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Evidence for Existence of Intermediate in Acid Hydrolyses of Sulfinamide and Carboxamide

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Hydrolyses of carboxamides, such as *N*-acylimidazoles, have been extensively studied in the aspect of similar role of histidine in enzyme reaction.[1] Most of them mainly investigated the structure-reactivity relationship and reaction mechanism. These results gave a lot of contribution to information on the reactivity of amides and the model of enzyme reaction. However, hydrolysis of sulfinamides is not studied extensively due to the low reactivity. In previous work, acid catalyzed hydrolysis of primary sulfinamides was reported by the authors.[2] Herein, acid catalyzed hydrolysis of sulfinamides involving electron-donating substituent in the aniline leaving group exhibited downward breaks for variation of the pH values. The results provided the first unequivocal evidence that nucleophilic substitution reaction at the sulfinyl sulfur may proceed through a two-step mechanism involving a hypervalent reaction intermediate.

In the present work, acid catalyzed hydrolyses of study, *N*-benzenesulfinyl benzimidazole (**1a**) and *N*-benzoyl benzimidazole (**1b**) are studied kinetically to gain further information on the hydrolysis mechanism of secondary sulfinamide and carboxamide.

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 well known method.[3] 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.

The substrates, **1a** and **1b**, were prepared by addition of benzenesulfinyl chloride and benzoyl chloride, respectively, to benzimidazole as previously described.[4] Benzenesulfinyl chloride was obtained by purging chlorine gas to reaction mixtures of 0.1 mol diphenyl disulfide and 0.2 mol acetic anhydride at 0 °C ~ −10 °C. Byproducts, acetyl chloride and excess chlorine were removed by heating to 50 °C under reduced pressure (15 mmHg). The two crude products were purified through silicagel column chromatography(*n*-hexane/ethylacetate = 1 : 2, v/v) and dried under vacuum condition for 48 hours. The physical properties and spectroscopic data of the substrates **1a** and **1b** are as follows.

***N*-Benzenesulfinyl benzimidazole (1a):** yellow solid; mp 63 - 65 °C; FT-IR (KBr, cm^{-1}): 1245 (C-N), 1290 (S=O); ^{1}H NMR ($CDCl_3$, 200MHz) δ 7.25-7.35 (m, 2H, ArH), 7.40-7.43 (m, 2H, ArH), 7.53-7.55 (m, 2H, ArH), 7.77-7.79 (d, J = 3.6 Hz, 2H, ArH), 8.21(s, 1H, ArH), 8.36(s, 1H, ArH); Mass: m/z 242 (M^+).

***N*-Benzoyl benzimidazole (1b):** pale yellow solid; mp 72 - 74 °C; FT-IR (KBr, cm^{-1}): 1308 (C-N), 1699 (C=O); ^{1}H NMR ($CDCl_3$, 200MHz) δ 7.43-7.47 (m, 1H, ArH), 7.53-7.69 (m, 3H, ArH), 7.73-7.87 (m, 2H, ArH), 8.13-8.18 (t, J = 4.8 Hz, 3H, ArH), 8.20-8.26 (s, 1H, ArH); Mass: m/z 222 (M^+).

Kinetic measurement. The hydrolysis rates of the substrates were measured spectrophotometrically in H_2O at 25 ± 0.1 °C by following the decrease in absorbance due to the disappearance of the substrates, **1a** and **1b**, at wavelengths in the range of 232 - 263 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. Kinetic runs were 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), cacodylate (pH = 5.0 - 7.4).

The hydrolysis reactions are catalyzed by buffer. Thus, the first-order rate constants were obtained in HCl solution or by extrapolation to zero buffer concentration. The pH values of reaction mixtures were measured at 25.0 ± 0.1 °C with a DP-215M Dong-Woo meter.

Results and Discussion

Acid hydrolyses of **1a** and **1b** were carried out under pseudo first-order conditions with the concentration of buffer in a large excess relative to the substrate. The pseudo first-order rate constant (k_{obsd}) was obtained from 89532K Kinetic Software (serial No. 325 G00380) of the Hewlett Packard company which was based on the slope value of the plot of $\ln(A_O\text{-}A_t)$ *vs*. time.

The observed rate constants (k_{obsd}) for the hydronium ion (H_3O^+) catalyzed reaction of the substrates, **1a** and **1b**, are proportional to H_3O^+ concentration in the pH range 2.0 - 5.3 and show constant value below pH 2.0. Therefore, the observed rate constanst (k_{obsd}) is given by equation (1).

$$k_{obsd} = k_1 + k_H[H_3O^+] \quad (1)$$

In eq. (1), k_1 stands for the first-oder rate constant for the water reaction of the conjugate acid (SH^+) of the neutral substrate (S), and k_H is the second order rate constant for the H_3O^+ catalysis. The rate constants for the hydrolyses of the substrates, **1a** and **1b**, are summerized in Table 1, and the plots of log k_{obs} against pH are shown in Figure 1.

The k_H value for the H_3O^+ catalyzed reaction of the sulfinamide (**1a**) is only slightly larger than that of the carboxamide (**1b**). This difference could be in part reflected the relatively high pK_a of the conjugate acid of the **1a** compared to that of **1b**. One can see the bent portion at low pH in Figure 1. This indicates that the pK_a values of the conjugate acids of the substrate, **1a** and **1b**, are around this pH region. We can estimate that the apparent pK_a values of the substrates, **1a** and **1b**, are 2.1 for **1a** and 2.0 for **1b** respectively, by drawing a pH rate profile. Thus, the k_H value of the substrate **1a** is relatively larger than those of 1b, since $k_H = k_1/K_a$ and the k_1 values are similar for the substrates, **1a** and **1b**, as shown in Table 1.

Table 1. Rate constants (k_1 and k_H) and thermodynamic parameters for the hydrolyses of *N*-benzenesulfinyl benzimidazole (**1a**) and *N*-benzoyl benzimidazole (**1b**) in H_2O (μ = 0.5 M with KCl) at 25.0 °C

Compound	k_1 (s^{-1})	k_H ($M^{-1}\cdot s^{-1}$)	$\Delta H^{\ddagger}$ (kcal/mol)	$-\Delta S^{\ddagger}$ (e.u)	p$K_{a_{app.}}$
1a	0.013	1.645[a] 8.912[b]	24.5	70.8	2.1
1b	0.010	1.00[a] 7.13[b]	24.0	71.4	2.0

[a]For lower pH, [b]For higher pH.

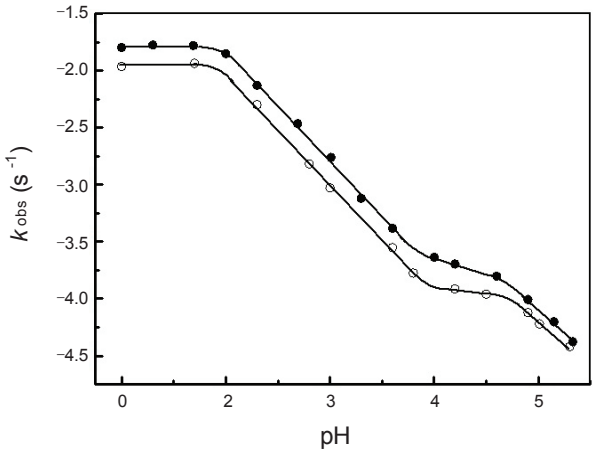


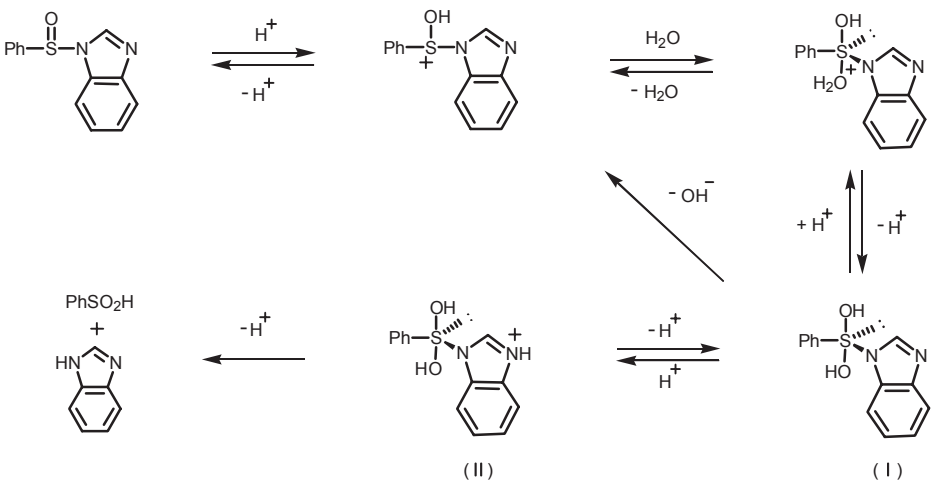
Figure 1. Plots of log k_{obs} against pH for the hydrolyses of *N*-benzenesulfinyl benzimidazole (**1a:** ●) and *N*-benzoyl benzimidazole (**1b:** ○) in H_2O and ionic strength 0.5 M with KCl at 25 °C.

As one can see in Figure 1, acid hydrolyses of the substrates, **1a** and **1b**, similarly take place in the whole pH ranges. The pH rate profiles for the two substrates, **1a** and **1b**, show a straight line with a slope of −1.0, but appear a break around pH 4.5.

This result may be accommodated by the mechanism involving the intermediate, i.e., a changeover of the rate determining step occurs around pH 4.5.

The rate determining step at the low pH should be the formation of the intermediate(II) in Scheme 1, because the protonation at the N-3 atom in the leaving group is more difficult than that at the sulfinyl oxygen atom. While, with increasing pH, the contribution from the neutral intermediate(I) becomes greater because of more favorable protonation at the sulfinyl oxygen atom. Then the decay of the intermediate should be the rate determining step. This suggestion implies that the protonation at the sulfinyl oxygen atom should be more favorable than that at the N-3 atom of *N*-benzenesulfinyl benzimidazole, which is in accord with our observation of the ^{18}O-leveled structure in the hydrolyses of benzenesulfinamide derivatives.[2] Likewise, the mechanism for acid hydrolysis of *N*-benzoyl benzimidazole should be similar to the one proposed in acid hydrolysis of sulfinamide, i.e., acid hydrolysis of carboxamide should proceed through a terahedral intermediate.

We have investigated the buffer effect on the hydrolysis of the substrates, **1a** and **1b**, in acetate buffer solutions. The observed first-order rate constants (k_{obsd}) in Table 2 show downward concave curve with increasing buffer concentration (Figure 2). This result can be taken as evidence for the existence of an intermediate during the hydrolysis. Hence, it could be reasonable that acid and alkaline hydrolyses of the substrates, **1a** and



Scheme 1

Table 2. Observed first-order rate constants for the hydrolyses of *N*-benzenesulfinyl benzimidazole (**1a**) and *N*-benzoyl benzimidazole (**1b**) in acetate buffer solutions (μ = 0.5 M with KCl) at 25.0 °C

Buffer	pH	Conc. (M)	$10^4\ k_{obsd}\ (s^{-1})$	
			1a	**1b**
Acetate	3.62	0.003	1.83	0.64
		0.005	2.87	9.76
		0.01	3.72	2.34
		0.02	3.89	2.51
		0.03	4.14	2.81
		0.06	4.41	2.86
		0.12	4.12	2.92

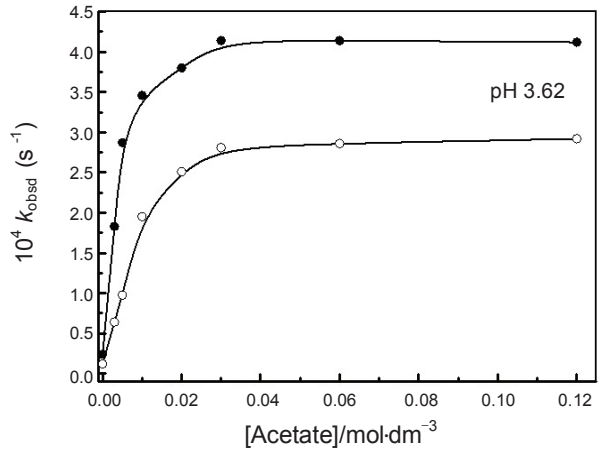


Figure 2. Buffer effects on the hydrolysis rates of *N*-benzenesulfinyl benzimidazole (**1a:** ●) and *N*-benzoyl benzimidazole (**1b:** ○) in acetate buffer solutions and ionic strength 0.5 M with KCl at 25 °C.

1b, proceed through the intermediate. Similar result has been observed for the hydrolysis of 4-hydroxybutyranilide in the phosphate buffer solution.[5] However, we could not observed downward concave curve for buffer effect in the hydrolysis of *N*-benzenesulfinyl-4-nitrobenzimidzole and *N*-benzoyl-4-nitrobenzimidzole.[6]

We have determined activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, for the substrates, **1a** and **1b**, and are listed in Table 1. Large negative $\Delta S^{\ddagger}$ values and small positive $\Delta H^{\ddagger}$ values are nearly the same tendency as those obtained for the hydrolysis of carboxamides.[7] Thus, this result supports that the reaction proceeds through a typical bimolecular reaction.[8]

In conclusion, (i) Acid hydrolysis reaction of sulfinamide and carboxamide takes place similarly and through an intermediate. (ii) A break of pH rate profile and the downward concave curve in buffer effect can be taken as definitive evidence for the existence of an intermediate.

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References

1. (a) Lee, J. P.; Bembe, R.; Fife, T. H. *J. Org. Chem.* **1997**, *62*, 2872. (b) Fife, T. H.; Natarajan, R.; Werner, M. H. *J. Org. Chem.* **1987**, *52*, 740. (c) Smith, J. H. *J. Am. Chem. Soc.* **1976**, *98*, 3598. (d) Fife, T. H.; Kogan, R. L. *J. Org. Chem.* **1984**, *49*, 5229.
2. Okuyama, T.; Lee, J. P.; Ohnishi, K. *J. Am. Chem. Soc.* **1994**, *116*, 6480.
3. Riddick, J. H.; Bunger, W. B. *Organic Solvents*, 4th ed.; Wiley Interscience: John Wiley & Sons, Inc.: 1970.
4. Lee, J. P.; Woo, R. K.; Lee, Y. H.; Koo, I. S. *Bull. Korean Chem. Soc.* **2006**, *27*, 941.
5. Cunningham, B. A.; Schmir, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 917.
6. Unpublished data.
7. (a) Lee, J. P.; Bang, H. Y.; Koo, I. S. *Bull. Korean Chem. Soc.* **2006**, *27*, 123. (b) Lee, J. P.; Lee, S. S. *Bull. Korean Chem. Soc.* **2002**, *23*, 151. (c) Lee, J. P.; Lim, G. T.; Lee, Y. H.; Lee, S. S.; Koo, I. S.; Ryu, Z. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 1357.
8. (a) Koo, I. S.; Kwon, E. J.; Choi, H. J.; Yang, K. Y.; Park, J. K.; Lee, J. P.; Lee, I. C.; Bentley, T. W. *Bull. Korean Chem. Soc.* **2007**, *28*, 2377. (b) Adhikary, K. K.; Kim, C. K.; Lee, B. S.; Lee, H. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 191. (c) Park, S. Y.; Oh, H. K. *Bull. Korean Chem. Soc.* **2009**, *30*, 749. (d) Oh, H. K.; Hong, H. K. *Bull. Korean Chem. Soc.* **2009**, *30*, 2453.