Synthesis and Hydrolysis of 4-Acetoxymethylbenzimidazoles. Effects of Freezing an Internal Rotation on Intramolecular Catalysis by a Benzimidazolyl Group

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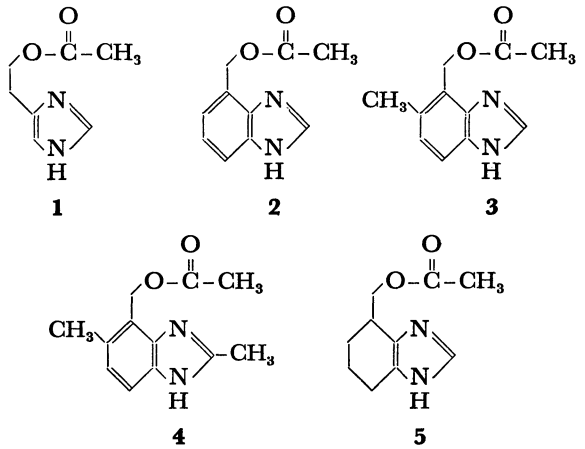
As models for acetyl-α-chymotrypsin, 4-acetoxymethylbenzimidazole (**2**), its 5-methyl derivative **3** and 2,5-dimethyl derivative **4** were synthesized from *o*-toluidine in moderate yields. Their hydrolytic reactivities were determined in water at 50 °C in comparison with their open-chain analog, 4-(acetoxyethyl)imidazole(**1**). The rate constant (k_1) for intramolecular general base catalysis by the imidazolyl group of **2** was 1.6 times larger than k_1 for **1**. A corrected relative rate of 4.1 is obtained by correcting the basicity difference and the polar substituent effect. The value of 4.1 is an expected magnitude of the effect of freezing an internal rotation as reported for 4,5-(1-acetoxymethyltetramethylene)imidazole. The 5-methyl group of **3** enhances the k_1 value 1.4 times as large as that for **2**. The enhancement can be attributed to restriction of the second internal rotation. The hydrolytic reactivity of **4** is discussed.

In a previous paper[1] we reported that intramolecular general base catalysis in the hydrolysis of acetate **5** by its imidazolyl group is 2.6 times more effective than the catalysis in acetate **1**. It was concluded that this enhancement of 2.6 can be rationalized from the entropy effect of freezing an internal rotation. This suggests that, even if the three remaining internal rotations in the acetoxymethyl group were frozen in **5**, the total enhancement would be a factor of about 50 at the highest, and that there remains a factor of about 500 to attain the deacylation rate constant of acetyl-α-chymotrypsin. This deficiency might possibly be provided by the presence of a carboxylate group which affords the so-called "charger-relay" system[2] in the enzyme, but such a large factor using a model system[3] has never been realized. Thus it is important to estimate the rate enhancement caused by freezing an internal rotation. In order to examine further the enhancement caused by the freezing, we have synthesized three new models **2**—**4** and compared their hydrolytic reactivities with the reactivity of **1** or **5**.

Acetate **2** is an unsaturated analog of acetate **5**. The former has a planar skeleton of benzene which is more rigid than that of cyclohexene in the latter.



1 **2** **3**

4 **5**

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Moreover, **2** has a slightly shorter distance between the carbonyl carbon and the imidazolyl nitrogen than **5**. It seems interesting to show the effect of these factors on the reactivity. The 5-methyl derivative **3** was designed to investigate the rate enhancement caused by restricting the second internal rotation by the methyl group. The dimethyl derivative **4** was prepared as a modification of **3**.

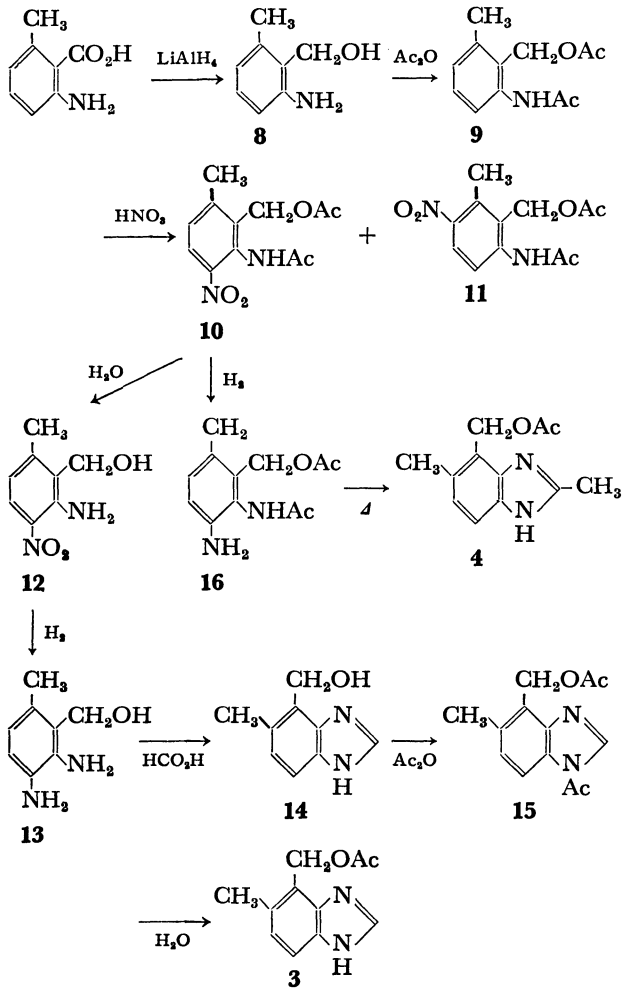
Results and Discussion

Synthesis. Acetate **2** was obtained by reduction and subsequent acetylation of methyl 4-benzimidazolecarboxylate prepared from *o*-toluidine according to the method of Williams and Salvadori.[4]

The 5-methyl derivative **3** was prepared as outlined in Scheme 1. Reduction of 2-amino-6-methylbenzoic acid with lithium aluminum hydride gave **8** in 73% yield, which, after acetylation, was nitrated with 70% nitric acid in acetic anhydride to give a 2:1 to 3:1 mixture of **10** and **11** in 79% yield. The isomer **10** crystallized with ease from the oily layer in the aqueous reaction mixture. Another isomer **11** was isolated by column chromatography. From their NMR spectra showing an AX pattern in the aromatic region with an intensity of two protons, 1,2,3,4-tetrasubstitution was evident for their benzene rings. Although it was not possible to distinguish **10** from **11** using their NMR and IR spectra, the former was distinguishable from the latter since only **10** could provide the benzimidazole derivative **14**.

Reduction of **12** with Urushibara nickel A[5] gave the expected diamino derivative **13** in 99% yield. To prevent coloration of **13**, the reaction mixture was worked up in a nitrogen atmosphere and the product was used immediately for formation of the benzimidazole ring. Use of tin and concd hydrochloric acid reduced not only the nitro group but also the hydroxyl group in 74% yield. The product was confirmed by the formation of 4,5-dimethylbenzimidazole.[6] Reduction with tin(II) chloride and hydrochloric acid[7] gave **13** in a yield of less than 10%.

The benzimidazole derivative **14** was prepared



Scheme 1.

conveniently by heating **13** with 80% formic acid[8] in an about 40% yield. Although acetylation of **14** was accompanied by unavoidable *N*-acetylation, model **3** was obtained in a good yield after selective hydrolysis of the *N*-acetyl group.

Reduction of **10** with Urushibara nickel A also gave the corresponding amine quantitatively. By refluxing **16** in xylene[9] and cooling for deposition, model **4** was obtained in 87% yield. Its NMR spectrum showed no signal near δ 8.0 for the hydrogen attached to the C-2 carbon, but indicated the presence of the 2-methyl group by a singlet at δ 2.55.

Kinetics. In Table 1 are given k_1 (min^{-1}) for intramolecular catalysis of the acetate hydrolysis by an imidazolyl or a benzimidazolyl group and k_{OH} (M^{-1} min^{-1}) for bimolecular hydroxide ion attack for **1**—**5**. These rate constants were derived from the observed pseudo-first-order rate constant k_{obsd} using the equation

$$k_{obsd} = \alpha k_1 + k_{OH}[OH^-],$$

where α is the mole fraction of the neutral imidazole. To calculate the concentration of OH^-, the ionization constant of water was taken as $10^{-13.2617}$ at 50 °C.[10] The plots of log k_{obsd} *vs.* pH for acetates **2** and **3** are given in Fig. 1. The curves in Fig. 1 were drawn using the above equation and the rate constants and pK_a values given in Table 1. For comparison the rate constants for **1** and **5** taken from the previous paper[1] are included in Table 1 and the relative rates corrected for the basicity and the polar substituent effect are also given.

Table 1. Hydrolytic rate constants of acetates **1**—**5** and pK_a values of their benzimidazolyl or imidazolyl groups in water[a]

	1[b]	2	3	4	5[b]
pK_a[c]	6.50	4.57	4.85	5.62	6.90
$k_{OH}\times10^{-2}$ (M^{-1} min^{-1})	0.63	2.0	1.95	1.8	0.54
Rel rate	1	3.2 (1)	(0.97)	(0.90)	0.86
$k_1\times10^4$ (min^{-1})	1.00	1.6	3.1	2.9	2.6
Rel rate	1	1.6 (1)	(1.9)	(1.8)	2.6
Corrected rel k_1 For basicity[d]	1	13 (1)	(1.4)	(0.58)	1.7
For polarity[e]	1	4.1			

a) At 50±0.1 °C, 0.1 M KCl. k_1 and k_{OH}, ±5%; pK_a, ±0.02. b) Taken from Ref. 1. c) For comparison the pK_a value for benzimidazole was determined to be 5.16 under the same conditions. d) Corrected for ΔpK_a using the Brönsted exponent β=0.47. e) Corrected for polar effects using the relative rate for k_{OH}.

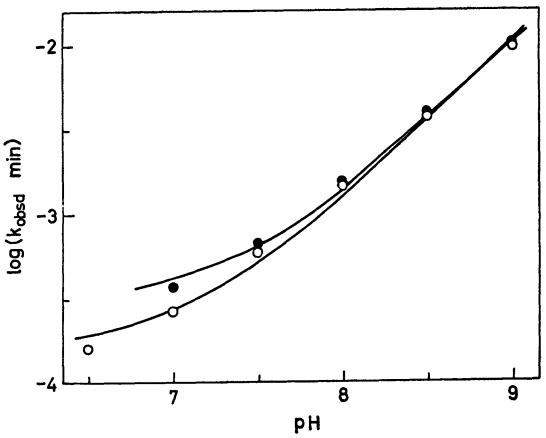


Fig. 1. Plots of log k_{obsd} *vs.* pH for the hydrolyses of **2** (○) and **3** (●) in water at 50 °C, 0.1 M KCl. The points are experimental and the lines theoretical using the equation $k_{obsd}=\alpha k_1+k_{OH}[OH^-]$ and the constants listed in Table 1.

*p*K$_a$ *Values.* As seen from Table 1 the pK_a value (4.57) for **2** is 0.59 pK_a units smaller than that (5.16) for benzimidazole. This magnitude of a base-weakening effect of an acetoxymethyl group attached to the C-4 position coincides with that for the saturated analog **5** (pK_a 6.90) and 4,5-tetramethyleneimidazole (pK_a 7.50).[1] This suggests that the acetoxymethyl group exerts its effect on the imidazolyl nitrogen through space or sterically. The pK_a value for **3** is 0.28 pK_a units larger than that for **2** and this increment is comparable to 0.33 pK_a units reported for 5-methylbenzimidazole (pK_a 5.81) and benzimidazole (pK_a 5.48) in water at 25 °C.[11] We find an additivity of the substituent effect on the pK_a value (5.62) for **4** as shown by the fact that

the increment (1.05) for the two methyl groups in **4** is equal to the sum of the increments (0.33 and 0.71) for the 5- and 2-methyl[11] groups, no anomaly being found in the pK_a values for **2**, **3**, and **4**.

Effects of Freezing an Internal Rotation. Acetate **2** can be characterized by the rigidity of its structure. It has one internal rotation frozen between the imidazolyl nitrogen and the carbonyl carbon in comparison with acetate **1**. As reported the hydrolysis of **1** is catalyzed by its intramolecular imidazolyl group as general base.[1] The catalytic activity is enhanced in the acetate **5** by a factor of 2.6 mainly because of the rigidity in structure. Thus we can except acetate **2** to show a similar enhancement in the catalysis.

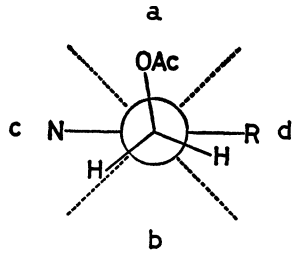
The catalytic rate constant k_1 for **2** was found to be 1.6 times as large as that for **1** (Table 1). This rate factor of 1.6 must be corrected for the basicity and polarity differences between **1** and **2**. Since **2** is less basic than **1** by 1.93 pK_a units, the general base catalysis in **2** is expected to decrease by a factor of 8.07 when we use the Brönsted exponent $\beta=0.47$ for the general base-catalyzed hydrolysis of ethyl dichloroacetate.[1,12] The correction gives a rate factor of 13 for **2**. A correction factor of 3.2 for the polarity difference was adopted from the relative rate for the hydroxide-ion hydrolysis. Although the polar substituent constants (σ^*) for the two alkoxyl groups in **1** and **2** have not been estimated, the observed rate factor of 3.2 seems reasonable as judged from the polar effect of ethyl and benzyl groups.[13]

Thus we obtain a rate factor of 4.1 for freezing an internal rotation in **2**. The value is about twice as large as the factor of 1.7 for **5**. However, the doubled factor is what had been expected previously.[1] In the imidazolyl group-catalyzed hydrolysis of **1** or **2**, two transition states, which are mirror images of each other and identical energetically, may take place during the imidazolyl residue rotation about the methylene-imidazolyl residue bond. But for **5**, since the acetoxymethyl group is expected to take a preferred pseudo-equatorial position, only one transition state can be realized.

We can thus concluded that the rigid structure of benzene in **2** gives rise to almost the same rate factor by freezing an internal rotation as the flexible structure of cyclohexene in **5**, and that the difference in the spatial alignments of the imidazolyl nitrogen and the carbonyl carbon between **2** and **5** is not critical for the intramolecular catalysis. These two conclusions are consistent with the looseness of the transition state in general base catalysis.[1]

Restriction of the Second Internal Rotation. The rate enhancement in k_1 by the 4-methyl group seems to be properly estimated using the concept of rotamer population.

Figure 2 shows the Newman projection for **2** and **3**, in which the horizontal line represents the benzimidazole plane. The projection formula indicates the existence of four rotamers **a**, **b**, **c**, and **d** with the acetoxyl group in a, b, c, and d regions, respectively. Rotamers **a** and **b** are considered to be active catalytically; rotamer **c** is thought to be inactive owing to the crowded and less



2 R=H
3 R=CH_3

Fig. 2. The projection formula for **2** and **3**. The horizontal line represents the benzimidazole plane.

favorable alignment of the acetoxyl group and rotamer **d** to be inactive because of the incorrect orientation of the acetoxyl group. Since the rotation about the carbon-carbon bond is expected to be essentially free for **2**, the four rotamer populations can be taken to be roughly equal to each other if the active region is accepted as shown in Fig. 2. Then the fraction of the active rotamer population is 2/4. If rotamer **c** is negligible owing to the steric repulsion between the nitrogen and the oxygen, the fraction will be 2/3.

On the other hand, rotamer **d** must be absent for the 4-methyl derivative **3**, whereas the remaining three rotamers are similar to the corresponding ones for **2**. Then the fraction of the active rotamer population is 2/3 or 2/2 for **3**. Thus we obtain a relative rate of 1.33—1.5 for the expected enhancement in k_1. Actually, the value of 1.4 was obtained for **3** after the correction for basicity (Table 1).

Effects of the 2-Methyl Group. Acetate **4** shows deceleration of the hydrolyses. A larger deceleration factor of 2.4 (=1.4/0.58) is obtained for k_1 in comparison with the small factor of 1.1 for k_{OH}, but the deceleration is not so large when compared with the deceleration factor of 92 reported for the intramolecular nucleophilic catalysis by 2-methylbenzimidazole of the hydrolysis of *p*-nitrophenyl acetate.[14]

Experimental

All melting points are uncorrected. Elemental analyses were carried out by Mr. E. Amano of our laboratory. ^1H NMR spectra were recorded at 60 MHz on a Hitachi Model R-24 spectrometer. Tetramethylsilane was used as internal standard unless otherwise noted.

Materials. Potassium chloride and benzimidazole of reagent grade were used after recrystallization. Hydrochloric acid, sodium hydroxide, and standard buffer solutions were obtained from Nakarai Chemicals (Kyoto). Deionized water was used in all kinetic runs.

4-Hydroxymethylbenzimidazole (6). Reduction of methyl 4-benzimidazolecarboxylate with lithium aluminum hydride in THF, prepared according to the method of Williams and Salvadori[4] from *o*-toluidine, gave crude yellow crystals of **6** in 74% yield. The crude crystals were recrystallized from hot water after treating with carbon, giving colorless needles: mp 140—144 °C; IR (KBr) 3400—2200 (OH and NH), 1620 (benzimidazole ring), and 1005 cm^{-1} (C–O); NMR (DMSO-d_6) δ (solvent peak as internal standard, δ 2.50) 8.22 (s, 1, N–CH=N), 7.7—7.1 (m, 3, benzene ring), 6.5 (s, NH and OH), and 4.92 ppm (s, 2, CH_2–O).

N-Acetyl-4-acetoxymethylbenzimidazole (7). In acetic anhydride **6** was heated at 70 °C for 1 h with stirring. The excess anhydride was distilled under reduced pressure, leaving white crystals of **7**. Recrystallization from carbon tetrachloride gave pure crystals in 95% yield: mp 96.0—97.5 °C; IR (KBr) 1730, 1725 (ester and amide C=O), 1600 (benzimidazole ring), and 1235 cm^{-1} (C–O); NMR ($CDCl_3$) δ 8.33 (s, 1, N–CH=N), 8.2—7.2 (m, 3, benzene ring), 5.53 (s, 2, CH_2–O), 2.71 (s, 3, N–$COCH_3$), and 2.10 ppm (s, 3, O–$COCH_3$).

4-Acetoxymethylbenzimidazole (2). In dil hydrochloric acid **7** was dissolved at 50 °C with stirring over a 50-min period. The solution was filtered and neutralized with aq potassium hydrogen carbonate. The neutral solution was extracted with chloroform, and the solvent was evaporated after drying over magnesium sulfate to leave white crystals of **2** in 94% yield. Recrystalliztion from chloroform gave a pure sample: mp 169.5—170.5 °C; IR (KBr) 3200—2200 (NH), 1723 (C=O), 1620—1605 (benzimidazole ring), 1242 (C–O), and 754, 715 cm^{-1} (1,2,3-trisubstituted benzene); NMR ($CDCl_3$) δ 8.06 (s, 1, N–CH=N), 7.9—7.1 (m, 3, benzene ring), 7.1 (s, 1, NH), 5.45 (s, 2, CH_2–O), and 2.08 ppm (s, 3, $COCH_3$). Found: C, 63.47; H, 5.50; N, 14.78%. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; 5.30; N, 14.73%.

2-Amino-6-methylbenzyl Alcohol (8). 2-Amino-6-methylbenzoic acid[15] prepared from *o*-toluidine was reduced with lithium aluminum hydride in ether at room temperature. The excess hydride was decomposed with water and the resulting mixture was filtered. The white solid was washed with ether repeatedly. The filtrate and washings were combined, the solvent being removed to leave white crystals of **8** in 73% yield. Recrystallization from carbon tetrachloride gave white needless: IR (KBr) 3400—2400 (NH_2 and OH), 1600 (NH_2), 1000 (C–O), and 785, 745 cm^{-1} (1,2,3-trisubstituted benzene).

2-Acetylamino-6-methylbenzyl Acetate (9). In excess acetic anhydride **8** was heated at 70 °C for 2 h with stirring. The excess anhydride was removed under reduced pressure to leave **9** in a quantitative yield. Recrystallization from carbon tetrachloride gave colorless needles: mp 118—118.5 °C; IR (KBr) 3250 (NH), 1735 (ester C=O), 1650 (amide C=O), and 790, 750 cm^{-1} (1,2,3-trisubstituted benzene); NMR ($CDCl_3$) δ 9.05 (s, 1, NH), 7.8—6.8 (m, 3, benzene ring), 5.12 (s, 2, CH_2–O), 2.41 (s, 3, CH_3), 2.19 (s, 3, N–$COCH_3$), and 2.05 ppm (s, 3, O–$COCH_3$). Found: C, 64.87; H, 6.59%. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83%.

2-Acetylamino-3-nitro-6-methylbenzyl Acetate (10). To a solution of 5.0 g (21.6 mmol) of **9** in 25 ml of acetic anhydride was added 4 ml of 70% nitric acid dropwise with stirring at 19—20 °C. After the addition was completed, the mixture was stirred for 1 h at the same temperature. The mixture was poured into 300 ml of cold water with stirring. Colorless needles separated were collected and recrystallized from ethanol to give pure **10** in 38% yield: mp 147—148 °C; IR (KBr) 3250 (NH), 1740 (ester C=O), 1655 (amide C=O), and 1510, 1355 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 8.9 (s, 1, NH), 7.81 (d, 1, J=9 Hz, H_4), 7.19 (d, 1, J=9 Hz, H_5), 5.15 (s, 2, CH_2–O), 2.50 (s, 3, CH_3), 2.19 (s, 3, N–$COCH_3$), and 2.08 ppm (s, 3, O–$COCH_3$). Found: C, 53.86; H, 5.07%. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30%.

From the mother liquor a mixture of **10** and **11** was recovered, giving a 79% yield for the nitration. The isomer **11** was separated by column chromatography using silica gel (Wakogel C-200) and dichloromethane, and recrystallized from carbon tetrachloride: mp 227—230 °C; IR (KBr) 3350 (NH), 1712 (ester C=O), 1688 (amide C=O), and 1520, 1350 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 9.5 (s, 1, NH), 8.03 (d, 1, J=9 Hz, H_4), 7.78 (d, 1, J=9 Hz, H_3), 5.20 (s, 2, CH_2–O), 2.58 (s, 3, CH_3), 2.25 (s, 3, N–$COCH_3$), and 2.12 ppm (s, 3, O–$COCH_3$).

2-Amino-3-nitro-6-methylbenzyl Alcohol (12). In aq methanol **10** was dissolved and hydrolyzed for 3 h at 60 °C after addition of aq sodium hydroxide. The solution was neutralized with hydrochloric acid and extracted four times with chloroform. After drying over magnesium sulfate, the solvent was removed to give orange crystals of **12** in 99% yield. Recrystallization from ethanol gave a pure sample: mp 135—136 °C; IR (KBr) 3460, 3350 (NH_2 and OH), 1636 (NH_2), 1498, 1321 (NO_2), and 816 cm^{-1} (1,2,3,4-tetrasubstituted benzene); NMR ($CDCl_3$) δ 7.89 (d, 1, J=9 Hz, H_4), 6.48 (d, 1, J=9 Hz, H_5), 4.76 (s, NH_2 and OH), 4.70 (s, 2, CH_2–O), and 2.35 ppm (s, 3, CH_3). Found: C, 52.45; H, 5.41%. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53%.

2,3-Diamino-6-methylbenzyl Alcohol (13). One hundred mg of **12** was dissolved in 5 ml of ethanol and reduced with hydrogen (1 atm) using about 20 mg of Urushibara nickel A.[5] Absorption of hydrogen ceased after the theoretical volume of hydrogen was taken up. The yellow solution was gradually decolorized as the hydrogen was absorbed. To dissolve a white precipitate 10 ml of hot ethanol was added and the reaction mixture was filtered with a glass filter with suction. Removal of ethanol gave 88 mg (99%) of white needles of **13**. The reaction mixture was worked up in a nitrogen atmosphere and **13** thus prepared was used immediately for the next step: mp 181—182 °C; IR (KBr) 3450—2400 (NH_2 and OH), 1660—1550 (NH_2), and 802 cm^{-1} (1,2,3,4-tetrasubstituted benzene); NMR (DMSO-d_6) δ 6.44 (d, 1, J=8 Hz, H_4 or H_5), 6.24 (d, 1, J=8 Hz, H_5 or H_4), 4.46 (s, 2, CH_2–O), and 2.16 ppm (s, 3, CH_3).

4-Hydroxymethyl-5-methylbenzimidazole (14). In 15 ml of 80% formic acid was dissolved 428 mg of freshly prepared **13**, and the solution was heated at 100 °C for 1 h with stirring. The resulting red solution was neutralized with concd aq sodium hydroxide to separate a red oil on the bottom. The decolorized supernatant solution was decanted and concentrated under reduced pressure to precipitate white needles. The needles were collected, washed with cold water, and dried, giving 171 mg (37%) of **14**: mp 205—205.5 °C; IR (KBr) 3300—2200 (NH and OH), 1590 (benzimidazole ring), and 811 cm^{-1} (1,2,3,4-tetrasubstituted benzene); NMR ($CDCl_3$) δ 8.00 (N–CH=N), 7.42 (d, 1, J=8 Hz, $H_{7(4)}$), 7.03 (d, 1, J=8 Hz, $H_{4(7)}$), 4.97 (s, 2, CH_2–O), and 2.45 ppm (s, 3, CH_3).

N-Acetyl-4-acetoxymethyl-5-methylbenzimidazole (15). Acetylation of **14** in the same way as for **6** gave crude **15**, which was recrystallized from carbon tetrachloride to give white needles in 80% yield: mp 156—157 °C; IR (KBr) 1725 (ester and amide C=O), 1595 (benzimidazole ring), and 817 cm^{-1} (1,2,3,4-tetrasubstituted benzene); NMR ($CDCl_3$) δ 8.32 (s, 1, N–CH=N), 8.06 (d, 1, J=9 Hz, H_7), 7.24 (d, 1, J=9 Hz, H_6), 5.59 (s, 2, CH_2–O), 2.71 (s, 3, N–$COCH_3$), 2.48 (s, 3, CH_3), and 2.07 ppm (s, 3, O–$COCH_3$).

4-Acetoxymethyl-5-methylbenzimidazole (3). Partial hydrolysis of **15** in the same way as for **7** gave white crystals of **3** in 83% yield after recrystallization from chloroform. The analytical and kinetic sample was purified further by sublimation *in vacuo*: mp 229—229.5 °C; IR (KBr) 3200—2400 (NH) 1720 (C=O), 1625, 1595 (benzimidazole ring), 1240 (C–O), and 820 cm^{-1} (1,2,3,4-tetrasubstituted benzene); NMR (CD_3OD) δ 8.02 (s, 1, N–CH=N), 7.46 (d, 1, J=9 Hz, $H_{7(4)}$), 7.05 (d, 1, J=9 Hz, $H_{6(5)}$), 5.42 (s, 2, CH_2–O), 4.74 (s, NH), 2.44 (s, 3, CH_3), and 2.02 ppm (s, 3, $COCH_3$). Found: C, 64.88; H, 5.98; N, 13.78%. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72%.

2-Acetylamino-3-amino-6-methylbenzyl Acetate (16). Using

the Urushibara nickel catalyst **10** was reduced with hydrogen in the same way as for **12**. White crystals of **16** were obtained in 100% yield: mp 149—151 °C; IR (KBr) 3390, 3230 (NH_2 and NH), 1732 (ester C=O), and 1650 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 8.8 (s, 1, NH), 6.90 (d, 1, J=8 Hz), 6.60 (d, 1, J=8 Hz), 5.07 (s, 2, CH_2–O), 2.30 (s, 3, CH_3), 2.20 (s, 3, N–$COCH_3$), and 2.01 ppm (s, 3, O–$COCH_3$).

4-Acetoxymethyl-2,5-dimethylbenzimidazole (4). A mixture of 2 ml of dry xylene and 50 mg of **16** was heated at 135 °C for 5 h with stirring. The reaction mixture was cooled to precipitate colorless needles, which were collected and washed with ether to give 40 mg (87%) of **4**. This was purified by recrystallization from carbon tetrachloride–chloroform and subsequent sublimation *in vacuo*: mp 220—221 °C; IR (KBr) 3500—2300 (NH), 1725 (C=O), 1625, 1595 (benzimidazole ring), 1235 (C–O), and 820 cm^{-1} (1,2,3,4-tetrasubstituted benzene); NMR (CD_3OD) δ 7.37 (d, 1, J=9 Hz, $H_{7(4)}$), 7.02 (d, 1, J=9 Hz, $H_{6(5)}$), 5.42 (s, 2, CH_2–O), 4.8 (s, NH), 2.55 (s, 3, CH_3), 2.44 (s, 3, CH_3), and 2.04 ppm (s, 3, $COCH_3$). Found: C, 65.94; H, 6.67; N, 13.12%. Calcd for $C_{12}H_{14}N_2O_4$: C, 66.04; H, 6.47; N, 12.84%.

Reduction of 12 with Tin and Hydrochloric Acid. To a mixture of 102 mg of **12** and 400 mg of tin was added 2.5 ml of concd hydrochloric acid, and the mixture was heated at 70 °C for 30 min. Then it was made basic (pH 11) by addition of 5 ml of 5 M sodium hydroxide and heated at 100 °C for a while. Extraction with chloroform gave 56 mg of white needles in 74% yield, which was identified as 3,4-*o*-xylenediamine: IR (KBr) 3400—3150 (NH_2), 1625 cm^{-1} (NH_2); NMR (CD_3OD) δ 6.45 (t, 2, CH=CH), 4.63 (s, 4, NH_2), 2.14 (s, 3, CH_3), and 2.03 ppm (s, 3, CH_3).

Kinetics. All kinetic measurements for hydrolysis were made at 50±0.1 °C (0.1 M KCl) in water by the titration of liberated acid with the titration assembly.[1] The initial concentration of acetate **2** was 0.0025 and 0.005 M. However, only 0.0025 M was used for **3** and **4** owing to their solbilities. Hydrolysis of the acetates were followed to 3 (at pH 6.5)—50 % (at pH 9.0) completion for **2**, to 2.4 (at pH 7.0)—47% (at pH 9.0) for **3**, and to 6.9 (at pH 6.5)—15% (at pH 9.0) for **4**. Deposition of **3** from the kinetic solution after 1 h or so from the start of kinetic run allowed only 2—3% completion for **3** at pH 6.5—7.0, although **3** could be dissolved initially in the acidic solution. All runs followed first-order kinetics. Values of k_{obsd} were reproduced within±5%.

pK_a *Determinations.* Values of pK_a were determined according to the method of Albert and Serjeant[16] using the apparatus for kinetics under the same conditions as for kinetics.

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