H	10.61 (0.86)	10.52 (0.78) ^c
2f	10.38 (0.87)	
2g R ¹ = Bu, R ² = <i>t</i> Bu	10.32 (0.79)	
2h R ¹ = Bu, R ² = Me	10.21 (0.82)	
2i R ¹ = Ph, R ² = Me	8.23 (0.81)	
2j	9.00 (0.98)	9.11 (0.88) ^c
2k	8.57 (0.84)	
2l	6.57 (0.93)	

^aNucleophilicity parameters *N* and *s_N* for **2a** were taken from ref 10, for **2b,c,e,i–l** from ref 6b, and for **2d,f–h** from ref 11. ^bNucleophilicity parameters *N* and *s_N* in CH₃CN for **2a** were taken from ref 12. ^cThe *N* and *s_N* parameters of the enamine **2b** and the ketene acetals **2c,e,j** in acetonitrile have not been reported previously and were determined by studying the rates of their reactions with benzhydrylium ions following previously reported procedures; for details, see Supporting Information.

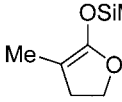
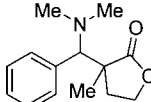
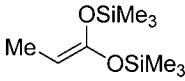
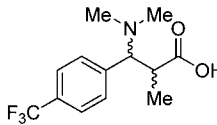
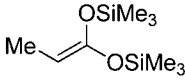
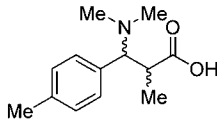
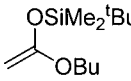
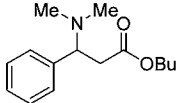
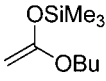
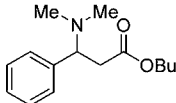
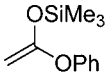
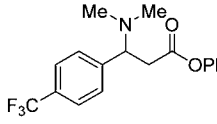
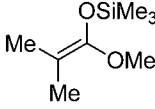
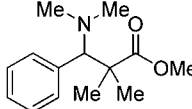
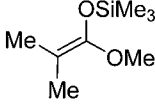
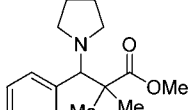
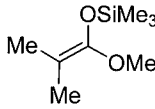
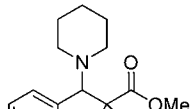
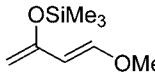
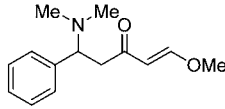
unambiguously characterized by NMR, the initial products were not hydrolyzed but methylated (**2c, 2l**) or oxidized (**2e**) and subsequently transferred into the α,β -unsaturated carbonyl compounds **5** (Scheme 5) by Hofmann or amine oxide elimination. The characterization of all products is given in the Supporting Information.

The imine **6** was obtained in 87% yield by the reaction of benzylamine with iminium triflate **1d**·OTf (Scheme 6).

Kinetic Investigations. The kinetics of the reactions of the nucleophiles **2** with the iminium triflates (**1a–f**)·OTf (and in some cases the iminium tetrafluoroborates (**1a,b**)·BF₄) were performed in CH₂Cl₂ or CH₃CN solution at 20 °C. All investigated reactions were monitored photometrically by following the disappearance of the iminium ions **1** at or close to their absorption maxima (265–330 nm). In order to achieve first-order conditions, the iminium ions **1** were combined with at least 10 equiv of the nucleophiles **2**. In case of the ketene acetals **2c,e**, stock solutions in CH₂Cl₂ were used, as these compounds slowly decompose in CH₃CN. Small portions of these stock solutions were dissolved in CH₃CN before each kinetic experiment.

From the resulting exponential decays of the UV–vis absorbances of the iminium ions **1** (Figure 1), the first-order rate constants *k_{obs}* were obtained. Plots of *k_{obs}* (s⁻¹) against the concentrations of the nucleophiles were linear with negligible intercepts as required by the relation *k_{obs}* = *k₂*[**2**]₀ (eq 4 and

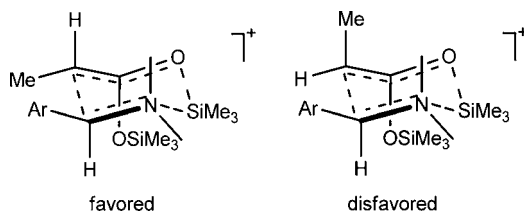
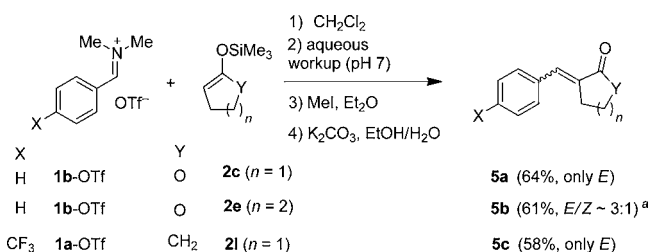
Table 2. Reactions of Iminium Triflates (1a–f)·OTf with the Silyl Ketene Acetals 2d,f–j and Danishefsky's Diene 2k in CH₂Cl₂ Followed by Aqueous Workup (pH 7)

Nucleophile	Electrophile	Product
 2d	1b	 3a (92%) ^a
 2f	1a	 3b (86%) ^b <i>anti:syn</i> = 4:1 ^{c,d}
 2f	1c	 3c (75%) ^b <i>anti:syn</i> = 5:1 ^c
 2g	1b	 3d (93%)
 2h	1b	 3d (91%)
 2i	1a	 3e (89%)
 2j	1b	 3f (86%)
 2j	1e	 3g (76%)
 2j	1f	 3h (66%)
 2k	1b	 4^e

^aOnly one diastereomer was obtained. ^bAqueous workup at pH 5. ^cBased on the ¹H NMR spectrum of the crude product ^d¹H NMR of the crude product isolated after the reaction in CH₃CN showed the same dr as in CH₂Cl₂. ^eProduct could not be isolated; reaction was performed in an NMR tube in CDCl₃ with subsequent addition of trace amounts of KOH in D₂O.

Figure 1). Only in case of the reaction of the enamine **2b** with iminium ion **1b**, the plot of k_{obs} vs $[\mathbf{2b}]_0$ showed a significant

positive intercept, indicating the high reversibility of the addition. However, in all cases the second-order rate constants,

Scheme 4. Zimmerman–Traxler Transition States for the Reactions of **2f** with Iminium Ions **2**Scheme 5. Reactions of the Silyl Ketene Acetals **2c,e** and the Silyl Enol Ether **2l** with the Iminium Ions **1a,b** and Subsequent Elimination Reactions to the α,β -Unsaturated Carbonyl Compounds **5**

^aAs treatment with MeI in Et₂O and K₂CO₃ in EtOH/H₂O gave poor yields, steps 3) and 4) were replaced by treatment with H₂O₂ (30% aq solution) in *i*-PrOH.

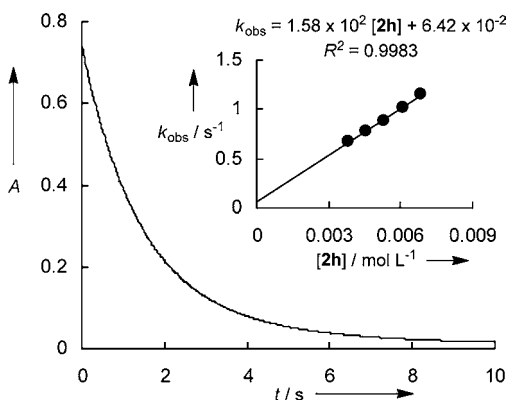
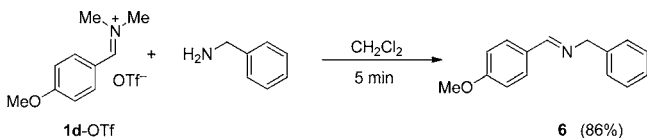
Scheme 6. Reaction of **1d**·OTf with Benzylamine

Figure 1. UV–vis spectroscopic monitoring of the reaction of the iminium ion **1d** ($2.16 \times 10^{-5} \text{ mol L}^{-1}$) with the silyl ketene acetal **2h** ($3.80 \times 10^{-3} \text{ mol L}^{-1}$) at 328 nm in CH₂Cl₂ at 20 °C. Inset: Determination of the second-order rate constant $k_2 = 1.58 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ from the dependence of the first-order rate constant k_{obs} on the concentration of **2h**.

which are summarized in Table 3, could be derived from the slopes of the linear correlations of k_{obs} versus $[2]_0$.

$$-d[1]/dt = k_2[2][1] \quad (2)$$

$$[2]_0 \gg [1]_0 \Rightarrow [2] \approx [2]_0 \quad (3)$$

$$-d[1]/dt = k_{\text{obs}}[1], \quad k_{\text{obs}} = k_2[2]_0 \quad (4)$$

Table 3. Second-Order Rate Constants ($\text{M}^{-1} \text{ s}^{-1}$) for the Reactions of the Iminium Triflates (**1a–d**)·OTf with the Nucleophiles **2** in CH₂Cl₂ at 20 °C

Electrophile	Nucleophile	k_2	
 1a	2d	7.20×10^3	
	2f	6.25×10^3	
	2h	3.36×10^4	
	2i	1.49×10^3	
	2j	4.22×10^1	
	2k	2.17×10^2	
	2l	2.62×10^{-1}	
	 1b	2b	1.08×10^4 ^a
		2c	1.16×10^4
		2d	3.70×10^2
2e		7.33×10^2	
2e		6.26×10^2 ^b	
2f		5.23×10^2	
2g		3.68×10^3	
2h		3.71×10^3	
2i		1.14×10^2	
2i		1.18×10^2 ^b	
2j	1.39		
2k	3.24×10^1		
2k	3.28×10^1 ^b		
 1c	2c	3.70×10^3	
	2d	1.04×10^2	
	2e	1.67×10^2	
	2f	1.23×10^2	
	2g	8.57×10^2	
	2h	9.37×10^2	
	2i	3.77×10^1	
	2j	7.23×10^{-1}	
2k	7.37		
 1d	2c	4.33×10^2	
	2d	9.91	
	2e	2.69×10^1	
	2f	1.81×10^1	
	2g	1.07×10^2	
	2h	1.58×10^2	

^aA significant positive intercept of the k_{obs} vs $[2]_0$ plot was observed, indicating a considerable degree of reversibility of the reaction.

^bIminium tetrafluoroborate **1b**·BF₄ was employed for the kinetic measurement.

As shown in Table 3, the rate constants of the reactions of iminium triflate **1b**·OTf with the nucleophiles **2e,i,k** varied by less than a factor of 1.2 when TfO[−] was replaced by BF₄[−] as a counterion. Therefore, we can conclude that the counterions (TfO[−] or BF₄[−]) are not involved in the rate-determining step under these reaction conditions. When the second-order rate constants for the reactions of the iminium ions **1a–d** with the nucleophiles **2** in CH₂Cl₂ (Table 3) were analyzed by eq 1, poor correlations of $(\log k_2)/S_N$ vs *N* were observed (Figure 2

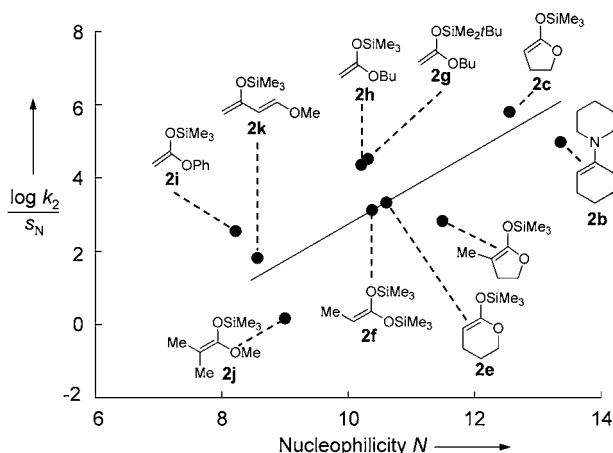


Figure 2. Poor correlation of the second-order rate constants ($\log k_2/s_N$) for the reactions of the iminium ion **1b** with the nucleophiles **2b–k** in CH_2Cl_2 at 20°C versus the corresponding nucleophilicity parameters N of **2b–k**. The slope is fixed to 1.0 as required by eq 1.

and Tables S8, S22, S32, and S39 of the Supporting Information), indicating that eq 1 does not provide reliable predictions for the reactions of the benzaldehyde-derived iminium ions **1** with nucleophiles **2** in CH_2Cl_2 .

Second-order rate constants of the reactions of the iminium ions **1** with the enamines **2a,b** and the ketene acetals **2c,e,j**, which have been determined in CH_3CN , are summarized in Table 4. As for the reactions in CH_2Cl_2 , significant counterion effects were also absent in CH_3CN solution, and with one exception (reaction with **2b**, factor 1.3) the reactivities of iminium triflates and tetrafluoroborates differed by less than 10% (Table 5).

Comparison of Tables 3 and 4 shows that the reactions of iminium ions with π -nucleophiles are generally faster in CH_2Cl_2 than in CH_3CN , and, as specified for the reactions of **1b**·OTf in Table 6, the reactivity ratio depends strongly on the nature of the nucleophile. While the reaction with the silyl ketene acetal **2j** proceeds only 1.55 times faster in CH_2Cl_2 than in CH_3CN , a much stronger acceleration was found for the reactions of compounds **2b,c,e** (factors of 7.25–56.0). A rationalization for this behavior will be attempted below.

In contrast to the poor correlation of the reactivities in CH_2Cl_2 (Figure 2), Figure 3 shows a good linear correlation between ($\log k_2/s_N$) and the corresponding nucleophilicity parameters N for the reactions of the C-nucleophiles **2a–c,e,j** with the iminium ions **1** in CH_3CN . Now eq 1 is applicable, and the electrophilicity parameters E of the iminium ions **1** (Table 4) were derived by least-squares minimizations, while fixing the slope at 1.0 as required by eq 1. For the sake of clarity only correlation lines for the iminium ions **1b,d** are shown in Figure 3. The correlations for **1a,c,e,f** are of similar quality and are shown in the Supporting Information (Tables S70, S82, S92, and S97).

As shown in Figure 4, the electrophilic reactivities of the benzaldehyde-derived iminium ions **1b** and **1d** are almost the same as those of the analogously substituted benzylidene malononitriles, i.e., the $\text{Me}_2\text{N}^+=$ group has a similar activating effect as a $(\text{NC})_2\text{C}=\text{C}$ group.

Figure 4 furthermore shows that the electrophilicities of benzaldehyde-derived iminium ions are similar to those of the conjugate positions of cinnamaldehyde-derived iminium ions. Nevertheless, α,β -unsaturated iminium ions undergo preferen-

Table 4. Second-Order Rate Constants ($\text{M}^{-1} \text{s}^{-1}$) for the Reactions of the Iminium Triflates **1** with the Nucleophiles **2a–c,e,j** in CH_3CN at 20°C

Electrophile	Nucleophile	k_2	E^a
 1a	2a	3.34×10^5	−8.34
	2b	1.06×10^4	
	2c	3.78×10^3	
	2e	8.01×10^1	
	2j	1.90	
	 1b	2a	7.93×10^4
2b		1.49×10^3	
2c		3.31×10^2	
2e		1.31×10^1	
2j		8.98×10^{-1}	
 1c		2a	3.14×10^4
	2b	6.16×10^2	
	2c	1.38×10^2	
	2e	5.85	
	2j	9.09×10^{-1}	
	 1d	2a	7.93×10^3
2b		1.44×10^2	
2c		3.20×10^1	
2e		1.10	
 1e		2a	8.32×10^4
	2b	1.51×10^3	
	2c	2.88×10^2	
	2e	1.04×10^1	
	 1f	2a	3.99×10^4
2b		7.46×10^2	
2c		2.38×10^2	
2e		9.60	

^aFor determination see text as well as Tables S70, S76, S82, S87, S92, and S97 of the Supporting Information.

Table 5. Second-Order Rate Constants ($\text{M}^{-1} \text{s}^{-1}$) for the Reactions of the Iminium Salts **1b**·OTf and **1b**·BF₄ with Various Nucleophiles in CH_3CN at 20°C

Nucleophile	k_2 (1b ·OTf) ^a	k_2 (1b ·BF ₄)	k_{rel}^b
2a	7.93×10^4	8.06×10^4	1.02
2b	1.49×10^3	1.96×10^3	1.32
2c	3.31×10^2	3.66×10^2	1.10
2e	1.31×10^1	1.27×10^1	0.97

^aFrom Table 4. ^b $k_{\text{rel}} = k_2(\text{BF}_4)/k_2(\text{OTf})$.

tially Michael additions with cyclic silyl ketene acetals,^{8a} which implies that the reactivity of the α -position of cinnamaldehyde-derived iminium ions is lower than that of their benzaldehyde-

Table 6. Comparison of the Second-Order Rate Constants k_2 ($M^{-1} s^{-1}$) for the Reactions of Iminium Ion **1b•OTf with Enamine **2b** and the Silyl Ketene Acetals **2c,e,j** in CH_2Cl_2 and CH_3CN**

Nucleophile	k_2 (CH_2Cl_2) ^a	k_2 (CH_3CN) ^b	k_{rel} ^c
2b	1.08×10^4	1.49×10^3	7.25
2c	1.16×10^4	3.31×10^2	35.0
2e	7.33×10^2	1.31×10^1	56.0
2j	1.39	8.98×10^{-1}	1.55

^aFrom Table 3. ^bFrom Table 4. ^c $k_{rel} = k_2(CH_2Cl_2)/k_2(CH_3CN)$

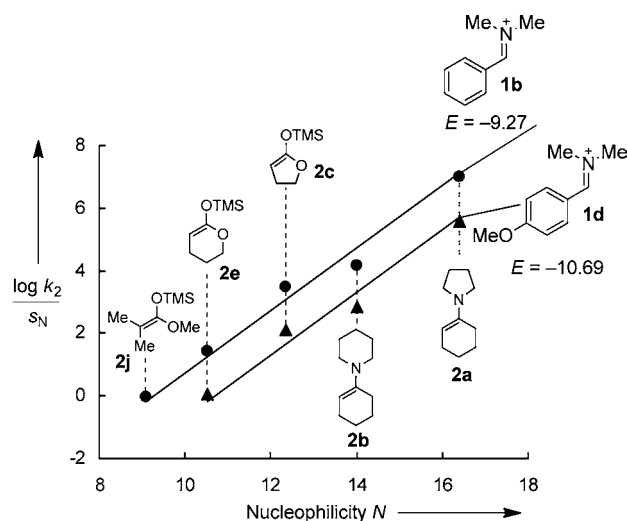


Figure 3. Correlation of the second-order rate constants ($\log k_2/s_N$) for the reactions of the iminium ions **1b,d** with the nucleophiles **2a–c,e,j** in CH_3CN at 20 °C versus the corresponding nucleophilicity parameters N .

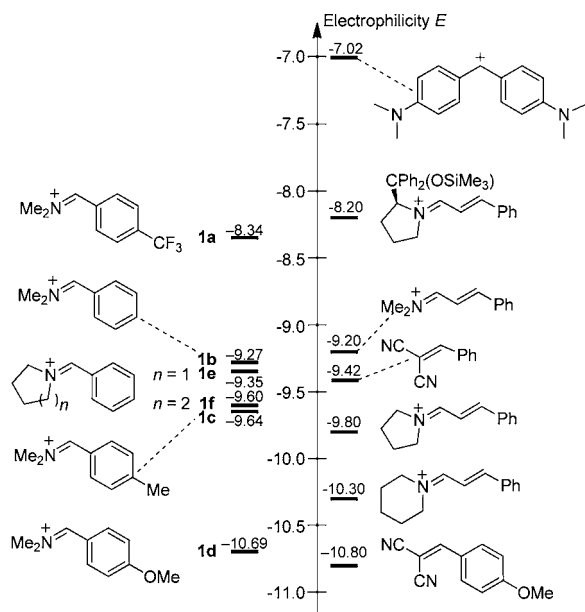


Figure 4. Comparison of the electrophilic reactivities E of the iminium ions **1** with those of analogously substituted α,β -unsaturated iminium ions, Michael acceptors, and benzhydrylium ions. E parameters were taken from Table 4 and refs 8a, 6b, and 6g.

derived analogues. Figure 4 also illustrates that the electrophilicities of the benzaldehyde-derived iminium ions **1b,e,f** are

less affected by the variation of the substituents on the nitrogen center than the reactivities of the vinylogous cinnamaldehyde-derived iminium ions.

In the parametrization of eq 1, solvent effects are included in the nucleophile-specific parameters N and s_N , while the electrophilicity parameters E of carbocations and Michael acceptors are treated as solvent-independent. Though limitations of this approximation have been mentioned,¹⁵ this procedure has been working reliably for a large number of electrophile–nucleophile combinations.

Our observation that the rate constants of the reactions of the iminium ions **1** with the nucleophiles **2** in acetonitrile follow eq 1 (Figure 3), while the same reactions in CH_2Cl_2 do not (Figure 2), is atypical and may be indicative of different stabilizing interactions in the transition states in these two solvents.

As the nucleophilicity parameters for compounds **2** were derived from their reactions with benzhydrylium ions in CH_3CN , the good correlations shown in Figure 3 indicate similar transition states for both reaction series in this solvent; i.e., the rates of the reactions of the π -nucleophiles **2** with the iminium ions **1**, like those of their reactions with benzhydrylium ions, are controlled by the interactions of only two reaction centers. The interaction between N and Si in the transition state depicted in Scheme 4 must be so weak in acetonitrile that it is not noticeable in the kinetics.

Assuming that the electrophilicity parameters E of the iminium ions **1** (Table 4) are also solvent-independent, one might combine them with the dichloromethane-specific N and s_N parameters of **2** (Table 1) to calculate the corresponding second-order rate constants by eq 1. The fact that the experimental rate constants determined in dichloromethane are 1.8–1800 times higher than the calculated ones shows that eq 1 does not hold. The large scatter of the deviations furthermore implies that the use of solvent-dependent E parameters for iminium ions would not solve the problem, as illustrated above by the poor correlation in Figure 2. A reason for the failure of eq 1 to describe reactions of iminium ions **1** with silyl enol ethers and ketene acetals **2c–k** in CH_2Cl_2 might be the interaction between the nitrogen of the iminium ion and the silicon of the silyl enol ether or ketene acetal (incipient metallo-ene reaction^{16,17}) in the Zimmerman–Traxler transition states (Scheme 4). This interaction, which does not exist in the reference reactions with benzhydrylium ions, may become strong enough in the less polar solvent CH_2Cl_2 that its influence on the kinetics is no longer negligible as it is in CH_3CN .

Reactions of O- and N-Nucleophiles with Iminium Ions in CH_3CN . In previous work, we have emphasized that eq 1 can only be applied when at least one of the reaction centers is carbon, because the N and s_N parameters of various nucleophiles have been derived from reactions with carbon electrophiles, and the E parameters of electrophiles are based on reactivities toward carbon nucleophiles. As a consequence, heteroatom–heteroatom bond formations are not covered by eq 1.¹⁸ Deviations from the predictions by eq 1 have also been expected⁷ for reactions which produce anomericly stabilized products, e.g., reactions of O- or N-substituted electrophilic C_{sp^2} centers with O- or N-nucleophiles, because the extra stabilization of the resulting acetals or aminals is not taken into account when the electrophilicities E are derived from the rates of the reactions with C-nucleophiles.

In order to examine whether the anomeric stabilization in O,N-acetals or N,N-aminals already affects the transition states of their formation, we have now investigated the kinetics of the reactions of the iminium ions **1** with water and with primary amines in acetonitrile as well as with hydroxide in aqueous acetonitrile. The kinetics were studied photometrically with the same experimental setup as described above. In case of the reactions with aqueous acetonitrile the expected first-order rate law and in case of the reactions with OH⁻ the expected second-order rate law were found. However, the reactions of the iminium ions **1** with primary amines, which were used in high excess (>10 equiv), showed an upward curvature of the plots of the pseudo-first-order rate constants k_{obs} against the amine concentrations, indicating the participation of two molecules of amines in the rate-determining step. A similar observation was previously reported for the reactions of secondary amines with quinone methides in CH₃CN solution.¹⁹ The evaluation of these kinetics, which follows previously reported procedures,¹⁹ is described in the Supporting Information. By using this formalism, the second-order rate constants for the initial attack of the amines at the iminium ions **1** can be extracted (Tables 7 and S111–S125).

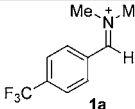
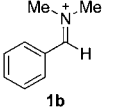
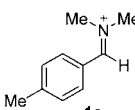
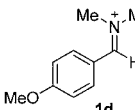
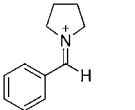
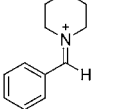
Using the electrophilicity parameters E of the iminium ions **1** listed in Table 4 and the previously published nucleophilicity parameters N and s_N of the O- and N-nucleophiles, which were derived from their reactivities toward benzhydrylium ions,^{19–21} we have now calculated the rate constants of their combinations by eq 1. As anomeric effects are not included in the reactivity parameters N , s_N , and E , the reactions of O- and N-nucleophiles with iminium ions **1** turned out to proceed 10^3 – 10^5 times faster than calculated by eq 1 (Table 7), indicating that the anomeric stabilization²² of the resulting products already affects the corresponding transition states.

Table 7 furthermore shows that the magnitude of the anomeric acceleration of the reactions of O- and N-nucleophiles with iminium ions depends on the nature of the electrophile as well as on the nature of the nucleophile. Thus, an anomeric rate acceleration of 3 orders of magnitude was found for the reactions of water/acetonitrile mixtures and of primary amines with the dimethylamino-derived iminium ions **1a–d**, while the reactions of OH⁻ with **1c,d** are 5 orders of magnitude faster than calculated. The substituents at the iminium nitrogen also affect the degree of anomeric acceleration. While the reactions with the piperidine-derived iminium ion **1f** are similarly accelerated as those of the dimethylamine-derived iminium ions **1a–d**, the reactions of the pyrrolidine-derived iminium ion **1e** with water/acetonitrile mixtures and primary amines are only 1–2 orders of magnitude faster than calculated by eq 1. The E -parameters for iminium ions **1** are thus restricted to their reactions with carbon nucleophiles, unlike the electrophilicity parameters E of ordinary carbocations and Michael acceptors, which can be employed for reactions with all types of nucleophiles (C-, N-, O-, P-, S-, etc.).⁶

CONCLUSION

We have shown that the reactions of the benzaldehyde-derived iminium ions **1** with electron-rich π -systems (enamines, silylated ketene acetals, and enol ethers) in acetonitrile can be described by eq 1, using the N and s_N parameters derived from the reactions of these π -nucleophiles with benzhydrylium ions. One can, therefore, conclude that the reactions of iminium ions Ar–CH=NMe₂⁺ and benzhydrylium ions Ar₂CH⁺ with

Table 7. Experimental and Calculated Rate Constants for the Reactions of the Iminium Ions **1 with O- and N-Nucleophiles in CH₃CN at 20 °C**

Electrophile	Nucleophile	k_{exp}	k_{calcd}^e
 1a	50W50AN ^a	3.53 ^b	1.18×10^{-3b}
	33W67AN ^a	4.20 ^b	1.03×10^{-3b}
	20W80AN ^a	4.51 ^b	1.11×10^{-3b}
	10W90AN ^a	3.04 ^b	2.80×10^{-4b}
 1b	50W50AN ^a	2.30×10^{-1b}	1.75×10^{-4b}
	33W67AN ^a	2.67×10^{-1b}	1.50×10^{-4b}
	20W80AN ^a	2.97×10^{-1b}	1.65×10^{-4b}
	10W90AN ^a	1.90×10^{-1b}	3.74×10^{-5b}
	Bn-NH ₂	3.65×10^6c	2.31×10^3
	<i>i</i> Pr-NH ₂	2.75×10^6c	1.41×10^3
<i>t</i> Bu-NH ₂	3.80×10^5c	1.65×10^2	
 1c	50W50AN ^a	8.88×10^{-2b}	8.22×10^{-5b}
	33W67AN ^a	1.05×10^{-1b}	6.95×10^{-5b}
	20W80AN ^a	1.07×10^{-1b}	7.73×10^{-5b}
	10W90AN ^a	5.94×10^{-2b}	1.68×10^{-5b}
	OH ⁻	3.76×10^5d	2.19
	Bn-NH ₂	2.26×10^6c	1.30×10^3
	<i>i</i> Pr-NH ₂	1.86×10^6c	7.78×10^2
<i>t</i> Bu-NH ₂	4.10×10^4c	8.94×10^1	
 1d	50W50AN ^a	2.39×10^{-2b}	9.56×10^{-6b}
	33W67AN ^a	2.70×10^{-2b}	7.89×10^{-6b}
	20W80AN ^a	3.21×10^{-2b}	8.99×10^{-6b}
	10W90AN ^a	1.49×10^{-2b}	1.73×10^{-6b}
	OH ⁻	1.28×10^5d	4.90×10^{-1}
	Bn-NH ₂	3.76×10^5c	2.58×10^2
	<i>i</i> Pr-NH ₂	2.85×10^5c	1.43×10^2
<i>t</i> Bu-NH ₂	1.74×10^4c	1.57×10^1	
 1e	50W50AN ^a	1.89×10^{-2b}	1.49×10^{-4b}
	33W67AN ^a	2.27×10^{-2b}	1.27×10^{-4b}
	20W80AN ^a	1.98×10^{-2b}	1.40×10^{-4b}
	10W90AN ^a	9.56×10^{-3b}	3.14×10^{-5b}
	Bn-NH ₂	1.66×10^5c	2.04×10^3
	<i>i</i> Pr-NH ₂	9.71×10^5c	1.24×10^3
<i>t</i> Bu-NH ₂	1.06×10^4c	1.45×10^2	
 1f	50W50AN ^a	3.45×10^{-1b}	8.92×10^{-5}
	33W67AN ^a	3.69×10^{-1b}	7.55×10^{-5}
	20W80AN ^a	3.58×10^{-1b}	8.39×10^{-5}
	10W90AN ^a	2.53×10^{-1b}	1.83×10^{-5}
	Bn-NH ₂	7.53×10^5c	1.39×10^3
	<i>i</i> Pr-NH ₂	6.08×10^5c	8.30×10^2
<i>t</i> Bu-NH ₂	6.71×10^4c	9.55×10^1	

^aHydrolysis in H₂O/CH₃CN (v/v) mixtures (W = water, AN = acetonitrile). ^bFirst-order rate constants k_1/s^{-1} for hydrolysis reactions. ^cSecond-order rate constants $k_2/L \text{ mol}^{-1} \text{ s}^{-1}$ were determined by eq S4 (see Supporting Information) and are less precise. ^dReaction was performed in a 9:91 (v/v) H₂O/CH₃CN mixture. ^eCalculated from eq 1 with the electrophilicity parameters E for the iminium ions **1a–f** (Table 4) and the N (s_N) parameters for the O- and N-nucleophiles in CH₃CN; for H₂O/CH₃CN (v/v) mixtures (50W50AN, 5.05 (0.89); 33W67AN, 5.02 (0.90); 20W80AN, 5.02 (0.89); 10W90AN, 4.56 (0.94)) from ref 20; for OH⁻ (10.19 (0.62)) in a 50/50 (v/v) H₂O/CH₃CN mixture from ref 21; and for primary amines (Bn-NH₂, 14.29 (0.67); *i*Pr-NH₂, 13.77 (0.70); *t*Bu-NH₂, 12.35 (0.72)) from ref 19.

C-nucleophiles in CH_3CN have analogous transition states, in which only the interactions of two reaction centers are of importance. Equation 1 does not properly describe the reactions of iminium ions with silylated enol ethers and ketene acetals in CH_2Cl_2 , which may be explained by the greater importance of secondary N–Si interactions in Zimmerman–Traxler-like transition states (incipient sila-ene reaction) in the less polar solvent CH_2Cl_2 .

As illustrated in Figure 5, the *N,N*-dimethyl-substituted iminium ion derived from benzaldehyde is 10 orders of

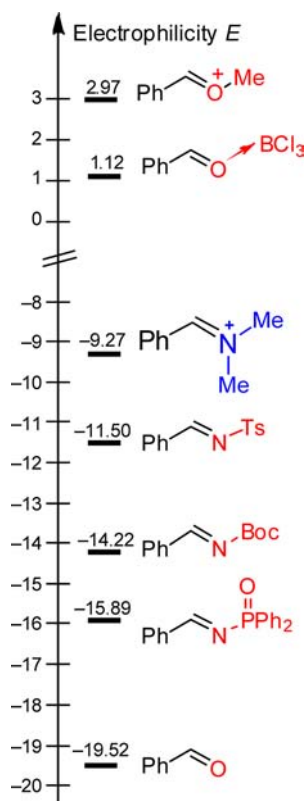


Figure 5. Comparison of the electrophilic reactivities E of benzaldehyde, O-methylated benzaldehyde, BCl_3 -activated benzaldehyde, benzaldehyde-derived imines, and benzaldehyde-derived iminium ions. E -parameters were taken from Table 4 and refs 6d and 7.

magnitude more electrophilic than benzaldehyde, which for the first time allows us to quantify the magnitude of iminium activation. Complexation with BCl_3 or O-methylation activates benzaldehyde significantly more, with the result that the electrophilicity of iminium ions is just between those of structurally analogous aldehydes and carboxonium ions,^{6d} somewhat higher than that of *N*-tosylated imines.

Because of the anomeric stabilization of O,*N*-acetals and *N,N*-aminals, the iminium ions **1** react 10^3 – 10^5 times faster with water and amines than calculated by eq 1, which implies that the E -parameters for iminium ions reported in this work are restricted to reactions with C-nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, product characterization, and details of the kinetic experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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