Kinetic Study on Michael-type Reactions of 1-Phenyl-2-propyn-1-one with Alicyclic Secondary Amines: Effect of Medium on Reactivity and Mechanism

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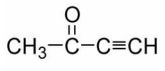
Second-order rate constants (k_N) have been measured for Michael-type addition reactions of a series of alicyclic secondary amines to 1-phenyl-2-propyn-1-one (**2**) in MeCN at 25.0 ± 0.1 °C. All the amines studied are less reactive in MeCN than in H_2O although they are more basic in the aprotic solvent by 7-9 pK_a units. The Brønsted-type plot is linear with β_{nuc} = 0.40, which is slightly larger than that reported previously for the corresponding reactions in H_2O (β_{nuc} = 0.27). Product analysis has shown that only *E*-isomer is produced. Kinetic isotope effect is absent for the reactions of **2** with morpholine and deuterated morpholine (*i.e.*, k^H/k^D = 1.0). Thus, the reaction has been concluded to proceed through a stepwise mechanism, in which proton transfer occurs after the rate-determining step. The reaction has been suggested to proceed through a tighter transition state in MeCN than in H_2O on the basis of the larger β_{nuc} in the aprotic solvent. The nature of the transition state has been proposed to be responsible for the decreased reactivity in the aprotic solvent.

Key Words : Michael-type reaction, Concerted mechanism, Stepwise mechanism, Brønsted-type plot, Medium effect

Introduction

Michael-type addition reactions of amines to carbon-carbon double bonds conjugated with a strong electron withdrawing group (EWG) have been intensively investigated due to the interests in reaction mechanisms as well as in synthetic applications. These reactions have been reported to proceed through either a concerted or a stepwise mechanism.[1-4] The corresponding reactions of carbon-carbon triple bonds conjugated with a strong EWG have also been studied widely.[5-12] However, most studies have been focused on the stereochemistry of the reaction products (*e.g.*, *Z*- or *E*-isomer) due to synthetic interests.[5-8] Only a few mechanistic studies are available.[9-12] Accordingly, the mechanism has not been fully understood.

We initiated a systematic study for Michael-type addition reactions of a series of aliphatic primary amines to activated acetylene derivatives such as 3-butyn-2-one (**1**)[9] and 1-phenyl-2-propyn-1-one (**2**).[10] The reactions were reported to proceed through an addition intermediate with its formation being the rate-determining step (RDS).[9,10] On the other hand, we have shown that the reactions of **1** with substituted anilines proceed through specific acid catalysis and the catalytic effect is remarkable for the reaction with weakly basic aniline (*e.g.*, 4-cyanoaniline).[11] The reactions of **2** with a series of alicyclic secondary amines were also performed in H_2O to investigate the effect of amine nature on reactivity and reaction mechanism.[12] We found that secondary amines are more reactive than isobasic primary amines, but the nature of amines does not influence the reaction mechanism.[12]



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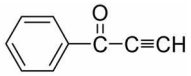

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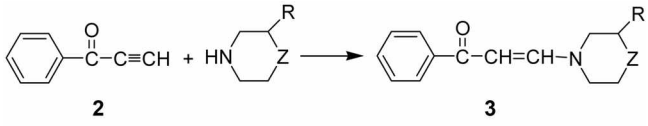


2 **3**

R = H or CH_3

Z = CH_2, NH, NCH_2CH_2OH, O, NCHO, NH_2^+

Scheme 1

Our study has been extended to the reactions of **2** with a series of alicyclic secondary amines in MeCN (Scheme 1). The kinetic data obtained in the current study have been compared with those reported previously for the corresponding reactions performed in H_2O to investigate the effect of medium on reactivity and reaction mechanism.

Results

All reactions in the current study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation, $\ln (A_\infty - A_t) = -k_{obsd}t + C$. The correlation coefficients were usually higher than 0.9995. The k_{obsd} values and reaction conditions are summarized in Table 1. The plots of k_{obsd} *vs.* amine concentrations were linear passing through the origin, indicating that general base catalysis by a second amine molecule is absent. Thus, the rate equation is given by eq. (1).

$$\text{Rate} = k_{obsd}[\text{substrate}], \text{ where } k_{obsd} = k_N[\text{amine}] \quad (1)$$

Five different concentrations of amines were used to determine the second-order rate constants (k_N) from the slope of the linear plots of k_{obsd} *vs.* amine concentrations. It is estimated from the replicate runs that the uncertainty in rate constants is less than 3%. The k_N values obtained in this way

Table 1. Summary of Kinetic Results for Michael-type Reactions of 1-Phenyl-2-propyn-1-one (**2**) with Alicyclic Secondary Amines in MeCN at 25.0 ± 0.1 °C

Entry	[amine]/mM	k_{obsd}/s^{-1}	n[a]
1 piperidine	10.2-50.8	0.338-1.55	5
2 3-methylpiperidine	10.0-50.0	0.277-1.33	5
3 piperazine	10.2-50.8	0.307-1.57	5
4 1-(2-hydroxyethyl)piperazine	10.1-50.3	0.0898-0.445	5
5 1-formylpiperazine	7.92-35.2	0.0447-0.200	10
6 morpholine	4.98-22.7	0.0106-0.0521	10

[a]Number of runs.

Table 2. Summary of Second-order Rate Constants (k_N) for Michael-type Reactions of 1-Phenyl-2-propyn-1-one (**2**) with Alicyclic Secondary Amines in MeCN and in H_2O (parentheses) at 25.0 ± 0.1 °C

	Amine	pK_a		k_N / M^{-1}s^{-1}	
1	piperidine	18.8[a]	(11.22)[b]	29.9	(41.9)[d]
2	3-methylpiperidine	18.6	(11.07)[b]	26.3	(-)
3	piperazine	18.2[a]	(9.82)[b]	31.3	(44.0)[d]
4	1-(2-hydroxyethyl)piperazine	17.6[a]	(9.38)[c]	8.81	(20.8)[d]
5	1-formylpiperazine	17.0[a]	(7.98)[c]	5.82	(8.67)[d]
6	morpholine	16.0[a]	(8.36)[b]	2.27	(11.5)[d]
7	piperazinium ion	-	(5.68)[b]	-	(2.21)[d]

[a]pK_a in MeCN taken from ref. 13a. [b]pK_a in H_2O taken from ref. 13b. [c]Data taken from ref. 13c. [d]Rate constants in H_2O taken from ref. 12.

are summarized in Table 2 together with the data reported previously for the corresponding reactions performed in H_2O for comparison purpose.

Discussion

Effect of Amine Basicity on Reactivity and Reaction Mechanism. As shown in Table 2, the second-order rate constant (k_N) for the reactions of 1-phenyl-2-propyn-1-one (**2**) in MeCN decreases as the basicity of amines decreases, i.e., k_N decreases from 29.9 M^{-1}s^{-1} to 8.81 and 2.27 M^{-1}s^{-1} as the pK_a of the conjugate acid of amines decreases from 18.8 to 17.6 and 16.0, respectively. A similar result is shown for the corresponding reactions performed in H_2O. The effect of amine basicity on reactivity is illustrated in Figure 1A for the reactions in MeCN. The Brønsted-type plot exhibits a good linear correlation with β_{nuc} = 0.40, when k_N and pK_a are statistically corrected using p and q (*i.e.*, p = 2 and q = 1 except q = 2 for piperazine).[14] A similar result is demonstrated in Figure 1B for the reactions performed in H_2O, although the slope of the linear Brønsted-type plot (β_{nuc} = 0.27) is slightly smaller for the reactions in H_2O than for those in MeCN.

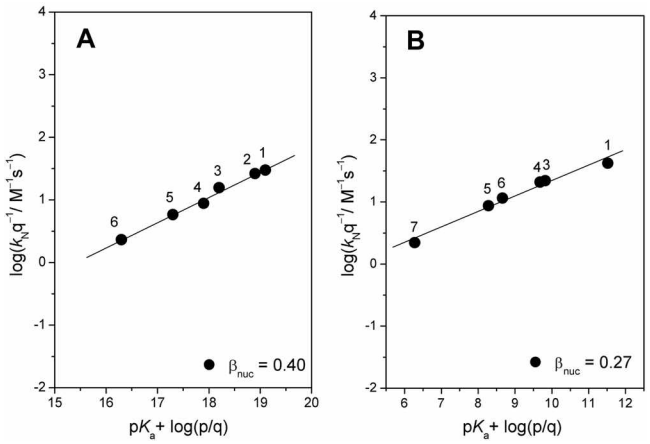


Figure 1. Brønsted-type plots for Michael-type reactions of 1-phenyl-2-propyn-1-one (**2**) with alicyclic secondary amines in MeCN (**A**) and in H_2O (**B**) at 25.0 ± 0.1 °C. The identity of the points is given in Table 2.

The magnitude of β_{nuc} values represents a relative degree of bond formation between the nucleophile and electrophilic center and/or a measure of reaction mechanism.[15] For example, β_{nuc} has been reported to be 0.8 ± 0.1 for aminolysis of esters which proceeds through a zwitterionic tetrahedral intermediate with its breakdown to products being the rate-determining step (RDS), while β_{nuc} = 0.2-0.3 for aminolysis which proceeds through rate-determining formation of an intermediate.[16-19] On the other hand, β_{nuc} has been reported to be 0.5 ± 0.1 for aminolysis of esters which proceeds through a concerted mechanism.[16-19]

Lee and his coworkers have recently reported that additions of anilines to an activated carbon-carbon double bond (*e.g.*, β-stilbenes) in MeCN proceed through a concerted mechanism with a 4-membered cyclic transition state (TS). One of the evidence provided is that β_{nuc} = 0.11-0.34.[3a] Similarly, addition reactions of benzylamines to benzylidene-3,5-heptadione have been proposed to proceed through a cyclic TS on the basis of the fact that β_{nuc} = 0.23.[3c]

On the contrary, Bernasconi *et al.* have concluded that additions of primary amines to 1,2,3,4-tetrachloro-6-phenylfulvene proceed through a stepwise mechanism based on the fact that β_{nuc} = 0.25.[2e] Similarly, β_{nuc} has been reported to be 0.26 for addition reactions of primary amines to benzylidene Meldrum's acid, which have been proposed to proceed through an intermediate.[2f] Thus, the β_{nuc} value of 0.40 obtained in the present reactions appears to be insufficient to determine whether the reaction proceed through a concerted or a stepwise mechanism. Clearly, more conclusive evidence is necessary to determine the reaction mechanism.

To get additional information on the reaction mechanism, product analysis has been performed through ^{1}H NMR spectroscopy. The current reactions may result in either an *E*- or a *Z*-isomer. We found that the coupling constant J between the two hydrogens in the –CH=CH– bond of product **3** is 12.6 Hz, a typical coupling constant for an *E*-isomer.

The fact that only the *E*-isomer is obtained suggests that the reaction may proceed through a 4-membered cyclic TS (*e.g.*, TS_1 for a concerted mechanism or TS_2 for a stepwise mechanism in which proton transfer from the nitrogen atom of the aminium moiety to the negatively charged carbon atom occurs at the RDS). Accordingly, one might expect a large primary kinetic isotope effect (KIE) if the reactions

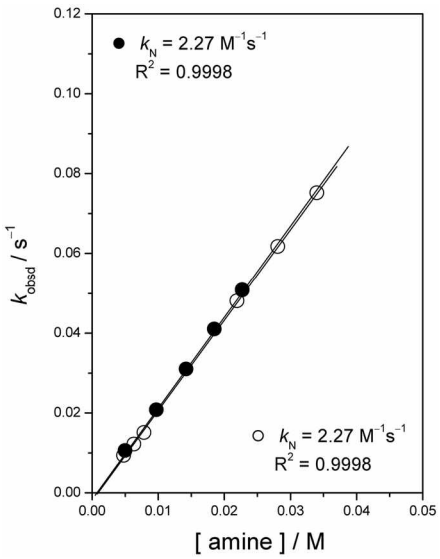
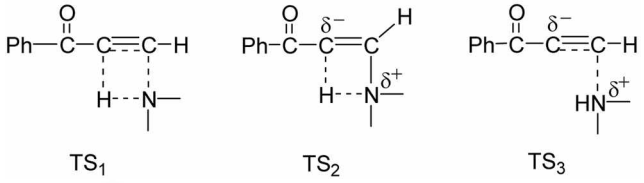


Figure 2. Plots of k_{obsd} *vs.* [amine] for the reaction of **2** with morpholine (●) and deuterated morpholine (○) in MeCN at 25.0 ± 0.1 °C.

proceed through TS_1 or TS_2, in which proton transfer is partially advanced in the RDS.



We performed the reaction of **2** with *N*-deuterated morpholine in MeCN at 25.0 ± 0.1 °C. It has been found that the KIE is absent (see Figure 2), indicating that the reaction does not proceed through TS_1 or TS_2. Thus, one can conclude that the reaction proceeds through a stepwise mechanism with TS_3, in which proton transfer does not occur at all in the RDS.

The above argument can be further supported by the fact that β_{nuc} = 0.40, an upper limit β_{nuc} value for reactions proceeding through a stepwise mechanism with rate-determining addition of amines to an unsaturated bond (*e.g.*, C=C or C=O bond). In fact, Bernasconi *et al.* have reported that β_{nuc} = 0.22-0.32 for addition of amines to benzylidene Meldrum's acids[2a,2f] and 1,2,3,4-tetrachloro-6-phenylfulvene.[2e] A similar β_{nuc} value (*e.g.*, β_{nuc} = 0.2-0.3) has often been reported for aminolysis of various esters, in which the RDS is the attack of amines on the C=O bond to form an addition intermediate.[16-19]

Effect of Medium on Reactivity and Transition-State Structure. It is well known that reactivity of anionic nucleophiles increases greatly on changing reaction medium from H_2O to a dipolar aprotic solvent such as DMSO or MeCN. In fact, the reactivity of OH^- toward 4-nitrophenyl acetate has been reported to increase up to 10^6 times on changing the medium from H_2O to 1 M H_2O in DMSO.[20] In contrast, we have shown that reactivity of neutral amines toward esters increases only slightly on changing the medium from H_2O to DMSO or MeCN.[21]

As shown in Table 2, all the amines are less reactive in MeCN than in H_2O, although they are more basic in the aprotic solvent by 7-9 pK_a units.[13] Clearly, the basicity of amines cannot account for the decrease in reactivity of these amines. One might then attribute the decreased reactivity of the amines to the nature of the TS structure. In the preceding section, TS_3 was proposed as the TS structure in the current reactions on the basis of the experimental results: (1) β_{nuc} = 0.40, (2) the enaminone **3** obtained is only the *E*-isomer, and (3) KIE is absent. The partially charged TS_3 can be stabilized in protic solvents through H-bonding interaction, but it would be destabilized in an aprotic solvent such as MeCN due to the repulsion between the partial negative charge in TS_3 and the negative dipole end of MeCN. Such destabilization of TS_3 might be one possible reason why the reactivity of the amines toward **2** decreases on changing the medium from H_2O to MeCN.

We have recently suggested that the addition reaction of amines to **2** in H_2O proceeds through TS_3.[12] The kinetic data for the current reactions in MeCN also support TS_3. Thus, the medium change from H_2O to MeCN does not alter the mechanism of the current Michael-type reactions. However, we found that the β_{nuc} value for the reactions of **2** with amines increases from 0.27 to 0.40 on changing the medium from H_2O to MeCN, indicating that the reactions proceed through a tighter TS in MeCN than in H_2O.

Conclusions

The present study has allowed us to conclude the following: (1) All the amines in this study are less reactive in MeCN than in H_2O, although they are 7-9 pK_a units more basic in the aprotic solvent. (2) Kinetic isotope effect is absent for the reaction of **2** with morpholine and deuterated morpholine (*i.e.*, k^H/k^D = 1.0), indicating that the reaction proceeds through a stepwise mechanism in which the proton transfer occurs after the RDS. (3) The Brønsted-type plots are linear with β_{nuc} = 0.40 in MeCN and β_{nuc} = 0.27 in H_2O, implying that the TS is slightly tighter in the aprotic solvent. (4) The nature of the TS contributes to the decreased reactivity of amines in the aprotic solvent.

Experimental Section

Materials. 1-Phenyl-2-propyn-1-one (**2**) was readily prepared from oxidation of 1-phenyl-2-propyn-1-ol,[22] which was obtained from the reaction of benzaldehyde with ethylmagnesium bromide in dried diethyl ether as reported in the literature.[23] The purity of **2** was checked by means of the melting point and ^1H NMR spectra. MeCN, amines and other chemicals employed were of the highest quality available.

Kinetics. The kinetic studies were performed using a UV-vis spectrophotometer equipped with a constant-temperature circulating bath. The reactions were followed by monitoring

the appearance of the enaminone **3** at a fixed wavelength corresponding to the maximum absorption. Typically, the reaction was initiated by adding 5 μL of *ca.* 0.02 M substrate stock solution in CH_3CN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and the amine nucleophile. All reactions were carried out under pseudo-first-order conditions in which the amine concentration was at least 20 times greater than that of **2**. The amine stock solution of *ca.* 0.2 M was prepared in a 25.0 mL volumetric flask under nitrogen. All transfers of solutions were carried out by means of gastight syringes.

Product analysis. The enaminone **3** was identified to be *E*-isomers only from its ^{1}H NMR spectrum (J = 12.6 Hz).

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