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Electrophilicities of Iminium Ions

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Abstract: Rate constants for the reactions of the iminium ions $Me_2N^+{=}CH_2$ (**1**), $^iPr_2N^+{=}CH_2$ (**2**), $Ph(Me)N^+{=}CH_2$ (**3**), and $Me_2N^+{=}C(Cl)H$ (**4**) with nucleophiles were determined by ^1H-NMR spectroscopy. By correlation, the electrophilicity parameters $E(\mathbf{1}) = -7.0$, $E(\mathbf{2}) = -8.0$, $E(\mathbf{3}) = -4.8$, and $E(\mathbf{4}) = -5.8$ were obtained, which allow to define scope and limitation of aminomethylations.
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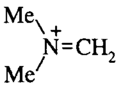
Aminomethylations are among the most important CC bond forming reactions.[1] The use of preformed iminium salts allows regioselective Mannich reactions with enamines, imines, boron enolates, and silyl enol ethers under mild conditions,[1, 2] and also enantioselective variants have successfully been performed.[3]

In previous work we have established that the Linear Free Enthalpy Relationship (LFER)

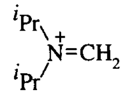
$$\lg k_{20°C} = s\,(E + N) \qquad (1)$$

allows to calculate the rates of a large number of electrophile-nucleophile reactions.[4a] Whereas neutral nucleophiles are characterized by the parameters N and s, the electrophilicities of carbocations, diazonium ions, and metal-π-complexes are expressed by the value of E. Despite numerous applications of iminium ions in organic syntheses there is a lack of kinetic data[5] which are necessary for the quantification of their electrophilic reactivity.

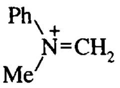
In this letter we report on the determination of the rate constants for the reactions of the iminium ions **1-4** with nucleophiles that possess known nucleophilicity parameters N and s. Based on these measurements, E-parameters for the Mannich reagents **1-3** and for the Vilsmeier-Haack ion **4** have been calculated.


$Me_2N^+{=}CH_2$

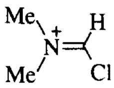
1


$^iPr_2N^+{=}CH_2$

2


$Ph(Me)N^+{=}CH_2$

3


$Me_2N^+{=}C(H)Cl$

4

All reactions reported in this paper follow second order kinetics, first order with respect to the iminium ion and first order with respect to the nucleophile. The rate constants remained unchanged - within experimental error - when iminium ions with different weakly nucleophilic counterions (OTf^-, $AlCl_4^-$, $SbCl_6^-$) were employed (Table 1). Though reactions with quite different types of nucleophiles (alkenes, arenes, silanes) have been studied, the E-parameters derived for each iminium ion with different reaction partners were fairly constant, indicating that these reactions also follow eq. (*1*).

The electrophilicity of the most frequently used aminomethylation agent **1** (k_{rel} = 1.0) can be enhanced when an *N*-methyl is substituted by an *N*-phenyl group (k_{rel}(**3**) = 158). Bulky *N*-substituents (isopropyl) retard the attack of the nucleophile and decrease the reactivity of the methyleneammonium ions by a factor of 10. The Vilsmeier-Haack reagent **4** where one of the methylene hydrogens of **1** is replaced by a chlorine atom turned out to be 16 times more reactive than the Mannich reagent **1**.

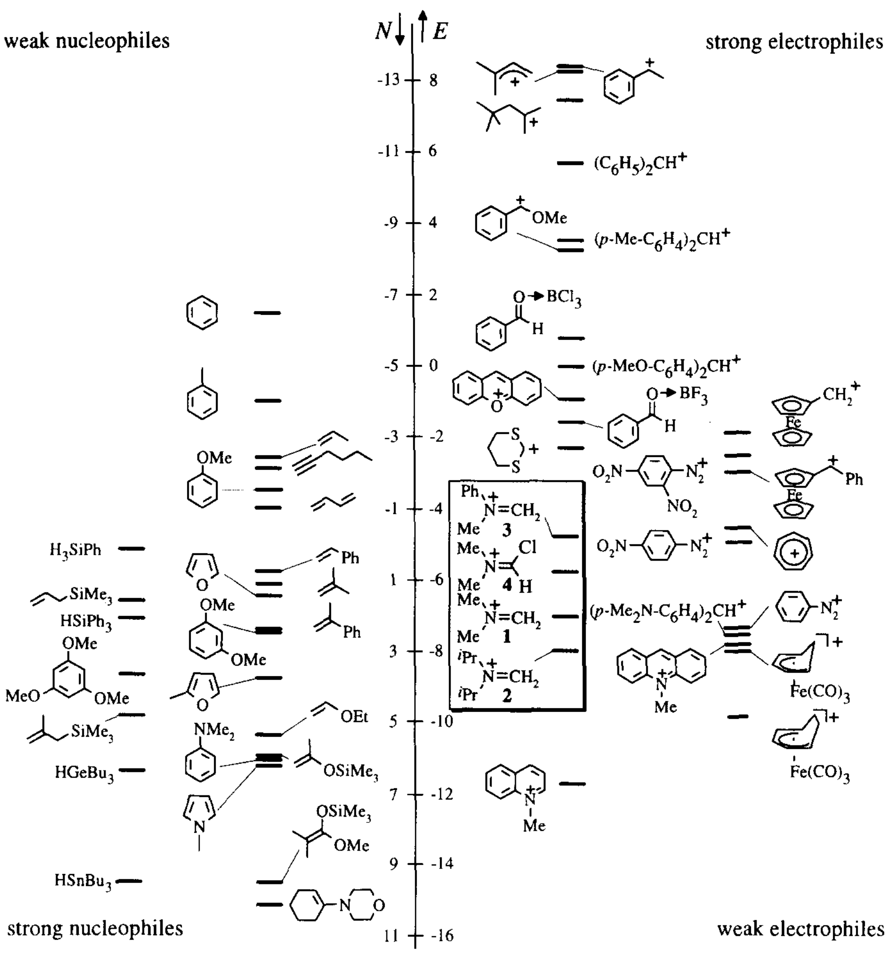
TABLE 1. *Rate Constants $k_{20°C}$ Determined by ^{1}H-NMR-Spectroscopy (in CD_3CN, 300 MHz) and Electrophilicity Parameters of the Iminium Ions 1-4.*[a]

Nucleophiles	*N*	*s*	$k_{20°C}$ / L mol^{-1} s^{-1}	*E*	E_{av}
- *N,N-Dimethylmethyleneammonium Ion* (**1**)					
2-methylfuran	3.86	1.05	3.78×10^{-4}	-7.12	E_{av}(**1**) = -7.0
1,3,5-trimethoxybenzene	3.40	1.30	5.88×10^{-5}	-6.65	
α-methylstyrene	2.39	1.00	3.12×10^{-5}	-6.90	
triphenylsilane	1.91	0.72	1.02×10^{-4}	-7.45	
- *N,N-Diisopropylmethyleneammonium Ion* (**2**)					
dimethylphenylsilane	3.39	0.72	9.53×10^{-4}	-7.59	E_{av}(**2**) = -8.0
triphenylsilane	1.91	0.72	1.83×10^{-5}	-8.49	
- *N-Methyl-N-phenylmethyleneammonium Ion* (**3**)[b]					
1,3-dimethoxybenzene	2.40	1.20	1.16×10^{-3}		*E*(**3**) = -4.8
- *Chloromethylenedimethylammonium Ion* (**4**)					
α-methylstyrene	2.39	1.00	1.55×10^{-4}	-6.20	E_{av}(**4**) = -5.8
1,3-dimethoxybenzene	2.40	1.20	2.60×10^{-4}	-5.39	

[a] Counterions: OTf^-, $AlCl_4^-$, and $SbCl_6^-$

[b] A stable solution of **3**-OTf was produced in CD_3CN by the addition of trimethylsilyl triflate to *N*-methoxymethyl-*N*-methylaniline. However, its isolation as a stable salt failed.

Scheme 1 shows the incorporation of the iminium ions **1**-**4** into the electrophilicity scale.[4] It can be seen that the *N,N*-dialkyliminium ions **1** and **2** have a similar electrophilicity as the *N*-methylacridinium ion, the irontricarbonyl-stabilized cyclohexadienylium ion, or the benzenediazonium ion. On the other hand, the reactivities of the more electrophilic iminium ions **3** and **4** are comparable to those of the tropylium ion and of the *p*-nitrobenzenediazonium ion. The nucleophilicity scale[4] is arranged in a way that reaction partners located on the same level fulfill the relationship ($N + E$) = -5. Since $s \approx 1$ for most nucleophiles, this corresponds to slow reactions at 20 °C, i. e., at room temperature electrophiles should only react with those nucleophiles that are located at the same or at a lower level. The preparative experience verifies the positioning of the cations **1**-**4** in Scheme 1: a) Many types of strong nucleophiles (silyl enol ethers, silyl ketene acetals, enamines, pyrroles and indoles) have been reported to undergo aminomethylation reactions.[1-3] b) 1,3,5-Trimethoxybenzene and



SCHEME 1. *Reactivity Scales for Nucleophiles and Electrophiles with the Iminium Ions 1-4 included.*

1,3-dimethoxybenzene can be converted to the corresponding Mannich bases,[6a] but all attempts to aminomethylate the less reactive anisole failed.[6] c) Furan reacts slowly with the dimethyliminium ion **1** at 20 °C but not with the corresponding diisopropyl derivative **2**.[7a] In contrast, 2-methylfuran - which is approximately 250 times more reactive than furan - gives products with both electrophiles **1** and **2**.[7] d) Toluene does not at all react with iminium ions and can be employed as a solvent for aminoalkylations.[6b, 8] e) Vilsmeier-Haack formylations of reactive arenes (pyrroles, furans, thiophenes, and selenophene derivatives) and of electron-rich alkenes (enamines, dienamines, enol ethers, styrene, isobutene) occur readily.[9] On the other hand, electrophilic substitutions of anisole can not be performed with **4**-Cl^- (100 °C / 24 h / < 5 %) and give only low yields with DMF/$POCl_3$ (100 °C / 24 h / 38 %).[10]

The *E*-parameters reported in this work can thus be used to rationalize known reactions of iminium ions and are valuable means to predict novel aminomethylation and formylation reactions. However, the methylene-ammonium ions **1-3** often take part in pericyclic reactions, e. g. Diels-Alder [11] or ene reactions[12]. Since the LFER (*1*) only holds for reactions where one new bond is formed in the rate determining step, the rates of cycloadditions and of ene reactions can only be predicted in this way when they proceed stepwise with a rate-determining first step.

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