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Michael-type Reactions of 1-(X-substituted phenyl)-2-propyn-1-ones with Alicyclic Secondary Amines in MeCN and H_2O: Effect of Medium on Reactivity and Transition-State Structure

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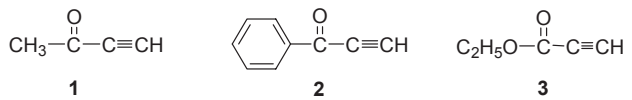
Second-order rate constants (k_N) have been measured spectrophotometrically for Michael-type reactions of 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) with a series of alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C. The k_N value increases as the incoming amine becomes more basic and the substituent X changes form an electron-donating group (EDG) to an electron-withdrawing group (EWG). The Brønsted-type plots are linear with β_{nuc} = 0.48 - 0.51. The Hammett plots for the reactions of **2a-f** exhibit poor correlations but the corresponding Yukawa-Tsuno plots result in much better linear correlations with ρ = 1.57 and r = 0.46 for the reactions with piperidine while ρ = 1.72 and r = 0.39 for those with morpholine. The amines employed in this study are less reactive in MeCN than in water for reactions with substrates possessing an EDG, although they are ca. 8 pK_a units more basic in the aprotic solvent. This indicates that the transition state (TS) is significantly more destabilized than the ground state (GS) in the aprotic solvent. It has been concluded that the reactions proceed through a stepwise mechanism with a partially charged TS, since such TS would be destabilized in the aprotic solvent due to the electronic repulsion between the negative-dipole end of MeCN and the negative charge of the TS. The fact that primary deuterium kinetic effect is absent supports a stepwise mechanism in which proton transfer occurs after the rate-determining step.

Key Words: Activated alkynes, Brønsted-type plot, Kinetic isotope effect, Yukawa-Tsuno plot, Transition-state structure.

Introduction

The term Michael reaction was given to nucleophilic addition of a carbanion to an activated alkene conjugated with an electron withdrawing group (EWG) such as CO, CN or NO_2.[1] Numerous studies have been performed to investigate reaction mechanisms.[2-6] However, the corresponding reactions of activated alkynes have much less been studied. Besides, most studies have been focused on the stereochemistry of reaction products (e.g., *E*- or *Z*-isomer) due to the interest in synthetic applications.[7-9] Thus, their mechanisms are not fully understood.

We have performed Michael-type reactions of activated alkynes such as 3-butyn-2-one (**1**) and 1-phenyl-2-propyn-1-one (**2**) with a series of primary amines in H_2O.[9,10] The reactions have been proposed to proceed through a stepwise mechanism, in which nucleophilic attack of the amine to the electrophilic carbon atom occurs in the rate-determining step (RDS).[9,10] In contrast, we have shown that reactions of **1** with substituted anilines proceed through specific acid catalysis and the catalytic effect increases as the pK_a of anilinium ion decreases.[11]



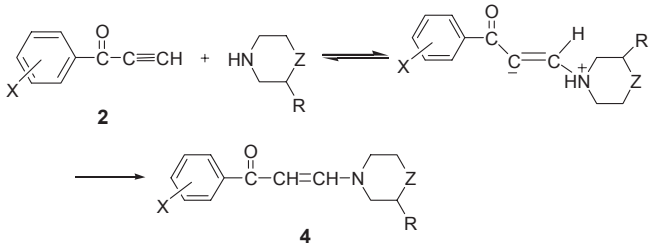
1 **2** **3**

Michael-type reactions of ethyl propiolate (**3**) with a series of alicyclic secondary amines have also been performed in H_2O and MeCN to investigate reaction mechanism.[12] The reactions in both solvents have been concluded to proceed through a stepwise mechanism with formation of an intermediate being the RDS, although the degree of bond formation at the transition state (TS) was suggested to be more advanced for the reaction in the aprotic solvent on the basis of the β_{nuc} values.[12]

Our study has been extended to the Michael-type reactions of 1-(X-substituted phenyl-2-proyn-1-ones (**2a-f**) with a series of alicyclic secondary amines in MeCN as shown in Scheme 1. The kinetic results have been compared with those obtained from the corresponding reactions performed in H_2O to investigate effect of solvent on reactivity and transition state (TS) structures.

Results and Discussion

Reactions of **2a-f** with the alicyclic secondary amines resulted in only the *E*-isomer. All reactions in this study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obsd}) were determined from the equation $\ln(A_\infty - A_t) = -k_{obsd}t + C$. The cor-



X = 4-MeO (**2a**), 4-Me (**2b**), H (**2c**), 4-Cl (**2d**), 4-CN (**2e**), 3-NO2 (**2f**).
R = H or Me; Z = CH_2, NH, NCH_2CH_2OH, NCHO, O.

Scheme 1

Table 1. Summary of second-order rate constants for Michael-type reactions of 1-(X-substituted phenyl)-2-propyn-1-ones **2a** (X = 4-MeO), **2c** (X = H), and **2d** (X = 4-Cl) with alicyclic secondary amines in MeCN at 25.0 ± 0.1 °C.

	Amine	pK_a[a]	k_N /$M^{-1}s^{-1}$		
			2a	**2c**[b]	**2d**
1	piperidine	18.8	7.22	33.0	75.4
2	3-methyl piperidine	18.6	5.82	26.3	55.1
3	piperazine	18.5	5.89	31.3	55.8
4	1-(2-hydroxyethyl) piperazine	17.6	1.84	8.81	14.3
5	morpholine	16.6	0.622 (0.654)[c]	2.67 (2.32)[c]	5.59 (5.79)[c]

[a]The pK_a data in MeCN were taken from ref. 12a. [b]The k_N values for the reactions of **2c** were taken from ref. 12b. [c]The k_N values for reactions with deuterated morpholine.

relation coefficients for the linear regressions were usually higher than 0.9995. The plots of k_{obsd} *vs*. amine concentration were linear and passed through the origin, indicating that general base catalysis by a second amine molecule is absent. Thus, the rate law is given by eq (1), in which [S] and [NH] represent the concentration of the substrate and amine, respectively. The second-order rate constants (k_N) were determined from the slope of the linear plots of k_{obsd} *vs*. [NH] and summarized in Tables 1 and 2. The uncertainty in the k_N values is estimated to be less than 3% from replicate runs.

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

Reaction mechanism. As shown in Table 1, the second-order rate constant (k_N) decreases as the amine basicity decreases, e.g., k_N for the reactions of 1-(4-methoxyphenyl)-2-propyn-1-one (**2a**) decreases from 7.22 $M^{-1}s^{-1}$ to 0.622 $M^{-1}s^{-1}$ as the pK_a of the conjugate acid of the amines decreases from 18.8 to 16.6. A similar reactivity trend is shown for the reactions of 1-phenyl-2-propyn-1-one (**2c**) and 1-(4-chlorophenyl)-2-propyn-1-one (**2d**) although the k_N value increases as the substrate changes from **2a** to **2c** and **2d** in turn.

The effect of amine basicity on reactivity is illustrated in Figure 1. The Brønsted-type plot for the reactions of **2a** with alicyclic secondary amines is linear with $\beta_{nuc} = 0.51$, when k_N and pK_a values are statistically corrected using p and q (i.e., $p = 2$ and $q = 1$ except $q = 2$ for piperazine).[14] The plots for the corresponding reactions of **2c** and **2d** are also linear with β_{nuc} value of 0.51 and 0.48, respectively, indicating that the current reactions proceed through a common mechanism.

The magnitude of β_{nuc} value has often been used as a measure of TS structures, since it represents the position of the TS along the reaction coordinate or a relative degree of bond formation between the nucleophile and electrophilic center.[15-21] A β_{nuc} value of 0.5 ± 0.1 is typical for reactions reported previously to proceed through a concerted mechanism.[16,17] On the other hand, β_{nuc} for a stepwise mechanism has often been reported to

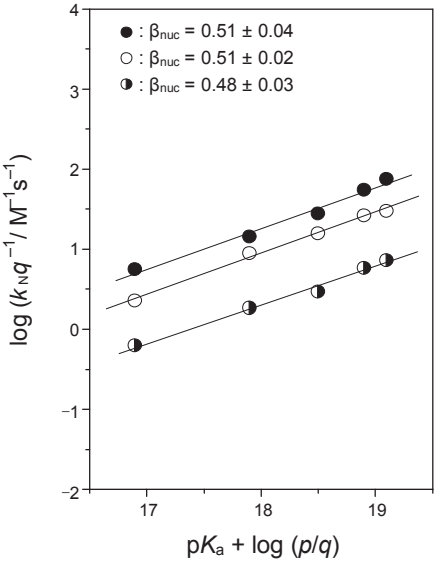
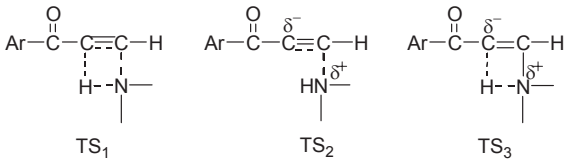


Figure 1. Brønsted-type plots for the Michael-type reactions of 1-(X-substituted phenyl)-propyn-1-ones, **2a** (X = 4-MeO, ◑), **2c** (X = H, ○), **2d** (X = 4-Cl, ●) with alicyclic secondary amines in MeCN 25.0 ± 0.1 °C. The identity of the points is given in Table 1.

be strongly dependent on the RDS, e.g., β_{nuc} decreases from 0.9 ± 0.2 to 0.3 ± 0.1 as the RDS changes from breakdown of an intermediate to its formation for aminolysis of carboxylic esters.[18-21]

One might expect that the current reactions proceed through a concerted mechanism with TS_1 as the transition state or through a stepwise pathway with TS_2 or TS_3 depending on the RDS. TS_1 shows that bond formation between the amine and the electrophilic center occurs simultaneously with proton transfer from the amine nucleophile to the substrate. One other hand, TS_2 is different from TS_3 in the timing of the proton transfer (i.e., the proton transfer occurs after the RDS in TS_2 but it is involved in the RDS in TS_3).



Since a β_{nuc} value of *ca*. 0.50 is typical for reactions reported previously to proceed through a concerted mechanism,[16,17] one might suggest that the reactions proceed through a concerted mechanism with a TS structure similar to TS_1. Such 4-membered cyclic TS has often been proposed for addition reactions of amines to activated C=C double bonds as well as aminolyses of esters and carbamates in MeCN.[5,22] Furthermore, the fact that only the *E*-isomer was formed also supports this mechanism.

If the current reactions proceed through TS_1 (or TS_3), in which proton transfer occurs in the RDS, one might expect primary kinetic isotope effect (KIE). To investigate deuterium KIE, the reactions of **2a**, **2c** and **2d** with deuterated morpholine have been performed. As shown in Table 1, the k_N values are slightly smaller for the reactions with morpholine than for those with deuterat-

Table 2. Summary of second-order rate constants for the Michael-type reactions of 1-(X-Substituted phenyl)-2-propyn-1-ones (**2a-f**) with piperidine and morpholine in MeCN and H_2O (in parentheses) at 25.0 ± 0.1 °C[a]

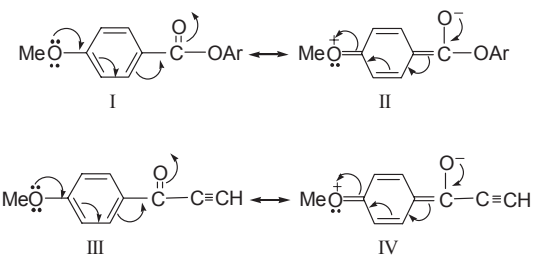
X	k_N / $M^{-1}s^{-1}$	
	piperidine	morpholine
2a, 4-MeO	7.22 (20.4)	0.622 (4.64)
2b, 4-Me	14.4 (31.4)	1.23 (8.59)
2c, H	33.0 (41.9)	2.67 (11.5)
2d, 4-Cl	75.4 (56.6)	5.59 (14.4)
2e, 4-CN	359 (121)	38.5 (31.4)
2f, 3-NO_2	438 (118)	34.8 (34.5)

[a]The k_N values determined in H_2O were taken from ref. 23.

ed morpholine (i.e., $k_N^H / k_N^D < 1$). The fact that primary deuterium KIE is absent indicates that the proton transfer occurs after the RDS. Thus, one can suggest that the current reactions proceed through TS_2 but not through TS_1 or TS_3, and the magnitude of β_{nuc} value alone is not sufficient to deduce reaction mechanism.

Hammett and Yukawa-Tsuno plots. To get further information on the TS structures, reactions of 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) with piperidine and morpholine, the most and least basic amines employed in this series in MeCN, respectively, have been performed. As shown in Table 2, the second-order rate constant for the reaction of **2a-f** with piperidine increases as the substituent X changes from an EDG to an EWG, e.g., k_N in MeCN increases from 7.22 $M^{-1}s^{-1}$ to 33.0 and 438 $M^{-1}s^{-1}$ as X varies from 4-MeO to H and 3-NO_2, respectively. A similar trend is shown for the corresponding reactions with morpholine although the k_N values are smaller for the reactions with the less basic amine.

The effect of substituent X on reactivity is illustrated in Figures 2A and 2B. The Hammett plots for the corresponding reactions in H_2O are also shown for comparison. As shown in Figures 2A and 2B, substrate **2a** deviates negatively from the linear Hammett plots for reactions with both piperidine and morpholine. Such negative deviation has been reported for aminolysis of 2,4-dinitrophenyl X-substituted benzoates[24a] and benzenesulfonates,[24b] and alkaline hydrolysis of 2,4-dinitrophenyl X-substituted benzoates[24c] and thionobenzoates.[24d] We have proposed that stabilization of the ground state (GS) through resonance interactions (e.g., I and II for aryl benzoates system) are responsible for the negative deviation.[24] Since such resonance structures are also possible for substrate **2a**, one might suggest that stabilization of the GS through resonance interactions III and IV is



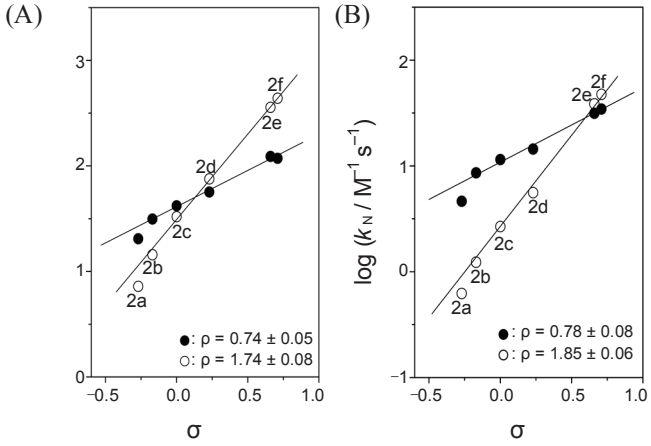


Figure 2. Hammett plots for the Michael-type reactions of 1-(X-substituted phenyl)-2-propyn-1-ones (**2a-f**) with piperidine (A) and morpholine (B) in H_2O (●) and MeCN (○) at 25.0 ± 0.1 °C. The identity of points is given in Table 2.

responsible for the negative deviation shown by **2a** in the linear Hammett plots

To further delineate the above argument, we have constructed the Yukawa-Tsuno plots in Figures 3A and 3B. The Yukawa-Tsuno equation (eq 2) has originally been derived to investigate solvolysis of benzylic systems. However, we have shown that it is highly effective to clarify ambiguities in reaction mechanism for aminolysis of aryl diphenylphosphinates[25a] and diphenylphosphinothioates,[25b] alkaline hydrolysis of aryl diphenylphosphinates[25c] as well as alkaline ethanolysis of aryl diphenylphosphinates.[25d] The *r* value in the Yukawa-Tsuno equation, eq. (2), represents the resonance demand of the reaction center or the extent of the resonance contribution, while the term ($\sigma^+ - \sigma^o$) represents the resonance substituent constant that measures the capacity for π-delocalization of a given π-electron donor substituent.[26]

$$\log (k_N^X / k_N^H) = \rho [\sigma^o + r(\sigma^+ - \sigma^o)] \quad (2)$$

As shown in Figure 3A, the Yukawa-Tsuno plots for the reactions of **2a-f** with piperidine exhibit excellent linear correlations, i.e., ρ = 1.57 and *r* = 0.46 in MeCN while ρ = 0.64 and *r* = 0.59 in H_2O. A similar result is shown in Figure 3B for the corresponding reactions with morpholine, i.e., ρ = 1.72 and *r* = 0.39 in MeCN while ρ = 0.62 and *r* = 0.83 in H_2O. The excellent linearity shown in the Yukawa-Tsuno plots clearly supports the preceding argument that the negative deviation shown by **2a** in the Hammett plots (Figures 2A and 2B) is caused by stabilization of the GS through the resonance interactions as modeled by III and IV.

Effect of medium on reactivity and TS structure. As shown in Figures 3A and 3B, the reactions in the aprotic solvent result in much larger ρ values than those in H_2O. This is consistent with the report that substituent effect becomes more sensitive in a less polar solvent, e.g., the ρ value for dissociation of substituted benzoic acids was defined to be 1.00 in H_2O but reported to be 2.05 ~ 2.4 in MeCN.[27]

Oh *et al*. have reported ρ = 0.62 for the Michael-type reactions

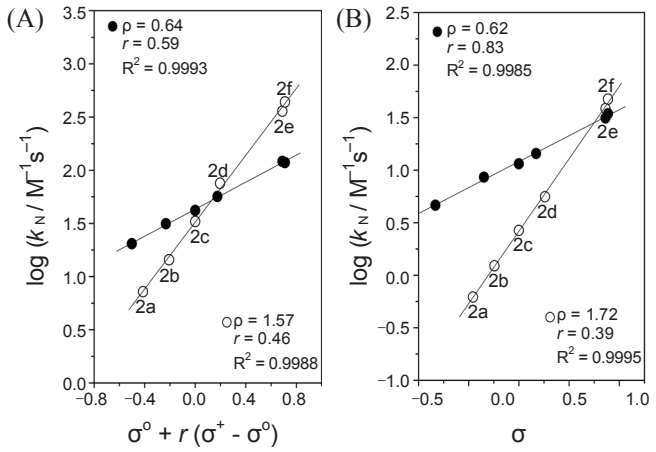


Figure 3. Yukawa-Tsuno plots for the Michael-type reactions of 1-(x-substituted phenyl)-2-propyn-1-ones (**2a-f**) with piperidine (A) and morpholine (B) in MeCN (○) and H_2O (●) at 25.0 ± 0.1 °C. The identity of points is given in Table 2

of benzylamine with β-cyanostilbenes in MeCN, which have been concluded to proceed through a concerted mechanism with a 4-membered cyclic TS similar to TS_1.[22] Thus, the large ρ values observed for the current reactions support the preceding argument that the reactions do not proceed through a concerted mechanism with TS_1.

It is demonstrated in Figure 3A that substrates possessing a strong EWG (e.g., **2e-f**) are more reactive in MeCN than in H_2O while others (e.g., **2a-c**) are less reactive in the aprotic solvent. The fact that **2a-c** are less reactive in MeCN is quite interesting since amines used in this study are ca. 8 pK_a units more basic in the aprotic solvent than in H_2O.[12,13]

It is well known that medium effect on reactivity is dependent on the type of reactants and TS structures.[28-30] Anionic nucleophiles would be stabilized in H_2O through H-bonding interaction. Since H-bonding is absent in aprotic solvents such as MeCN and DMSO, anions would be strongly destabilized in aprotic solvents due to strong repulsion between the anion and the negative dipole end of the aprotic solvents. In fact, reactions with anionic nucleophiles have been reported to result in rate enhancements up to 10^6 times upon changing medium from H_2O to aprotic solvents.[29] On the contrary, reactions between neutral species, which proceed through a partially charged TS, have been reported to exhibit a decrease in reactivity due to destabilization of the charged TS in aprotic solvents.[30]

As mentioned above, piperidine and morpholine are less reactive in MeCN than in H_2O in the reactions with substrates possessing an EDG although these amines are significantly more basic in MeCN. This is consistent with the preceding proposal that the current reactions proceed through TS_2, since such a charge separated TS would be stabilized in H_2O but destabilized in MeCN due to the electronic repulsion between the negative charge of TS_2 and the negative dipole end of MeCN.

Furthermore, the negative charge of TS_2 would be more significant for the reaction of substrates possessing a stronger EDG. Accordingly, one might expect that the electronic repulsion would be more significant for the reaction of substrates possessing a stronger EDG. This idea accounts for the fact that substrates possessing a strong EDG are significantly less reactive in the aprotic solvent than in H_2O.

Conclusions

The current study has allowed us to conclude the following for the Michael-type reactions of **2a-f** with alicyclic secondary amines: (1) The Brønsted-type plots are linear with a β_{nuc} value of 0.5 ± 0.2. (2) Absence of primary KIE indicates that the reactions proceed through a stepwise mechanism, in which proton transfer occurs after the RDS. (3) The Yukawa-Tsuno plots result in much better correlation coefficients than the Hammett plots with ρ = 1.57 ~ 1.72 and r = 0.39 ~ 0.46. (4) The reactions of amines with substrates possessing an EDG are slower in MeCN than in H_2O, although the amines are *ca*. 8 pK_a units more basic in the aprotic solvent. (5) Destabilization of TS in MeCN is responsible for the lower reactivity found in the aprotic solvent.

Experimental Section

Materials. 1-(X-substituted phenyl)-2-propyn-1-ones were prepared from oxidation of the respective 1-(X-substituted phenyl)-2-propyn-1-ols as reported previously.[31] 1-(X-substituted phenyl)-2-propyn-1-ols were synthesized from the reactions of X-substituted benzaldehydes with ethylmagnesium bromide in dried diethyl ether as reported in the literature.[32] Their purity was checked by means of melting points and ^{1}H NMR spectra. Other chemicals including alicyclic secondary amines and MeCN were of the highest quality available.

Kinetics. The kinetic study was performed using a UV-vis spectrophotometer for slow reactions ($t_{1/2}$ > 10 s) or a stopped-flow spectrophotometer for fast reactions ($t_{1/2} \leq$ 10 s) equipped with a constant temperature circulating bath. The reactions were followed by monitoring the appearance of enaminones **4a-f**.

Typically, the reaction was initiated by adding 5 μL of a 0.02 M substrate stock solution in MeCN by a 10 μL syringe to a 10 mm UV cell containing 2.50 mL of MeCN and amine. 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 20 times greater than the substrate concentration.

Product analysis. Enaminone **4c** was identified by means of Uv-vis and ^{1}H NMR spectrum. ^{1}H NMR study has shown that **4c** is only the *E*-isomer (e.g., $J_{-CH=CH-}$ = 12.6 Hz).

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