Effect of Leaving Group in the Hydrolyses of *N*-Cyclopropanecarbonylimidazoles

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Received March 1, 2008

Key Words : *N*-Cyclopropanecarbonylimidazole, pH-rate profile, Hydrolysis, Appearent pKa

The hydrolysis reactions of *N*-acylimidazole derivatives have been extensively studied in view of the reactivity study of amides.[1,2] The most interesting results[3] are that the rate determining step in the hydrolyses of *N*-furoyl- and *N*-thenoyl-2-phenylimidazole changes in acidic region and that[4] of *N*-benzoyl-2-phenylimidazole is related with diprotonated species in acidic region. However, in the hydrolysis of *N*-benzoyl-4,5-diphenylimidazole, a change in the rate determining step or the existence of diprotonated species in acidic region was not observed, even though the structure of substrate is varied from phenyl to diphenyl group in the imidazole ring. The hydrolytic reactivity of *N*-acylimidazoles depends on the acyl group and the leaving group.

In the present study, our interest is on how the hydrolysis reaction may occur when the substituent of the leaving group of *N*-acylimidazole changes. Therefore, we have performed the hydrolysis reactions of *N*-cyclopropanecarbonylimidazole (**1a**), *N*-cyclopropanecarbonyl-4-nitroimidazole (**1b**) and *N*-cyclopropanecarbonyl-4-methylimidazole (**1c**).

Materials. All materials used for synthesis of the substrates were purchased from Aldrich or Tokyo Kasei. All organic solvents were purified by the well known method.[5] Deionized water were distilled using a Streem III Glass Still and kept under nitrogen atmosphere. Buffer materials for kinetic studies were analytical reagent grade.

The substrates can be prepared as previous reported method.[3] The *N*-cyclopropanecarbonylimidazole (**1a**) was prepared by dissolving 10 mmol of imidazole in dry acetonitrile with cooling and slowly adding 10 mmol of cyclopropanecarbonyl chloride dissolved in dry acetonitrile in the presence of TEA. The reaction mixture was generally refluxed for 48 hours with stirring. After the reaction mixture was cooled and filtered, the filtrate was evaporated. The residue was dissolved in dichloromethane and washed with water several times and separated from the organic layer. The solution was dried over magnesium sulfate and the solvent was removed by rotary evaporation. The crude oil product was purified through silicagel column chromatography (*n*-hexane/ethylacetate = 1:2) and dried under vacuum condition for 48 hours. Other compounds (**1b-c**) were prepared similarly as above described method. The physical properties and spectroscopic data of the compounds **1a**, **1b** and **1c** are as follows.

***N*-Cyclopropanecarbonyllimidazole (1a):** brown oil; FT-IR (KBr, cm^{-1}): 1234 (C-N), 1720 (C=O), 3410 (N-H); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.99-1.09 (dd, J = 3.36 Hz, 2H), 1.14-1.22 (dd, J = 3.03 Hz, 2H), 2.04-2.16 (m, 1H), 6.94 (s, 1H), 8.13 (s, 1H); Mass: m/z 136 (M^-).

***N*-Cyclopropanecarbonyl-4-nitrolimidazole (1b):** pale yellow solid; m.p. 80-82 °C; FT-IR (KBr, cm^{-1}): 1382 (C-N), 1740 (C=O), 3460 (N-H); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.31-1.40 (dd, J = 3.36 Hz, 2H), 1.42-1.49 (dd, J = 3.03 Hz, 2H), 2.21-2.27 (m, 1H), 8.22 (s, 1H), 8.35 (s, 1H); Mass: m/z 180 (M^+).

***N*-Cyclopropanecarbonyl-4-methylimidazole (1c):** brown solid; m.p. 70-73 °C; FT-IR (KBr, cm^{-1}): 1254 (C-N), 1717 (C=O), 3404 (N-H); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.09-1.19 (dd, J = 3.36 Hz, 2H), 1.21-1.34 (dd, J = 3.03 Hz, 2H), 2.10-2.23 (m, 1H), 2.24 (s, 3H), 7.25 (s, 1H), 8.18 (s, 1H); Mass: m/z 150 (M^+).

Kinetics. The rates of hydrolysis of the substrates were measured spectrophotometrically in H_2O at 25 ± 0.1 °C by following the decrease in absorbance due to disappearance of the substrates **1a, 1b** and **1c** at wavelengths in the range of 214-244 nm. The rate measurements were carried out using a Hewlett Packard 8452 Diode Array spectrophotometer equipped with a Shimadzu TB-85-thermo bath to keep the temperature of the reaction mixture at 25 °C ± 0.1 °C. The pseudo first order rate constant (k_{obs}) obtained from 89532 K Kinetic Software (serial No. 325 G00380) of the Hewlett Packard company which was based on the slope of the plot in $\ln(A_O\text{-}A_t)$ *vs.* time. Buffer solutions were maintained at a constant ionic strength of 0.5 M with KCl. Typically, kinetic run was initiated by injecting 30 μL of 1.0×10^{-2} M stock solution of the substrate in acetonitrile into 3.0 mL of buffer solution maintained at 25 °C ± 0.1 °C. The buffer solution employed were HCl (pH = 1.0-2.4), formate (pH = 2.51-4.15), acetate (pH = 4.15-4.92), MES (5.5-6.7), cacodylate (5.0-7.4), imidazole (6.2-8.0), *N*-ethylmorpholine (6.6-8.6), tris (7.0-9.0) and carbonate (9.6-10.5).

The hydrolysis reactions are catalyzed by buffer. Therefore, rate constants were obtained by extrapolation to zero buffer concentration. The catalytic rate constants were obtained from plots of k_{obs} versus concentration of catalyst. pH values of reaction mixtures ere measured at 25 °C with a DP-215M Dong-Woo meter.

Results and Discussion

The hydrolysis reactions of **1a**. **1b** and **1c** were carried out under pseudo first order conditions with the concentration of buffer in large excess relative to the substrate. The pH rate profiles for the hydrolysis reactions of substrate **1a**. **1b** and **1c(in Inset)** are presented in Figure 1. These profiles are similar in shape to those for hydrolysis of corresponding *N*-acylimidazoles.[2] The hydrolysis reactions of the substrates **1a** and **1c** show four distinct regions corresponding to the hydroxide ion (OH^-) catalyzed reactions above pH 8.0, the hydronium ion (H_3O^+) catalyzed reaction between pH 6.0 and pH 4.0, the pH independent reaction by the protonated species of the substrate below pH 4.0, and the water reaction by the neutral species around pH 7.0. But the pH rate profile for the substrate **1b** shows a wide plateau region and the hydroxide ion catalyzed reaction.

Therefore, the observed rate constant (k_{obs}) for the substrates **1a** and **1c** is given by equation (1), whereas that of the substrate **1b** involves only the second term of equation (1). In equation 1 k_1 and k_o are the rate constants

$$k_{obs} = k_1 \left\{ \frac{[H^+]}{K_a + [H^+]} \right\} + (k_o + k_{OH}[OH^-]) \frac{K_a}{K_a + [H^+]} \quad (1)$$

for water catalyzed reaction of the protonated species (SH^+) and that of the neutral substrate (S), k_{OH} is the second order rate constant for hydroxide ion catalysis and K_a is the dissociation constant of the conjugate acid of the substrate. The rate constants for hydrolysis reactions of the substrate **1a**. **1b** and **1c** are listed in Table 1.

The k_H value for H_3O^+ catalyzed reaction of *N*-cyclopropanecarbonylimidazole (**1a**) is less than that of *N*-cyclopropanecarbonyl-4-methylimidazole (**1c**). This difference can be due to the relatively lower pKa of the conjugate acid of *N*-cyclopropanecarbonylimidazole (**1a**) than that of *N*-cyclopropanecarbonyl-4-methylimidazole (**1c**). The bent portion is observed at low pH in Figure 1. This indicates that

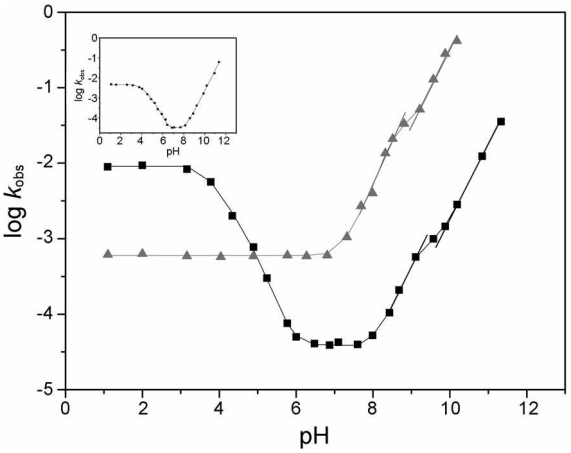


Figure 1. Plots of logk_{obs} *vs* pH for hydrolysis of *N*-cyclopropanecarbonylimidazole (■), *N*-cyclopropanecarbonyl-4-nitroimidazole (▲) and *N*-cyclopropanecarbonyl-4-methylimidazole in inset (●) in H_2O at 25 °C and ionic strength 0.5 M with KCl.

Table 1. Rate constants for hydrolysis reactions of *N*-cyclopropanecarbonylimidazole (**1a**), *N*-cyclopropanecarbonyl-4-nitroimidzole (**1b**) and *N*-cyclopropanecarbonyl-4-methylimidazole (**1c**) in H_2O (μ = 0.5 M with KCl) at 25 °C

Compound	k_1 (s^{-1})	k_H ($M^{-1}\cdot s^{-1}$)	k_o (s^{-1}) (k_{H_2O}/k_{D_2O})	k_{OH} ($M^{-1}\cdot s^{-1}$)	$pKa_{app.}$
1a	0.01	50.3	4.05×10^{-5} (1.21)	42.5[a] 17.5[b]	3.7
1b	–	–	5.74×10^{-4} (1.07)	5874[c] 3429[d]	–
1c	0.007	70.0	3.38×10^{-5} (1.12)	22.2	4.0

[a]pH < 9.11. [b]pH > 9.11. [c]pH < 8.51. [d]pH > 9.22

pKa values of the conjugate acids of the substrates **1a** and **1c** are around this pH region. We can estimate that the apparent pKa values of the substrates **1a** and **1c** are 3.7 for **1a** and 4.0 for **1c** respectively, by drawing pH rate profile. Thus, the k_H value of the substrate **1a** is relatively small because $k_H = k_1/K_a$ and the k_1 values are nearly similar for the two substrates **1a** and **1c**.

The k_H values for hydrolyses of *N*-acylimidazoles normally decrease as the acyl group changes from aliphatic to aromatic. For example, the k_H value of *N*-acetylimidazole is 183 $M^{-1}\cdot s^{-1}$, whereas that of *N*-benzoylimidazole is 5.3×10^{-2} $M^{-1}\cdot s^{-1}$ at 25 °C even though the pKa values of the two compounds are nearly same.

However, H_3O^+-catalyzed reaction for the substrate **1b** was not observed, indicating that the protonated species is not made due to the strong electron withdrawing group in the leaving group. These results support that H_3O^+ catalyzed reaction should be proceeded through the protonated species which is protonated at N-3 atom of the leaving group imidazole. This explanation is in accord with the molecular orbital calculation result for the *N*-acetylimidazole which shows a more negative charge at the N-3 atom of imidazole than at the carbonyl oxygen atom.[6]

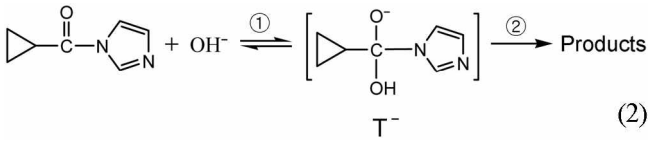
On the other hand, the water reaction of the substrates **1a** and **1c** appears around pH 7.0, while that of the substrate **1b** is observed in a wide regions from pH 7.0 to pH 1.0. This means that there is no indication of any reaction of the protonated species even at pH 1.0. Therefore, the pKa value of the substrate **1b** should be less than 1.0.

As indicated in Table 1, the k_o value for the water reaction of the substrate **1a** is slightly larger than that of the substrate **1c**, even though the water reaction is more favorable for high pKa of the conjugate acid. This result could be explained that pKa of 4-methylimidazole (pKa = 15.1)[7] leaving group is relatively larger than that of the unsubstituted imidazole (pKa = 14.5)[8] leaving group. Therefore, the facilitation of attack of the water molecule to the substrate **1a** provided by the lower pKa of the unsubstituted imidazole leaving group would be compensated by the difficulty of proton transfer to N-3 atom of the substrate **1a**; *i.e.*, the ease of C-N bond breaking by the attack of the water molecule is more important than the protonation on the N-3 atom of the leaving group. Similar results for the water reaction were

observed in the hydrolyses of *N*-acetylimidazole,[9] *N*-acetyl-1,2,4-triazole[10] and *N*-acetylbenzotriazole.[11] However, the k_o value for the substrate **1b** is larger than those of the substrates **1a** and **1c**. This result could be explained by the two factors that the relatively low pKa (nitroimidazole; pKa = 9.1)[12] and the strong electron withdrawing ability of the leaving group will allow both facile nucleophilic attack by the water and ease C-N bond breaking. However, the D_2O solvent isotope effect was not observed in the water reaction.

As indicated in Figure 1, the pH-rate profile for OH^- catalyzed reaction of the substrate **1c** shows a straight line with increasing pH, while those for the substrates **1a** and **1b** appear a break at around pH 9.0. This means that a change of the rate determining step occurs around pH 9.0.

To clarify the OH^- catalyzed reaction of the substrates **1a** and **1b**, we have been applied the Bronsted type plot ($\log k_{OH}$ *vs.* pKa of leaving group). The Bronsted type plot of Figure 2 exhibits a good straight line with a slope (β_{lg}) of −0.4 (r = 0.9997) for OH^- catalyzed reaction in low pH range, from pH 7 to pH 9. The small β_{lg} value reflects that the rate determining step should be the formation of a tetrahedral intermediate (T^-) in low pH region, between pH 7 and pH 9 (① step in equation 2). On the contrary, the correlation of $\log k_{OH}$ *vs* pKa of leaving group in high pH region exhibits a poor with a nonlinear. This result suggests that the rate determining step in high pH region should be changed in comparison with that in low pH region; *i.e.*, the rate determining step at higher pH should be a break down of the intermediate (② step in equation 2).



(2)

The β_{lg} values for OH^- catalyzed reaction of several *N*-acylimidazoles have been observed −0.44 for *N*-aryl-β-lactams,[13] −0.3 for β-phenyl-propionylimidazole derivatives.[14] These β_{lg} values are nearly similar to those obtained in this study. However, the change over the rate determining step in OH^- catalyzed reaction of the substrate **1c** was not observed.

To find out the most effective buffer in the hydrolysis reaction of *N*-cyclopropanecarbonylimidazole derivatives, the effect of total concentration of acetate buffer and cacodylate buffer has been investigated. The catalytic rate constants (k_{cat}) for the hydrolysis of all compounds at each buffer concentrations are listed in Table 2. A plot of k_{cat} for the hydrolysis of the substrate **1b** *vs* the total concentration of acetate buffer and cacodylate buffer has shown in Figure 2. The effective catalyst is cacodylate, but acetate buffer is not nearly as effective although they contain equal concentration. The catalyses of the other compounds showed same results. Accordingly, the effect of free base concentration of cacodylate buffer for the hydrolysis of the substrates **1a** and **1b** was employed. As is shown in Figure 3, the catalysis of cacodylate in the hydrolyses of the substrates **1a** and **1b** indicates completely different pattern each other with increasing the free base concentration. The k_{cat} for the substrates **1b** and **1c** increases with increasing the free base concentration of cacodylate buffer, whereas that for the substrate **1a** shows in contrast to the substrates **1b** and **1c**.

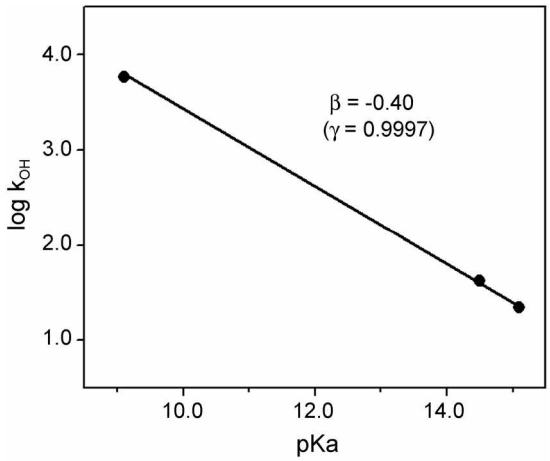


Figure 2. Plot of $\log k_{OH}$ for alkaline hydrolysis of *N*-cyclopropanecarbonylimidazole (**1a**), *N*-cyclopropanecarbonyl-4-nitroimidazole (**1b**) and *N*-cyclopropane-4-methylimiazole (**1c**) *vs* pKa of the leaving group in H_2O (μ = 0.5 M) at 25 °C.

This means that the basic form of cacodylate buffer acts predominantly in the hydrolysis of the substrates **1b** and **1c**, while the substrate **1a** is subject to strong catalysis by the acidic form of cacodylate buffer. Even though the cacodylate buffer acts as bifunctional acid and base catalyst as shown in Scheme 1, this result is very unique in comparison to that obtained for *N*-propionylimidazoles, which have been

Table 2. Effect of acetate and cacodylate buffer concentrations for hydrolysis of *N*-cyclopropanecarbonylimidazole (**1a**), *N*-cyclopropanecarbonyl-4-nitroimidazole (**1b**) and *N*-cyclopropanecarbonyl-4-methylimidazole (**1c**) in H_2O (μ = 0.5 M with KCl) at 25 °C

Buffer	pH	Conc. range (M)	k_{cat} ($M^{-1}\cdot s^{-1}$)		
			1a	**1b**	**1c**
Acetate	3.78	0.03 - 0.50		5.60×10^{-4}	
	4.04	0.03 - 0.50	3.24×10^{-3}		2.05×10^{-3}
Cacodylate	5.10 (0.10)*	0.03 - 0.50	8.89×10^{-2}	3.39×10^{-2}	1.04×10^{-1}
	5.54 (0.25)*	0.03 - 0.50	7.52×10^{-2}	7.64×10^{-2}	9.06×10^{-2}
	6.33 (0.50)*	0.03 - 0.50	4.84×10^{-2}	1.49×10^{-1}	6.56×10^{-2}
	6.89 (0.75)*	0.03 - 0.50	2.52×10^{-2}	2.43×10^{-1}	3.31×10^{-2}

( )* ratio of free base concentration to total buffer concentration.

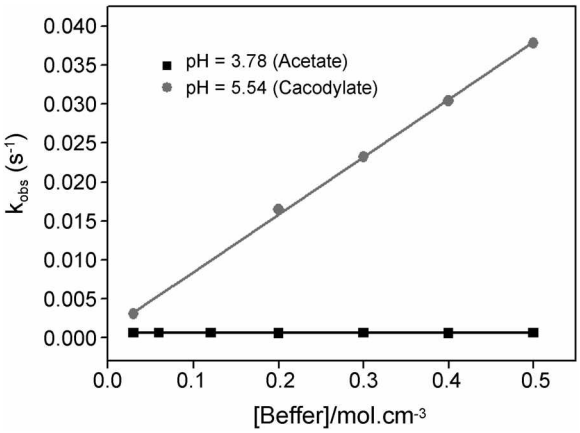
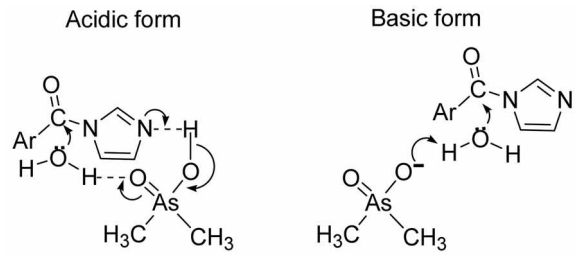


Figure 3. plot of k_{obs} for hydrolysis of *N*-cyclopropanecarbonyl-4-nitroimidazole (**1b**) *vs* total concentration of cacodylate buffer (●) and acetate buffer (■) in H_2O (μ = 0.5 M) at 25 °C.



Scheme 1

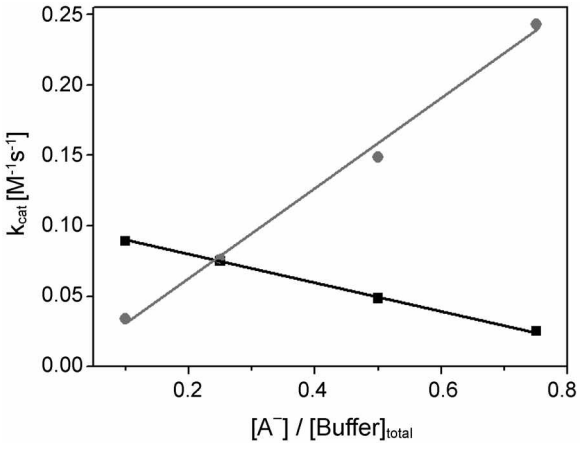


Figure 4. Plot of k_{cat} (slope of a plot of k_{obs} *vs* total cacodylate buffer concentration) *vs* the free base concentration in cacodylate buffer for hydrolysis of *N*-cyclopropanecarbonylimidazole (■) and *N*-cyclopropanecarbonyl-4-nitroimidazole (●) in H_2O (μ = 0.5 M) at 25 °C.

observed the maximum rate at 0.25 M free base concentration of cacodylate buffer.[15]

The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, for all compounds in acidic and basic regions are summarized in Table 3. A large negative $\Delta S^{\neq}$ value and a small positive $\Delta H^{\neq}$ value are nearly the same tendency as those obtained for the hydrolysis of *N*-propionylimidazoles.[15] Thus, this result supports that the reaction proceeds through a typical bimolecular reaction[16] in both acidic and basic regions.

In conclusion, (i) the apparent pKa values of the substrates

Table 3. Thermodynamic parameters for hydrolysis reactions of *N*-cyclopropanecarbonylimidazole (**1a**), *N*-cyclopropanecarbonyl-4-nitroimidazole (**1b**) and *N*-cyclopropanecarbonyl-4-methylimidazole (**1c**) in H_2O (μ = 0.5 M with KCl) at 25 °C

Compound	Ea$^{\neq}$ (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$-\Delta S^{\neq}$ (e.u)
1a	6.95^a	6.35^a	69.6^a
	17.3^b	16.7^b	68.7^b
1b	8.14^a	7.53^a	73.4^a
	3.23^b	2.64^b	67.0^b
1c	13.7^a	13.1^a	69.8^a
	11.8^b	11.2^b	64.0^b

^{a}in acidic region. ^{b}in basic region

reflect the differences in the k_H values. (ii) A break of pH rate profile around pH 9.0 supports that the OH^- catalysed reaction of *N*-cyclopropanecarbonylimidazole (**1a**) and *N*-cyclopropanecarbonyl-4-nitroimidazole (**1b**) is proceeded through an anionic intermediate. (iii) the cacodylate buffer is more effective catalyst than the acetate buffer. (iv) The D_2O solvent isotope effect is not observed for the pH independent reaction. (v) The observed rate constants for the hydrolyses of *N*-cyclopropanecarbonylimidazole derivatives are less than those of *N*-propionylimidazole derivatives.

Acknowledgments. This paper was supported by Dong-A University Research Fund in 2007.

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