Influence of Bifunctional Catalysts in the Hydrolysis Reactions of *N*-Benzoyl-4(5)-methylimidazoles

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Received July 19, 2004

Key Words : *N*-Benzoyl-4(5)-methylimidazole, Bifunctional catalyst, pH-rate profile, Catalysis

Acetate, cacodylate, phosphate and imidazole are well known as the bifunctional acid and base catalysts. Catalysis of these bifunctional catalysts depends on the structure of the reaction substrates. For example, in nucleophilic substitution reaction at the carbonyl carbon, imidazole has been found to be 100-4000 fold as reactive as phosphate dianion,[1] whereas imidazole and phosphate dianion or imidazolium and phosphate monoion exhibit nearly equal effect in the general acid or general base catalysis in nucleophilic substitution reactions of imine derivatives.[2,3]

However, there are little reports on the catalysis of acid and base bifunctional catalysts for the hydrolysis of amides. So, we have performed the hydrolysis of *N*-benzoyl-4(5)-methylimidazole (**1**) and *N*-toluoyl-4(5)-methylimidazole (**2**) to compare with the structure of substrate and the catalytic effects of bifunctional acid and base catalysts.

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.[4] Deionized water were distilled using a Streem Glass Still and kept under a nitrogen atmosphere. Buffer materials for kinetic studies were analytical reagent grade.

N-benzoyl-4(5)-methylimidazole (**1**) was prepared by dissolving 10 mmol of 4(5)-methylimidazole in methylene chloride with cooling and slowly adding 10 mmol of 2-benzoyl chloride dissolving in methylene chloride in the presence of triethylamine as a catalyst. The reaction mixture was generally refluxed with stirring for 3 days. After the mixture was cooled and filtered, the filtrate was washed with water several times and separated the organic layer. The organic layer was dried over sodium sulfate and the solvent removed by rotary evaporation. The crude product was dried under vacuum condition and recrystallized from ether-hexane mixture (white, mp. 70-71 °C).

FT-IR (KBr), 1705 (C=O), 1597, 1478 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 2.27 (s, 3H), 7.26 (s, 1H), 7.54-7.80 (m, 5H), 7.97 (s, 1H). Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 69.63; H, 5.517; N, 14.54.

N-toluoyl-4(5)-methylimidazole (**2**) was prepared by same method as that for the substrate (**1**). After recrystallization from ether-hexane mixture, the product melted at 73-74 °C. FT-IR (KBr), 1625 (C=O), 1594, 1460 (C=C, aromatic); ^{1}H NMR ($CDCl_3$, 200 MHz), δ 2.27 (s, 3H), 2.58 (s, 3H), 7.25 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.97 (s, 1H). Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 69.97; H, 6.168; N, 13.51.

Kinetics. The rates for hydrolysis reactions of *N*-benzoyl-4(5)-methylimidazole (**1**) and *N*-toluoyl-4(5)-methyl-imidazole (**2**) were measured spectrophotometerically in H_2O at 25 ± 0.1 °C by following the decrease in absorbance due to disappearance of the substrate (**1**) and (**2**) at wavelengths in the range of 262-266 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 ± 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 of (**1**) and (**2**) 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

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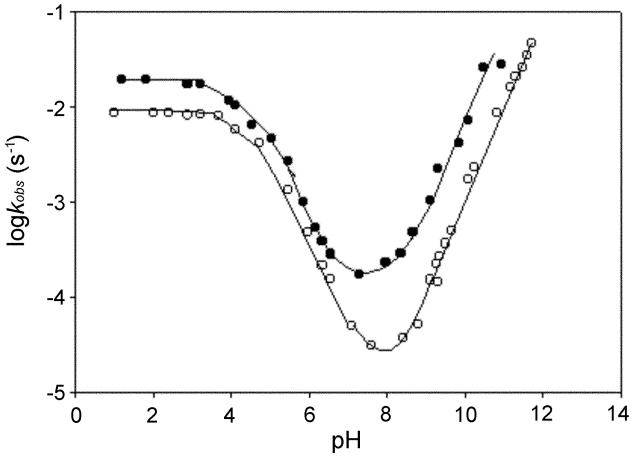


Figure 1. Plots of k_{obs} *vs.* pH for hydrolysis of *N*-benzoyl-4(5)-methylimidazole (●) and *N*-toluoyl-4(5)-methylimidazole (○) in H_2O at 25 °C and μ = 0.5 M with KCl.

company which was based on the slope value of the plot of $\ln(A_O\text{-}A_t)$ *vs.* time.

The pH rate profiles for the hydrolysis reactions of substrate (**1**) and (**2**) are presented in Figure 1. These profiles are similar in shape to those for hydrolysis of corresponding *N*-acylimidazoles.[5,6] There are three distinct regions corresponding to the hydroxide ion catalyzed reactions above pH 8.0, the hydronium ion catalyzed reaction between pH 7.5 and pH 4.0 and below pH 4.0, the pH independent reaction by the protonated species of the substrate. Therefore, the overall reactions should be described as following each pH regions, where S and P stand for the substrate and the product.

$$S + H^+ \underset{K_a}{\rightleftharpoons} SH^+ + H_2O \xrightarrow{k_1} P \text{ (below pH 7.0)}$$

$$S + H_2O \xrightarrow{k_o} P \text{ (around pH 8.0)}$$

$$S + OH^- \xrightarrow{k_{OH}} P \text{ (around pH 8.0)}$$

Then, the observed rate constant (k_{obs}) is given by equation (1), where k_1

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

and k_o are the rate constants for water catalyzed reaction of the protonated species (SH^+) and that of the neutral substrate (S), k_{OH} is the catalytic rate constant of hydroxide ion and K_a is the dissociation constant of the conjugate acid of the substrate. The rate constants for hydrolysis reactions of the substrate (**1**) and (**2**) are listed in Table 1.

The catalytic rate constants for the hydrolysis of *N*-benzoyl-4(5)-methylimidazole (**1**) are larger than those of *N*-toluoyl-4(5)-methylimidazole (**2**). These results mean that the electron donating substituent in the acyl group should be affected the catalytic rate constant, that is, the electron density on carbon atom of carbonyl moiety should be increased by the -CH_3 group. Then, the rate constants of the substrate (**2**) are less than those of the substrate (**1**).

One can see the bent portion at low pH in the pH-rate profile of Figure 1. This indicates that p*K*a value of the conjugate acid of the substrate is around this pH region. We can estimate that the p*K*a values of the substrate (**1**) and (**2**) are 4.7 and 4.5 by drawing a pH-rate profile though not accurate. Thus, the k_H value of the substrate (**1**) is relatively larger than that of the substrate (**2**). And also k_1 values of the substrate (**1**) and (**2**) show similar tendency because of $k_H = k_1/K_a$.[7]

The catalytic rate constants for catalysis of bifunctional acid-base catalysts in the hydrolysis of substrate (**1**) and (**2**) are listed in Table 2.

As one can see in Figure 2 and Figure 4, the most effective catalyst is cacodylate while other catalysts are not nearly as effective although they contain equal concentrations of catalysts. To make sure how the bifunctional catalyst, cacodylate, operates in this reaction, we have investigated

Table 2. Effect of total buffer concentration of bifunctional acid-base catalysts on rates of hydrolysis of *N*-benzoyl-4(5)-methylimidazole (**1**) and *N*-toluoyl-4(5)-methyl-imidazole **(2)** in H_2O at 25 °C and μ = 0.5 M with KCl

Buffer	pH	Conc. range (M)	k_{cat} (**1**)	k_{cat} (**2**)
Acetate	4.10	0.10-0.40	7.050×10^{-3}	6.624×10^{-4}
	4.54	0.005-0.50	7.620×10^{-3}	3.472×10^{-3}
Cacodylate	5.22	0.005-0.50	–	0.1523
	5.94	0.005-0.12	0.2991	0.1797
	6.51	0.005-0.50	0.3274	0.2054
	7.10	0.005-0.50	0.2276	0.1402
	7.46	0.005-0.50	0.1502	0.0914
Phospate	6.61	0.005-0.20	9.820×10^{-3}	5.474×10^{-3}
Imidazole	7.97	0.005-0.50	1.420×10^{-3}	–

Table 1. Rate constants and activation parameters for hydrolysis of *N*-benzoyl-4(5)-methylimidazole (**1**) and *N*-toluoyl-4(5)-methylimidazole (**2**) in H_2O at 25 °C and μ = 0.5 M with KCl

compound	$^*k_H$ ($M^{-1}s^{-1}$)	k_1 (s^{-1})	k_0 (s^{-1})	k_{OH} ($M^{-1}s^{-1}$)	$\Delta H^{\ddagger}$ (kcal/mol)	$-\Delta S^{\ddagger}$ (eu)
(**1**)	927	1.85×10^{-2}	1.74×10^{-4}	86.7	7.50[a]	70.3[a]
					16.3[b]	69.4[b]
(**2**)	269	8.52×10^{-3}	1.34×10^{-5}	10.8	7.90[a]	71.7[a]
					10.9[b]	73.7[b]

$^*k_H = k_1/K_a$. [a]acidic region. [b]basic region.

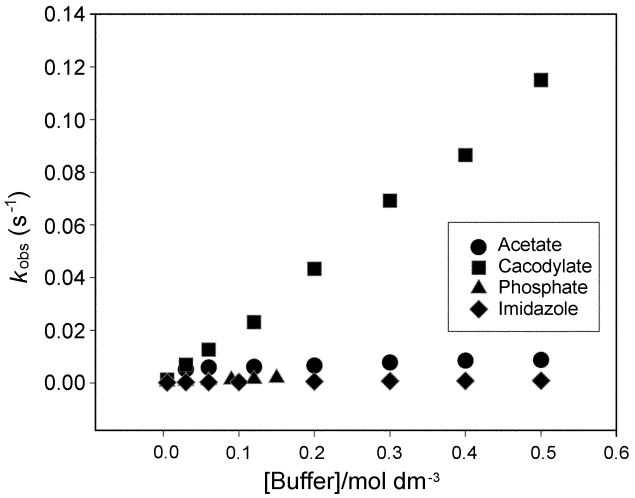


Figure 2. Total buffer effects on rate for hydrolysis of *N*-benzoyl-4(5)-methylimidazole in H_2O at 25 °C and μ = 0.5 M with KCl.

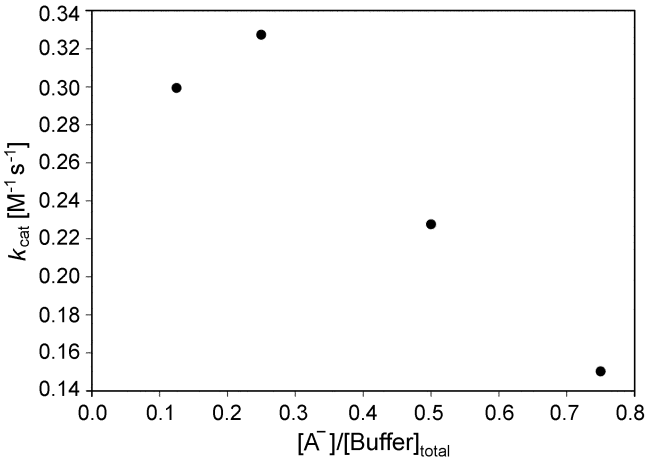


Figure 3. Effect of bifunctional acid-base catalyst, cacodylate, on rate for hydrolysis of *N*-benzoyl-4(5)-methylimidaole in H_2O at 25 °C and μ = 0.5 M with KCl.

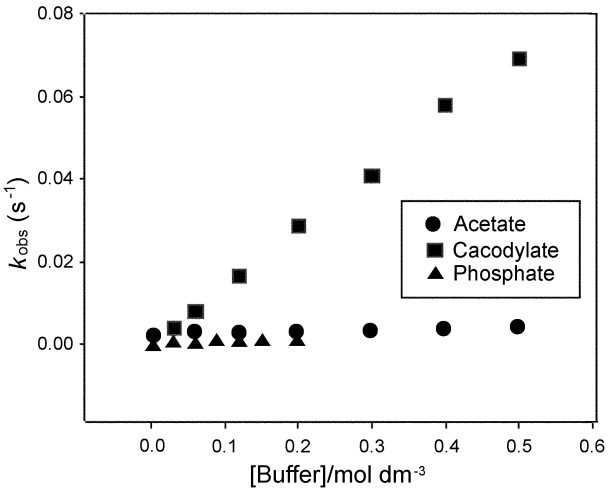


Figure 4. Total buffer effects on rate for hydrolysis of *N*-toluoyl-4(5)-methylimidazole in H_2O at 25 °C and μ = 0.5 M with KCl.

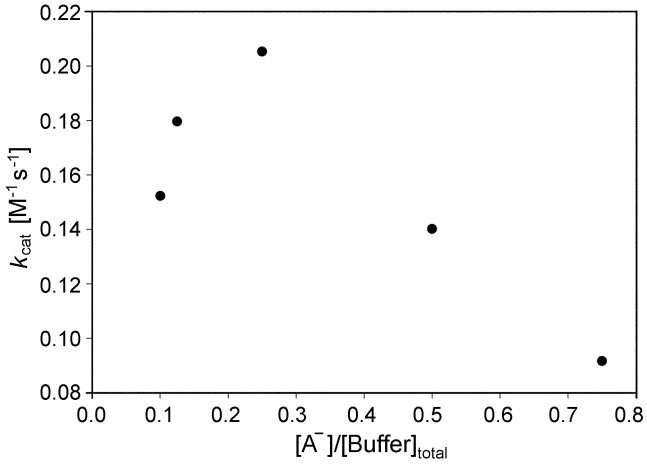


Figure 5. Effect of bifunctional acid-base catalyst, cacodylate, on rate for hydrolysis of *N*-toluoyl-4(5)-methylimidaole in H_2O at 25 °C and μ = 0.5 M with KCl.

the effect on concentration of cacodylate buffer.

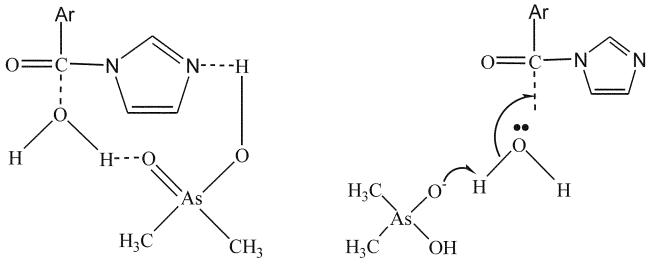
As one can see from Figure 3 and Figure 5, when the concentration of free base of cacodylate buffer to total buffer concentration, that is, $[base]/[buffer]_T$ is 0.3 M, the catalytic rate constant shows the maximum value. It is very difficult to explain the reason for this maximum phenomenon because 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 that the catalytic rate constant (k_{cat}) is combination of catalytic rate constants for general acid catalysis and general 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 acid and general base of the bifunctional acid and base catalyst, respectively.

One can see that the acidic form is more favorable than the basic form in the catalysis of cacodylate buffer from Figure 3 and Figure 5. Then, the possible catalyses of the acidic form and the basic form of cacodylate buffer should be described as following;

Acidic Form **Basic Form**



This result is very characteristic, although, sometimes, the catalysis of bifunctional catalysts has been observed the saturation effect with increasing catalyst concentration.[8]

We have determined activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in acidic and basic regions as shown in Table 1. 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.[9] Thus, this result supports that this reaction should be proceeded *via* the tetrahedral intermediate in both acidic and basic regions.

Finally, in this work, we have found that the cacodylate buffer is the most effective catalyst of bifunctional catalysis, whereas acetate, phosphate and imidazole have nearly no effect on the hydrolysis of *N*-benzoylimidazole derivatives. In addition, the acidic form of bifunctional catalyst, cacodylate, is more sensitive than the basic form in the hydrolysis reaction.

Acknowledgment. This paper was supported by Dong-A University Research Fund in 2002.

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