

Counterion effects in iminium-activated electrophilic aromatic substitutions of pyrroles†

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Electrophilic substitution of pyrroles by α,β -unsaturated iminium ions is slow in acetonitrile when only weakly basic counterions are present. When the reactions are carried out in the presence of KCF_3CO_2 , fast deprotonation of the intermediate σ -adducts occurs, and the rate constant for the rate-determining CC bond-forming step can be predicted from the electrophilicity parameter E of the iminium ion and the N and s parameters of the pyrroles.

Iminium activation has become one of the most important methods for the enantioselective formation of CC bonds.¹ Recently, much attention has been paid to the mechanism of these reactions including the isolation and characterisation of the intermediates.²

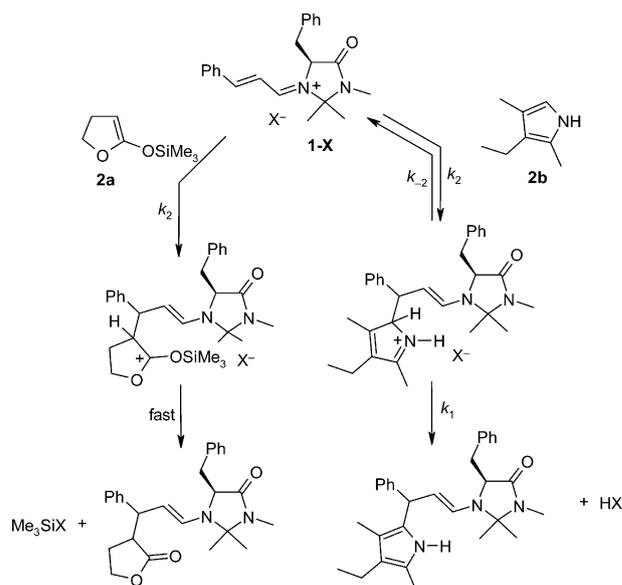
In previous work, we have studied the kinetics of a series of α,β -unsaturated iminium ions with ketene acetals in order to determine their electrophilicity parameters E according to eqn (1)³ where electrophiles are characterised by one parameter (E), while two parameters (N and s) are used for the characterisation of nucleophiles.⁴

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

We now report on the applicability of eqn (1) for predicting the scope and limitations of iminium-activated electrophilic aromatic substitutions.⁵ As the rate constants accessible by eqn (1) refer to the electrophile–nucleophile combination step, knowledge of the rate-determining step of this reaction cascade was needed. Paras and MacMillan reported that imidazolidinone-catalysed reactions of α,β -unsaturated aldehydes with pyrroles proceed well with $\text{CF}_3\text{CO}_2\text{H}$ as a cocatalyst, but give low yields and enantioselectivities, when strong acids such as $\text{CF}_3\text{SO}_3\text{H}$, TsOH or HCl are employed.⁶ As this observation may be due to reversible formation of the σ -adduct from the iminium ion **1** and the pyrroles,⁶ we have systematically studied the effect of the counterions on the rates of these reactions.

The kinetics of the reactions of the iminium ion **1** with the ketene acetal **2a** and the pyrrole **2b** (Scheme 1) were determined photometrically by following the disappearance of the absorbance of **1** at 360 nm according to the procedure described previously.^{3,7}

All kinetic experiments were performed under first-order conditions using 25 to 800 equivalents of **2**. The reactions of



Scheme 1 Mechanism of the reactions of different iminium salts **1-X** with π -nucleophiles.

Table 1 Counterion effect on the second-order rate constants k_2 ($\text{M}^{-1} \text{s}^{-1}$) for the reactions of the iminium salts **1-X** with the ketene acetal **2a** in CH_2Cl_2 and the apparent second-order rate constants k'_2 ($\text{M}^{-1} \text{s}^{-1}$) for the reactions of **1-X** with kryptopyrrole **2b** in CH_3CN at 20°C

1-X	k_2 (2a)	k'_2 (2b)
1-PF₆	1.14×10^4	6.27×10^1
1-BF₄	1.19×10^4	5.60×10^1
1-OTf	9.06×10^3 ^a	2.32×10^1
1-Br	4.53×10^3	6.43×10^1
1-CF₃CO₂ ^b	6.76×10^3	5.94×10^2

^a From ref. 3. ^b **1-CF₃CO₂** was generated by addition of an equimolar amount of cinnamaldehyde to imidazolidinium trifluoroacetate in acetonitrile.

1-X with the ketene acetal **2a** showed monoexponential decays over more than 4 half-lives. Deviations from the first-order rate law were observed for the reactions of **1-X** with **2b** at conversions above 70%. The second-order rate constants k_2 and k'_2 listed in Table 1 are the slopes of the linear plots of the observed first-order rate constants k_{obs} vs. $[\mathbf{2}]$.

Table 1 shows the different counterion effects on the reactions with the nucleophiles **2a** and **2b**. While the second-order rate constants of the reactions of **1-X** with **2a** vary by less than a factor of 3, the rates of the reactions of **1-X** with **2b** are significantly affected by the counterions; in the concentration range investigated, the iminium trifluoroacetate **1-CF₃CO₂** reacts 26 times faster with **2b** than the iminium triflate **1-OTf**.

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This behaviour may be rationalised by the reversible attack of **1** at the pyrrole **2b** and subsequent deprotonation of the intermediate σ -adduct.⁸ Due to its higher basicity,⁹ CF_3CO_2^- can be assumed to abstract the proton faster than the other anions investigated, all of which are conjugate bases of very strong acids.

In line with this hypothesis, first-order kinetics over more than four half-lives have been observed when the reaction of the iminium salt **1**- BF_4 with **2b** was studied in the presence of high concentrations of potassium trifluoroacetate. With the assumption that CF_3CO_2^- serves as the base to deprotonate the intermediate σ -adduct, the rate law for the reaction of **1**- BF_4 with **2b** is given by eqn (2), where the last term corresponds to the ratio of deprotonation of the intermediate $k_1[\text{CF}_3\text{CO}_2^-]$ divided by the sum of the forward plus backward reaction (the meaning of the rate constants is specified in Scheme 1). For $[\mathbf{2b}] \gg [\mathbf{1}]$, the concentration of **2b** can be considered to be constant, and one obtains eqn (3).

$$-\frac{d[\mathbf{1}]}{dt} = k_2[\mathbf{1}][\mathbf{2b}] \frac{k_1[\text{CF}_3\text{CO}_2^-]}{k_1[\text{CF}_3\text{CO}_2^-] + k_{-2}} \quad (2)$$

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k_2[\mathbf{2b}]} + \frac{k_{-2}}{k_1 k_2 [\mathbf{2b}] [\text{CF}_3\text{CO}_2^-]} \quad (3)$$

According to eqn (3), the intercept of the plot of $1/k_{\text{obs}}$ vs. $1/[\text{CF}_3\text{CO}_2^-]$ yields the rate constant for the first step of the reaction cascade (Fig. 1). Comparison of this value ($k_2 = 1.3 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) with the entries 1 to 4 in the right column of Table 1 shows that the rate constants k_2' observed in the absence of CF_3CO_2^- are 202 to 560 times smaller than k_2 , indicating that triflate, tetrafluoroborate, hexafluorophosphate, and bromide ions are poor bases for the removal of protons from the pyrrolium species. It should be noted that also the last entry in the right column of Table 1 is 22 times smaller than the second-order rate constant derived from Fig. 1, indicating that at low ion concentrations, also the first step of the reaction of **1**- CF_3CO_2 with **2b** is reversible.

The method described in Fig. 1 for determining the second-order rate constant k_2 for the attack of **1** at the pyrrole **2b** has analogously been employed for determining the rate constant of attack of **1** at the pyrroles **2c**–**g**. Table 2 shows that the experimental rate constants k_2 agree within a factor of 8 with

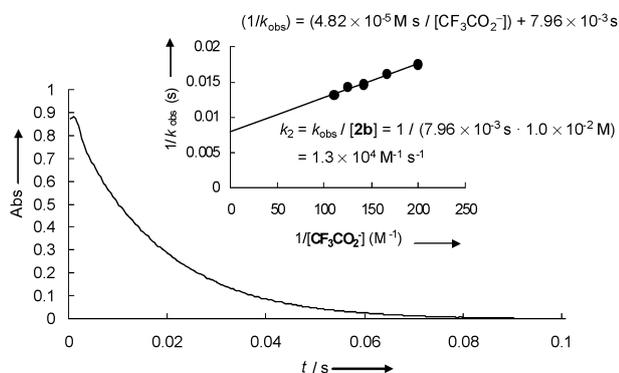
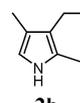
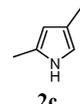
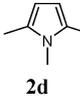
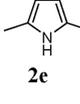
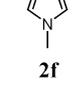
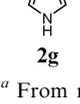


Fig. 1 Exponential decay of the absorbance at 360 nm during the reaction of **1**- BF_4 ($5.0 \times 10^{-5} \text{ M}$) with **2b** ($1.0 \times 10^{-2} \text{ M}$) and CF_3CO_2^- ($5.0 \times 10^{-3} \text{ M}$). Inset: determination of the second-order rate constant k_2 .

Table 2 Comparison of calculated and experimental second-order rate constants ($\text{M}^{-1} \text{ s}^{-1}$) of the reactions of pyrroles **2b**–**g** with the iminium ion **1** (20°C , CH_3CN) in the presence of added trifluoroacetate

Pyrroles 2	N, s^a	$k_2^{\text{calcd } b}$	$k_2^{\text{exp } c}$	$k_2^{\text{calcd}}/k_2^{\text{exp}}$
 2b	11.63, 0.95	2.3×10^4	1.3×10^4	1.8
 2c	10.67, 0.91	2.1×10^3	3.5×10^3	0.60
 2d	8.69, 1.01	3.9×10^1	5.3	7.4
 2e	8.01, 0.96	5.9	3.6	1.6
 2f	5.85, 1.03	4.1×10^{-2}	7.2×10^{-3}	5.7
 2g	4.63, 1.00	2.7×10^{-3}	6.8×10^{-4}	4.0

^a From ref. 10. ^b Calculated by eqn (1) by using the electrophilicity parameters $E = -7.2$ for **1** from ref. 3. ^c Derived from the intercepts of the linear correlations of $1/k_{\text{obs}}$ with $1/[\text{CF}_3\text{CO}_2^-]$. Details are given in the ESI.†

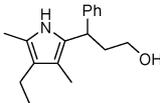
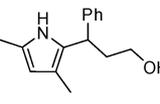
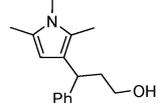
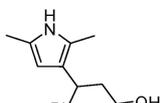
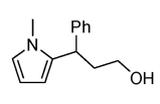
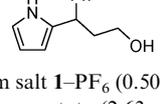
those calculated from eqn (1), *i.e.*, the E , N , and s parameters can be employed for determining the scope and limitations of iminium-catalysed reactions.

As the N and s parameters of the pyrroles **2b**–**g**¹⁰ have been derived from their reactions with benzhydrylium ions (reference electrophiles) and the parameter E for **1** has been derived from its reactivity toward ketene acetals,³ this agreement is further evidence for the power of the three parameter eqn (1) to provide reliable estimates for second-order rate constants in a reactivity range presently covering 40 orders of magnitude.

Accordingly, treatment of an acetonitrile : water (1 : 1) solution of the iminium salts **1**- PF_6 with 5 equivalents of the pyrroles **2b**–**g** in the presence of 5 to 6 equivalents of potassium trifluoroacetate and subsequent reduction with NaBH_4 allowed us to isolate the alcohols **3b**–**g** in 78 to 99% yield (Table 3).¹¹ In contrast, the reaction of **2b** with **1**- PF_6 gave only 15% of **3b** when the reaction was carried out under the same conditions but without potassium trifluoroacetate. These observations show clearly that the presence of base is essential for the success of the reaction.¹²

The high reversibility of the attack of the iminium ions at pyrroles in the absence of CF_3CO_2^- not only accounts for the lower conversion rates of **1**- X ($X = \text{PF}_6, \text{BF}_4, \text{OTf}, \text{Br}$) but also for the erosion of enantioselectivity which was reported

Table 3 Products of the reactions of 1-PF₆ with pyrroles 2b–g in the presence of potassium trifluoroacetate^a

Pyrrole	Product	Yield ^b (%)
2b		94 (15) ^c
2c		97
2d		83
2e		99
2f		78 ^d
2g		80

^a Reaction conditions: iminium salt 1-PF₆ (0.50 mmol), pyrroles 2b–g (2.46 mmol), potassium trifluoroacetate (2.63 mmol) in acetonitrile–water mixture 1 : 1 at –20 °C, 30 min. Then, *in situ* reduction of the aldehydes by NaBH₄ to the corresponding primary alcohols 3b–g. ^b Yield of isolated product after column chromatography on silica gel. ^c Without potassium trifluoroacetate. ^d ee > 99% (for details see p S31 of the ESI†).

by Paras and MacMillan for the imidazolidinium catalysed reaction of cinnamaldehyde with 2f.⁶ Only when high concentrations of the more basic trifluoroacetate counterion are present, are the σ-adducts formed irreversibly. As a consequence, the high enantioselectivity of the addition step, which has been studied computationally by Houk *et al.*,¹³ is fully transmitted into the final product. In line with this interpretation, the reaction of 2f with 1-PF₆ gave 3f with >99% ee, when the reaction was carried out in CH₃CN–H₂O (1 : 1) in the presence of KCF₃CO₂ (Table 3). Presently, we are investigating the effect of the co-catalyst on the formation of the iminium ion, in order to achieve a quantitative description of the whole organocatalytic cycle.

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