JOC Article

Kinetic and Mechanistic Studies of NEt_3-Catalyzed Intramolecular Aminolysis of Carbamate

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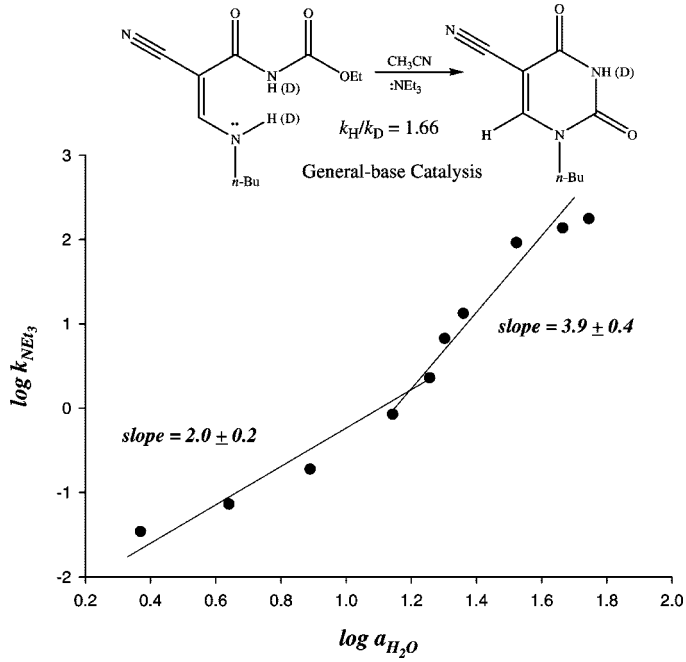

The mechanism of the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in acetonitrile or aqueous acetonitrile solutions is suggested to involve rate-determining collapse of $T^{\pm}$ through simultaneous H-abstraction and ethoxide expulsion of E2 process. The evidence for that includes the primary isotope effect of $k_H/k_D = 1.66$ in acetonitrile, general-base catalysis in aqueous buffer solutions, salt effect, and the proposed water-stabilized rate-determining transition states (TS1 and TS2) in the water-titration experiments.

Introduction

Modification of nucleosides or their organic bases sometimes shows useful biological activities due to inhibition of nucleic acid metabolism.[1] For instance, cancer cells can be killed by 5-fluorouracil,[2] which can be prepared from 5-cyanouracil.[3] We prepared analogues of 5-cyanouracil by a multicomponent reaction (MCR),[4] where we found that an amine as a base helps the intramolecular aminolysis of *Z*-**1**, forming 5-cyanouracils (Scheme 1). Hence, in this paper we try to explore the mechanism of this reaction by means of kinetic studies in acetonitrile with various water concentrations (water-titration experiments), investigation of base catalysis, kinetic isotope effect, and salt effect.

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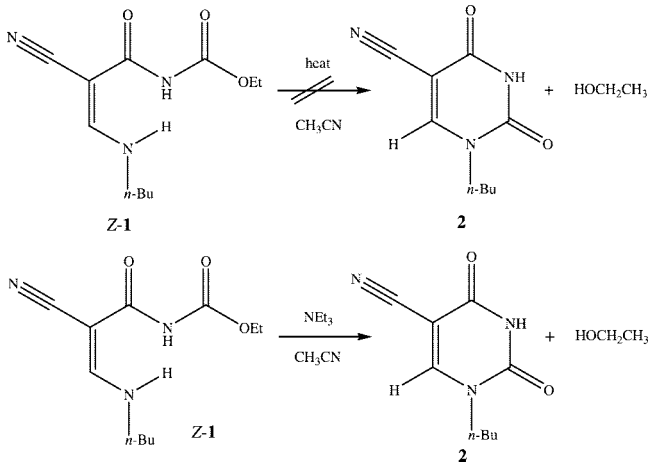
SCHEME 1



There are two important issues on the mechanisms of acyl-transfer reactions.[5] One is whether a tetrahedral addition intermediate ($T^{\pm}$ or T^{-}) is involved and the other is whether the rate-determining step involves formation of the tetrahedral addition intermediate or its collapse if the tetrahedral addition intermediate is involved.

For the aminolysis of carbamates, the $E1_{CB}$ mechanism[6] involving an isocyanate intermediate was proposed but it was questioned with an alternative stepwise mechanism involving the tetrahedral addition intermediate $T^{\pm}$.[7a] The stepwise mechanism for the aminolysis of carbamates[7] was usually confirmed by a change of the rate-determining step, implying that the tetrahedral addition intermediate $T^{\pm}$ is involved, and so were the stepwise mechanisms for the aminolysis of esters[8] and carbonates.[9] However, the aminolysis of carbamates, carbonates and their thio-analogues may be switched from a stepwise mechanism to a concerted mechanism,[7c,10] provided that the amine nucleophiles have high expulsive rates from $T^{\pm}$ and the substrates have a very good leaving group and π-donating nonleaving group.

In this paper, the substrate *Z*-**1** provides a good opportunity to study the mechanism for the NEt_3-catalyzed intramolecular aminolysis of carbamate. Since the mechanism for the aminolysis of carbamates in aprotic solvents was proposed to involve the rate-determining collapse of the tetrahedral addition intermediate $T^{\pm}$,[7a,b] the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** would be checked to see if it follows the similar mechanism in acetonitrile or aqueous acetonitrile solutions.

Results

It has been confirmed by ^1H NMR spectroscopy that NEt_3-catalyzed intramolecular aminolysis of carbamate *Z*-**1** completely produces **2** without any detectable byproduct,[4a] so a UV spectrophotometer was used to obtain the following data for kinetic studies of the aminolysis reaction. The intramolecular aminolysis of *Z*-**1** (5×10^{-5} M) in 0.1 M NEt_3 of acetonitrile solution was monitored by UV spectrophotometry for 21 h until *Z*-**1** was completely converted into **2** (Figure 1). The *Z*-**1** has a maximum UV absorption at 294 nm with molar absorptivity (ϵ) of 21380 M^{-1} cm^{-1}. The UV absorption at 294 nm kept decreasing as the intramolecular aminolysis was going. When the intramolecular aminolysis was complete, molar absorptivity (ϵ) of **2** at 294 nm was measured to be 6000 M^{-1} cm^{-1}, which is much smaller than that of *Z*-**1**. Hence, kinetic studies for the intramolecular aminolysis of *Z*-**1** were carried out in dried and excess NEt_3 of acetonitrile solution at 298 K by following the decreasing UV absorption at 294 nm with UV spectrophotometer. All of the kinetic curves showed first-order exponential decays, and the observed rate constants (k_{obs}) are shown in Table 1. According to eq 1, the second-order rate constant of k_{NEt3} was calculated to be 1.79×10^{-3} M^{-1} s^{-1} by correlation of the observed rate constants (k_{obs}) with [NEt_3].

$$\text{rate} = \frac{-\text{d}[Z\text{-}\mathbf{1}]}{\text{d}t} = k_{NEt3}[NEt_3][Z\text{-}\mathbf{1}] = k_{obs}[Z\text{-}\mathbf{1}] \qquad (1)$$

N-Deuterium *Z*-**1** was prepared by treating *Z*-**1** in dry CD_3CN with 3−4 drops of D_2O (Scheme 2). The reaction was monitored by proton NMR spectroscopy until the N−H resonance peaks at $\delta = 9.81$ and 7.74 disappeared and the resonance peak of vinyl hydrogen at $\delta = 7.32$ turned into a singlet from a doublet. To remove any residual water, the resulting solution of *N*-deuterium *Z*-**1** was dried by 4 Å molecular sieves. The dried solution of *N*-deuterium *Z*-**1** was used to do kinetic studies of its intramolecular aminolysis in dried and excess NEt_3 of acetonitrile solution at 298 K. The observed pseudo-first-order rate constants (k_{obs}) and the second-order rate constants (k_{NEt3}) for the NEt_3-catalyzed intramolecular aminolysis of *N*-deuterium *Z*-**1** were obtained and are shown in Table 1. The kinetic isotope effect[11] (k_H/k_D) for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** was calculated to be 1.66.

The base-catalyzed intramolecular aminolysis of *Z*-**1** was also measured in aqueous $NEt_3/NEt_3 \cdot HCl$ buffer solutions at 298 K with constant buffer ratio [NEt_3]/[$NEt_3 \cdot HCl$] of 1 and various total buffer concentrations of [NEt_3] and [$NEt_3 \cdot HCl$] (Figure 2). All of the buffer solutions have the same pH value of 11.0,[12a] and their ionic strength was kept as 0.01 with NaCl. The observed pseudo-first-order rate constants (k_{obs}) were obtained and are shown in Table 2. The observed pseudo-first-order rate constant (k_{obs}) for the acid-catalyzed intramolecular aminolysis of *Z*-**1** in 2 M HCl aqueous solution at 298 K is 4.0×10^{-6} s^{-1}, so the second-order rate constant of k_H^+ is around 2.0×10^{-6} M^{-1} s^{-1}, which is very small in comparison with base catalysis. Therefore, $k_{NEt3 \cdot HCl}$[$NEt_3 \cdot HCl$] and k_H^+[H^+] can be neglected from eq 2 for the intramolecular aminolysis of *Z*-**1** in aqueous $NEt_3/NEt_3 \cdot HCl$ buffer solutions. According to eq 2, the linear

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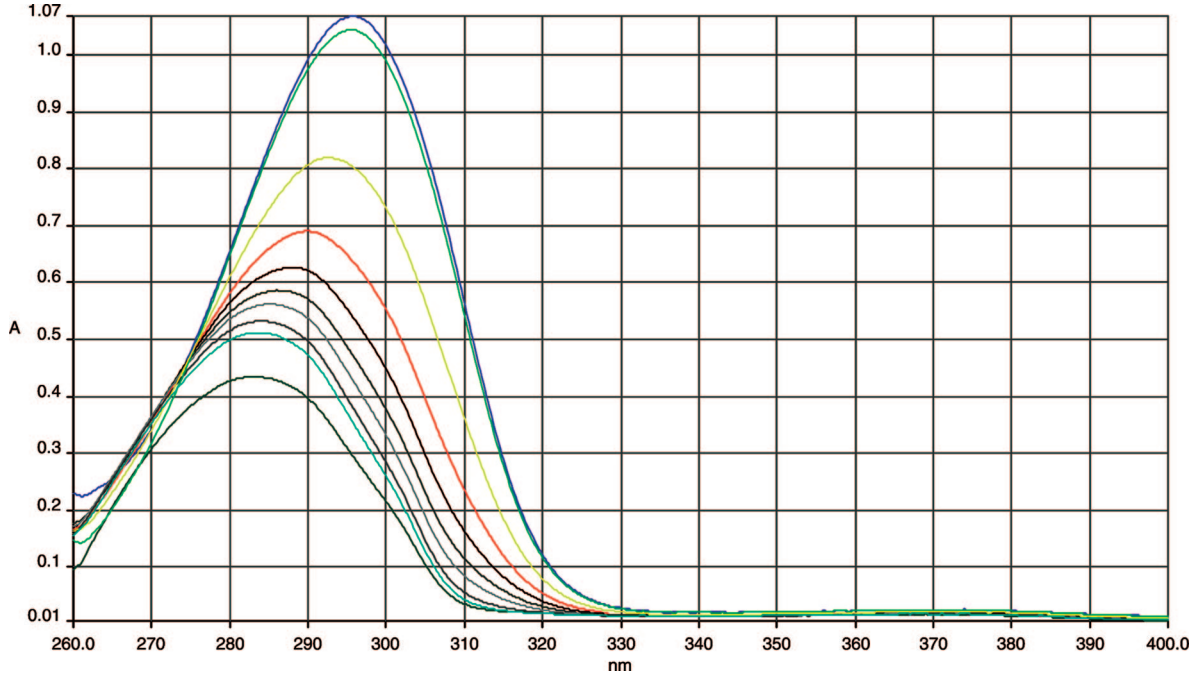


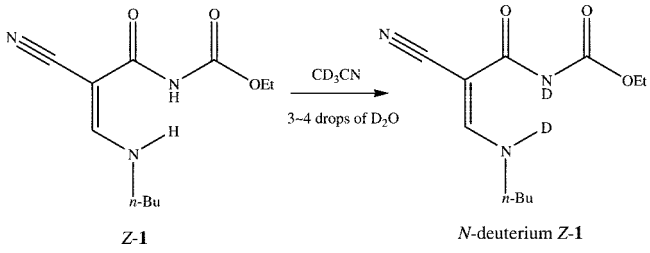
FIGURE 1. UV absorption spectra for the intramolecular aminolysis of *Z*-**1** (5×10^{-5} M, $\epsilon = 21380$ M^{-1} cm^{-1} at 294 nm) in 0.1 M NEt_3 of acetonitrile solution obtained at 5, 60, 120, 180, 240, 300, 420, 660, and 1260 min with decreasing absorption at 294 nm until **2** ($\epsilon = 6000$ M^{-1} cm^{-1} at 294 nm) was formed completely.

TABLE 1. Observed Pseudo-First-Order and Second-Order Rate Constants of the NEt_3-Catalyzed Intramolecular Aminolysis of *Z*-1 and *N*-Deuterium *Z*-1 in Acetonitrile at 298 K[a]

substrate	*Z*-**1**							
base	NEt_3							
base concn, M	0.500	0.350	0.204	0.183	0.163	0.143	0.100	0.050
$10^4 k_{obs}$, s^{-1}	8.95 ± 0.23	6.25 ± 0.15	3.69 ± 0.10	3.32 ± 0.06	2.94 ± 0.09	2.59 ± 0.10	1.76 ± 0.04	0.850 ± 0.03
10^3 k_{NEt3}, $M^{-1}s^{-1}$	1.79 ± 0.03							
substrate	*N*-deuterium *Z*-**1**							
base	NEt_3							
base concn, M	0.500	0.350	0.204	0.183	0.163	0.143	0.100	0.050
$10^4 k_{obs}$, s^{-1}	5.44 ± 0.15	3.75 ± 0.09	2.19 ± 0.08	1.96 ± 0.05	1.75 ± 0.03	1.53 ± 0.05	1.10 ± 0.03	0.577 ± 0.020
10^3 k_{NEt3}, M^{-1} s^{-1}	1.08 ± 0.02							

[a] k_H/k_D was calculated to be 1.66 ± 0.04.

SCHEME 2



Z-**1** *N*-deuterium *Z*-**1**

plot of k_{obs} versus [NEt_3] was drawn and the second-order rate constant of k_{NEt3} was calculated to be 177 M^{-1} s^{-1}.

$$\text{rate} = \frac{-\text{d[Z-}\mathbf{1}\text{]}}{dt} = \{k_H + [H^+] + k_{NEt3HCl}[NEt_3HCl] + k_{OH^-}[OH^-] + k_{NEt3}[NEt_3]\}[\text{Z-}\mathbf{1}] \simeq \{k_{OH^-}[OH^-] + k_{NEt3}[NEt_3]\}[\text{Z-}\mathbf{1}] = k_{obs}[\text{Z-}\mathbf{1}] \quad (2)$$

To study the salt effect, ionic strength (μ) for one of the buffer solutions was varied from 0.01 to 0.40 with NaCl. The observed

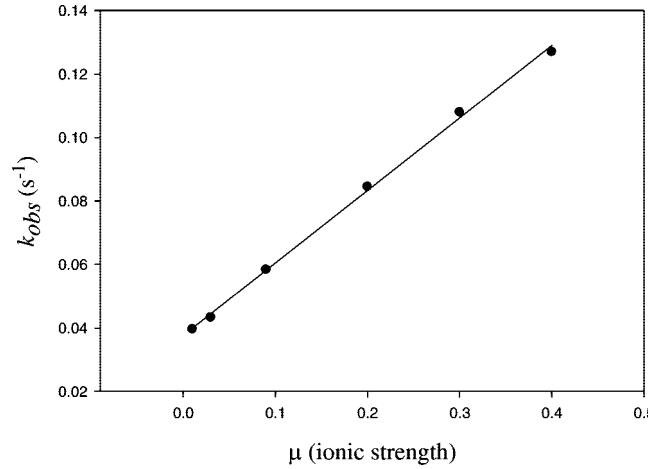


FIGURE 2. Salt effect for the base-catalyzed intramolecular aminolysis of *Z*-**1** in aqueous $NEt_3/NEt_3 \cdot HCl$ buffer solutions at 298 K.

pseudo-first-order rate constants (k_{obs}) were obtained and are shown in Table 3. Correlation of the observed pseudo-first-order rate constants (k_{obs}) with μ is linear (Figure 3) with $r^2 = 0.998$

TABLE 2. Rate Constants for the Base-Catalyzed Intramolecular Aminolysis of *Z*-1 in Aqueous $NEt_3/NEt_3 \cdot HCl$ Buffer Solutions at 298 K[a]

entry	[NEt_3] (M)	[$NEt_3 \cdot HCl$] (M)	μ (ionic strength)	k_{obs} (s^{-1})
1	2×10^{-4}	2×10^{-4}	0.01	$(3.96 \pm 0.05) \times 10^{-2}$
2	4×10^{-4}	4×10^{-4}	0.01	$(7.41 \pm 0.08) \times 10^{-2}$
3	5×10^{-4}	5×10^{-4}	0.01	$(9.09 \pm 0.08) \times 10^{-2}$
4	6×10^{-4}	6×10^{-4}	0.01	$(1.11 \pm 0.04) \times 10^{-1}$

[a] pH of all the buffer solutions = 11.0; $k_{NEt3} = 177 \pm 4\ M^{-1}\ s^{-1}$

TABLE 3. Salt Effect for the Base-Catalyzed Intramolecular Aminolysis of *Z*-1 in Aqueous $NEt_3/NEt_3 \cdot HCl$ Buffer Solutions at 298 K[a]

entry	[NEt_3] (M)	[$NEt_3 \cdot HCl$] (M)	μ (ionic strength)	k_{obs} (s^{-1})
1	2×10^{-4}	2×10^{-4}	0.40	$(1.27 \pm 0.03) \times 10^{-1}$
2	2×10^{-4}	2×10^{-4}	0.30	$(1.08 \pm 0.03) \times 10^{-1}$
3	2×10^{-4}	2×10^{-4}	0.20	$(8.45 \pm 0.23) \times 10^{-2}$
4	2×10^{-4}	2×10^{-4}	0.09	$(5.84 \pm 0.15) \times 10^{-2}$
5	2×10^{-4}	2×10^{-4}	0.03	$(4.33 \pm 0.12) \times 10^{-2}$
6	2×10^{-4}	2×10^{-4}	0.01	$(3.96 \pm 0.05) \times 10^{-2}$

[a] pH of all the buffer solutions = 11.01.

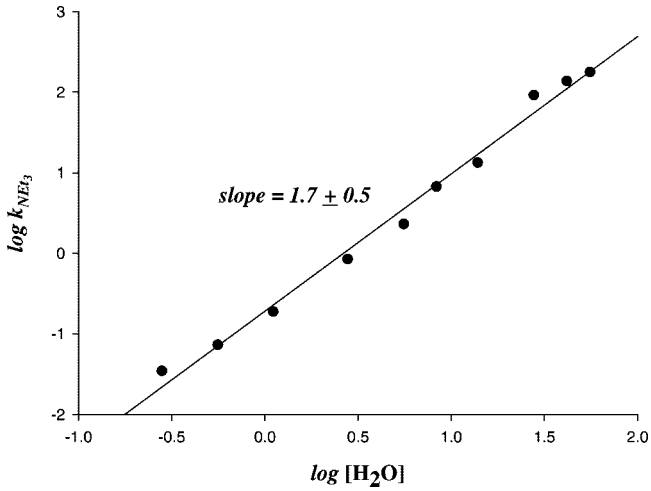


FIGURE 3. Correlation of logk_{NEt3} with log[H_2O] for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in aqueous acetonitrile solutions at 298 K.

from $\mu = 0.01$ to $\mu = 0.4$. The correlation equation (eq 3) has a positive slope of 0.23.

$$k_{obs} = (0.23 \pm 0.01)\mu \pm (0.038 \pm 0.001)\ (r^2 = 0.998) \quad (3)$$

Since the second-order rate constant of k_{NEt3} for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in water is 5 orders of magnitude larger than that in acetonitrile, it is necessary to investigate the influence of water concentration on the second-order rate constant of k_{NEt3}. Thus, the reaction was titrated by aqueous acetonitrile solutions with various water concentrations,[13] and the corresponding kinetics was analyzed. The observed pseudo-first-order rate constants (k_{obs}) and the corresponding second-order rate constants (k_{NEt3}) for these titration experiments were obtained and are shown in Table 4. The logk_{NEt3} was correlated with log[H_2O] and that showed a linear relationship with a slope of 1.7 ± 0.5 (Figure 3). Since aqueous acetonitrile solutions are deviated from an ideal solution, activity, a_{H2O}, is supposed to replace [H_2O] in the correlation with logk_{NEt3}, and their relation is shown in eq 4, in which activity

TABLE 4. Observed Pseudo-First-Order and Second-Order Rate Constants for the NEt_3-Catalyzed Intramolecular Aminolysis of *Z*-1 in Acetonitrile Solutions with Various Water Concentrations at 298 K

x_{H2O} ([H_2O], a_{H2O}, % v/v)	89.7% (41.67, 46.16, 75% v/v)					74.5% (27.78, 33.34, 50% v/v)		
[NEt_3], M	2×10^{-3}	1.5×10^{-3}	1×10^{-3}	5×10^{-4}	2×10^{-4}	2.5×10^{-3}	1.5×10^{-3}	1×10^{-3}	5×10^{-4}	2.5×10^{-4}
$10^2 k_{obs}$, s^{-1}	27.0 ± 0.7	20.9 ± 0.5	14.0 ± 0.3	6.85 ± 0.14	2.47 ± 0.07	22.9 ± 0.4	13.9 ± 0.2	9.38 ± 0.11	4.52 ± 0.09	2.21 ± 0.06
k_{NEt3},M^{-1} s^{-1}	137.0 ± 4.1					92.0 ± 2.3				
x_{H2O} ([H_2O], a_{H2O}, % v/v)	49.3% (13.89, 22.92, 25% v/v)					33.9% (8.33, 20.06, 15% v/v)				
[NEt_3], M	1×10^{-2}	7×10^{-3}	5×10^{-3}	3×10^{-3}	1×10^{-3}	2×10^{-2}	1.5×10^{-2}	1×10^{-2}	5×10^{-3}	2×10^{-3}
$10^2 k_{obs}$, s^{-1}	13.3 ± 0.3	9.25 ± 0.18	6.82 ± 0.11	4.01 ± 0.07	1.26 ± 0.04	13.5 ± 0.4	9.99 ± 0.21	6.71 ± 0.13	3.34 ± 0.07	1.38 ± 0.03
k_{NEt3}, M^{-1} s^{-1}	13.3 ± 0.34					6.72 ± 0.14				
x_{H2O} ([H_2O], a_{H2O}, % v/v)	24.7% (5.56, 18.05, 10% v/v)					13.4% (2.78, 13.90, 5% v/v)				
[NEt_3], M	2×10^{-2}	1.5×10^{-2}	1×10^{-2}	5×10^{-3}	2×10^{-3}	2×10^{-2}	1.5×10^{-2}	1×10^{-2}	5×10^{-3}	2×10^{-3}
$10^2 k_{obs}$, s^{-1}	4.65 ± 0.06	3.45 ± 0.03	2.21 ± 0.04	1.15 ± 0.02	$0.515\ 0.018$	1.70 ± 0.04	1.28 ± 0.03	0.837 ± 0.019	0.420 ± 0.011	0.178 ± 0.005
k_{NEt3},M^{-1} s^{-1}	2.30 ± 0.05					0.849 ± 0.025				
x_{H2O} ([H_2O], a_{H2O}, %v/v)	5.6% (1.11, 7.76, 2% v/v)					3.1% (0.56, 4.37, 1% v/v)				
[NEt_3], M	2×10^{-2}	1.5×10^{-2}	1×10^{-2}	5×10^{-3}	2×10^{-3}	2×10^{-2}	1.5×10^{-2}	1×10^{-2}	5×10^{-3}	2×10^{-3}
$10^3 k_{obs}$, s^{-1}	3.76 ± 0.05	2.85 ± 0.03	1.94 ± 0.02	0.920 ± 0.014	0.356 ± 0.009	1.47 ± 0.03	1.09 ± 0.02	0.713 ± 0.015	0.371 ± 0.011	0.152 ± 0.005
k_{NEt3},M^{-1} s^{-1}	0.190 ± 0.004					0.073 ± 0.002				
x_{H2O} ([H_2O], a_{H2O}, %v/v)	1.6% (0.28, 2.34, 0.5% v/v)									
[NEt_3], M	2×10^{-2}	1.5×10^{-2}	1×10^{-2}	5×10^{-3}	2×10^{-3}					
$10^4 k_{obs}$, s^{-1}	6.90 ± 0.18	5.21 ± 0.15	3.47 ± 0.11	1.71 ± 0.05	0.680 ± 0.02					
k_{NEt3},$M^{-1}s^{-1}$	0.0346 ± 0.0009									

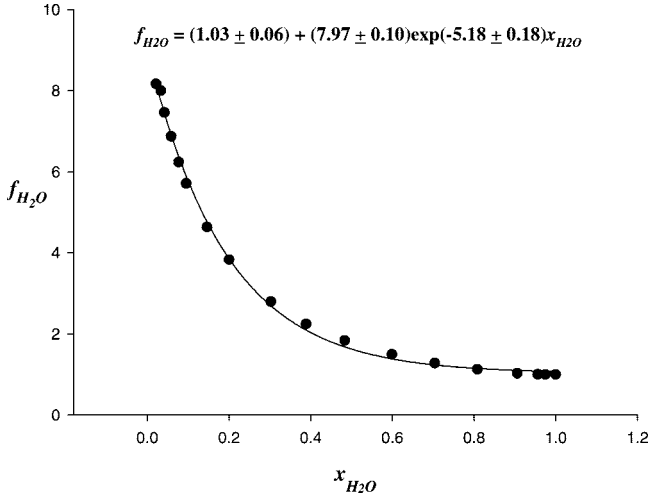


FIGURE 4. Correlation of activity coefficients, f_{H2O}, with mole fraction of water, x_{H2O}, in aqueous acetonitrile solutions at 298 K.

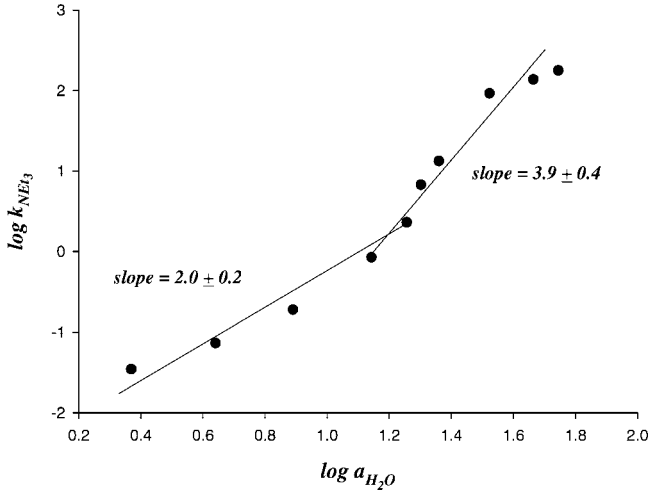


FIGURE 5. Correlation of logk_{NEt3} with loga_{H2O} for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in aqueous acetonitrile solutions at 298 K.

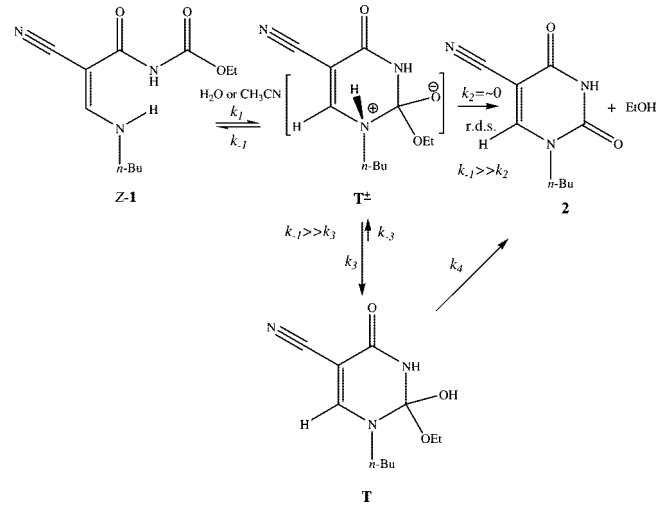
coefficients, f_{H2O}, were obtained from the literature,[14] correlated with x_{H2O} and depicted in Figure 4. When log k_{NEt3} was plotted against log a_{H2O}, two linear correlation lines were obtained. One has a slope of 2.0 ± 0.2 in the range of 0% < x_{H2O} < 19%, and the other has a slope of 3.9 ± 0.4 in the range of 19% < x_{H2O} ≤ 100% (Figure 5).

$$a_{H_2O} = f_{H_2O}[H_2O] \quad (4)$$

Discussion

According to the current accepted mechanisms,[7] the reversible addition of enamine moiety to carbamate of *Z*-**1**, forming the transient $T^{\pm}$, is supposed to be thermodynamically favorable

SCHEME 3. *Z*-1 in Water or Acetonitrile



(Scheme 3). However, *Z*-**1** does not undergo any intramolecular aminolysis in water or acetonitrile in the absence of acids or bases. This is probably due to a high barrier of H-abstraction from the transient $T^{\pm}$. The H-abstraction from the transient $T^{\pm}$ by acetonitrile or water solvent should be thermodynamically unfavorable because the protonated enamine moiety (its pK_a in water ≃ pK_a of *N*,*N*-diethylanilinium[12b] in water = ca. 6.6) of the transient $T^{\pm}$ is much less acidic than the conjugated acid of acetonitrile or water (pK_a of H_3O^+ = ca. −1.74).[12c] Thus, a base like NEt_3 is needed in carrying out the intramolecular aminolysis of *Z*-**1**. On the other hand, is it possible that proton on the protonated enamine moiety of $T^{\pm}$ is transferred to oxygen anion or amide nitrogen moiety? Since pK_a values of alcohol[12d] and protonated amide[12e] in water are ca. 15.5 and 5.3, respectively, proton transfer from the protonated enamine moiety to the oxygen anion moiety is thermodynamically favorable, but proton transfer from the protonated enamine moiety to the amide moiety is not thermodynamically favorable, resulting in formation of the tetrahedral addition intermediate T (Scheme 3). Because enamine (its pK_a in DMSO ≃ pK_a of aniline[12d,f] in DMSO = ca. 30.6) is less acidic than ethanol (its pK_a in DMSO ≃ pK_a of methanol[12d,f] in DMSO = ca. 29.0), expulsive rate of ethoxide from T is faster than that of enamine anion, leading to formation of **2**. If any of the intermediate T were formed, it would be very hard to return back to $T^{\pm}$ but would go further to **2**, because protonated enamine moiety is much acidic than hydroxyl moiety. However, *Z*-**1** is stable for a long time (many months) in water or acetonitrile in the absence of acids or bases, and in the meantime, no tetrahedral intermediate T can be detected in the solutions. Hence, the rate for the reverse of addition (k_{-1}) is supposed to be much greater than the proton transfer rate of $T^{\pm}$ (k_3), i.e., $k_{-1} \gg k_3$.

According to the current accepted mechanisms for the aminolysis of carbamates,[7a,b] the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** is assumed to follow a stepwise mechanism, instead of a concerted mechanism, because ethoxide is not a very good leaving group.[10b] The next issue is whether the rate-determining step involves the formation of the tetrahedral addition intermediate or its collapse.

In aqueous NEt_3/NEt_3·HCl buffer solutions, the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** is subjected to general-base catalysis (Table 2), which is also found in the

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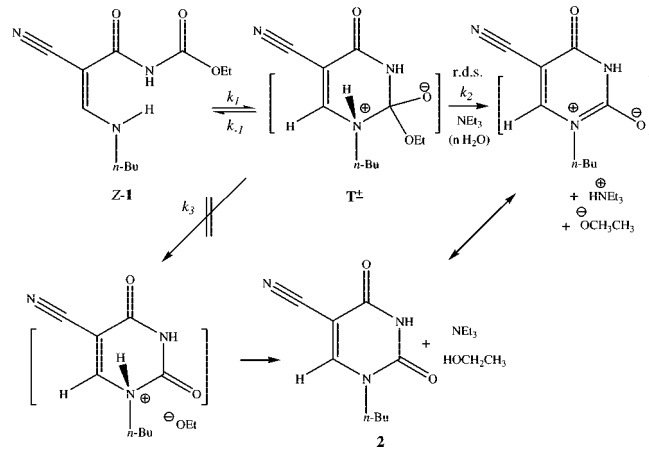
aminolysis of some esters.[15,16] In other words, its rate-determining step in protic aqueous solution involves proton transfer. Conversely, the ring closure of phenyl *N*-(2-hydroxyphenyl)carbamate[17b] in aqueous solutions is subjected to specific-base catalysis, probably because its phenol moiety (pK_a = ca. 10.0 in water[12g] and 18.0 in DMSO[12d,f]) is much more acidic than enamine moiety (its pK_a in DMSO $\simeq$ pK_a of aniline[12d,f] in DMSO = ca. 30.6) of *Z*-**1**.

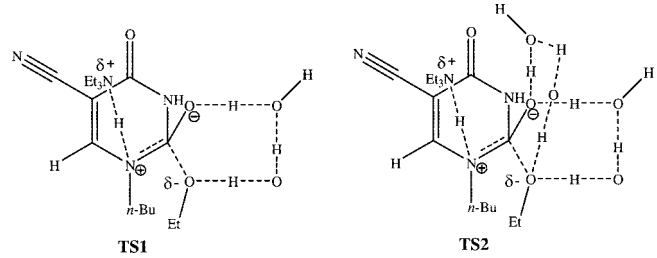
In aprotic acetonitrile, the kinetic isotope effect of k_H/k_D = 1.66 shown in Table 1 for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1**, and *N*-deuterium *Z*-**1** in dry CH_3CN is similar to that found for the aminolysis of ester (k_H/k_D = 1.57),[16a] carbamates (k_H/k_D = 1.62∼1.82),[7b] and thiocarbamates (k_H/k_D = 1.48∼1.74),[10b] indicating that the kinetic isotope effect is a primary kinetic isotope effect (PKIE).[11] It implies that the rate-determining step involves cleavage of the N−H bond of *Z*-**1** by general bases such as NEt_3. It was reported that imide N−H(D) of *p*-nitrophenyl *N*-phenylcarbamate displayed very little isotope effect in its aminolysis,[7b] so the isotope effect of imide N−H(D) of *Z*-**1** may be neglected. In addition, the $E1_{CB}$ mechanism[6] involving an isocyanate intermediate for the aminolysis of carbamates was suggested to work only in a very strong base condition with a very good leaving group,[17] which cannot be found in the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1**. Hence, the rate-determining proton transfer for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in aprotic acetonitrile is suggested to involve cleavage of enamine N−H(D) in *Z*-**1**.

The water concentration on the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** is quite significant with k_{NEt3} = 177 M^{-1} s^{-1} in H_2O and k_{NEt3} = 1.79 × 10^{-3} M^{-1} s^{-1} in dry CH_3CN. The former is 5 orders of magnitude larger than the latter. When the reaction was titrated with water in aqueous acetonitrile solutions, the plot of log k_{NEt3} against log a_{H2O} showed two linear correlation lines. According to the literature,[18] the plot of log k_{NEt3} vs log a_{H2O} may indicate the number of water molecules involved in the rate-determining step. One correlation line with a slope of 2.0 in the region of 0% < x_{H2O} < 19% indicates that two water molecules are involved in the rate-determining step. The other with a slope of 3.9 in the region of 19% < x_{H2O} ≤ 100% implies that the rate-determining step involves four water molecules. Since the mechanism for the aminolysis of carbamates in aprotic solvents is known to involve the rate-determining collapse of the tetrahedral addition intermediate $T^{\pm}$,[7a,b] the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** is assumed to follow the same mechanism, and the rate-determining transition-state structures in the regions of 0% < x_{H2O} < 19% and 19% < x_{H2O} ≤ 100% are proposed as TS1 and TS2, respectively. Stabilization of the developing charge on ethoxy oxygen through hydrogen bonding with water is a plausible explanation for the water-assisted NEt_3-catalyzed

SCHEME 4. Proposed Mechanism for NEt_3-Catalyzed Intramolecular Aminolysis of *Z*-1 in Acetonitrile or Aqueous Acetonitrile Solutions



intramolecular aminolysis of *Z*-**1**. At low water concentrations (0% < x_{H2O} < 19%), TS1 is suggested to involve one eight-membered water-linking ring; at high water concentrations (19% < x_{H2O} ≤ 100%), TS2 is suggested to involve two eight-membered water-linking rings. These transition-state structures are consistent with those of other water-catalyzed reactions.[18] The advantage of this eight-membered transition state over a six-membered transition state involving one water molecule is that it accommodates linear hydrogen bonds as suggested by Gandour.[19] Wolfe also suggested that the linearity of hydrogen bonds formed in the transition state balances the entropic disadvantage of bringing these molecules together.[20]



According to the kinetic isotope effect of k_H/k_D = 1.66 in acetonitrile, the general-base catalysis in aqueous NEt_3/NEt_3·HCl buffer solutions, and the proposed water-stabilized rate-determining transition states (TS1 and TS2) in the water-titration experiments, the mechanism involving the collapse of the tetrahedral addition intermediate $T^{\pm}$ is suggested in Scheme 4 for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in acetonitrile or aqueous solutions. The rate law in acetonitrile or aqueous acetonitrile is also suggested in eq 5 or 6.

In acetonitrile,

$$-d[Z\text{-}\mathbf{1}]/dt = k_{obs}[Z\text{-}\mathbf{1}] = k_{NEt3}[NEt_3][Z\text{-}\mathbf{1}] \quad (5)$$

where

$$k_{NEt3} = k_1k_2/(k_{-1} + k_2) = k_1k_2/k_{-1}$$

In aqueous acetonitrile,

$$-d[Z\text{-}\mathbf{1}]/dt = k_{obs}[Z\text{-}\mathbf{1}] = k_{NEt3}[NEt_3][Z\text{-}\mathbf{1}] = k(a_{H2O})^n[NEt_3][Z\text{-}\mathbf{1}] \quad (6)$$

where

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$$k = k_1k_2/k_{-1} \text{ and } n = 2 \text{ or } 4$$

For this mechanism, the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** may undergo reversible addition of the enamine moiety to the carbamate, forming the transient $T^{\pm}$, followed by the rate-determining collapse of the tetrahedral intermediate $T^{\pm}$ through H-abstraction from the protonated enamine moiety by NEt_3.[7] As we mentioned earlier, proton transfer from the protonated enamine moiety of $T^{\pm}$ to the amide moiety is not thermodynamically favorable. Even though proton transfer from the protonated enamine moiety $T^{\pm}$ to the oxygen anion moiety is thermodynamically favorable, its rate is much less than that for the reverse of addition. However, increasing [NEt_3] may raise proton-transfer rate of $T^{\pm}$ through proton transfer from the protonated enamine moiety to NEt_3. The protonated enamine moiety (its pK_a in water $\simeq$ pK_a of *N*,*N*-diethylanilinium[12b] in water = ca. 6.6) is more acidic than the amide proton (pK_a = ca. 15.1 in water),[12d] so the former is easier to remove by NEt_3 than the latter in the k_2 process. The protonated enamine is not a strong acid, and NEt_3 is not a strong base, so H-abstraction in the k_2 process is likely to follow E2 mechanism,[11] instead of $E1_{CB}$, with simultaneous ethoxide expulsion with the help of the neighboring oxygen anion. When some water is involved in the reaction, the ethoxide expulsion is accelerated possibly by stabilization of the developing charge on ethoxy oxygen through hydrogen bonding with water in the rate-determining E2 process. The number of water molecule which is involved in the rate-determining E2 process may depend on the water concentration; it may be 2 at $0\% < x_{H2O} < 19\%$ or 4 at $19\% < x_{H2O} \leq 100\%$. The k_3 process can be neglected because *Z*-**1** is very stable in H_2O and CH_3CN in the absence of any acid or base.

The salt effect is significant and increases k_{obs} for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in aqueous NEt_3/NEt_3·HCl buffer solutions. (Table 3) The addition of inert NaCl salt into water increases aqueous ionic strength and polarity, which stabilize TS2 better than its precursor in the rate-determining E2 process because the former has more charge separation than the latter, resulting in rate acceleration of the reaction. Similar E2 processes were also reported to be accelerated by more polar solvents.[21] Hence, the salt effect is also consistent with the mechanism involving the collapse of the tetrahedral addition intermediate $T^{\pm}$.

Conclusion

Based on the primary kinetic isotope effect of $k_H/k_D = 1.66$ in acetonitrile, the general-base catalysis in aqueous NEt_3/NEt_3·HCl buffer solutions, salt effect, and the proposed water-stabilized rate-determining transition states (TS1 and TS2) in the water-titration experiments, the mechanism of the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** in acetonitrile or aqueous acetonitrile is suggested to involve the collapse of the tetrahedral addition intermediate $T^{\pm}$.

Experimental Section

General Methods. The carbamate *Z*-**1** was prepared according to the literature.[4a]

Preparation of *N*-Deuterium *Z*-1. Four drops of D_2O was added to 1 mL of 0.2 M *Z*-**1** solution in dry CD_3CN (Scheme 4). The reaction was monitored by proton NMR spectrometry until the N−H resonance peaks at $\delta = 98.1$ and 7.74 disappeared and the resonance peak of vinyl hydrogen at $\delta = 7.32$ turned from doublet to singlet. The solution was dried with 4 Å molecular sieves before it was ready for the experiment of isotope effect.

Kinetic Studies of NEt_3-Catalyzed Intramolecular Aminolysis of *Z*-1 and *N*-Deuterium *Z*-1 in Dry CH_3CN. Kinetic studies for the NEt_3-catalyzed intramolecular aminolysis of *Z*-**1** or *N*-deuterium *Z*-**1** were carried out by injecting 4 μL of approximately 0.025 M *Z*-**1** or *N*-deuterium *Z*-**1** of CH_3CN solution into 1 mL of NEt_3 CH_3CN solutions, whose concentrations were 0.50, 0.35, 0.204, 0.183, 0.163, 0.143, 0.10, or 0.05 M, in the thermostatic UV cell at 25 °C, and monitoring the decrease in absorption at 294 nm with Perkin-Elmer Lambda 12 spectrometer. The SigmaPlot software was used to fit the exponential decays to get the rate constants. All rate constants were measured at least in duplicate with maximum deviations of ± 5%.

Kinetic Studies of Intramolecular Aminolysis of *Z*-1 in Aqueous NEt_3/NEt_3·HCl Buffer Solutions at 298 K. Kinetic studies for the intramolecular aminolysis of *Z*-**1** were carried out by injecting 1 μL of approximately 0.005 M *Z*-**1** of CH_3CN solution into 1 mL of aqueous 1:1 NEt_3/NEt_3·HCl buffer solutions, whose ionic strength was 0.01−0.4 (NaCl) and concentrations were 2×10^{-2}, 4×10^{-4}, 5×10^{-4}, and 6×10^{-4} M, in the thermostatic UV cell at 25 °C, and monitoring the decrease in absorption at 294 nm with Perkin-Elmer Lambda 12 spectrometer. The SigmaPlot software was used to fit the exponential decays to get the rate constants. All rate constants were measured at least in duplicate with maximum deviations of ± 5%.

Kinetic Studies of NEt_3-Catalyzed Intramolecular Aminolysis of *Z*-1 in Aqueous CH_3CN with Various Water Concentrations. The kinetic studies were carried out by injecting 4 μL of approximately 0.025 M *Z*-**1** of CH_3CN solution into 1 mL of NEt_3 of aqueous CH_3CN solutions with various NEt_3 and H_2O concentrations in the thermostatic UV cell at 25 °C and monitoring the decrease in absorption at 294 nm with Perkin-Elmer Lambda 12 spectrometer. The SigmaPlot software was used to fit the exponential decays to get the rate constants. All rate constants were measured at least in duplicate with maximum deviations of ± 5%.

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