Kinetics and Mechanism for Hydrolysis Reaction of *N*-Benzoyl-2-phenylimidazole

Jong-Pal Lee* **and Sung-Sik Lee†**

Department of Chemistry, Dong-A University, Pusan 604-714, Korea
†Department of Chemical Engineering, Dong-A University, Pusan 604-714, Korea
Received October 26, 2001

Keywords : *N*-Benzoyl-2-phenylimidazole, Protonation, Di-protonated species.

Recently, we have reported the mechanism for hydrolyses of *N*-thenoyl-2-phenylimidazole[1] and *N*-furoyl-2-phenylimidazole.[2]

The pH-rate profiles for the hydrolysis of these two compounds exhibited three distingtive regions corresponding to hydronium ion catalyzed reaction, pH independent reaction and hydroxide ion catalyzed reaction above pH 8. Surprisingly, a character of hydrolysis reaction of these two compounds is a change in rate determining step (RDS) in acidic region. These results were very interesting in comparison with hydrolyses[3-9] of *N*-acylimidazoles having an aromatic or aliphatic acyl group, even though the change in the structure of *N*-acylimidazole, sometimes, gives rise to an abnormal reactivity in hydrolysis reactions.[10,11]

In this study, our aim is to examine how the reaction mechanism changes in acidic region when the acyl group varies from a heteroaryl group to a benzoyl group. We have performed hydrolysis of *N*-benzoyl-2-phenylimidazole in order to compare with our previous results obtained from hydrolyses of *N*-furoyl-2-phenylimidazole and *N*-thenoyl-2-phenylimidazole.

Experimental Section

Materials. Materials for synthesis of the substrate were purchased from Aldrich or Merck. THF was distilled from $LiAlH_4$ and stored over molecular sieves (Aldrich 4.0 Å). Acetonitrile(HPLC grade) was dried with CaH_2, and stored over molecular sieves(Aldrich 4.0 Å). Deionized water was distilled using a Streem III Glass Still and kept under a nitrogen atomosphere. Buffer materials for kinetic studies were analytical reagent grade. *N*-benzoyl-2-phenylimidazole (**1**) was prepared by adding 1.40 g (10 mmol) of 2-phenylimidazole and 1.44 g (10 mmol) of benzoyl chloride in THF in the presence of pyridine (0.79 g) as a catalyst. The reaction mixture was stirred for 24 hrs at room temperature, and filtered. The filtrate was evaporated under vacuum. The crude product was recrystallized from hexane (yellow, mp 84-86 °C), ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19-7.29 (d, 2H, J = 1.65 Hz, imidazole), 7.79-8.62 (m, 5H, phenyl), 7.42-7.56 (m, 5H, 2-phenyl); FT-IR (KBr, cm^{-1}) 1180 (ν(C-N)), 1780 (ν(C=O)), 3150 (ν(C-H)). Anal. Calcd. for $C_{16}H_{12}ON_2$: C, 77.39; H, 4.83; N, 11.27. Found: C, 77.42; H, 4.80; N, 11.32.

Kinetics. The rate constants for hydrolysis of *N*-benzoyl-2-phenylimidazole were measured in H_2O at 25 ± 0.1 °C by monitoring the decrease in absorbance due to disappearance the substrate at wavelengths in the range of 242-304 nm. The measurement of rate constants was carried out using a Hewlett Packard 8452 A Diode Array spectrophotometer equipped with a Shimdzu TB-85 thermo bath to keep the temperature of the reaction mixture at 25.0 ± 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 a 1.0×10^{-2} M stock solution of the substate in acetonitrile into 3.0 mL of buffer solution maintained at 25.0 ± 0.1 °C. The buffer solutions employed were formate (pH = 2.98-3.94), acetate (pH = 4.62-4.90), calcodylate (pH = 5.04-5.92), Tris (pH = 6.72-8.80) and carbonate (pH = 9.06-10.7).

Results and Discussion

Hydrolysis has generally been understood to be catalyzed by buffer. Therefore, the observed rate constants were calculated by extrapolation to the zero buffer concentration. The observed rate constants for hydrolysis of *N*-benzoyl-2-phenylimidazole (**1**) in a wide range of pH are summarized

Table 1. Pseudo First Order Rate Constants for the Hydrolysis of *N*-benzoyl-2-phenylimidazole in H_2O at 25 ± 0.1 °C and μ = 0.5 M KCl

Buffer	pH	k_{obs} (s^{-1})
HCl	2.66	3.13×10^{-3}
Formate	2.98	1.64×10^{-3}
Formate	3.20	1.00×10^{-3}
Formate	3.94	2.62×10^{-4}
Acetate	4.62	2.28×10^{-4}
Acetate	4.90	2.80×10^{-4}
Calcolate	5.04	2.78×10^{-4}
Calcolate	5.84	2.49×10^{-4}
Calcolate	5.92	2.44×10^{-4}
Tris	6.72	1.16×10^{-5}
Tris	7.07	5.62×10^{-6}
Tris	7.58	5.01×10^{-6}
Tris	7.96	1.07×10^{-5}
Tris	8.80	8.86×10^{-5}
Carbonate	9.06	8.71×10^{-5}
Cardonate	9.60	9.56×10^{-5}
Carbonate	10.0	2.99×10^{-4}
Carbonate	10.7	1.92×10^{-3}

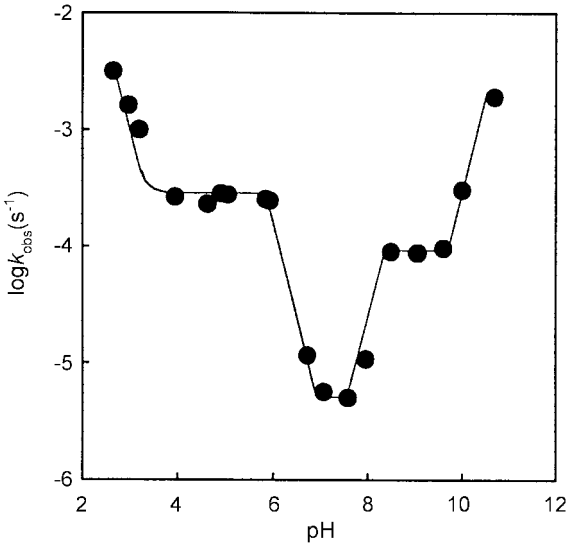
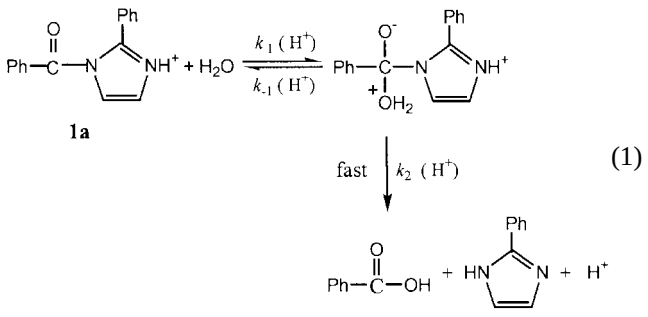


Figure 1. Plot of logk_{obs} *vs*. pH for hydrolysis of *N*-benzoyl-2-phenylimidazole in H_2O at 25 ± 0.1 ºC with μ = 0.5 M KCl.

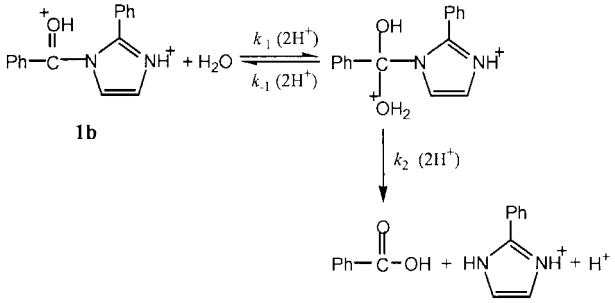
in Table 1 and demonstrated graphically in Figure 1 as a function of pH of the reaction medium. The pH-rate profile has two distinct regions corresponding to the hydronium ion catalyzed reaction below pH 7.0 and the hydroxide ion catalyzed reaction above pH 7.5. In acidic region, the hydrolysis of **1** seems to be related with the two different protonated species. The two different protonated species might be formed by protonation on the carbonyl oxygen atom and the N-3 atom in the leaving group, 2-phenylimidazole moeity. Between pH 6.0 and pH 7.0, the observed rate constants increase with increasing hydronium ion concentration with a slope *ca*. 1 as shown in Figure 1. This indicates that the hydrolysis of **1** proceeds through the protonated species **1a**, in which the protonation occurs on the N-3 atom of the leaving group as shown in Eq. (1). Such a protonation would increase the leaving ability of the leaving group. Therefore the rate determining step in this pH range is considered to be the attack of water molecule to the mono protonated species



(1)

1a.

Likewise, the hydronium ion catalyzed reaction takes place below pH 4.0 as shown in Figure 1. In this pH region, the hydrolysis reaction might be related with the diprotonated species **1b**, one on the carbonyl oxygen atom and another on the N-3 atom in the 2-phenylimidazole leaving group of the substrate **1**. Since this pH region is strongly acidic, it might be possible to form the diprotonated species **1b** as shown in Eq. (2). The protonation on the carbonyl oxygen would increase the electrophilicity of the carbonyl carbon and the protonation on the N-3 atom of the leaving group would lead to increase the leaving ability of the leaving group. Thus, the rate determining step of the hydrolysis of

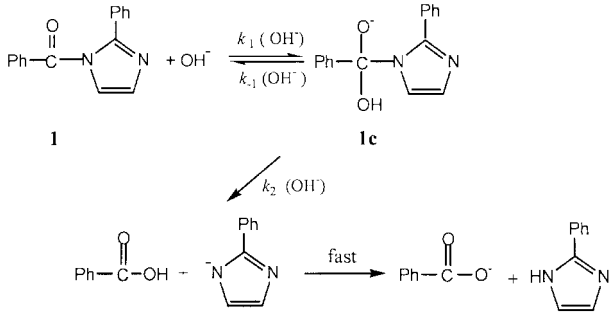


(2)

the diprotonated species **1b** is not clear.

One can see a plateau region in the pH rate profile around pH 5.0. One might attribute the plateau to an equilibrium between **1a** and **1b**. There is no evidence for a change in the **RDS** for the hydrolysis of **1** in acidic media. However, we have recently reported that there is an **RDS** change for the hydrolysis of *N*-heteroaryl-2-phenylimidazoles in acidic media. One might attribute the difference in reaction mechanism between the hydrolysis of **1** and that of *N*-heteroaryl-2-phenylimidazoles to the difference in stability of these substrates in the transition state, since the benzoyl moiety in **1** is expected to exert higher stability than the furoyl or the thenoyl moeity in the *N*-heteroaryl analogues. This expectation is in accord with the order of the emprical resonance energy, *e.g.*, 94.6 kJ/mol for benzene, 18.0 kJ/mol for furan and 27.2 kJ/mol for thiophene.[12]

As shown in Figure 1, the observed rate constant increases with increasing hydroxide ion concentration from pH 7.5 to pH 8.5. This can be explained that the rate determining step is the attack of hydroxide ion to the neutral substrate as in



(3)

Eq. (3). But one can see that the rate constant remains nearly constant between pH 8.5 and pH 9.5. This result might indicate that there is a transient region of change in rate determining step. Above pH 10, the rate determining step for the hydrolysis of **1** is considered to vary from formation of the addition intermediate to breakdown of **1c**.

Finally, hydrolysis of *N*-benzoyl-2-phenylimidazole seems

to be charaterized by the mono-, and diprotonated species in acidic region and a change in a rate determining step in alkaline region.

Acknowledgment. This paper was supported by the Dong-A University Research Fund, 2000. The authors thank professors Rory More O'Ferrall (University College Dublin, Ireland) and Tadashi Okuyama (Himeji Institute of Technology, Japan) for their useful comments.

References

1. Lee, J. P.; Park, H. S.; Uhm, T. S. *Bull. Korean Chem. Soc*. **1998**, *19*, 1298.
2. Lee, J. P.; Uhm, T. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 29.
3. Lee, J. P.; Bembi, R.; Fife, T. H. *J. Org. Chem*. **1997**, *62*, 872.
4. (a) Jencks, W. P. *Catalysis in Chemistry and Enzymolgy*; McGraw-Hill: New York, 1969. (b) Bruice, T. C.; Benkovic, S. *Bioorganic Mechanism*; New York, 1966.
5. Choi, M.; Thornton, E. R. *J. Am. Chem. Soc*. **1974**, *96*, 1428.
6. (a) Hogg, J. L.; Phillips, M. K.; Jergens, D. E. *J. Org. Chem*. **1977**, *42*, 2495. (b) Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem*. **1983**, *48*, 2038.
7. Fife, T. H.; Natarajan, R.; Werner, M. H. *J. Org. Chem*. **1987**, *52*, 741.
8. (a) Oakenful, D. G.; Jencks, W. P. *J. Am. Chem. Soc*. **1971**, *93*, 178. (b) Oakenful, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem Soc.* **1971**, *93*, 188.
9. Kogan, R. L.; Fife, T. H. *Biochemistry* **1984**, *23*, 2983.
10. Jencks, W. P.; Carriuolo, J. *J. Biol. Chem*. **1959**, *234*, 1272, 1280.
11. Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 1778.
12. Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press Inc.: New York, 1985; p 77.