Kinetics Studies on the Hydrolysis Reactions of *N*-Heteroaryl-4(5)-nitroimidazoles

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There is little study on the hydrolysis reactions of *N*-heteroarylimidazole derivatives in comparison with those of *N*-acylimidazoles. Some years ago, we reported the hydrolysis reactions of *N*-heteroaryl-2-phenylimidazoles, *N*-furoyl-2-phenylimidazole and *N*-thenoyl-2-phenylimidazole.[1,2] In the hydrolysis reactions of these compounds, we found a change of the rate dertermining step in acidic regions. These results are very unique even though the feature of hydrolysis reactivity of *N*-acylimidazole derivatives depends on the structure of *N*-acylimidazole. But, when one changes the acyl group with the heteroaryl group to the benzoyl group having same leaving group, the pH rate profile for the hydrolysis reaction of *N*-benzoyl-2-phenylimidazole observed to be related with the diprotonated species of the substrate in acidic region.[3]

If *N*-heteroarylimidazole having the strong electron withdrawing group in the leaving group is hydrolyzed, how does the feature of the hydrolysis reaction appear? This is our concerns in this study. And so, we have performed the hydrolysis reactions of *N*-furoyl-4(5)-nitroimidazole (**1**) and *N*-thenoyl-4(5)-nitroimidazole (**2**) in order to compare with the previous results of the hydrolysis of *N*-heteroarylimidazoles having the phenyl group in the leaving group.

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. 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-Furoyl-4(5)-nitroimidazole (**1**) prepared by adding 10 mmol of 4(5)-nitroimidazole and 10 mmol of 2-furoylchloride in dry acetonitrile in the presence of triethylamine as a catalyst. The reaction mixture was generally refluxed with stirring for 48 hrs. The mixture was cooled and filtered, and the acetonitrile was removed by rotary evaporation. The residue was dissolved in dry chloroform and water was added to this solution to remove the amine salt. After the aqueous layer was separated and the methylene chloride was removed by rotary evaporation. The crude product was dried under vacuum condition, and recrystallized from a chloroform-hexane mixture (pale yellow, mp. 121-122 °C).

FT-IR (KBr), 1318 (C-N), 1719 (C=O), 3140 (C-H); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 8.66 (1H, d, J = 1.4 Hz, imidazole), 8.51 (1H, d, J = 1.4 Hz, imidazole), 7.86 (1H, d, J = 0.9 Hz, furan), 7.73 (1H, d, J = 3.7 Hz, furan), 6.80 (1H, dd, J = 3.7, 0.9 Hz, furan). Anal. Calcd. for $C_8H_5N_3SO_3$: C, 43.06; H, 2.24; N, 18.82. Found: C, 42.78; H, 2.19; N, 19.03.

N-Thenoyl-4(5)-nitroimidazole (**2**) was prepared by same methods above described. The product was oil phase (yellow). FT-IR (KBr), 1105 (C-N), 1692 (C=O), 2675 (C-H); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 8.65 (1H, d, J = 1.4 Hz, imidazole), 8.49 (1H, d, J = 1.4 Hz, imidazole), 7.84 (1H, d, J = 2.7 Hz, thiophene), 7.57 (1H, d, J = 4.7 Hz, thiophene), 7.11 (1H, dd, J = 4.7, 2.7 Hz, thiophene). Anal. Calcd. for $C_8H_5N_3O_4$: C, 46.40; H, 2.41; N, 20.28. Found: C, 45.92; H, 2.33; N, 21.07.

Kinetics. The rates for hydrolysis reactions of *N*-furoyl-4(5)-nitroimidazole (**1**) and *N*-thenoyl-4(5)-nitroimidazole (**2**) were measured spectrophotometerically in H_2O at 25 ± 0.1 °C by following the decrease in absorbance due to disappearance of the substrate at wavelengths in the range of 274-312 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 ± 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 (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 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

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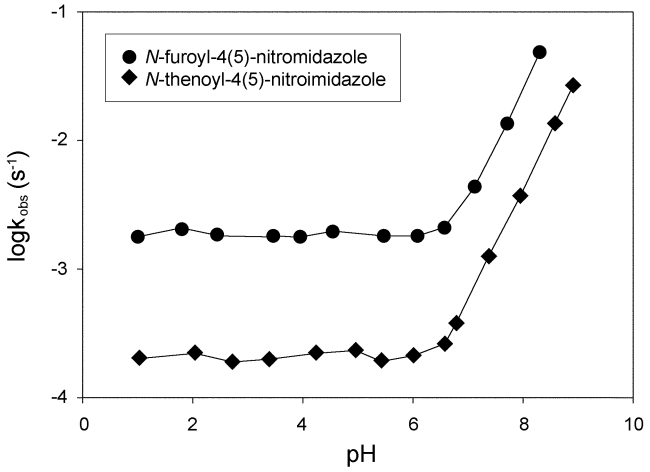


Figure 1. Plots of log kobs *vs.* pH for hydrolysis of *N*-furoyl-4(5)-nitroimidazole (●) and *N*-thenoyl-4(5)-nitroimidazole (■) at 25 °C and μ = 0.5 M with KCl.

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 value of the plot of $\ln(A_O-A_t)$ *vs.* time.

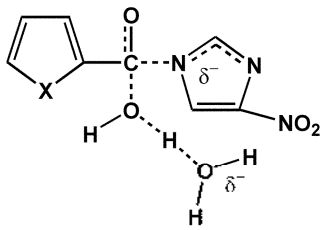
The pH rate profiles for the substrate (**1**) and (**2**) and presented in Figure 1. The pH profiles are similar in shape to those for hydrolysis of corresponding *N*-acylimidazoles.[4] There are two regions corresponding to the pH independent reaction below pH 7.0 and the hydroxide ion catalyzed reaction above pH 7.0. Therefore, the observed rate constant (k_{obs}) is given by equation (1)

$$k_{obs} = k_o + k_{OH}[OH^-] \quad (1)$$

where k_o and k_{OH} are the rate constants for water catalyzed and hydroxide catalyzed reactions, respectively. The rate constants for hydrolysis reactions of the substrate (**1**) and (**2**) are listed in Table 1.

The catalytic rate constants k_o and k_{OH} of *N*-furoyl-4(5)-nitroimidazole are larger than those of *N*-thenoyl-4(5)-nitroimidazole. These difference should be explained by the polar substituent constant (σ^*)[5] of the Taft's equation which is 1.06 for furoyl group and 0.92 for thenoyl group. Since the magnitude of the polar substituent constant means the degree of the electron withdrawing ability of the substituent, the substituent having a large value in the polar substituent constant should lead more positive charge at the reaction center. Therefore, the catalytic rate constants of *N*-furoyl-4(5)-nitroimidazole is larger than those of *N*-thenoyl-4(5)-nitroimidazole. Above explanation is consistent with the p*K*a values of the parent acid of carbonyl moiety, *i.e.*, 2-furoic acid (p*K*a = 3.16) and thiophene 2-carboxylic acid (p*K*a = 3.53).[6] A similar results have been observed for the aminolyses of aryl thiophene 2-carboxylate and aryl 2-furoate.[7,8]

As one can see in Table 1, *N*-furoyl-4(5)-nitroimidazole (**1**) in the pH independent reaction hydrolyzes about 16 fold faster than unsubstituted *N*-furoylimidazole at 40 °C, whereas *N*-thenoyl-4(5)-nitroimidazole (**2**) is only enhanced about 6 fold by the nitro group substitution at same temperature.[9] These results are similar to those for the hydrolysis of *N*-(3,3-dimethylbutyryl-4(5)-nitroimidazole (k_o = 1.25 × 10^{-4} s^{-1} at 30 °C) and *N*-(3,3-dimethylbutyryl-4(5)-imidazole (k_o = 2.0 × 10^{-5} s^{-1} at 30 °C).[4] Therefore, in this study, the rate accelerating effect of a 4(5)-nitro group on the pH independent reactions is small, even though the D_2O solvent isotope effect was found. This result might be considered that the substituent effect of nitro group is not quite effective due to the resonance interaction with imidazole ring and nitro group, producing a partial negative charge on the imidazole ring, like in Scheme 1.



X=O, S

Scheme 1

Then, the nucleophilic attack by water to the carbonyl carbon might be not affected greatly by the substituent, nitro group.

On the other hand, in the OH^- catalyzed hydrolysis reaction, the catalytic rate constants (k_{OH}) of the substrate (**1**) and (**2**) show very large values.

Generally, the rates of OH^- catalyzed hydrolysis of *N*-acylimidazoles are remarkably rapid even though the p*K*a

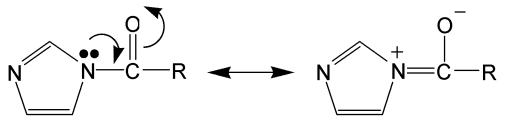
Table 1. Rate constants and activation parameters for hydrolysis of *N*-furoyl-4(5)nitroimidazole (**1**) and *N*-thenoyl-4(5)-nitroimidazole (**2**) in H_2O at 25 °C, 40 °C and μ = 0.5 M

compound	k_o (s^{-1})	k_{OH} (M^{-1}·s^{-1})	k_{H2O}/k_{D2O}	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e·u)
(**1**)	1.86 × 10^{-3}	28147	2.0	9.97[a]	-36.6[a]
	*6.65 × 10^{-3}	*129000		8.51[b]	-67.1[b]
N-furoyl-imidazole	*4.11 × 10^{-4}	*2180			
(**2**)	2.11 × 10^{-4}	4407	2.1	13.3[a]	-29.8[a]
	*9.09 × 10^{-4}	*7820		12.5[b]	-70.3[b]
N-thenoyl-imidazole	*1.50 × 10^{-4}	*871			

*taken from ref. 7. [a]acidic region. [b]basic region.

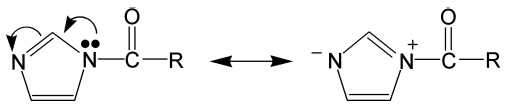
value of the leaving group has quite low. For example, the k_{OH} for OH^- catalyzed hydrolysis reaction of *N*-acetylimidazole is 316.6 $M^{-1}\cdot s^{-1}$ at 25°C,[10] whereas the k_{OH} for hydrolysis of the reactive ester *p*-nitrophenylacetate is 14.8 $M^{-1}\cdot s^{-1}$ at 25 °C,[11] even though the p*K*a of the imidazole is 14.5,[12] over 7 p*K*a unit greater than that of *p*-nitrophenol.

Such like hydrolytic behavior of *N*-acylimidazole derivatives should be due to partial positive charge on the carbonyl carbon. This means that there is little resonace interaction between N-1 atom of the imidazole and the carbonyl carbon as shown in eq. 1.



(1)

If such a resonance interaction occurs, the carbonyl carbon should be deactivated, and then the rate of OH^- catalyzed reaction should be slow. However, in acylimidazoles there will be opposed resonance in which N-3 atom of the imidazole has net negative charge as shown in eq. 2.



(2)

Molecular orbital calculations on *N*-acetylimidazole[13] have indicated that N-3 atom has a negative charge of -0.23, whereas N-1 atom and the carbonyl carbon have charge of +0.475 and +0.287, respectively.

As a consequence, the rate accelerating effect of nitro group produces small and the k_{OH} value must be large.

Finally, in this study, we have found that the rate accelerating effect by the substituent, NO_2 group in the leaving group is small. The large k_{OH} value in OH^- catalyzed hydrolysis reaction should be explained that the resonance interaction of the leaving group itself is more important than that between N-1 atom of the imidazole and the carbonyl carbon.

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