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Kinetics and mechanism of reactions of substituted (methylthio)benzylidene Meldrum's acids with primary amines in aqueous DMSO

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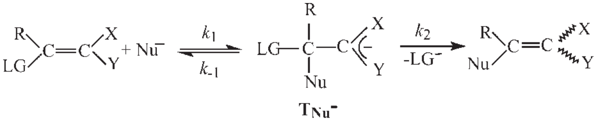
ABSTRACT: A kinetic study of the aminolysis of substituted (methylthio)benzylidene Meldrum's acids, **2-SMe-Z** with the aliphatic primary amines, *n*-butylamine, glycinamide, methoxyethylamine, and aminoacetonitrile, in aqueous DMSO at 20 °C is reported. With all amines the reaction is strictly second-order, that is, first-order in **2-SMe-Z** and first-order in the amine. A three steps mechanism has been proposed. The first step is a rate-limiting attachment of the amine to form the tetrahedral intermediate ($\mathbf{T_A^{\pm}}$), and the subsequent steps are a fast acid–base equilibrium followed by a fast $R'''CH_2NH_3^+$ or H_2O catalyzed expulsion of the leaving group. The Brönsted plot for k_1 for the reaction of **2-SMe-H** with four primary amines showed a good correlation between log k_1 and pK_a^{AH} with $\beta_{nuc} = 0.32 \pm 0.02$, a slightly lower value than that for the reactions of secondary amines ($\beta_{nuc} = 0.41 \pm 0.01$). The Hammett plot for *n*-butylamine yields $\rho(k_1) = 0.40 \pm 0.05$ which is smaller than that for the reaction of piperidine with the same substrates ($\rho(k_1) = 0.72 \pm 0.07$) and also for the reactions of $HOCH_2CH_2S^-$ ($\rho(k_1) = 1.18$), $CF_3CH_2O^-$ ($\rho(k_1) = 1.14$) and OH^- ($\rho(k_1) = 1.11$) addition to **2-H-H** ($\rho(k_1) = 1.11$). All these observations are consistent with the suggested mechanism.

Supplementary electronic material for this paper is available in Wiley Interscience at http://www.interscience.wiley.com/jpages/0894-3230/suppmat/

KEYWORDS: nucleophilic substitution reactions; (methylthio)benzylidene Meldrum's acids; primary amines; three steps mechanism; tetrahedral intermediate

INTRODUCTION

Studies of substituent effects on rates and equilibrium constants of reactions lie at the heart of understanding structure-reactivity relationships and probing transition state structures. It is well understood that the addition-elimination nucleophilic vinylic substitution (S_NV) reactions with anionic nucleophiles (Nu^-) on substrates activated by electron-withdrawing groups proceeds in two steps as in Eqn (1), where, LG^- is the leaving group and X and Y are the activating substituents.[1]



(1)

A number of studies have been reported where the intermediates ($\mathbf{T_{Nu}^-}$) accumulate to detectable levels and allow the determination of rate constants (k_1, k_{-1}, and k_2) as functions of the nucleophile, the leaving group, the activating substituents X and Y, the R group and the solvent polarity.[2–5] These studies provide the opportunity to understand the structure-reactivity relationships in S_NV reactions. Accumulation of the intermediate to detectable levels during the reaction depends on two conditions which must be met: (i) thermodynamic or equilibrium condition: $K_1[Nu^-] > 1$, $K_1 = (k_1/k_{-1})$ and (ii) kinetic condition: $k_1[Nu^-] > k_2$. The former requires a combination of strong nucleophile and strongly electron-withdrawing groups (X, Y) while the latter requires a combination of strong nucleophile and relatively sluggish leaving group. The reactions of some alkoxide and thiolate ions with **1-OMe**,[3,4] **1-SMe**,[3,4] **2-OMe**,[5] **2-SMe**,[5] **3-SMe**[2], and **4-OMe**[2] were shown to easily meet the above requirements.

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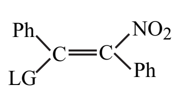
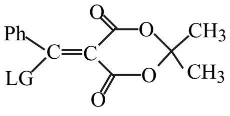
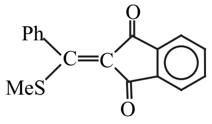


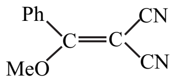
1-OMe (LG =MeO)
1-SMe (LG = SMe)



2-OMe (LG =MeO)
2-SMe (LG = SMe)
2-H-H (LG = H)

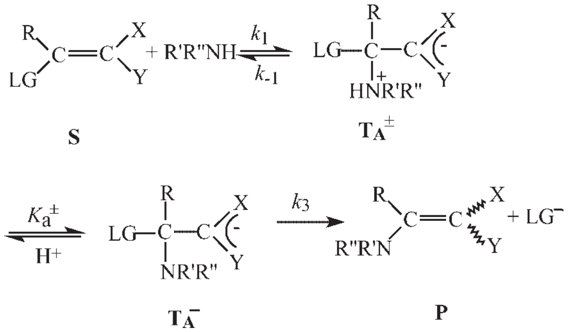


3-SMe



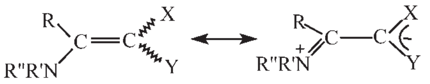
4-OMe

On the other hand, for the reactions with amine nucleophiles, the mechanism is more complex. Compared with their reactions with anionic species like MeO^-, RS^- etc, it includes a proton transfer as an additional step (Eqn (2), and it is difficult to find conditions where an intermediate may be directly detectable.[6]



(2)

Whereas it is easy to meet the equilibrium condition ($K_1K_a^{\pm}$ [R′R″NH])/[H$^+$] > 1,[7] the kinetic condition k_1[R′R″NH] > k_3 is rather difficult to meet, as the leaving group departure (k_3) is much more enhanced by the electronic push of the nitrogen lone pair than from the oxygen or sulfur lone pairs in $\mathbf{T}_{\mathbf{Nu}}^-$. This extra stabilization of the transition state results from the developing higher product (P) resonance.

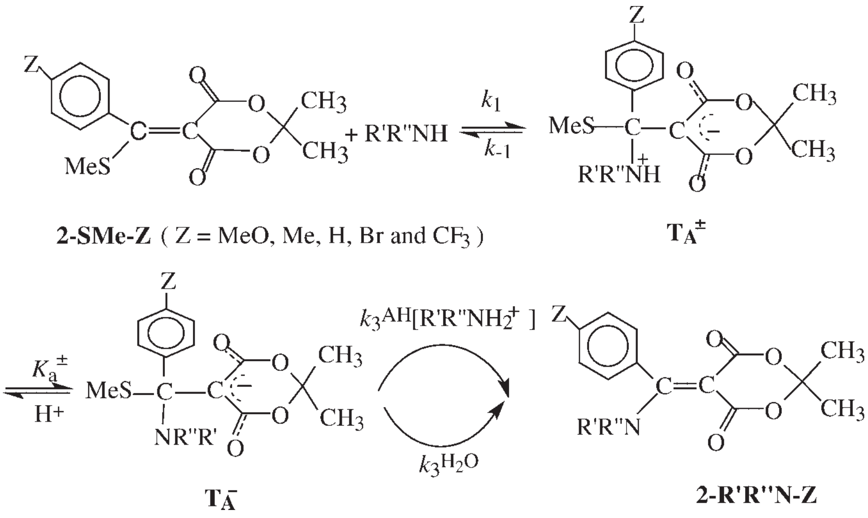


P **P**$^{\pm}$

In fact, reducing this push by choosing a weakly basic amine as nucleophile was the key in making $\mathbf{T}_{\mathbf{A}}^-$ detectable in the reactions of **1-OMe** with methoxyamine[6] (pK_a 4.70). On the other hand, despite the higher nucleophilicity of the more basic amines, for example, *n*-butylamine (p$K_a = 10.65$), piperidine (p$K_a = 11.02$) or morpholine (p$K_a = 8.70$), the intermediate could not be observed[8] as the effect of increased nucleophilicity is more than offset by the increased push.[6a] Thus the three-step mechanism has generated particular interest because of possible changes in the rate-limiting step with changing reaction conditions.

In the reaction of **2-SMe-Z** with a series of secondary amines[9] (Scheme 1) it was shown that general acid catalyzed MeS^- departure (k_3^{AH}, $k_3^{H_2O}$) is rate limiting, at least for piperidine, while for piperazine, 1-(2-hydroxyethylpiperazine) and morpholine deprotonation of $\mathbf{T}_{\mathbf{A}}^{\pm}$ to $\mathbf{T}_{\mathbf{A}}^-$ is rate-limiting at low amine concentrations and relatively low pH. At high amine concentrations or high pH nucleophilic addition (k_1) is rate limiting.[9]

It was observed that the order of the reaction in the amine was dependent on the substrate **2-SMe-Z** and also on the solvent.[10] In C_2H_5OH only **2-SMe-OMe** having the least electron withdrawing aryl group displayed a second-order reaction in the amine while for other substrates the order in the amine was between 1 and 2 and base catalysis was extensive. In the reaction of **2-SMe-(CF$_3$)$_2$** with piperidine the k_{obs} (sec^{-1}) *versus* [piperidine] plot was a first-order limiting curve with leveling off at higher amine concentrations.[10a] On the other hand, the



Scheme 1

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reactions of **2-SMe-Z** with four secondary amines in 50% DMSO-50% water displayed an order in amine between 1 and 2 with significant base catalysis.[10]

We present here the reactions of **2-SMe-Z** with a series of primary aliphatic amines in 50% DMSO-50% H_2O at 20 °C in order to examine how the change from secondary amines to primary amines as nucleophiles may affect what step(s) is (are) rate limiting and how the overall reactivity may change. The interesting finding is that these reactions involve rate limiting nucleophilic attack of the amines on the electrophilic α-carbon followed by rapid leaving group expulsion, resulting in an overall second-order:first-order in both substrate and amine concentration and found to be the first report on such substituted benzylidene Meldru's acid systems.

EXPERIMENTAL SECTION

Materials and reagents

The substituted (methylthio)benzylidene Meldrum's acids were available from a previous study.[9] DMSO was refluxed over CaH_2 and distilled under vacuum. Reagent grade amines were from Aldrich chemicals and solid amines were recrystallized from water–ethanol solution and the liquid amines were distilled over CaH_2 before use.

Synthesis of (*n*-Butylamino)benzylidene Meldrum's acid

This compound was prepared by following the procedure reported earlier on the synthesis of 2,2-dimethyl-5-[piperidino(*p*-methoxyphenyl)methylene-1,3-dioxane-4, 6-dione.[10] In a typical method a $CaCl_2$- protected 15 mL MeCN solution containing 1 mmol **2-SMe-H** and 1 mmol *n*-butylamine was stirred at room temperature for 48 h. The solvent was evaporated and the solid mass was recrystallized from EtOH to give (*n*-butylamino)-benzylidene Meldrum's acid. It was characterized by ^{1}H NMR and GC-MS as follows: ^{1}H NMR (300 MHz, δ, $CDCl_3$): 7.26, 7.19, and 7.47 (5H, *m*, Ph), 0.91 (6H, *m*, $(CH_2)_3$), 2.67 (3H, *t*, CH_3), 1.72 (6H, *s*, CMe_2), 2.06 (1H, *t*, NH); MS (*m/z*, electrospray):304 (MH^+), 246 (MH^+—$OCMe_2$), 115 (MH^+—CMe_2—$2CO_2$—$CH_3(CH_2)_2CH_3$), 58 ($OCMe_2$).

Kinetics and pH measurements

Most reactions were followed by monitoring the disappearance of the substrates at around 330 nm using Hewlett-Packard 8453 Agilent UV–Vis spectrophotometer. The pH in 50% DMSO-50% H_2O (v/v) at an ionic strength 0.50 M (KCl) at 20 °C (maintained by using water jacketed container and flowing water through it from a thermostatic water bath) was determined by a digital pH-meter (Systronics-335, India) equipped with a glass electrode and a reference electrode calibrated with standard aqueous buffers in 50% DMSO-50% H_2O (v/v) before use. Stock solutions of the substrates were prepared in anhydrous acetonitrile. The pseudo-first-order rate constants (k_{obs}, sec^{-1}) were obtained by fitting the kinetic traces with suitable computer-fit program and the results were found to fall within the error limit of ±5%.

RESULTS AND DISCUSSION

General features

All reactions were conducted in 50% DMSO-50% H_2O (*v/v*) at 20 °C, at an ionic strength of 0.5 M maintained with KCl. Pseudo-first-order conditions were applied throughout, with the substrate as the minor component. Rates were measured for the reactions of **2-SMe-Z** with Z = OMe, Me, H, Br, and CF_3 with *n*-butylamine (Table 1) and of **2-SMe-H** with *n*-butylamine, glycinamide, 2-methoxyethylamine and aminoacetonitrile (Table 2). Figure 1, which is representative, shows time-resolved spectra of the reaction of aminoacetonitrile with **2-SMe-H**. The presence of an isosbestic point indicates that the reaction is quite clean. The conversion

Table 1. Second-order rate constants for the reaction of **2-SMe-Z** with *n*-butylamine in 50% DMSO-50% water at 20 °C

Z	σ^a	k_1 ($M^{-1}sec^{-1}$)
OMe	−0.27	4.05
Me	−0.17	4.76
H	0.00	5.37
Br	0.23	6.4
CF_3	0.54	8.86

[a] Ref. [9].

Table 2. Second-order rate constants for the reaction of **2-SMe-H** with primary amines in 50% DMSO-50% water at 20 °C

Amine	$pK_a^{BH,a}$	k_1 ($M^{-1}sec^{-1}$)
n-Butylamine	10.61	5.36
2-Methoxyethylamine	9.63	2.63
Glycinamide	8.28	1.30
Aminoacetonitrile	5.39	0.115

[a] Ref. [11].

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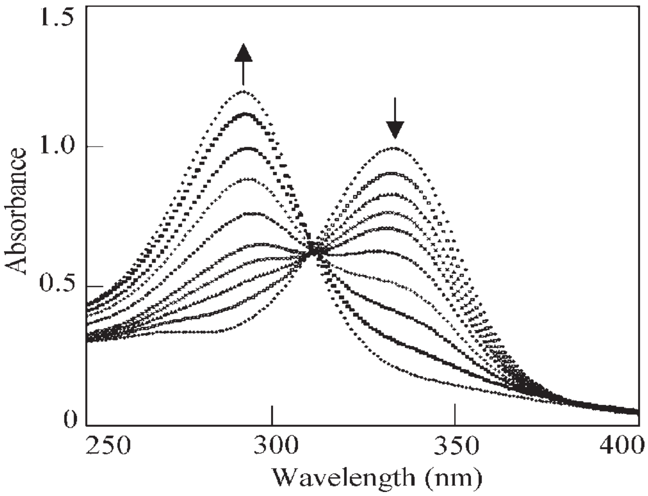


Figure 1. Time resolved spectra for **2-SMe-H** + $NCCH_2NH_2$ reaction in 50% DMSO-50% water at 20 °C. First spectrum was generated within 5 sec of mixing and subsequent spectra at a time interval of 15 sec

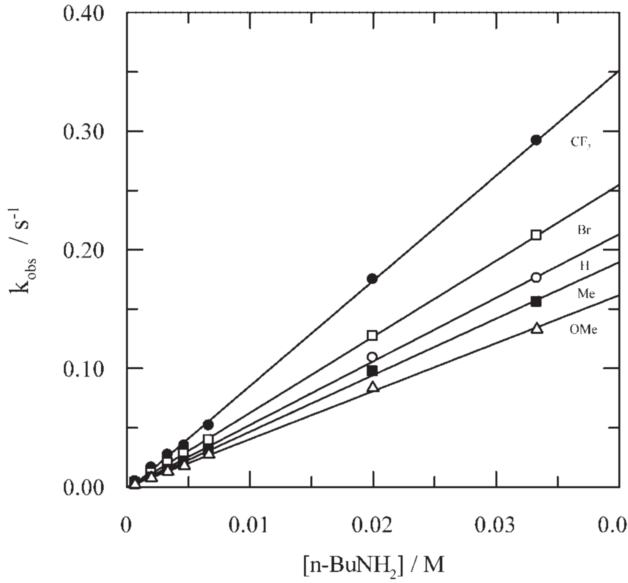
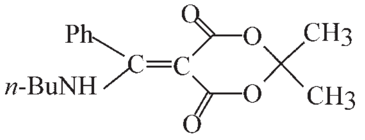


Figure 2. Plots of k_{obs} (sec^{-1}) vs. [*n*-$BuNH_2$] for **2-SMe-Z** + *n*-$BuNH_2$ reactions in 50% DMSO-50% water at 20 °C

of **2-SMe-H** to **7** produces a blue shift in the UV region, which is typical for the reaction of amines with **2-OMe** and **2-SMe**. Formation of the amine-substituted product (**7**) was confirmed from the GC-MS and ^1H NMR spectrum of the product and also by comparing the spectrum of a reaction solution at infinite time to that obtained synthetically.



7

The reactions of **2-SMe-Z** with the primary aliphatic amines (data are listed in Table S1–S8 and corresponding plots are given in Figure S1–S8), all showed strictly overall second-order kinetics, that is, k_{obs} is given by Eqn (3), with k_A being the second-order rate constant for aminolysis. Plots of k_{obs} *versus* [$R'''CH_2NH_2$] are all linear with no positive intercept on the k_{obs} axis.

$$k_{obs} = k_A[R'''CH_2NH_2] \qquad (3)$$

Figure 2 shows plots of k_{obs} *versus* [$R'''CH_2NH_2$] for the reaction of **2-SMe-H** with four primary aliphatic amines at $pH \sim pK_a$ of the amines, where $[R'''CH_2NH_2]:[R'''CH_2NH_3^+] = 1:1$ is prevailing. Reactions were carried out in few cases at pH where $[R'''CH_2NH_2]$: $[R'''CH_2NH_3^+] \sim 9:1$ and no significant change in the slope (k_A) values was observed.

Consequently, it can be concluded that k_A remains constant at different pH values showing no general base catalysis. It is expected that there should be no major change in mechanism on moving from the reaction of secondary amines to that of primary aliphatic amines. Hence, as for the reactions of secondary alicyclic amines with **2-SMe-Z**[9] the discussion will be based on the mechanism of Scheme 1. Since no intermediate was observed in most aminolysis reactions,[9] $\mathbf{T_A^{\pm}}$ and $\mathbf{T_A^{-}}$ may be treated by the steady-state approximation which leads to Eqn (4) for k_A, where K_a^{AH} and $K_a^{\pm}$ are the acid dissociation constants of $R'''CH_2NH_3^+$ and $\mathbf{T_A^{\pm}}$, respectively and K_w is the ionic product of the solvent.

$$k_A = \frac{k_1\left(\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] + \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-]\right)}{1+\left(\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] + \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-]\right)} \qquad (4)$$

Analysis of Eqn (4) shows that three special cases may arise:

1) Formation of $\mathbf{T_A^{\pm}}$ is rate limiting, that is, the conversion of $\mathbf{T_A^{\pm}}$ via $\mathbf{T_A^{-}}$ to products is much faster than return of $\mathbf{T_A^{\pm}}$ back to reactants (k_{-1}). This is expressed here by Eqn (5) and Eqn (4) simplifies to Eqn (6).

$$\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] + \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-] \gg 1 \qquad (5)$$

$$k_A = k_1 \qquad (6)$$

2) Concurrent ammonium ion catalyzed (k_3^{AH}) and solvent assisted ($k_3^{H_2O}$) loss of MeS^- from $\mathbf{T_A^{-}}$ is rate limiting, with the first two steps of Scheme 1 being

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preequilibria, that is, Eqn (7) holds, and k_A is given by Eqn (8).

$$\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] + \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-] \ll 1 \qquad (7)$$

$$k_A = k_1\left(\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] + \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-]\right) \qquad (8)$$

Here, k_A should increase linearly on increasing $[R'''CH_2NH_2]$ and $[OH^-]$, particularly at lower concentrations of these bases.

3) This is a special case where only OH^- catalysis but not amine catalysis would occur. This situation applies if both the relationships of Eqns (9) and (10) hold throughout the concentration ranges used and if, $(k_3^{H_2O}K_a^{\pm}/k_{-1}K_W)$ $[OH^-]$ changes from <1 to >1 as $[OH^-]$ is increased.

$$\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] \ll 1 \qquad (9)$$

$$\frac{k_3^{AH}K_a^{\pm}}{k_{-1}K_a^{AH}}[R'''CH_2NH_2] \ll \frac{k_3^{H_2O}K_a^{\pm}}{k_{-1}K_w}[OH^-] \qquad (10)$$

In the present investigation, the absence of amine and OH^- catalysis implies that $(k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH})$ and/or $(k_3^{H_2O}K_a^{\pm}/k_{-1}K_W)$ ratios are larger than those for the reactions with secondary amines and become $(k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH})[R'''CH_2NH_2] > 1$ and $(k_3^{H_2O}K_a^{\pm}/k_{-1}K_W)[OH^-] > 1$ under all reaction conditions, which means that k_1 is rate limiting.

Factors responsible for the absence of base catalysis

As mentioned in the Introduction, for the reactions of **2-SMe-Z** with a series of secondary amines in 50% DMSO-50% water a general acid catalyzed leaving group (MeS^-) departure was found to be the rate-limiting step. On the other hand, for the reactions of a series of primary amines with the same substrates under identical conditions, as observed in this study, the nucleophilic attack on the α-carbon is found to be rate-limiting followed by a rapid leaving group departure.

In these reactions both the substrate (**2-SMe-Z**) and the solvent (50% DMSO-50% water) are identical and the only variable parameter is the steric effect in the transition state, which is much more pronounced in the reactions of secondary amines. This effect would increase k_{-1}, decrease k_1, and enhance both $k_3^{H_2O}$ and k_3^{AH}. Consequently, $\{(k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH})[R'''CH_2NH_2] + (k_3^{H_2O}K_a^{\pm}/k_{-1}K_W)[OH^-]\} < 1$ at low $[R'''CH_2NH_2]$ and $[OH^-]$ and $\{(k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH})[R'''CH_2NH_2] + (k_3^{H_2O}K_a^{\pm}/k_{-1}K_W)[OH^-]\} > 1$ at high $[R'''CH_2NH_2]$ and high $[OH^-]$, and Eqn (4) accounts for the observed dependence. The steric effect in the transition state for the reactions with primary amines is less pronounced than in the case of secondary amines with a consequent slight enhancement of k_1 and decrease in k_{-1}, $k_3^{H_2O}$ and k_3^{AH}. The effect on k_{-1} and on $k_3^{H_2O}$ or k_3^{AH} tends to offset each other. The effect on k_{-1} is likely to be stronger, and as a consequence the combined effects lead to the increase in $k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH}$ and $k_3^{H_2O}K_a^{\pm}/k_{-1}K_W$ ratios and $\{(k_3^{AH}K_a^{\pm}/k_{-1}K_a^{AH})[R'''CH_2NH_2] + (k_3^{H_2O}K_a^{\pm}/k_{-1}K_W)$ $[OH^-]\}$ becomes always $\gg$1, which accounts for the observed dependence on the amine (Eqn (5)).

The nucleophilic attack step (k_1)

A Bronsted plot for k_1 for the reaction of **2-SMe-H** with four primary aliphatic amines (Fig. 3) displays a good correlation between log k_1 and pK_a^{AH} with $\beta_{nuc} = 0.32 \pm 0.02$. The β_{nuc} (k_1) value for the reactions of secondary amines with **2-SMe-H** is 0.41 ± 0.01[9] which is slightly higher than that for the primary amine reactions.

This slight difference in $\beta_{nuc}(k_1)$ between the secondary alicyclic amines and the primary amines indicates that:

1) At the transition state, C—N bond formation is more advanced for the reaction with secondary amines. This mainly represents a Hammond effect[12,13] resulting from a thermodynamically less favorable $\mathbf{T_A^{\pm}}$ formation in the reaction of the secondary amines due to increased steric crowding in $\mathbf{T_A^{\pm}}$.

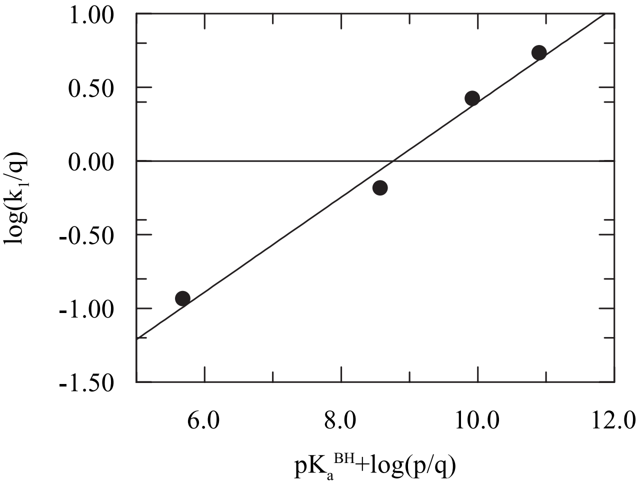


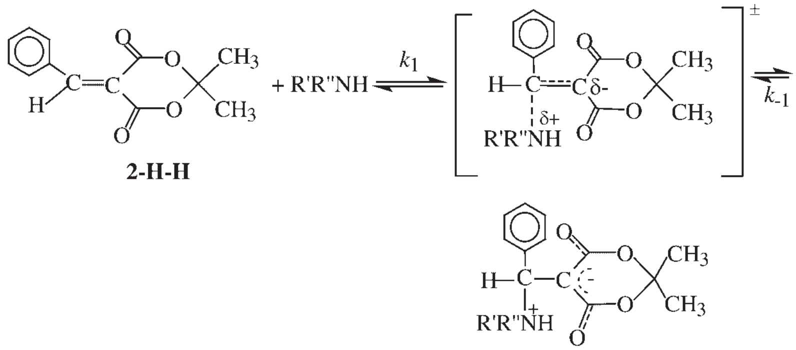
Figure 3. Bronsted plot for the nucleophilic attachment of primary amines for **2-SMe-H** + $R'''CH_2NH_2$ reactions

2) In the addition reaction of piperidine/morpholine to **2-H-H** (Eqn (11) $\beta_{nuc}(k_1) = 0.14$[14] indicating that in this reaction the C—N bond is less advanced than in the reaction of **2-SMe-H** with both primary and secondary amines. This is again consistent with the Hammond[12]–Leffler principle,[13] because **2-H-H** is much more reactive than **2-SMe-H**. For example, for (**2-H-H** + morpholine) reaction k_1 ($3.19 \times 10^5\,M^{-1}\,sec^{-1}$) is much higher than for the addition step of morpholine to **2-SMe-H** ($k_1 = 0.49\,M^{-1}\,sec^{-1}$), K_1 for the same reaction is also higher for **8-H-H**[15] ($7.76 \times 10^4\,M^{-1}$) than for **2-SMe-H** which is approximated to be $1.9 \times 10^{-8}\,M^{-1}$.[9] The inverse correlation between β_{nuc} and the reactivity of activated PhCH=CXY systems appears to be quite general and has been observed before.[16]

Substituent effects

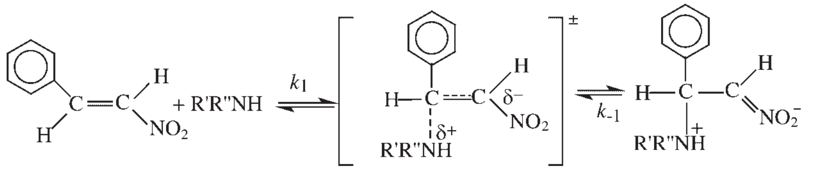
The change in the substituents **Z** on **2-SMe-Z** covers a wide range from the resonative electron donating MeO to the strong electron withdrawing CF_3 groups. Electron withdrawal increases the rate of nucleophilic attack (k_1) on the electrophiles due to the increased electrophilicity of C_α as shown by the k_1 values for reaction of *n*-butylamine with **2-MeS-Z** (Z = CF_3, Br, H, Me, and OMe) (Table 1). A Hammett plot (Fig. 4) yields a slope $\rho(k_1) = 0.40 \pm 0.05$. This value is smaller than that ($\rho(k_1) = 0.72 \pm 0.07$)[9] for the reaction of piperidine, and for the reactions of $HOCH_2CH_2S^-$ ($\rho(k_1) = 1.18$), $CF_3CH_2O^-$ ($\rho(k_1) = 1.14$), and OH^- ($\rho(k_1) = 1.11$) reaction with the same substrates.[5d] The smaller $\rho(k_1)$ for the additions of the amines compared to the $\rho(k_1)$ for the additions of the anionic nucleophiles is most likely the result of the developing positive charge on the amine nitrogen, that is, the stabilizing substituent effect on the developing negative charge is partially offset by the destabilizing effect on the developing positive charge. The lower ρ value for primary than for secondary amines is in line with the lower $\beta_{nuc} = 0.32 \pm 0.02$ for primary amines cited above, manifesting an earlier transition state for secondary amines, which is partly stabilized by the electron-withdrawing phenyl substituents.

In the absence of extraneous factors, such as a π-donor group, one would expect the substituent effect on a reaction that leads to a zwitterionic transition state to be small as long as the distances of the substituent from the sites of positive and negative charges are about the same. These conditions are met with the transition states of the reactions of amines with **2-H-H** (Eqn (11)[14] and **8-H-H** (Eqn (12).[15]



2-H-H

(11)



8-H-H

(12)

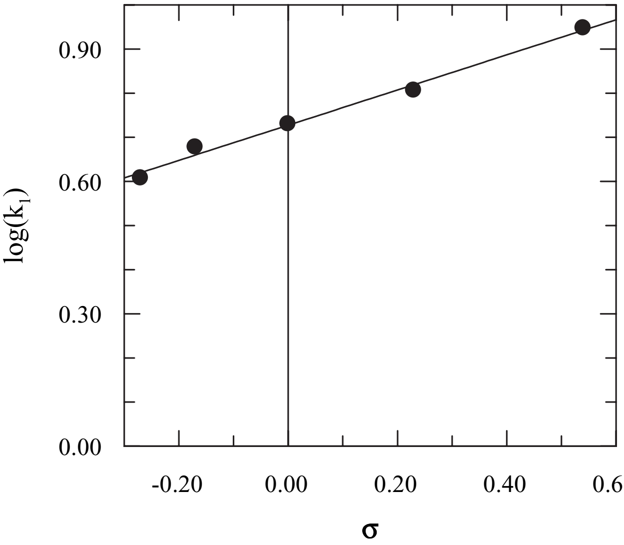


Figure 4. Hammett plot for the nucleophilic attachment of primary amines for **2-SMe-H** + $R'''CH_2NH_2$ reactions

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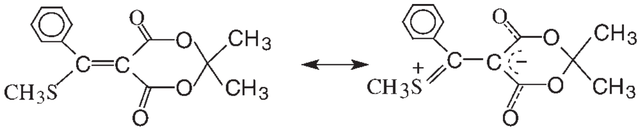
The comparatively higher $\rho(k_1)$ values for the reactions of **2-MeS-Z** with secondary (0.35) and primary (0.27) amines than those for their reactions with **2-H-H** and **8-H-H** is ascribed to be a π-donor effect of the MeS group (cf. **9**) which partly offsets the destabilizing effect of positive charge by the electron withdrawing substituents.


2-SMe-H **9**

CONCLUSIONS

(1) In the reactions of **2-SMe-Z** with four primary aliphatic amines no base catalysis was observed, implying that the k_1 step is rate limiting. (2) The k_1 values for the reactions with secondary amines are smaller than those for the reactions with primary amines of comparable basicity. These results suggest the presence of strong steric effect that mainly reduces the reactivity of bulkier secondary amines. (3) The higher $\beta_{\mathrm{nuc}} = 0.41 \pm 0.01$ for secondary amines than $\beta_{\mathrm{nuc}} = 0.32 \pm 0.02$ for primary amines indicates an earlier transition state in the reaction of primary amines with **2-SMe-Z**. (4) The smaller $\rho(k_1)$ (0.40) value for the reaction of **2-SMe-Z** with *n*-butylamine than that for piperidine with the same substrates ($\rho(k_1) = 0.72 \pm 0.07$) point out that the early transition state is comparatively less stabilized by the electron withdrawing substituents.

Supporting information available

Tables S1–S8 (kinetic data). This material is available free of charge via the Internet at http://pubs.acs.org.

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