Kinetics Studies on the Hydrolysis of *N*-Benzoyl-4,5-diphenylimidazole Derivatives

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Recently, we have reported hydrolysis reactions of three *N*-acylimidazoles compounds having one phenyl substituent in the imidazole leaving group.[1] In the hydrolysis reaction of *N*-furoyl- and *N*-thenoyl-2-phenylimidazole of these three compounds observed a change in rate determining step in acidic region, whereas, that of *N*-benzoyl-2-phenylimidazole found to be related with the diprotonated species in acidic region. Even though, the change in the structure of *N*-acylimidazoles, sometimes, give rise to an abnormal reactivity in hydrolysis reaction,[2] the feature of the hydrolysis of the above three *N*-acyl-2-phenylimidazoles compounds was very unique in comparison with the previous obtained results from hydrolysis of *N*-acylimidazole derivatives.[3-9]

In this study, our interest is to examine how the substituent effect of the acyl group in the hydrolysis of *N*-acylimidazoles exhibits when the leaving group imidazole has two phenyl group. So, we have performed the hydrolyses reactions of *N*-benzoyl-4,5-diphenylimidazole, *N*-toluoyl-4,5-diphenylimidaozole and *N*-anisoyl-4,5-diphenylimidazole.

Materials. Materials of synthesis of the substrates were purchased from Aldrich or Tokyo Kasei. Acetonitrile was dried with CaH_2 stored over molecular sieves. Deionized water was distilled using a Streem III Glass Still and ketp under a nitrogen atomosphere. Buffer materials for kinetic studies were analytical grade.

N-benzoyl-4,5-diphenylimidazole (**1-a**) was prepared by mixing benzoyl chloride and 10 mmol of 4,5-dephenylimidazole in 100 mL of dichloromethane in the presence of triethylamine a catalyst. The reaction mixture was refluxed for 48 hr and filterd. The filtrate was evaproated under vaccum. The product was recrystallized from ether-hexane (pale yellow), m.p. 186-187 °C, FT-IR (KBr), 1340 (C-N), 1718 (C=O), 3109 (C-H); ^{1}H NMR ($CDCl_3$, 200 MHz), 7.24-7.52 (m, 10H), 7.54 (d, J = 5.6 Hz, 2H), 7.64 (m, 1H), 7.81 (d, J = 7.4 Hz, 2H), 7.95 (s, 1H). Anal. Cald. for $C_{22}H_{16}N_2O$: C, 81.48; H, 4.93; N, 8.64. Found: C, 80.74; H, 5.07; N, 8.49.

N-toluoyl-4,5-diphenylimidazole (**1-b**) and *N*-anisoyl-4,5-dipheylimidazole (**1-c**) were prepared by the same method as that for *N*-benzoyl-4,5-diphenylimidazole. After recrystallization from ether-hexane (dark brown), the compound (**1-b**) melted at 153-155 °C. FT-IR (KBr), 1373 (C-N), 1713 (C=O), 3163 (C-H); ^{1}H NMR ($CDCl_3$, 200 MHz), 7.98 (d, J = 8.2 Hz, 2H), 7.95 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.23-7.55 (m, 10H), 2.63 (s, 3H). Anal. Calcd. for $C_{23}H_{18}ON_2$: C, 81.65; H, 5.32; N, 8.28. Found: C, 82.77; H, 5.46; N, 8.13.

After recrystallization from ether-hexane (yellow brown), the compound (**1-c**) melted 105.3 °C. FT-IR (KBr), 1358 (C-N), 1711 (C=O), 3153 (C-N); ^{1}H NMR ($CDCl_3$, 200 MHz), 8.12 (d, J = 8.9 Hz, 2H), 7.95 (s, 1H), 7.82 (d, J = 8.9 Hz, 2H), 7.54-7.25 (m, 10H), 3.91 (s, 3H). Anal. Calcd. for $C_{23}H_{18}O_2N_2$: C, 77.96; H, 5.08; N, 7.90. Found: C, 78.03; H, 5.01; N, 8.06.

Kinetics. The rates of the hydrolysis of (**1-a**), (**1-b**) and (**1-c**) were measured spectrophotometrically in H_2O at 25 °C ± 0.1 °C by monitoring the decrease in absorbance due to disappearence the substrate at the wavelengths in the range of 266-285 nm. The rate mesurement was carried out using a Hewlett Packard 8452 A Diode Array spectrophotometer equipped with a Shimatzu TB-85 thermo bath to keep the temperature of the reaction mixure 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 at 2.5 °C ± 0.1 °C. The buffer solutions employed were HCl (1.0-2.2), formate (2.6-4.8), acetate (3.6-5.6), 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), carbonate (9.6-11.0), phosphate (10.9-12.0). The hydrolysis reactions are catalyzed by buffer. Therefore, rate constants were obtained by extrapolation to zero buffer concentration. Catalytic rate constants were obtained from plots of k_{obs} versus concentration of catalyst. Reaction mixture pH values were measured with a DP-215M pH meter from Dong Woo Medical company.

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 and pseudo first order rate constant (kobs) 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. From these k_{obs} values, we could draw the

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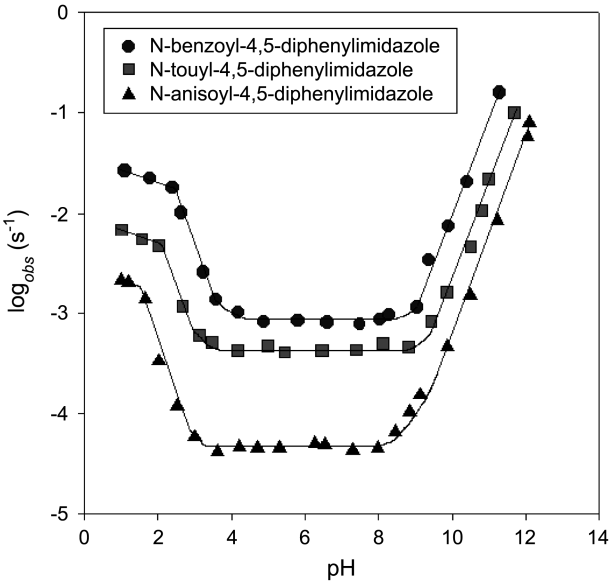


Figure 1. Plots of log k_{obs} *vs*. pH for hydrolysis of *N*-benzoyl-4,5-diphenylimidazole (■), *N*-toluoyl-4,5-diphenylimidazole (●) and *N*-anisoyl-4,5-diphenylimidazole (▲) at 30 °C and $\mu = 0.5$ M with KCl.

pH rate profile for the substrates (**1-a**), (**1-b**) and (**1-c**) as shown in Figure 1.

The pH-rate profiles, log k_{obs} *vs*. pH, for the hydrolysis reaction of all compounds are similar in shape to those from the hydrolysis of corresponding *N*-acylimidazoles.[1-3] There are three regions corresponding to the hydroxide ion catalyzed reaction above pH 9.0, the pH independent reaction between pH 4.0 and pH 8.5 and the hydronium ion catalyzed reaction around pH 3.0. Therefore, the rate constant is given by equation (1)

$$k_{obs} = k_H[H_3O^+] + k_o + k_{OH}[OH^-] \qquad (1)$$

where k_H, k_o and k_{OH} are the rate constants for the hydronium ion catalyzed, water catalyzed and hydroxide ion catalyzed reactions, respectively.

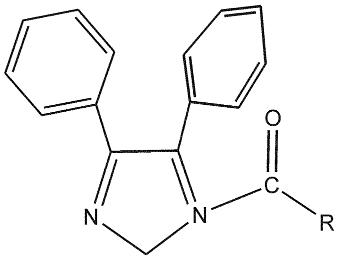
The rate constants for the hydrolysis of the substrates (**1-a**), (**1-b**) and (**1-c**) are listed in Table 1.

As one can see in Table 1, the catalytic rate constants k_H, k_o and k_{OH} decrease with increasing electron donating ability of the substituent in the acyl group. This means that the strong electron donating group, like -CH_3 group, in the acyl group should be increased the electron density on carbon atom of carbonyl moity. And then, the catalytic rate constant of *N*-anisoyl-4,5-diphenylimidazole is less than those of *N*-benzoyl-4,5-diphenylimidazole and *N*-toluoyl-4,5-diphenylimidazole.

The rate constants k_H and k_o for reactions involving the attack of the water molecule to the protonated species or the neutral species show that the k_H value of *N*-benzoyl-4,5-diphenylimidazole (**1-a**) is about 2-20 fold larger than and the k_o value is about 9-93 fold larger than those of *N*-toluoyl-4,5-diphenylimidazole (**1-b**) and *N*-anisoyl-4,5-diphenylimidazole (**1-c**). These results can be in part reflected the relatively low pKa value of the conjugate acid of the substrate (**1-c**) than those of the substrates (**1-a**) and (**1-b**). One can see the bent portion in the pH-rate profiles of Figure 1 at low pH. This means that the appearent p$K_{app.}$ values of the substates (**1-a**), (**1-b**) and (**1-c**) are 2.5, 2.0 and 1.5, respectively. Thus, the k_H and k_o values of the substrate (**1-c**) is relatively small because the p*K*a value of the conjugate acid of the substrate (**1-c**) is low. One can see similar results from the hydrolysis reaction of *N*-acylbenzimidazole derivatives.[9]

Generally, the rate for the OH^- catalyzed reaction of *N*-acylimidazoles depends on the p*K*a value of the leaving group. In our previous paper,[8] the rate constants, k_{OH}, for the OH^- catalyzed reaction of *N*-acylbenzimidazoles are less than those for the corresponding 4,5-diphenyl substituted compounds, even though the p*K*a values of the leaving group, 4,5-diphenylimdazole and benzimidazole are identical (p*K*a = 12.8 at 25 °C). In this study, we can see the same tendency; *N*-benzoyl-4,5-diphenylimidazole hydrolyzed 2 fold faster than *N*-benzoybenzimidazole in the OH^- catalyzed reaction at the same temperature.

For the reason that the catalytic rate constant, k_{OH}, for hydrolysis of *N*-acyl-4,5-diphenylimidazole is faster than that of *N*-acylbenzimidazole, we should be explained by the geometry of the leaving group, 4,5-diphenylimidazole. In molecular orbital calculation,[8] the energy minimized structure of the leaving group, 4,5-diphenylimidazole in the *N*-acyl-4,5-diphenylimidazole can not be coplanar with the imidazole ring. Therefore, the phenyl groups in the imidazole ring are each twisted out of the plane of the imidazole ring so that the alignment in propellar like, as shown in



Scheme

Table 1. Rate constants for hydrolysis of *N*-(*p*-substituted benzoyl)-4,5-diphenylimidazoles in H_2O at 30 °C with $\mu = 0.5$ M KCl

Compound	k_H ($M^{-1}\cdot s^{-1}$)	k_o (s^{-1})	k_{OH} ($M^{-1}\cdot s^{-1}$)	pKa$_{app}$
N-benzoyl-4,5-diphenylimidazole	4.617	8.09×10^{-4}	240	2.5
N-toluoyl-4,5-diphenylimidazole	0.526	4.59×10^{-4}	26.3	2.0
N-anisoyl-4,5-diphenylimidazole	0.0492	4.57×10^{-5}	7.25	1.5

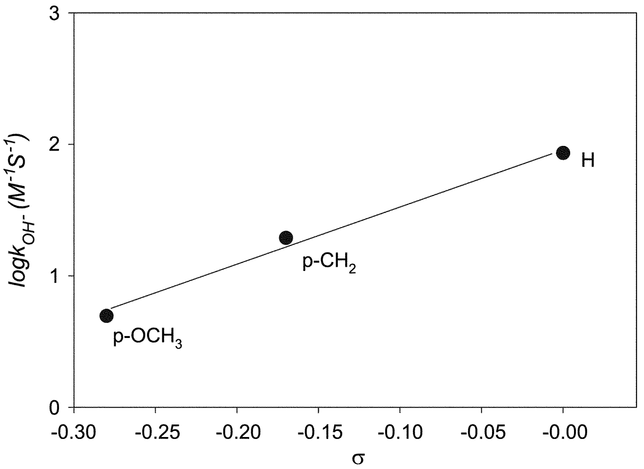


Figure 2. Plot of log k_{OH^-} *vs*. σ for hydrolysis of *N*-benzoyl-4,5-diphenylimidazole derivatives in H_2O at 30 °C, μ = 0.5 M with KCl.

Scheme. Thus, the positive charge of the carbonyl carbon in the transition state should be more developed by the electronic interaction between the hydrogen atom of the benzene ring in the leaving group and the carbonyl oxygen atom. As a result, the attack of the OH^- should be more easy. The steric distortion of amide has been found to give rise to enhanced rates of hydrolysis.[10,11]

As one can see in Table 1, the k_{OH} values for the hydrolysis of the substrates (**1-b**) and (**1-c**) show 9-33 fold less than that of the unsubstituted substrate (**1-a**). These results may be considered to be due to the electronic interaction with the substituent and the reaction center. Thus, we have been investigated the Hammett plot to obtain information on the effect of the substituent in the OH^- catalyzed reaction in Figure 2.

The ρ value has been calculated to be *ca*. 5.44 (r = 0.9992). This value is very large. Generally, the ρ value for the hydrolysis of amides is small because of the relatively low reactivity of amide. However, somtimes, the ρ value for the bimolecular reaction with anionic nucleophile appears to be large. For example, the ρ value for the OH^- catalyzed reaction of ethyl benzoates was found 2.55.[12] In this reaction, the ρ value is almost 2 fold larger than that of the above reaction. These results might be in accord with the hypothesis of the geometry of the 4,5-diphenyl leaving group in the transition state. Therefore, the OH^- catalyzed reaction of *N*-benzoyl-4,5-diphenylimidazole derivatives should be influenced by the two effects of the substituent and the geometry of the leaving group.

To make sure whether the hydrolysis reaction of *N*-benzoyl-4,5-diphenylimidazoles is or is not catalyzed by the general base, we have been measured the rate constants in the total concentration of acetate buffer at pH 5.11. As one can see in Figure 3, the hydroysis reaction is not subjected to catalysis by the general base.

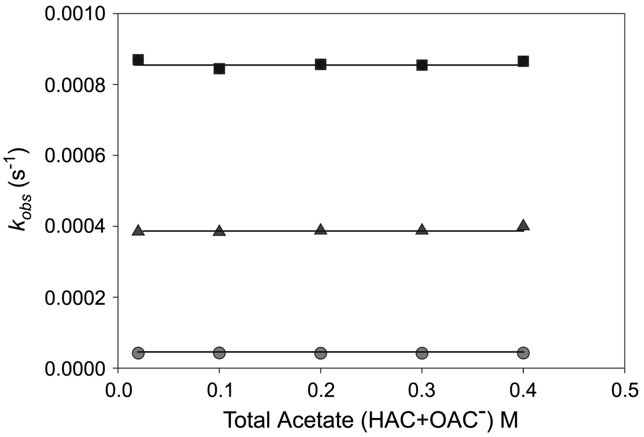


Figure 3. Plot of k_{obs} *vs*. the total concentration of acetate buffer (HAC + OAC$^-$) for hydrolyses of *N*-benzoyl-4,5-diphenylimidazole (■), *N*-toluoyl-4,5-diphenylimidazole (▲), and *N*-anisoyl-4,5-diphenylimidazole (●) at 30 °C in H_2O and μ = 0.5 M with KCl.

The D_2O solvent isotope effect in the pH independent reactions of all compounds observed k_{H_2O}/k_{D_2O} = 0.98-1.2. This means that there is no general base catalysis in the pH independent reaction of the 4,5-diphenylimidazole *N*-benzoyl derivatives. This result is in accord with the obtained data that the total buffer effect was not observed for the hydrolysis of 4,5-diphenylimidazole *N*-benzoyl derivatives. Generally, the pH independent reactions of N-acylimidazole derivatives proceed more slowly in D_2O than in H_2O, which indicates proton transfer in the transition state.[13] In this study, the D_2O solvent isotope effect is not observed. It is not obvious that the reason is due to the steric effect of the leaving group or another factor.

The activation parameters for the pH independent reaction of all compounds are summarized in Table 2. The values of activation enthalpy of all compounds in the pH independent reaction are larger than those of activation entropy. Generally, the activation parameters for the pH independent reaction of *N*-acylimidazole derivatives are observed to have a large negative value of activation entropy and a small positive value of activation enthalpy. If the pH independent reaction takes place by general base catalysis, the value of activation entropy should be large value relatively to the value of the activation enthalpy. However, in this reaction, the large value of activation enthalpy may be considered to be due to the obtained results of the total buffer effect and

Table 2. Thermodynamic parameters for the pH independent reaction of *N*-(*p*-substituted benzoyl)-4,5-diphenylimidazoles in H_2O at 30 °C

Compound	$Ea^{\neq}$ (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$-\Delta S^{\neq}$ (e.u)
N-benzoyl-4,5-diphenylimidazole	18.9	18.3	12.1
N-toluoyl-4,5-diphenylimidazole	31.2	30.6	27.1
N-anisoyl-4,5-diphenylimidazole	34.3	33.7	29.8

the D_2O solvent isotope effect. Therefore, the structure of transition state in the pH independent reaction may be more developed the bond breaking than the bond formation. This work shows very interesting results, like the larger value of ρ and the activation enthalpy and so on. So, we are planning to further study on the hydrolysis reaction of *N*-(4-substituted)benzoylbenzimidaoles which a geometry of the leaving group is coplanar and compare it with the present work.

In summary, we have concluded that (i) the appearent p*K*a values of the substrates reflect the differences in the k_H values and k_o values, (ii) the hydrolysis reactions of *N*-benzoyl-4,5-diphenylimidazoles are not catalyzed by the general base, (iii) the geometry of the leaving group in the hydroxide ion catalyzed reaction is very important and (iv) the substituent effect on the hydroxide ion catalyzed reaction appears very large.

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