

Reactions of α -isobutyl- α -(methylthio)methylene Meldrum's acid with primary amines in aqueous DMSO

Supriya Biswas, Mahammad Ali, Zvi Rappoport, and Hatim Salim

Abstract: The aminolysis of α -isobutyl- α -(methylthio)methylene Meldrum's acid **7** with primary amines, namely, *n*-butylamine, glycynamide, and methoxyethylamine in DMSO–H₂O (50:50, v/v) at 20 °C is overall second-order but first-order in both **7** and amines. The reaction with aminoacetonitrile (AA) is overall third-order, first-order in substrate, and second-order in amine at low amine concentration, while at high amine concentration and high pH the dependence on amine is first-order. A general three-step mechanism has been proposed for all these reactions. For the former group of amines, the first step is a rate-limiting attack of the amine to form the tetrahedral intermediate (T_A^\ddagger), followed by a fast acid–base equilibrium and a fast RNH₃⁺- or H₂O-assisted leaving group expulsion. For AA, general base catalysis was confirmed from the dependence of k_A on [AA]_f and on [OH⁻]. For all four amines, a good Brønsted plot of log k_1 vs. pK_a^{AH} in DMSO–H₂O (50:50, v/v) with $\beta_{nuc} = 0.34 \pm 0.02$ was observed. These observations are consistent with the suggested mechanism.

Key words: nucleophilic vinylic substitution reactions, primary amines, α -isobutyl- α -(methylthio)methylene Meldrum's acid, three-step mechanism.

Résumé : L'aminolyse du dérivé α -isobutyl- α -(méthylthio)méthylène de l'acide de Meldrum (**7**) avec des amines primaires telles la butylamine, le glycynamide et la méthoxyéthylamine, dans des solutions contenant 50% de DMSO et 50% d'eau, à 20 °C, est une réaction globalement du deuxième ordre, du premier ordre en composés **7** et du premier ordre en amines. À faible concentration d'amine, la réaction avec l'aminoacétonitrile (AA) est globalement du troisième ordre, soit du premier ordre en substrat et du deuxième ordre en amine; à des concentrations plus élevées d'amine et à des pH plus élevés, la dépendance sur l'amine est toutefois du premier ordre. D'une façon générale, on suggère que la réaction se produit par un mécanisme en trois étapes. Pour le premier groupe d'amines, la première étape est une attaque cinétiquement limitante de l'amine qui conduit à la formation de l'intermédiaire tétraédrique (T_A^\ddagger) et qui est suivie par un équilibre acide-base rapide et une expulsion rapide du groupe partant assistée par RNH₃⁺ ou H₂O. Dans le cas de l'aminoacétonitrile, on a confirmé l'existence d'une catalyse basique générale à partir de la dépendance de k_A sur les [AA]_f et [OH⁻]. Pour les quatre amines, dans des solutions contenant 50% de DMSO et 50% d'eau, on a observé une bonne corrélation de Brønsted entre log k_1 et pK_a^{AH} avec $\beta_{nuc} = 0,34 \pm 0,02$. Ces résultats sont en accord avec le mécanisme suggéré.

Mots clés : réactions de substitution vinylique nucléophile, amines primaires, dérivé α -isobutyl- α -(méthylthio)méthylène de l'acide de Meldrum, mécanisme en trois étapes.

[Traduit par la Rédaction]

Introduction

The mechanism of the addition–elimination variant of nucleophilic vinylic substitution (S_NV) reactions of electrophilic alkenes (**1**), where X and Y are the activating substituents (**1**), with anionic nucleophiles (Nu⁻) may occur either in a single-step (concerted type) process via a transition state (**2**) or in a two-step process via an intermediate (**3**, T_{Nu}^-), which expels the leaving group (LG⁻) to form the product **4** (Scheme 1). Whereas the concerted route is relatively rare

(*1h*), reactions with most anionic nucleophiles proceed by a two-step mechanism (**1**).

The reactions with amine nucleophiles go through a two-step route with the involvement of acid–base equilibrium as an additional step, as depicted in Scheme 2 (**2**).

In the reactions of **6-SMe-Z** (Chart 1) with a series of secondary amines (**2**), it was shown that general-acid-catalyzed MeS⁻ departure (k_3^{AH} , $k_3^{H_2O}$) from T_A^- is rate-limiting for piperidine, while with piperazine, 1-(2-hydroxyethylpiperazine), and morpholine deprotonation of T_A^\ddagger to T_A^- is

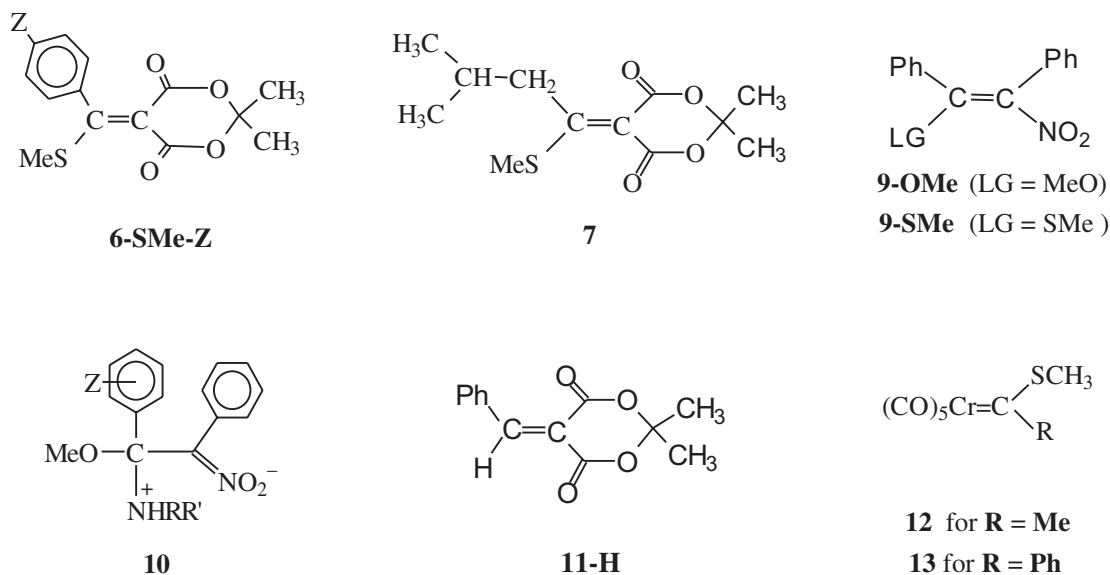
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S. Biswas and M. Ali.¹ Department of Chemistry, Jadavpur University, Kolkata 700 032, India.

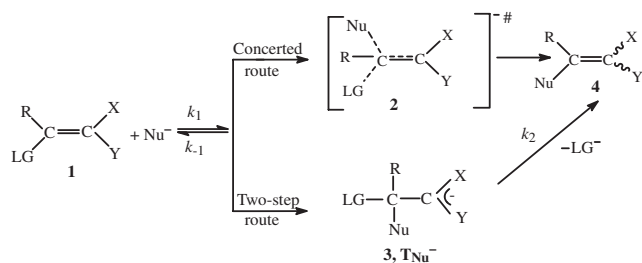
Z. Rappoport and H. Salim. Department of Organic Chemistry, the Hebrew University of Jerusalem, Jerusalem 91904, Israel.

¹Corresponding author (e-mail: mali@chemistry.jdvu.ac.in).

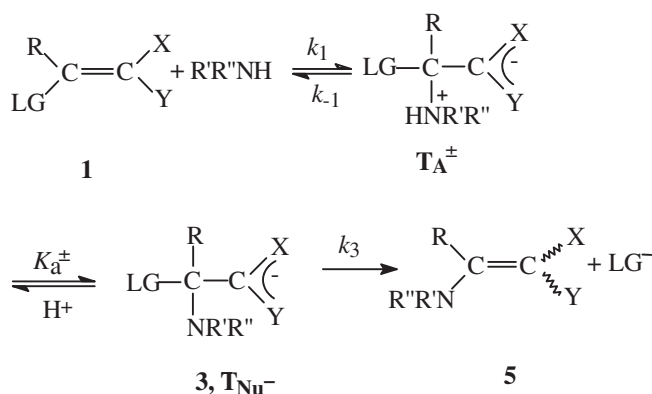
Chart 1.



Scheme 1.



Scheme 2.



rate-limiting. This conclusion is based on the $k_3^{\text{OH}}/k_3^{\text{A}}$ ratios of 18:36, indicating the independence of k_1 values on the amine $\text{p}K_{\text{a}}^{\text{AH}}$ for the former, while for the latter, the ratio was 179, higher than the observed limit of 5:25 (2, 3) manifesting the dependence of $k_3^{\text{OH}}/k_3^{\text{A}}$ ratio on $\text{p}K_{\text{a}}^{\text{AH}}$ of the amines.

In the present paper, we examine how the change from a substituted phenyl group in **6-SMe-Z** ($\text{Z} = \text{H}$) to the isobutyl group in **7** (see Chart 1) affects the rate-limiting step(s) and

how the overall reactivity changes in the reactions with a series of primary amines.

Results and discussion

General features

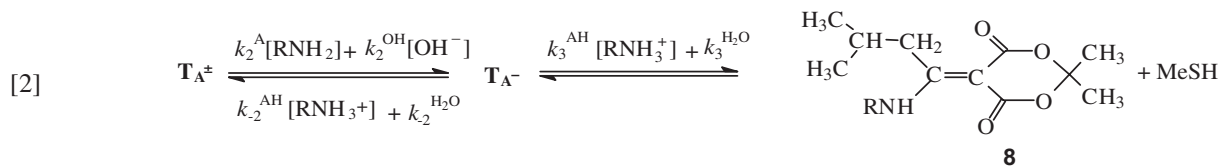
All reactions were conducted in DMSO–H₂O (50:50, v/v) at 20 °C, at an ionic strength of 0.5 mol dm⁻³ maintained with KCl. Pseudo-first-order conditions were applied throughout, with the substrate being the minor component. Rates were measured for the reactions of **7** with *n*-butylamine, glycylamide, methoxyethylamine, and aminoacetonitrile. The representative Fig. 1 shows time-resolved spectra of the reaction with aminoacetonitrile. The presence of an isobestic point indicates a clean reaction. As observed in the literature, the formation of amine-substituted product **8** produces a blue shift in the UV–vis spectrum (2), and the spectrum of the reaction mixture at infinite time is identical with that of the synthetically prepared **8**. This was further supported by ¹H NMR and HR-MS studies.

Based on the observations from the reaction of aliphatic primary (4) and alicyclic secondary amines with **6-SMe-Z** (2), we adopt Scheme 3 for the reactions of primary aliphatic amines (RNH₂) with **7**.

As the intermediate does not accumulate to a detectable level, a steady-state approximation to T_A[±] leads us to derive an expression for the second-order rate constant, k_{A} , as given by eq. [1].

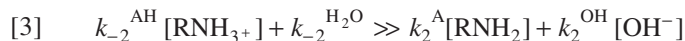
$$[1] \quad k_{\text{A}} = \frac{k_1 \left(\frac{k_3^{\text{A}}}{k_{-1}} [\text{RNH}_2] + \frac{k_3^{\text{OH}}}{k_{-1}} [\text{OH}^-] \right)}{1 + \left(\frac{k_3^{\text{A}}}{k_{-1}} [\text{RNH}_2] + \frac{k_3^{\text{OH}}}{k_{-1}} [\text{OH}^-] \right)}$$

The rate constants corresponding to the conversion of T_A[±] via T_A⁻ and then to product **8** are shown in eq. [2].

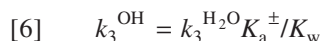
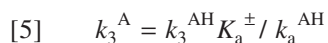
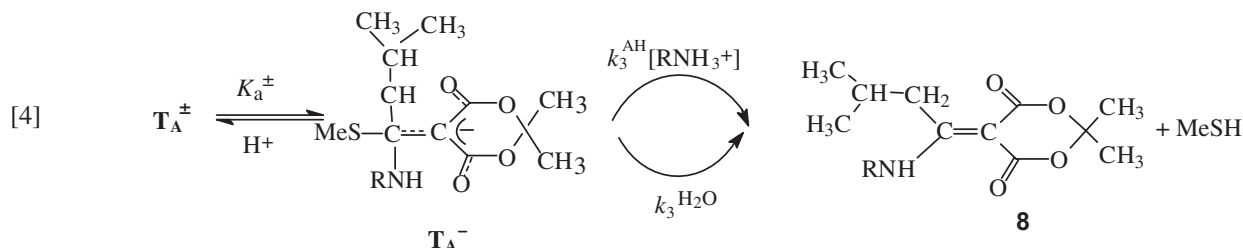


Three cases may arise:

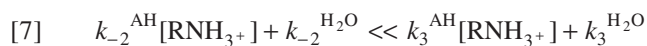
(i) When the acid-catalyzed conversion of \mathbf{T}_A^- to \mathbf{T}_A^\pm is much faster than its reversal, eq. [3] applies.



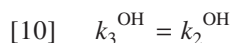
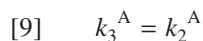
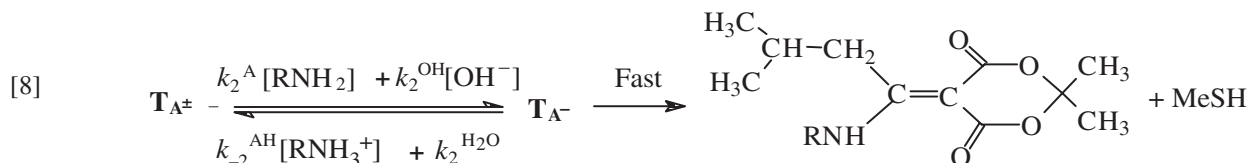
The interconversion of \mathbf{T}_A^- and \mathbf{T}_A^\pm can be treated as a rapid pre-equilibrium followed by a rate-limiting MeS^- departure (eq. [4]) and eqs. [5] and [6] hold, where K_a^{AH} is the acidity constant and K_w is the ionic product of the solvent ($\text{p}K_w = 15.89$ in DMSO– H_2O (50:50, v/v) at 20 °C, $\mu = 0.50 \text{ mol dm}^{-3}$ KCl) (5).



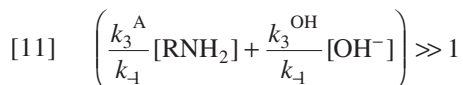
(ii) When the inequality in eq. [7] holds, \mathbf{T}_A^\pm deprotonation is the rate-limiting step for the conversion



of \mathbf{T}_A^\pm to **8**, and eq. [8] and relationships [9] and [10] then hold.



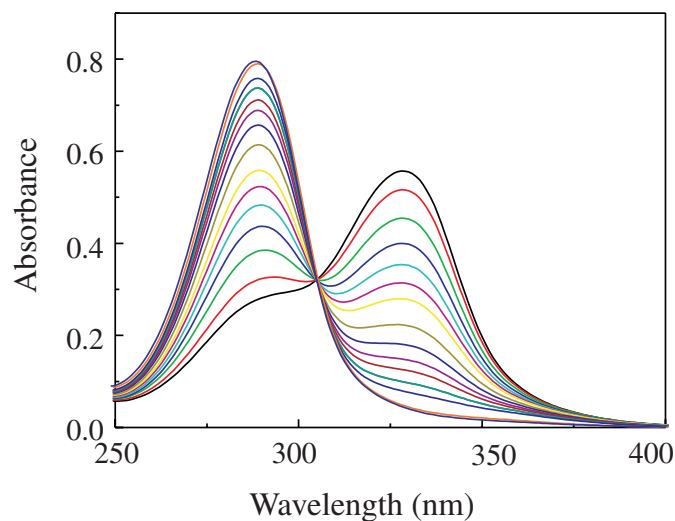
(iii) The nucleophilic attack becomes the rate-limiting step either via a concerted route or through the formation of \mathbf{T}_A^\pm (Scheme 2) with subsequent faster steps. For reactions with amines, it is generally accepted that the nucleophilic vinylic substitution ($\text{S}_{\text{N}}\text{V}$) occurs through the formation of \mathbf{T}_A^\pm (2, 6–7), and eqs. [11] and [12] hold (at high pH, this condition is easily met).



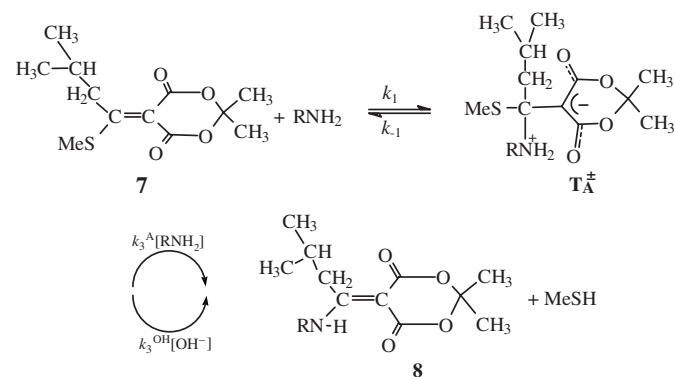
Reactions of *n*-BuNH₂, MeOCH₂CH₂NH₂, and NH₂COCH₂NH₂

For the reactions of these three primary amines, a strict second-order kinetics (eq. [12] with $k_{\text{A}} = k_1$) was observed under all conditions. All the plots of k_{obs} vs. $[\text{RNH}_2]_{\text{f}}$ at $\text{pH} \sim \text{p}K_{\text{a}}$ of the amines, where $[\text{RNH}_2]_{\text{f}}:[\text{RNH}_3^+]_{\text{f}}$ is 1:1, are linear with negligible or no intercept on the rate axis (Fig. 2). A contribution from H_2O or OH^- -catalyzed hydrolysis ($k_1^{\text{H}_2\text{O}}$, k_1^{OH}) of **7** was excluded by the small values of the independently determined $k_1^{\text{H}_2\text{O}} = 3.27 \pm 0.01 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and $k_1^{\text{OH}} = (5.52 \pm 0.03) \times 10^{-6} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$.

Fig. 1. Time resolved spectra generated from a kinetic trace for the reaction between **7** and $\text{H}_2\text{NCH}_2\text{CN}$ in DMSO– H_2O (50:50, v/v) with $[\text{H}_2\text{NCH}_2\text{CN}] = 0.02 \text{ mol dm}^{-3}$ at pH 5.30 and 20 °C.



Scheme 3.



$$[13] \quad k_{\text{obs}} = k_A[\text{RNH}_2]$$

Consequently, experimental eq. [13] fits the previously mentioned situation (iii), and k_A can be identified as k_1 according to eq. [12].

In few cases, reactions were carried out at pH where $[\text{RNH}_2]:[\text{RNH}_3^+] \sim 9:1$, and no significant changes were observed in slope (k_A) values. Consequently, k_A is pH-independent, showing no general base catalysis.

Reaction with $\text{H}_2\text{NCH}_2\text{CN}$

The kinetics were performed under pseudo-first-order conditions with **7** as the minor component. A plot of the observed pseudo-first-order rate constants, k_{obs} , vs. $[\text{H}_2\text{NCH}_2\text{CN}]_f$ showed upward curvatures with an increasing slope (Fig. 3), while a plot of k_A ($k_A = k_{\text{obs}}/[\text{H}_2\text{NCH}_2\text{CN}]_f$) showed an initial rapid increase in k_A with the increase in [amine] followed by leveling off at higher amine concentration (Fig. 4), which is reminiscent of the reactions of **6-SMe-Z** with secondary amines (2). To check for a general base catalysis in this reaction, a variation of $[\text{NMM}]_f$ (NMM is *N*-methylmorpholine) in the range of 0.0005–0.10 mol dm^{-3}

Fig. 2. Plot of k_{obs} vs. $[\text{RNH}_2]_f$ for the reaction of **7** with primary amines in DMSO– H_2O (50:50, v/v) at 20 °C.

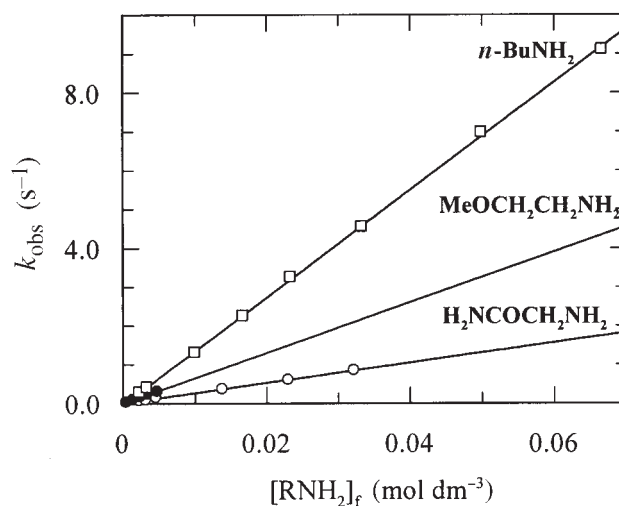
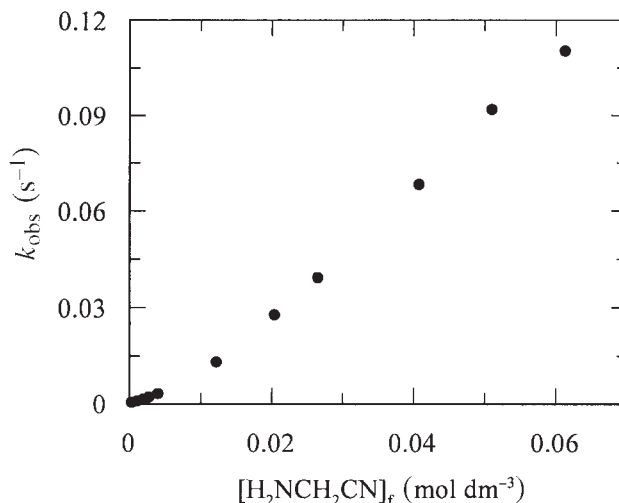


Fig. 3. Plot of k_{obs} vs. $[\text{H}_2\text{NCH}_2\text{CN}]_f$ for the reaction of **7** with aminoacetonitrile in DMSO– H_2O (50:50, v/v) at 20 °C.

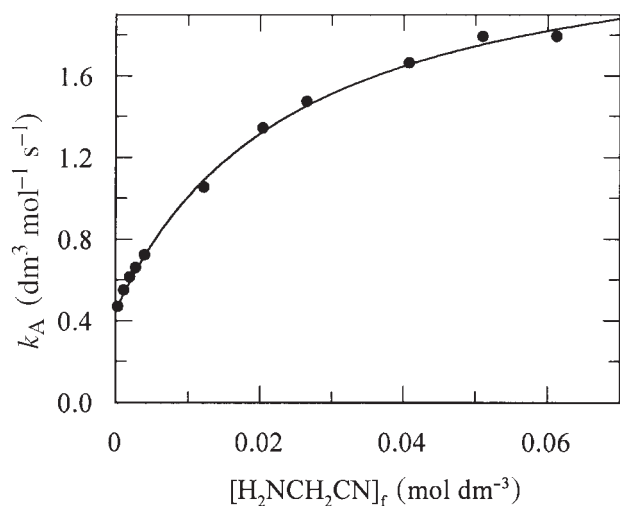


at pH 7.40 with $[\text{H}_2\text{NCH}_2\text{CN}]_f = 0.002 \text{ mol dm}^{-3}$ and pH variation in the range of 6.70–8.45 at constant $[\text{NMM}]_f = 0.002 \text{ mol dm}^{-3}$ and $[\text{H}_2\text{NCH}_2\text{CN}]_f = 0.002 \text{ mol dm}^{-3}$ were carried out. The k_A value remained almost independent of $[\text{NMM}]_f$ with a value $2.26 \pm 0.04 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, while it increased with $[\text{OH}^-]$ at the low $[\text{OH}^-]$ region and became independent at high $[\text{OH}^-]$ (Fig. 5). This behaviour seems to be a special case of Scheme 2, where only OH^- catalysis but not amine catalysis occurs, particularly at high pH. This can be understood if eqs. [14] and [15] hold throughout the whole concentration ranges used, and if simultaneously the ratio $(k_3^{\text{H}_2\text{O}}K_a^\pm/k_1K_w)[\text{OH}^-]$ changes from <1 to >1 as $[\text{OH}^-]$ is increased and eq. [3] changes to eq. [16].

$$[14] \quad \frac{k_3^{\text{AH}}K_a^\pm}{k_1k_a^{\text{AH}}}[\text{RNH}_2] \ll 2$$

Table 1. Comparison of rate constants for the nucleophilic attack on **6-SMe-H** and **7** by nucleophiles in DMSO–H₂O (50:50, v/v) at 20 °C.

Amine or other nucleophile	p <i>K</i> _a ^{AH}	<i>k</i> ₁ (7) (dm ³ mol ⁻¹ s ⁻¹)	<i>k</i> ₁ (6-SMe-H) (dm ³ mol ⁻¹ s ⁻¹)	<i>k</i> ₁ (7)/ <i>k</i> ₁ (6-SMe-H)
<i>n</i> -Butylamine	10.61	138.4	5.36	25.8
Methoxyethylamine	9.63	65.0	2.63	24.7
Glycinamide	8.28	26.1	1.30	22.9
Aminoacetonitrile	5.39	2.38	0.12	20.3
OH ⁻	17.30	3.27	0.63	5.2
H ₂ O	17.33	5.52 × 10 ⁻⁶	2.80 × 10 ⁻⁶	2.0

Fig. 4. Plot of *k*_A vs. [aminoacetonitrile]_f for the reaction of **7** with aminoacetonitrile in DMSO–H₂O (50:50, v/v) at 20 °C.

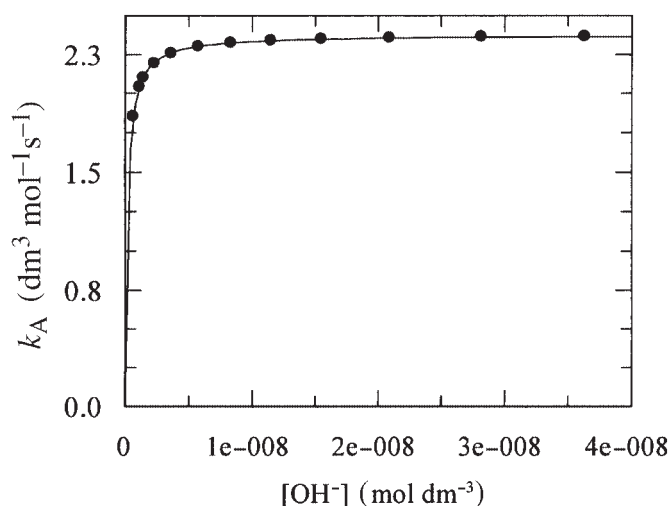
$$[15] \quad \frac{k_3^{\text{AH}} K_a^\pm}{k_1 k_a^{\text{AH}}} [\text{RNH}_2] \ll \frac{k_3^{\text{H}_2\text{O}} K_a^\pm}{k_1 K_w} [\text{OH}^-]$$

$$[16] \quad k_A = \frac{k_1 \left(\frac{k_3^{\text{H}_2\text{O}} K_a^\pm}{k_1 K_w} [\text{OH}^-] \right)}{1 + \left(\frac{k_3^{\text{H}_2\text{O}} K_a^\pm}{k_1 K_w} [\text{OH}^-] \right)}$$

A non-linear least-squares fit of the data to eq. [3] for [H₂NCH₂CN]_f gives *k*₁ = 2.37 ± 0.07 dm³ mol⁻¹ s⁻¹ and *k*_{3^A}/*k*₋₁ = 50.8 ± 5.15 s⁻¹. Similar treatment for the change in [OH⁻] (eq. [16]) yields *k*₁ = 2.48 ± 0.05 dm³ mol⁻¹ s⁻¹ and *k*_{3^{OH}}/*k*₋₁ = 8.13 ± 0.78 × 10⁸ s⁻¹ (Table 1). The *k*₁ value obtained from the variation of [H₂NCH₂CN]_f at constant pH is almost the same as that obtained from the variation of [OH⁻] at constant [NMM]_f and [H₂NCH₂CN]_f, thus confirming the proposed mechanism.}}

The rate-limiting step

The catalysis by both OH⁻ and H₂NCH₂CN demonstrates a general base catalysis, which is most likely accounted by Scheme 2. The lack of NMM catalysis may be attributed to its bulkiness, which precludes its closer approach to **T**_A[±] in the transition state. Either the conversion of **T**_A[±] to **T**_A⁻ or

Fig. 5. Plot of *k*_{obs} vs. [OH⁻] for the reaction of **7** with aminoacetonitrile with [H₂NCH₂CN]_f = 0.002 mol dm⁻³ in DMSO–H₂O (50:50, v/v) at 20 °C.

LG departure from **T**_A⁻ is rate-limiting. The very high *k*_{3^{OH}}/*k*_{3^A}} ratio (3.28 × 10⁸) implies a rapid acid–base equilibrium between **T**_A[±] and **T**_A⁻ followed by a rate-limiting, general-acid-catalyzed LG departure (2). Similar observations were encountered in the aminolysis of the electrophilic β-methoxy-α-nitrostilbene (**9-OMe**) (see Chart 1) where the deprotonation of the corresponding zwitterionic intermediate (**10**) is fast, and methoxide ion departure is rate determining (7).}

Based on the reaction in eq. [8], the reaction of OH⁻ is expected to be a diffusion-controlled proton transfer with a *k*_{2^{OH}}/*k*_{2^A}} value around 10¹⁰ dm³ mol⁻¹ s⁻¹ (8); hence, *k*_{2^{OH}}} should be independent of the amine basicity. *k*_{2^A}} is also expected to be essentially independent of the amine basicity irrespective of whether the reaction is diffusion-controlled (*K*_a^{AH} >> *K*_a[±]) or diffusion-separation-controlled (*K*_a^{BH} < *K*_a[±]) (9). In the latter case, *k*_{2^A}} is independent of the amine basicity because the p*K*_a difference (*K*_a[±] – *K*_a^{AH}) should be constant. Furthermore, if *K*_a^{AH} < *K*_a[±] of **T**_A[±], the proton transfer from **T**_A[±] to RNH₂ will be thermodynamically favorable and close to diffusion controlled limit. Hence, *k*_{3^{OH}}/*k*_{3^A}} ratios should be independent of the amine basicity and have values of 5–25 (3). Because this contrasts our experimental observation, we ascribe the very high *k*_{3^{OH}}/*k*_{3^A}} value for the H₂NCH₂CN reac-}}}

tion to a rate-limiting leaving group departure rather than to a rate-limiting proton transfer from T_A^\ddagger .

The nucleophilic attack step (k_1)

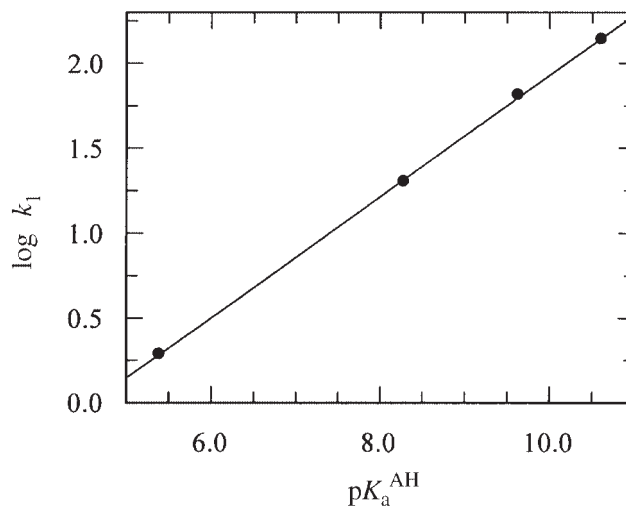
The good linearity of a Brønsted plot of $\log(k_1)$ vs. pK_a^{AH} ($\beta_{\text{nuc}} = 0.34 \pm 0.004$) for the reaction of **7** with the four primary amines is shown in Fig. 6. The corresponding β_{nuc} for k_1 values for the reaction of secondary amines with **6-SMe-H** is 0.41. It was found that the k_1 values for the reactions with secondary amines are smaller than those for the primary amines of comparable basicity. For example, for the **11-H**-HEPA (HEPA is *N*-(2-hydroxyethyl)piperazine) reaction ($pK_a^{AH} = 9.51$), k_1 is $1.06 \pm 0.34 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, while for **11-H**-MeOCH₂CH₂NH₂ reaction ($pK_a^{AH} = 9.63$), k_1 is $2.63 \pm 0.05 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. These results reflect a strong steric effect that reduces the reactivity of the bulkier secondary amines. When steric effects are absent, secondary amines generally react faster than primary amines of comparable basicity (9, 10).

The substitution reactions of **7** are 20–26 times faster than the **6-SMe-H**-RNH₂ reactions. Hence, the formation of T_A^\ddagger with RNH₂ is thermodynamically more favorable for **7** than for **6-SMe-H**. However, based on both inductive and steric effects a reverse trend is expected. We ascribe this discrepancy to an additional effect, i.e., π -donation by the phenyl group (Ph), which may reduce the reactivity of **6-SMe-H** (11). A similar reactivity trend, which was observed for the reactions of H₂NCH₂CN and morpholine with the Fischer carbene complexes **12** and **13** (see Chart 1) was attributed to a different π -donation effect of the Ph group which lowers the reactivity of **13** over **12** (12–15).

The higher β_{nuc} value for **6-SMe-H**-RR'NH (0.41 ± 0.01) compared with that for the **6-SMe-H**-RNH₂ reactions (0.32 ± 0.01) (4) implies that at the transition state, C–N bond formation is more advanced with the secondary amines. Similarly, the β_{nuc} value for the **7**-RNH₂ reaction (0.34 ± 0.02) is almost the same as that for **6-SMe-H**-RNH₂ reaction and manifests the fact that the bond formations in the transition states progress equally in both reactions.

In the reaction of **14-H** with piperidine or morpholine (16) (eq. [17]), $\beta_{\text{nuc}}(k_1) = 0.14$, suggesting that the C–N bond is less advanced than in the reaction of **11-H** and **7** with both primary and secondary amines. This is again consistent with the Hammond–Leffler (17, 18) principle, because **14-H** (19) and **15-H** (16) are much more reactive, e.g., k_1 for the **14-H**-morpholine reaction ($3.19 \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$) is much higher than k_1 for the addition of morpholine to **11-H** ($0.49 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$), and K_1 for the same reaction is also higher for **15-H** ($7.76 \times 10^4 \text{ dm}^3 \text{ mol}^{-1}$) than for **11-H**, which is $\sim 1.9 \times 10^{-8} \text{ dm}^3 \text{ mol}^{-1}$. The inverse correlation be-

Fig. 6. Brønsted Plot for the reaction of **7** with primary amines.



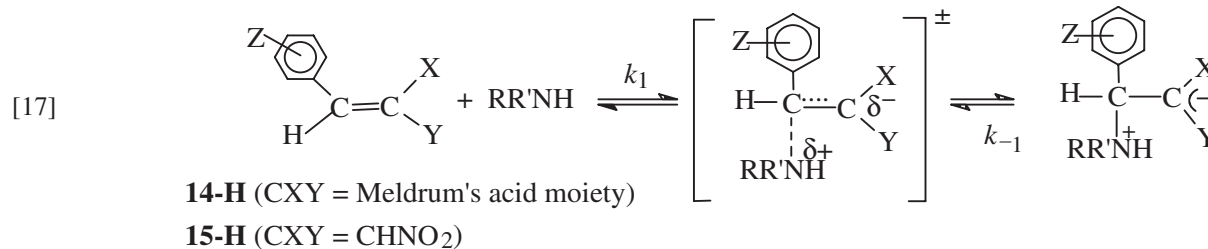
tween β_{nuc} and the reactivity of electrophilic olefins (PhCH=CXY) appears to be quite general and has been observed before (20).

Conclusions

- (1) In the reactions of **7** with the more basic amines, namely, H₂NCH₂CONH₂, MeOCH₂CH₂NH₂, and *n*-BuNH₂, no base catalysis is observed; thus, implying a rate-limiting k_1 step because of the strong electronic push from the nitrogen lone pair in the product leading to the stabilization of the transition state resulting from the developing product resonance. For the less basic amine, H₂NCH₂CN, general base catalysis is observed as the electronic push is not so prominent here.
- (2) The k_1 values for **6-SMe-H**-RNH₂ reactions are lower than those for the **7**-RNH₂ reactions, suggesting that a strong π -donation by the phenyl group reduces the reactivity of **6-SMe-H**.

Experimental section

Compound **7** was synthesized by following the literature method (20). DMSO was refluxed over CaH₂ and distilled under vacuum. Reagent grade amines were purchased from Aldrich chemicals (USA). The solid amines were recrystallized from a water–ethanol solution, and the liquids were distilled over CaH₂ before use.



Synthesis of α -isobutyl- α -(*n*-butylamino)methylene Meldrum's acid (6)

Compound **7** was prepared analogous to the procedure reported for the synthesis of 2,2-dimethyl-5-[piperidino(*p*-methoxyphenyl)methylene-1,3-dioxane-4,6-dione (**21**). CaCl₂-protected MeCN solution (15 mL) containing 1 mmol of each of **7** and *n*-butylamine was stirred for 48 h at room temperature. The solvent was evaporated, and the remaining solid was recrystallized from EtOH to give α -isobutyl- α -(*n*-butylamino)methylene Meldrum's acid in 35% yield. ¹H NMR (300 MHz, CDCl₃, ppm) δ : 1.00 (2Me of *i*-Bu), 1.02 (Me), 1.24 (CH₂), 1.41 (CH₂), 1.67 (2Me of Meldrum's acid moiety), 2.04 (CH₂ of *i*-Bu), 2.58 (NH), 2.68 (CH of *i*-Bu), 3.45 (CH₂ α - to NH). ES-MS *m/z*: 284 (MH⁺), 241 (MH⁺ - CMe₂), 226 (MH⁺ - OCMe₂), 197 (MH⁺ - HCMe₂-CH₃(CH₂)₂), 171 (MH⁺ - *i*-BuN-CMe₂), 114 (M - MA-CH₂-CH₂, MA is Meldrum's acid moiety).

Kinetics and pH measurements

Details of the kinetic and pH measurements are reported elsewhere (2, 4). Most reactions were followed by monitoring the disappearance of the substrates around 330 nm using a Hewlett-Packard 8453 Agilent UV-vis spectrophotometer. The pH in DMSO-H₂O (50:50, *v/v*) at an ionic strength of 0.50 mol dm⁻³ KCl at 20 °C was determined by a digital pH-meter (Systronics-335, India) equipped with a glass electrode and a reference electrode calibrated with standard aq. buffers in DMSO-H₂O (50:50, *v/v*) before use. Stock solutions of the substrates were prepared in anhyd. acetonitrile. The pseudo-first-order rate constants (*k*_{obs}, s⁻¹) were obtained by fitting the kinetic traces with a suitable computer-fit program and the results were within an error limit of $\pm 5\%$.

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