Kinetics and Mechanism of the Hydrolysis Reaction of *N*-Furoyl-2-phenylimidazole

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For a couple of dacades, hydrolysis reactions of *N*-acylimidazoles have been extensively studied in the view of the similar role of histidine in biological acyl group transfer reactions.[1-10] Hydroxide ion and hydronium ion catalysis have been observed in these reactions and a pH independent reaction occurs near pH 6-7. However, sometimes, the hydrolytic reactivity of *N*-acylimidazole derivatives has showed exceptional reactivity depending on the structural features.[11,12] For example, the second order rate constant k_{OH} for alkaline hydrolysis of *N*-trimethylacetylbenzimidazole is 612 $M^{-1} \cdot s^{-1}$ at 30 °C,[13] whereas k_{OH} for hydrolysis of acetylbenzimidazole is 204 $M^{-1} \cdot s^{-1}$ at the same temperature.[14] Likewise, we can observe the similar tendency in the hydrolysis reaction of *N*-acetylimidazole (k_{OH}: 316 $M^{-1} \cdot s^{-1}$, 25 °C)[11] and that of *N*-trimethyl-2,4,5-triphenylimidazole (k_{OH}: 4720 $M^{-1} \cdot s^{-1}$, 15 °C).[13] But the hydrolytic reactivity of *N*-acylimidazole derivatives does not always exhibit such a tendency.

Recently, we reported on the hydrolysis of *N*-thenoyl-2-phenylimidazole,[15] in which the rate determining step changes in the acidic region. This hydrolysis reaction is very interesting, even though the change in the structure of *N*-acylimidazole, sometimes, gives rise to an abnormal reactivity in hydrolysis reaction.

This study concerns with how the reaction mechanism is changed when the acyl group is changed from thenoyl group to furoyl group. So, we performed the hydrolysis reaction of *N*-furoyl-2-phenylimidazole in order to compare with the previous result of the hydrolysis *N*-thenoyl-2-phenylimidazole.

The substrate, *N*-furoyl-2-phenylimidazole, can be obtained easily from the reaction of 2-phenylimidazole with 2-furoylchloride in methylene chloride. The rates of the hydrolysis were measured spectrophotometrically in H_2O at 40 °C by following the absorbance decrease due to disappearance of the substrate at wavelengths between 254 and 265 nm. Buffer solutions were maintained at a constant ionic strength (μ) 0.5 M with potassium chloride (KCl). The buffer solutions employed were hydrogen chloride, formate, acetate, calcodylate, imidazole, tris, and carbonate. The hydrolysis reactions are catalyzed by buffer. Therefore, rate constants were obtained by extrapolation to zero buffer concentration.

Figure 1 is a plot of log k_{obs} at zero buffer concentration *vs*. pH for the hydrolysis of *N*-furoyl-2-phenylimidazole in H_2O at 40 °C, μ = 0.5 M with KCl. Hydroxide ion catalyzed reactions are observed above pH 8. The second order rate constant k_{OH} is 1590 $M^{-1} \cdot s^{-1}$. This value is a little bit larger than that obtained for reaction of *N*-thenoyl-2-phenylimidazole at the same reaction conditions (k_{OH} = 1320 $M^{-1} \cdot s^{-1}$).[15] This

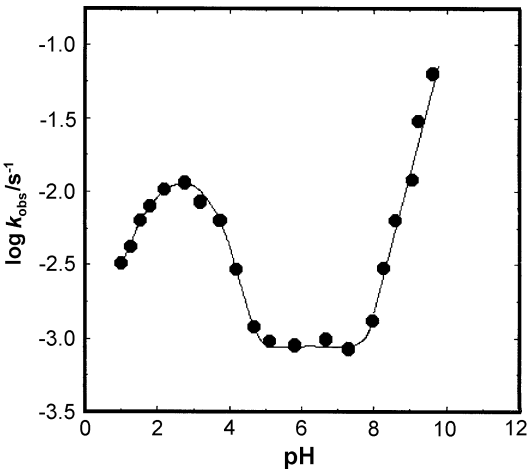
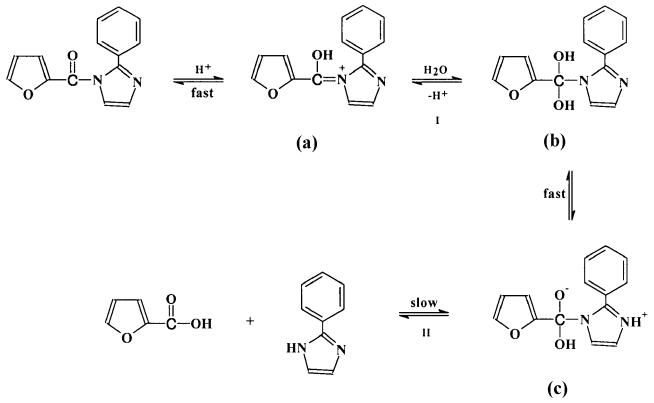


Figure 1. A plot of log k_{obs} *vs*. pH for the hydrolysis of *N*-furoyl-2-phenylimidazole in H_2O at 40 °C, μ = 0.5 M with KCl.

difference may be caused by the different acyl group. In the previous report[16] on the aminolysis of esters which have the different acyl group, that is, 4-nitrophenyl-2-furoate and 4-nitrophenyl-2-thiophenate, the rate constant for the aminolysis of furoate was observed to be larger than that of thiophenate. This result should be explained by the polar substituent constant (σ^*) of the Taft's equation[17] 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, a larger value in the polar substituent constant should lead to more positive charge at the reaction center. Therefore, the second order rate constant k_{OH} for hydroxide ion catalyzed hydrolysis of *N*-furoyl-2-phenylimidazole should be larger than that of *N*-thenoyl-2-phenylimidazole.

The pH independent reaction of *N*-furoyl-2-phenylimidazole was observed between pH 5 and pH 8, whereas that of *N*-thenoyl-2-phenylimidazole was in more acidic region, below pH 4. This result may reflect that the neutral species of *N*-furoyl-2-phenylimidazole is more stable than that of *N*-thenoyl-2-phenylimidazole between pH 5 and pH 8.

However, the hydrolysis reactions of *N*-furoyl-2-phenylimidazole at pH < 5 occur more complicatedly. This means that the hydrolysis reaction in this pH range is related to the protonated species and should change the rate determining step. As shown in Figure 1, the rate constants (k_{obs}) increase with increasing hydronium ion concentration from pH 5 to pH 3. This could be explained that the first protonation of the substrate would occur at the carbonyl oxygen. Therefore, the rate determining step I would be the formation of the intermediate (b) by attacking the water molecule



Scheme

to the carbonyl carbon of the protonated substrate (a) as shown in Scheme.

On the other hand, one can see that the rate constants decrease with increasing hydronium ion concentration below pH 3. This result may reflect that the proton from the intermediate (b) would be rapidly transfered to *N*-3 atom of the 2-phenylimidazole leaving group and then the rate determining step II would be breakdown of the intermediate (c).

The pH-rate profile for the hydrolysis of *N*-furoyl-2-phenylimidazole is similar to that of *N*-thenoyl-2-phenylimidazole, but the stability of the protonated species and the neutral species of *N*-furoyl-2-phenylimidazole seems to be different compared with that of *N*-thenoyl-2-phenylimidazole.

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