Hydrolysis Reactions of *N*-Propionylimidazole Derivatives

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An unusual reactivity in the hydrolysis of *N*-acylimidazoles, sometimes, has been observed depending on the structure of *N*-acylimidazole and the reaction medium.[1] For example, the second order rate constant for pH independent reaction of *N*-acetyl-4,5-diphenylimidzole was 20 times larger than that of simple *N*-acylimidazole even though the leaving group is bulk.[2] And also we have observed an unusual reactivity in the hydrolysis of several compounds, like *N*-benzoyl-2-phenylimidazole which relates with diprotonated species in acidic region[3] and *N*-furoyl-2-phenylimidazole that rate determining step changes in acidic region, etc.[4]

The hydrolytic reactivity of *N*-acylimidazoles has been studied on many compounds in view of similar role of histidine in enzyme reaction, however there are few studies on the compounds having the aliphatic acyl group. In this study, our interest is to examine the substituent effect of the leaving group of *N*-acylimidazoles having simple aliphatic acyl group. So, we have performed the hydrolysis reactions of *N*-propionylimidazole (**1-a**), *N*-propionyl-4-methylimidazole (**1-b**), *N*-propionylbenzimidazole (**2-a**) and *N*-propionyl-5-methylbenzimidazole (**2-b**).

Experimental Section

Materials. All materials used for synthesis of the substrates were purchased from Aldrich or Tokyo Kasei. All organic solvents were purified by the known method.[6] Deionized water were distilled using a Streem III Glass Still and kept under a nitrogen atmosphere. Buffer materials for kinetic studies were analytical reagent grade.

N-Propionylimidazole (**1-a**) was prepared by mixing 10 mmol of propionyl chloride and 10 mmol of imidazole in 100 mL of methylene chloride in the presence of triethylamine as a catalyst. The reaction mixture was refluxed for 40 hours with stirring. The precipitated amine hydrochloride in the reaction mixture was removed by several time washing with water. Then, the filterate was rotary evaporated and dried with vacuum pump. After recrystallization from chloroform-hexane mixture, the compound was melted sharply at 63-64 °C (pale yellow crystal). FT-IR (KBr, cm^{-1}) 1384 (C-N), 1740 (C=O), 3134 (N-H); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 2.84 (q, J = 7.2 Hz, 2H), 7.41 (s, 1H), 7.86 (s, 1H), 8.15 (s, 1H); Mass (m/z): 124 (M^+).

The other compounds, *N*-propionyl-4-methylimidazole (**1-b**) and *N*-propionylbenzimidazole (**2-a**) and *N*-propionyl-5-methylbenzimidazole (**2-b**) were prepared by the same general method outlined for the *N*-propionylimidazole (**1-a**). After recrystallization from chloroform-hexane, the compound (**1-b**) was melted at 67-68 °C (pale yellow crystal). FT-IR (KBr, cm^{-1}) 1732 (C=O), 1338 (C-N), 3445 (N-H); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.2 Hz, 3H), 2.28 (s, 3H), 2.84 (q, J = 7.2 Hz, 2H), 7.15 (s, 1H), 8.06 (s, 1H); Mass (m/z): 138 (M^+).

The compound (**2-a**) was melted at 80-82 °C (white crystal). FT-IR (KBr, cm^{-1}) 1715 (C=O), 1276 (C-N), 3421 (N-H); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.38 (t, J = 7.3 Hz, 3H), 3.05 (q, J = 7.3 Hz, 2H), 7.39 (dd, J = 2.1 Hz, 2H), 7.79 (dd, J = 2.5 Hz, 2H), 8.40 (s, 1H); Mass (m/z): 174 (M^+).

The compound (**2-b**) was melted at 87-89 °C (dark brown crystal). FT-IR (KBr, cm^{-1}) 1729 (C=O), 1375 (C-N), 3618 (N-H); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 1.37 (t, J = 7.3 Hz, 3H), 2.49 (s, 3H), 3.02 (q, J = 7.3 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.56 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H); Mass (m/z): 188 (M^+).

Kinetics. The rates for hydrolysis reactions of reaction substrates (**1-a**), (**1-b**), (**2-a**) and (**2-b**) were measured spectrophotometerically in H_2O at 25 ± 0.1 °C by following the decrease in absorbance due to disappearance of the substrates at wavelengths in the range of 232-254 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. 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 (pH = 5.5-6.7), cacodylate (pH = 5.0-7.4), imidazole (pH = 6.2-8.0), *N*-ethylmorpholine (pH = 6.6-8.6), tris (pH = 7.0-9.0), carbonate (pH = 9.6-10.9) and phosphate (pH = 11.0-11.6).

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 were measured at 25 °C with a DP-215M Dong-Woo meter.

Results and Discussion

The hydrolysis reactions were carried out under pseudo first order conditions with the concentration of buffer in large excess relative to the substrate. The pseudo first order rate constant (k_{obs}) obtained from 89532K Kinetic Software (serial No. 325 G00380) of the Hewlett Packard company which was based on the slope value of the plot of ln(Ao-At) *vs*. time.

The pH rate profiles for the substrates (**1-a**), (**1-b**), (**2-a**) and (**2-b**) are presented in Figure 1. There are three distinct regions corresponding to the hydronium ion catalyzed reaction, hydroxide ion catalyzed reaction and pH independent reaction in acidic region except *N*-propionylbenzimidazole. Therefore, the observed rate constant (k_{obs}) is given by equation (1), where k_1 and k_o are the rate constants for hydrolysis of conjugate acid (SH^+) of the substrate (S) and that of the pH independent reaction of the neutral substrate (S) and k_{OH} is the catalytic rate constant of hydroxide ion catalyzed reation and Ka is the dissociation constant of the conjugate acid of the substrate.

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

The rate constants for hydrolysis reactions of the substrate (**1-a**), (**1-b**), (**2-a**) and (**2-b**) are listed in Table 1.

The values of the rate constants k_H ($k_H = k_1/Ka$) and k_o for hydrolysis of *N*-propionylbenzimidazoles are less than those obtained for hydrolysis of propionylimidazoles having same leaving group. The k_H values for hydrolysis of the *N*-propionylbenzimidazole derivatives are about 150 fold less and k_o values are about 20 fold less than those of the corresponding *N*-propionylimidazoles. These differences could be in part reflected the relatively low pKa of the conjugated acid of the *N*-propionylbenzimidazole derivatives.

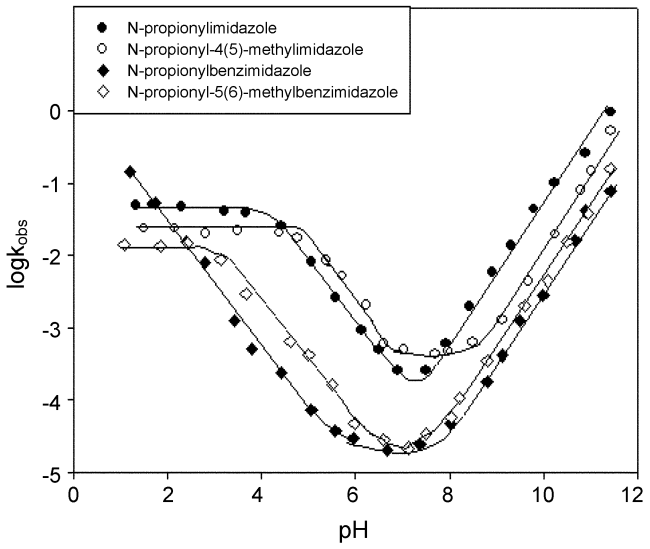


Figure 1. pH-rate profiles for hydrolysis of *N*-propionylimidazoles and *N*-propionylbenzimidazoles in H_2O (μ = 0.5 M with KCl) at 25 °C.

Table 1. Rate constants for hydrolysis of *N*-propionylimidazole (**1-a**), *N*-propionyl-4-methylimidazole (**1-b**), *N*-propionylbenzimidazole (**2-a**) and *N*-propiony-5-methylbenzimidazole (**2-b**) in H_2O (μ = 0.5 M with KCl) at 25 °C

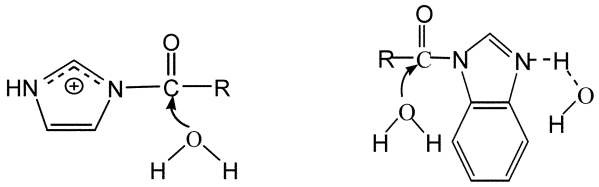
Compound	k_1 (s^{-1})	k_H ($M^{-1}\cdot s^{-1}$)	k_o (s^{-1})	k_{OH} ($M^{-1}\cdot s^{-1}$)	$pKa_{app.}$
1-a	0.113	2257	2.05×10^{-4}	199.5	4.1
1-b	0.740	9363	3.63×10^{-4}	119.0	5.0
2-a	–	15.59	3.50×10^{-5}	54.45	–
2-b	0.068	53.56	1.99×10^{-5}	45.08	2.9

One can see the bent portion at low pH in Figure 1. This means that the pKa value of the conjugate acid of the substrate is around this pH region. We can estimate that the pKa values of the substrate (**1-a**), (**1-b**) and (**2-b**) are 4.1, 5.0 and 2.9 by drawing a pH-rate profiles, respectively. However, in the case of the substrate (**2-a**), one can not see the bent portion even at pH 1.0. This means that the pKa of the conjugate acid of the substrate (**2-a**) is less than 1.0. Therefore, the values of k_H for (**1-b**) and (**1-a**) are larger than those of (**2-b**) and (**2-a**) because of $k_H = k_1/Ka$. Likewise, the differences in k_o values for the substrates (**1-a**), (**1-b**) and (**2-a**), (**2-b**) show similar tendency as well as the variation in k_H for the compounds (**1-a**), (**1-b**) and (**2-a**), (**2-b**). The reason that the relatively small values of k_o for the substrates (**2-a**) and (**2-b**) should be explained by the greater difficulty of proton transfer to the N-3 atom of the benzimidazole in comparison with that of the imidazole as shown in below Scheme 1.

This explanation might be in accord with the fact that the k_{OH} values of the substrates (**1-a**) and (**1-b**) are larger than those of the substrates (**2-a**) and (**2-b**) even though the pKa of the benzimidazole leaving group (12.5) is small than that of the imidazole leaving group (14.5).[7]

In other word, the expected rate accelerating effect on OH^- catalyzed reaction provided by the lower pKa of the benzimidazole leaving group would be offset by the greater difficulty of proton transfer to N-3 atom of the benzimidazole. We can see similar results in alkaline hydrolyses of *N*-acetylimidazole (k_{OH} = 316 $M^{-1}\cdot s^{-1}$, at 30 °C) and *N*-acetylbenzimidazole (k_{OH} = 204 $M^{-1}\cdot s^{-1}$, at 30 °C).[5(a)]

To make sure which one is the most effective buffer in the



Scheme 1

Table 2. Effect of acetate and cacodylate buffer concentrations on the hydrolysis of *N*-propionylimidazole (**1-a**), *N*-propionyl-4-methylimidazole (**1-b**), *N*-propionylbenzimidazole (**2-a**) and *N*-propionyl-5-methylbenzimidazole (**2-b**) in H_2O (μ = 0.5 M with KCl) at 25 °C

Buffer	pH	Conc. range (M)	k_{cat} ($M^{-1}\cdot s^{-1}$)			
			(**1-a**)	(**1-b**)	(**1-c**)	(**1-d**)
Acetate	4.42	0.03~0.5	6.52×10^{-3}		2.93×10^{-4}	
	4.61	0.03~0.5		1.04×10^{-3}		3.59×10^{-4}
Cacodylate	5.10(0.10)*	0.03~0.5	0.202	0.349	3.39×10^{-3}	1.16×10^{-1}
	5.24(0.125)*	0.03~0.5	0.223	0.482	7.88×10^{-3}	1.22×10^{-1}
	5.54(0.25)*	0.03~0.5	0.303	0.659	2.97×10^{-3}	1.81×10^{-2}
	6.33(0.50)*	0.03~0.5	0.215	0.467	2.31×10^{-3}	1.91×10^{-3}
	6.64(0.67)*	0.03~0.5	0.167	0.384	1.63×10^{-3}	2.03×10^{-3}
	6.79(0.75)*	0.03~0.5	0.132	0.226	1.74×10^{-3}	1.19×10^{-3}

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

hydrolysis reaction of *N*-propionylimidazole derivatives, we have investigated the total buffer concentration effects of acetate and cacodylate buffers. The catalytic rate constants for hydrolysis of all compounds at each buffer concentrations are listed in Table 2. As one can see in Figure 2, the effective catalyst in the hydrolysis of *N*-propionylimidazole is cacodylate, whereas acetate buffer is not nearly as effective although they contain equal concentration. And also the other compounds showed same results. In the previous report,[8] we have been observed that the cacodylate buffer among employed catalysts is the most effective in the hydrolysis reactions of *N*-benzoyl-4-methylimidazoles.

An unusual buffer catalysis of cacodylate might be caused by two methyl groups in the cacodylate molecule. And then, the cacodylate molecule should have higher electron density on the oxygen atom in comparison with that of acetate.

To get more information on the character of cacodylate catalyst in the hydrolysis reaction, we have investigated the effect of free base concentration of cacodylate buffer for all compounds. As one can see in Table 2 and Figure 3, when the ratio of free base concentration to the total buffer concentration of the cacodylate buffer, that is, [base]/[buffer]$_T$ is 0.25, the catalytic rate constants of the compounds (**1-a**) and (**1-b**) show the maximum value, whereas those of the compounds (**2-a**) and (**2-b**) observe at 0.125 fraction of base as seen in Table 2. It is very difficult to explain the reason for this maximum phenomenon because the catalytic rate constants of changing pH is usually not very precise due to poor constancy of pH with changing buffer concentration. Nevertheless, a significant meaning that these results give us should be related with the catalytic rate constant (k_{cat}) is combination of catalytic rate constants for general acid and base catalysis as following equation;

$$k_{cat} = (k_{HA}[HA] + k_B[B])/([HA] + [B])$$

where k_{HA} and k_B are the catalytic rate constants for general

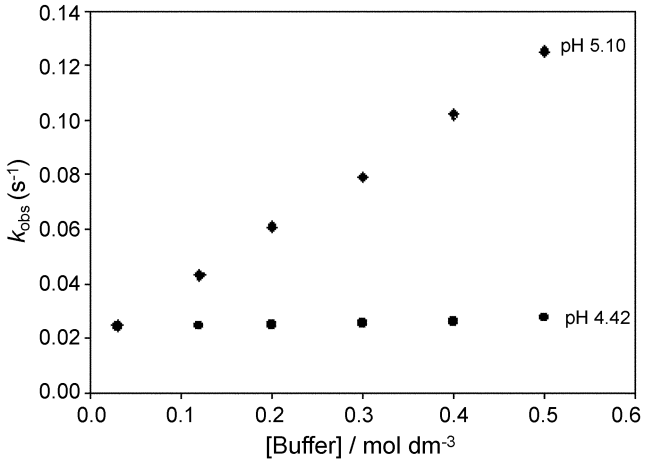


Figure 2. Total buffer effects of acetate (●) and cacodylate (◆) on rate for hydrolysis of *N*-propionylimidazole in H_2O (μ = 0.5 M with KCl) at 25 °C.

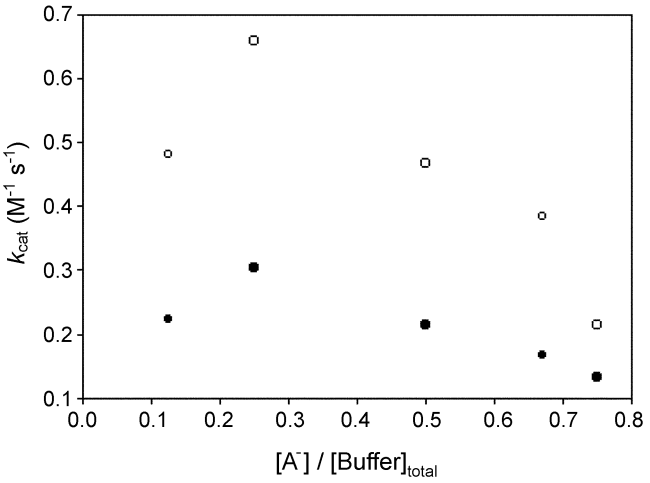


Figure 3. Effect on free base of cacodylate buffer on rate for hydrolysis of *N*-propionylimidazole (●) and *N*-propionyl-4-methylimidazole (○) in H_2O (μ = 0.5 M with KCl) at 25 °C.

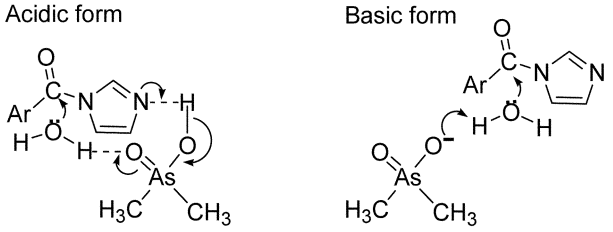


Table 3. Thermodynamic parameters for the hydrolysis reactions of *N*-propionylimidazole (**1-a**), *N*-propionyl-4-methyl-imidazole (**1-b**), *N*-propionylbenzimidazole (**2-a**) and *N*-propionyl-5-methyl-benzimidazole (**2-b**) in H_2O at 25 °C

Compound	$Ea^{\neq}$ (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$-\Delta S^{\neq}$ (e.u)
(**1-a**)	1) 16.7	1) 16.3	1) 65.7
	2) 24.0	2) 22.9	2) 68.3
(**1-b**)	1) 16.6	1) 16.0	1) 66.9
	2) 18.8	2) 17.8	2) 66.3
(**2-a**)	1) 18.9	1) 17.9	1) 72.6
	2) 18.5	2) 17.7	2) 74.5
(**2-b**)	1) 6.63	1) 5.92	1) 73.0
	2) 16.5	2) 15.3	2) 73.4

acid and base catalysis of the cacodylate catalyst, respectively. As a result, the catalysis of cacodylate buffer might be acted by acidic form and basic form. Then, the possible catalyses of acidic form and basic form of the cacodylate buffer should be described as following;

This result is very characteristic, although, sometimes, the catalysis of bifunctional catalysts has been observed the saturation effect with increasing catalyst concentration.[9]

We have determined activation parameter, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, for all compounds in acidic and basic regions and are summarized in Table 3. A large negative value of activation entropy and a small positive value of activation enthalpy are consistent within the range of values expected for the hydrolysis of *N*-acylimidazole derivatives.[7] Thus, this result supports that reaction should be proceeded via the tetrahedral intermediate in both acidic and basic regions.

In summary, we have concluded that (i) the apparent pKa values of the substrates reflect the differences in the k_H and k_o values, (ii) The k_{OH} values are influenced by the protonation to the N-3 atom of the leaving group and the pKa value of the leaving group, (iii) the cacodylate buffer is more effective catalyst than the acetate buffer in the hydrolysis of *N*-propionylimidazole derivatives.

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