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Kinetics and Mechanism of Michael-type Reactions of Ethyl Propiolate with Alicyclic Secondary Amines in H_2O and MeCN: Solvent Effect on Reactivity and Transition-State Structure

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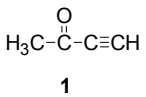
The amines studied in this study are less reactive toward ethyl propiolate (**3**) in MeCN than in H_2O although they are 7 to 9 pK_a units more basic in the aprotic solvent. The reactivity of morpholine and deuterated morpholine toward **3** is found to be identical, indicating that proton transfer occurs after rate-determining step (RDS). The fact that kinetic isotope effect is absent excludes a stepwise mechanism in which proton transfer occurs in RDS as well as a concerted mechanism in which nucleophilic attack and proton transfer occur concertedly through a 4-membered cyclic transition state (TS). Thus, the reactions have been concluded to proceed through a stepwise mechanism in which proton transfer occurs after RDS. Brønsted-type plots are linear with small β_{nuc} values, i.e., β_{nuc} = 0.29 in H_2O and β_{nuc} = 0.51 in MeCN, indicating that bond formation is not advanced significantly in RDS. The small β_{nuc} value also supports the conclusion drawn from the study of kinetic isotope effect.

Key Words: Ethyl propiolate, Michael-type reaction, Kinetic isotope effect, Rate-determining step, Brønsted-type plot

Introduction

Reactions of electron deficient alkynes have been intensively investigated due to synthetic interests.[1-8] It is well known that alkynes conjugated with an electron withdrawing group (EWG) such as alkynones and acetylenic esters undergo Michael-type reactions with various nucleophiles.[1-8] 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]

We performed Michael-type reactions of activated acetylene derivatives such as 3-butyn-2-one (**1**)[9] and 1-(X-substituted phenyl)-2-propyn-1-ones (**2**)[10] with a series of primary amines to investigate reaction mechanism. The reactions were reported to proceed through a stepwise mechanism with rate-determining nucleophilic attack on the electrophilic carbon atom followed by fast proton transfer.[9,10] In contrast, the reactions of **1** with substituted anilines were reported to proceed through specific acid catalysis and the catalytic effect is remarkable for the reaction with weakly basic aniline such as 4-cyanoaniline.[11]



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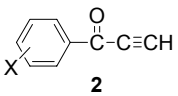

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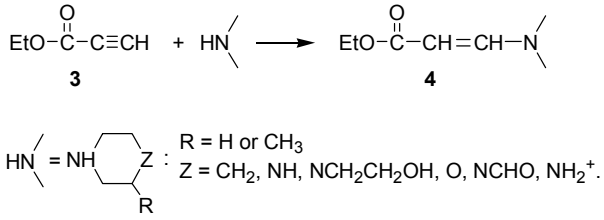
Our study has been extended to Michael-type reactions of ethyl propiolate (**3**) with a series of alicyclic secondary amines in H_2O and MeCN (Scheme 1). We wish to report the reaction mechanism and the effect medium on reactivity and transition-state structures.



Scheme 1

Results and Discussion

^{1}H NMR spectra revealed that product **4** formed from the reactions of ethyl propiolate (**3**) with alicyclic secondary amines is only the *E*-isomer (i.e., $J_{CH=CH}$ = 13.5 Hz). The kinetic study was performed under pseudo-first-order conditions with the concentration of amines in excess over the substrate concentration. All reactions obeyed first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were calculated from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. Plots of k_{obsd} *vs.* [amine] were linear passing through the origin for reactions in H_2O and MeCN, indicating that general base catalysis by a second amine molecule is absent. Thus, the rate law is given as eq. (1) and the second-order rate constants (k_N) were calculated from the slope of the linear plots. It is estimated from replicate runs that the uncertainty in the rate constants is less than ±3%.

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

Effect of Changing Solvent from H_2O to MeCN on Reactivity of Amines. Reactivity of anionic nucleophiles has been reported to increase significantly upon changing solvent from H_2O to dipolar aprotic solvents (e.g., DMSO and MeCN). This is

Table 1. Summary of Second-Order Rate Constants for Reactions of Ethyl Propiolate (**3**) with Alicyclic Secondary Amines in H_2O and MeCN at 25.0 ± 0.1 °C

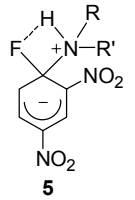
	amine	H_2O		MeCN	
		pK_a	k_N / $M^{-1}s^{-1}$	pK_a	k_N / $M^{-1}s^{-1}$
1	piperidine	11.22[a]	1.24	18.8[c]	0.902
2	3-methyl-piperidine	11.07[a]	1.43	18.6[d]	0.837
3	piperazine	9.82[a]	0.935	18.5[c]	0.783
4	1-(2-hydroxyethyl)-piperazine	9.38[b]	0.399	17.6[c]	0.207
5	morpholine	8.36[a]	0.245	16.6[e]	0.0748
6	piperzinium ion	5.68[a]	0.0386	-	-

[a,b,c,d,e] pK_a from ref. 12a, b, c, d, e, in turn.

because anions are strongly destabilized due to repulsion between anions and the negative dipole end of dipolar aprotic solvents.

However, the rate of reactions between neutral molecules is dependent on reaction types. As shown in Table 1, all amines are less reactive in MeCN than in H_2O (e.g., morpholine is *ca*. 3-fold less reactive in MeCN than in H_2O), although the amines are more basic in the aprotic solvent by 7 - 9 pK_a units.[12a-e] Similarly, alicyclic secondary amines have been reported to exhibit decreased reactivity in reactions with carboxylic esters upon changing the medium from H_2O to MeCN.[13a,b] In contrast, we have recently shown that S_NAr reaction of 1-fluoro-2,4-dinitrobenzene (DNFB) with piperazine exhibits *ca*. 72 times higher reactivity in MeCN than in H_2O.[13c]

Reaction mechanism is an important factor to account for the contrasting medium effects on reactivity. We have reported that reactions of DNFB with alicyclic secondary amines proceed through a Meisenheimer complex (**5**), in which the positive charge is dispersed through the 4-membered H-bonding structure while the negative charge is delocalized on the two NO_2 groups through resonance interaction. Destabilization of such charge dispersed Meisenheimer complex would not be significant in the aprotic solvent. Consequently, the enhanced amine basicity in the aprotic solvent outweighs destabilization of the charge dispersed Meisenheimer complex, which accounts for the result that amines are more reactive in MeCN than in H_2O.



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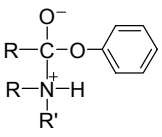
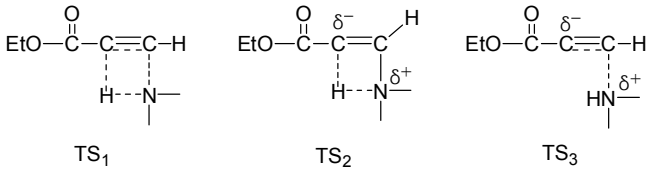


6

Aminolysis of carboxylic esters has generally been understood to proceed through a zwitterionic tetrahedral intermediate (**6**), in which the negative and positive charges are mainly localized on the O and N atom, respectively. Water molecules can stabilize such charge-localized species through H-bonding interaction. However, H-bonding by MeCN is absent. Furthermore, there would be strong repulsions between the negative charge in **6** and the negative dipole end of MeCN. This idea accounts for the fact that amines are less reactive in MeCN, although they are much more basic in the aprotic solvent.

The fact that the amines used in this study are less reactive in MeCN toward **3** is an important clue to deduce the reaction mechanism including TS structures. The mechanism will be discussed in the following section.

Reaction Mechanism and Solvent Effect on TS Structure. The reactions of **3** with alicyclic secondary amines would proceed through a concerted mechanism with TS_1 or through a stepwise mechanism with TS_2 or TS_3 depending on the rate-determining step (RDS). One might suggest that the reaction would proceed through TS_1 on the basis of the fact that only the *E*-isomer is produced. In fact, such a 4-membered cyclic TS structure was reported previously for Michael-type additions of amines to activated C=C double bonds.[14]



TS_1 TS_2 TS_3

Since charge separation in TS_1 is negligible, TS_1 would not experience strong desolvation upon the medium change from H_2O to MeCN. Accordingly, if the current reaction proceeds through a concerted mechanism with TS_1, one might expect that amines are more reactive in the aprotic solvent due to the enhanced amine basicity. However, as shown in Table 1, amines are less reactive in MeCN, indicating that the reaction would not proceed through TS_1. In contrast, charge separation is advanced partially in TS_2 and TS_3. Thus, one might expect that TS_2 and TS_3 would be destabilized significantly in the aprotic solvent. The fact that amines are less reactive in MeCN implies that the reaction proceeds through a stepwise mechanism with charge localized TS_2 or TS_3.

To get further information on the TS structure of the current reaction, Brønsted-type plots have been constructed in Figures 1A and 1B using the kinetic data in Table 1. The Brønsted- type

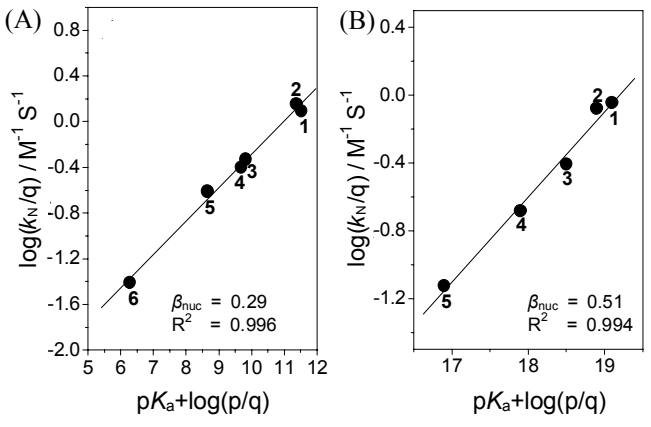


Figure 1. Brønsted-type plots for reactions of ethyl propiolate (3) with alicyclic secondary amines in H_2O (A) and MeCN (B) at 25.0 ± 0.1 °C. The identity of numbers is given in Table 1.

plots are linear with $\beta_{nuc} = 0.29$ in H_2O and $\beta_{nuc} = 0.51$ in MeCN when k_N and pK_a values are statistically corrected using p and q (i.e., $p = 2$ except $p = 4$ for piperazinium ion and $q = 1$ except $q = 2$ for piperazine).[15] The reactions carried out in MeCN result in a little larger β_{nuc} value than those in H_2O. This is consistent with the report that electronic effect is more sensitive in less polar solvents, e.g., $\rho = 1.00$ in H_2O but $\rho = 2.5$ in MeCN for dissociation of benzoic acids.[16]

Magnitude of β_{nuc} values represents a relative degree of bond formation between the nucleophile and electrophilic center in the transition state. In TS_2, bond formation is fully advanced. Accordingly, if the current reaction proceeds through TS_2, one might expect a large β_{nuc} value. The β_{nuc} value of 0.29 in H_2O is very small, indicating that bond formation is little advanced in the RDS. Thus, one can exclude TS_2 and conclude that the reactions of **3** with alicyclic secondary amines proceed through a stepwise mechanism with TS_3 on the basis of the β_{nuc} value.

The above argument can be further supported by the β_{nuc} value of 0.29 in H_2O, which is typical of reactions reported to proceed through a stepwise mechanism with addition of amines to an unsaturated bond (e.g., C = C or C = O bond) being the RDS. In fact, Bernasconi *et al*. have reported that β_{nuc} = 0.22 ~ 0.32 for addition reactions of amines to benzylidene Meldrum's acids[2a, 2f] and 1,2,3,4-tetrachloro-6-phenylfulvene.[2e] Similarly, a β_{nuc} value of 0.2 ~ 0.3 has been reported for aminolysis of various esters, in which formation of a zwitterionic tetrahedral intermediate is the RDS.[16-19] Although the β_{nuc} value of 0.51 for the reactions in MeCN may represent a concerted mechanism,[20] we propose the reaction does not proceed through TS_1 on the basis of the fact that: (1) The amines are less reactive in MeCN than in H_2O. (2) Hammett ρ values were reported to be larger in the aprotic solvent than in H_2O.[16]

To examine the above argument, reaction of **3** with deuterated morpholine has been performed in MeCN. One might expect primary kinetic isotope effect (KIE) if the reaction proceeds through TS_1 or TS_2, since the proton transfer from the nitrogen to the carbon atom is involved in RDS in $TS_1$and TS_2. On the contrary, KIE would be absent if the reaction proceeds through TS_3 since the proton transfer occurs after RDS in TS_3. As shown in Figure 1, the reactivity of morpholine is identical to that of deuterated morpholine, indicating that the proton transfer occurs after RDS. Thus, one can conclude that the current reaction proceeds through TS_3 but not TS_1 or TS_2.

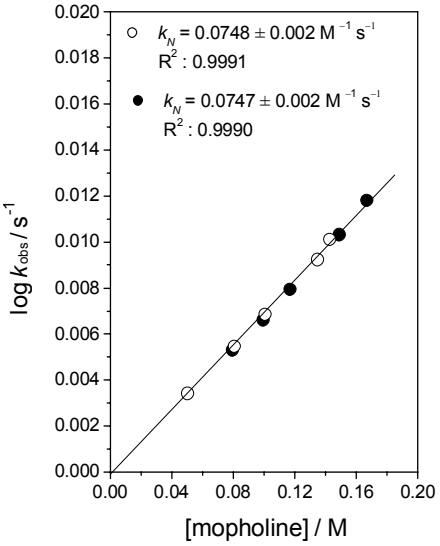


Figure 2. Plots showing absence of primary KIE for the reaction of 3 with morpholine (○) and deuterated morpholine (●) in MeCN at 25.0 ± 0.1 °C.

Conclusions

The current study has allowed us to conclude the following: (1) Reactions of **3** with alicyclic secondary amines yield only the *E*-isomer. (2) Amines are less reactive in MeCN than in H_2O toward **3**, although they are 7 to 9 pK_a units more basic in the aprotic solvent. This excludes TS_1, in which charge separation is little advanced. (3) The linear Brønsted-type plot with a β_{nuc} value of 0.29 suggests that the reaction proceeds through TS_3 but not through TS_2. (4) The fact that primary KIE is absent also excludes TS_1 and TS_2. (5) The current reactions proceed through a stepwise mechanism, in which proton transfer occurs after RDS (TS_3).

Experimental Section

Materials. All chemicals including ethyl propiolate and alicyclic secondary amines were of the highest quality available. MeCN was distilled over P_2O_5 and stored under nitrogen. Doubly glass-distilled water was further boiled to remove dissolved CO_2 and cooled under nitrogen just before use.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of product **4** at a fixed wavelength corresponding the maximum absorption (e.g., λ_{max} = 285 and 280 nm for the reaction of **3** with piperidine in H_2O and MeCN.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M ethyl propiolate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of the reaction medium and amine. The amine sock solution of *ca*. 0.2 M for the reactions in H_2O was prepared in 25.0 mL volumetric flask under nitrogen by adding 2 equiv of amine to 1 equiv of standardized HCl solution to obtain a self-buffered solution. Transfers of solutions were carried out by means of gas-tight syringes. All reactions were carried out under pseudo-first-order conditions in which amine concentrations were at least 30 times greater than the substrate concentration.

Product Analysis. Product **4** was identified to be the *E*-isomer from ^{1}H NMR spectra (e.g., $J_{-CH=CH-}$ = 13.5 Hz).

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