General Acid Catalytic Activity of 2-Substituted Imidazoles for Hydrolysis of Diethyl Phenyl Orthoformate

Masao Ihjima,* Masahiro Fukuyama, Takashi Kobayashi, and Takayuki Hirakawa
Department of Industrial Chemistry, Tsuruoka Technical College, Tsuruoka, Yamagata 997, Japan
Masayasu Akiyama *
Department of Applied Chemistry for Resources, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184, Japan

Hydrolysis of diethy phenyl orthoformate catalysed by a series of 2-substituted imidazoles has been studied in 50% dioxane–water (v/v) at 30 °C. The substituents are H, Me, Et, Pr^{i}, Bu^{t}, 2-hydroxypropyl, and 1,1-dimethyl-2-hydroxyethyl groups. General acid catalysis is observed for hydrolysis by these imidazoles but not general base catalysis. The rate data are analysed in terms of the second-order rate constants for imidazoles *versus* the Taft steric constant parameter, E_s. The steric effect of substituents is small. Activation parameters determined for a few imidazoles contain large negative entropies. These results and a D_2O solvent isotope effect indicate that solvent water molecules participate in the transition state of the reaction.

Studies on imidazolium ions in chemical reactions are of importance in an attempt to understand the mechanism of enzyme actions.[1-3] In serine proteases, a histidine imidazolyl group is considered to accept a proton from a serine hydroxy group and to give the proton to the leaving amine moiety of a substrate to form an acyl enzyme intermediate.[1,4] In the papain-catalysed hydrolysis of an amide substrate, a rate-determining proton transfer from a protonated imidazolyl group to a tetrahedral intermediate is suggested,[5] and in the action of ribonuclease a protonated imidazolyl group is thought to act concertedly on a substrate with another nearby imidazolyl group.[6] Although general base and nucleophilic catalysis by imidazoles has been extensively studied for the hydrolysis of esters and amides, only a few reports have been published on general acid catalysis by imidazolium ions; it has been shown that the hydrolysis of *N*-acylimidazoles proceeds partially through general acid catalysis by imidazolium ions,[7] and that cyclic acetals with ring strain[8] or phenyl ketene acetals[9] are hydrolysed by the action of general acid catalysts involving imidazolium ion.

Previously we have reported that the nucleophilic reactivity of 2-substituted imidazoles is markedly diminished by bulky substituents,[10] while the general base catalytic activity is little affected.[11] In this context, it was of interest to study substituent effects of imidazolium ions upon general acid catalytic activity.

A number of studies have been made to delineate the requirements for general acid catalysis in the hydrolysis of acetals and orthoesters,[12] dealing with the effects of substituents on these substrates.[13] However, the hydrolysis has not been studied in terms of steric effects on the catalysts. In this study, we chose diethyl phenyl orthoformate as substrate, since it has been shown to be hydrolysed through general acid catalysis by a series of carboxylic acid.[14] Because of the partial resemblance of an orthoester to a tetrahedral intermediate this hydrolysis could be taken as a model reaction for the breakdown of a tetrahedral intermediate to an acyl enzyme.[15]

Experimental

Materials.—Diethyl phenyl orthoformate was distilled before use, b.p. 93 °C at 3 mmHg, n_D^{21} 1.4796. The sources of the imidazoles were described previously.[10] Dioxane was purified by the standard method.[16] Spectroscopic grade acetonitrile was used. Water and deuterium oxide (Merck 99.75%) were glass distilled.

Kinetic Procedure.—The solvent used was 50% dioxane–water (v/v). Imidazole buffers were prepared by partial neutralisation of an appropriate imidazole free base with 1 mol l^{-1} hydrochloric acid: their total concentrations were in the range of 0.04—0.2 mol l^{-1}, the buffer ratio ([ImH$^+$]:[Im]) was mostly 1:1, and ionic strength was maintained at 0.1 with KCl. Rates of the hydrolysis were determined by following the increase in absorbance at 272.3 nm due to the product phenol at constant temperature with a Hitachi 100-50 recording spectrophotometer fitted with a constant-temperature cell holder (±0.1 °C). To initiate the reaction diethyl phenyl orthoformate in acetonitrile (10 µl) was added to buffer solution (3 ml) in a cuvette with vigorous stirring. All runs were performed under pseudo-first-order conditions, with an initial orthoester concentration of 1.0×10^{-4} mol l^{-1}. The absorbance was recorded continuously over three or four half-lives and the infinite-time recording was made after 10 half-lives to obtain observed first-order rate constants (k_{obs}). In slower runs the data were treated by the method of Guggenheim.[17] Each run was at least duplicated. An average deviation of the individual rate constants was <5%. Second-order rate constants (k_{imH^+}) were obtained from the slopes of the plots of the first-order rate constants against the imidazolium ion concentrations at three or four buffer concentrations. The pH of each solution was measured with a Denkikagakukeiki HG-2 pH meter equipped with a combination electrode type 6035.

Product Analysis.—Diethyl phenyl orthoformate (final concentration 0.01 mol l^{-1}) was added to 0.2 mol l^{-1} imidazole buffer (1 ml) ([Im] = [ImH$^+$] = 0.1 mol l^{-1}) in 50% aqueous dioxane. When the hydrolysis was over (*ca.* 30 min), the solution (1 µl) was chromatographed on a Varian Aerograph 920 TCD gas chromatograph using SE-30 on Chromosorb W at 130 °C. The products were ethanol, phenol, and ethyl formate. In a kinetic run, any other intermediate could not be detected with repeat scanning of the u.v. spectra.

Results

Figure 1 shows typical plots of k_{obs} for hydrolysis by imidazole buffer at different buffer ratios against the total buffer concentration. Similar plots were obtained for 2-methylimidazole, which is the most basic of the imidazoles used. An increase in slope with decreasing pH in Figure 1 was taken as

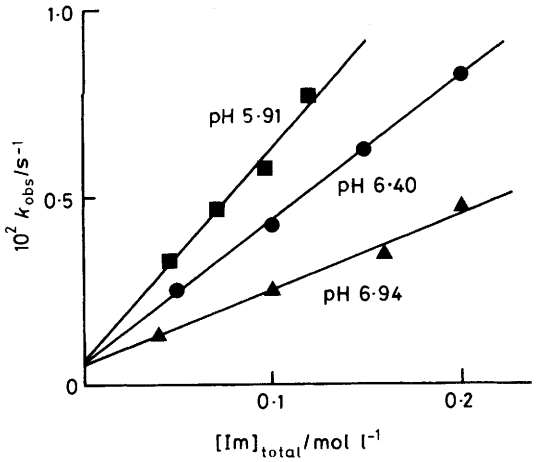


Figure 1. Plots of k_{obs} for hydrolysis of diethyl phenyl orthoformate *versus* total imidazole buffer concentration in 50% dioxane–water at 30 °C and ionic strength 0.1: ●, 1:1 buffer; ▲, 1:3 buffer; ■, 3:1 buffer

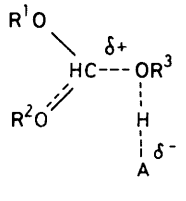
evidence for general acid catalysis by imidazolium ions. Thus, equation (1) holds. A k_{imH^+} value obtained for 1:1 imidazole

$$k_{obs} = k_0 + k_{imH^+}[ImH^+] \quad (1)$$

buffer is in accord with values for 1:3 and 3:1 buffer within experimental error. The value obtained at zero buffer concentration (Figure 1) is the rate constant due to spontaneous hydrolysis, k_0, by water and hydronium ion. The values of k_{imH^+} for 1:1 buffer at 30 °C and at additional temperatures for some of the imidazoles are given in Table 1 together with the pK_a values. The k_{imH^+} value for imidazole (pK_a 6.50) at 25 °C was close to a value of 0.078 l mol^{-1} s^{-1} reported[14] for succinic acid (pK_a 6.90). The rate constants were also determined for 1:1 imidazole buffer in 50% dioxane–deuterium oxide at 30 °C and listed in Table 1. A deuterium oxide solvent isotope effect, $k_{imH^+}(H_2O)/k_{imH^+}(D_2O)$, for imidazolium ion was calculated to be 2.1 and this was of the same magnitude as the value[14] reported for acetic acid as a catalyst. The values of activation parameters determined for a few imidazoles are given in Table 2. Although amide acetal formation in the reaction of triethyl orthoformate with imidazole has been reported,[18] no such intermediate was detected during kinetic runs.

Discussion

General Acid Catalysis.—Protonated imidazole in buffer was the active form of the catalyst for hydrolysis of diethyl phenyl orthoformate. Scheme 1 represents the accepted structure of the



Scheme 1.

transition state of the acid-catalysed hydrolysis of orthoesters. To confirm general acid catalysis by imidazolium ions, $(k_{obs} - k_0)/[Im]_{total}$ is plotted against the fraction of acidic component of the buffer, as shown in Figure 2. A good linear

Table 1. Rate constants for hydrolysis of diethyl phenyl orthoformate catalysed by 2-substituted imidazoles in 50% dioxane–water (v/v)[a]

	Imidazole substituent	pK_a[b]	$10^2 k_{imH^+}$/l mol^{-1} s^{-1} 30 °C	35 °C	40 °C
1	2-H[c]	6.40	7.74	10.8	15.6
	(Dioxane-D_2O)		3.74		
2	2-Me	7.34	3.05		
3	2-Et	7.31	3.13		
4	2-HOCH(Me)CH_2	7.06	3.25		
5	2-Pr^i	7.20	2.56	4.00	6.11
6	2-Bu^t	7.10	1.97		
7	2-$HOCH_2C(Me)_2$	6.99	1.64	2.68	3.80

[a] Ionic strength 0.1 (KCl); diethyl phenyl orthoformate 1×10^{-4} mol l^{-1}. [b] Taken as the pH of the half-neutralised buffer solution in 50% dioxane–water at 30 °C and ionic strength 0.1. [c] At 25 °C, $10^2 k_{imH^+}$ 5.07 l mol^{-1} s^{-1}.

Table 2. Activation parameters for hydrolysis of diethyl phenyl orthoformate in 2-substituted imidazole buffers[a]

Buffer	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal K^{-1} mol^{-1}
Imidazole	13.2 ± 0.4	−20.3 ± 1.2
2-Isopropylimidazole	15.8 ± 0.1	−13.7 ± 0.4
2-(1,1-Dimethyl-2-hydroxyethyl)imidazole	15.6 ± 1.2	−15.4 ± 4.0

[a] Obtained as values at 25 °C in 50% dioxane–water; the standard errors were estimated from the deviation of a plot of ln (k_{imH^+}/l mol^{-1} s^{-1}) *versus* $(T/K)^{-1}$.

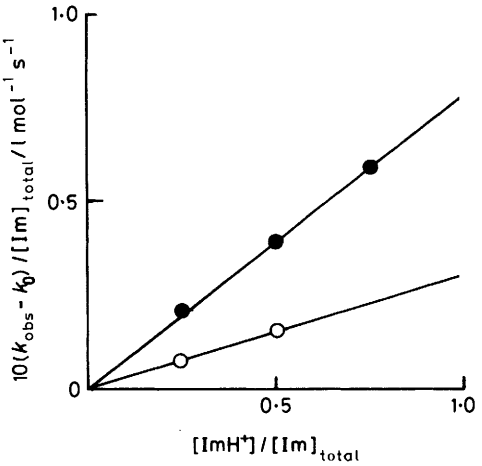


Figure 2. Plots of $(k_{obs} - k_0)/[Im]_{total}$ *versus* fraction of imidazolium ion concentration: ●, imidazole; ○, 2-methylimidazole

relationship with zero intercept on the left-hand ordinate indicates that only the acidic component of the buffer acts as catalyst.[19] Since no particular stable intermediate is detected by product analysis, the mechanism of the present hydrolysis involves rate-determining proton transfer with concurrent C–O bond cleavage as observed for the same hydrolysis by carboxylic acids catalysts. The deuterium oxide solvent isotope effect of 2.1 is also evidence for the general acid catalysis.[12]

The value of k_{imH^+} for imidazole at 25 °C was slightly smaller when compared with an acid of the same pK_a:[14] the point for imidazole deviates by 0.3 log unit below a Brönsted line with a slope of 0.47. Since no steric hindrance by imidazole

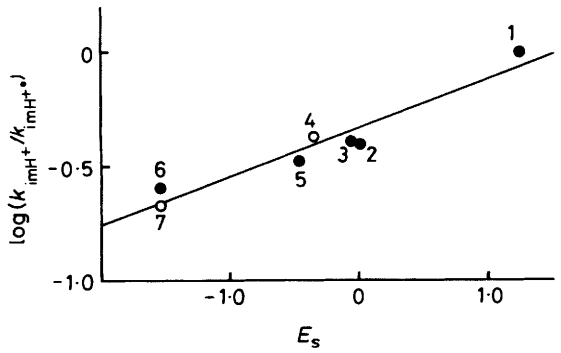


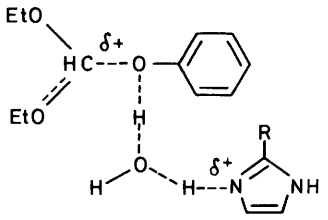
Figure 3. Plot of log ($k_{imH^+}/k_{imH^+}^{\circ}$) *versus* Taft E_s steric constant parameter: E_s values are given in ref. 23; hydroxyalkyl groups (○) are tentatively plotted on the same scale as the corresponding alkyl groups (●). For key, see Table 1

ring itself has been found in the general acid-catalysed hydrolysis of 2-methoxy-3,3-dimethyloxetane[8] and phenylketene acetal,[9] the lower deviation is thought to be due to a polar interaction[20] between imidazolium ion and a partially positively charged substrate which is different from the interaction between a partially negatively charged carboxylic acid catalyst and a partially positively charged substrate.

The entropies of activation in Table 2 are large negative values, which indicate the participation of two or more molecules in the transition state.[21] These activation parameters are comparable with those reported by Kirby and his coworkers[22] for hydrolysis of 2-(4-nitrophenoxy)-1-oxa-*trans*-decalin catalysed by chloroacetic acid. Upon entering into the transition state in 50% aqueous dioxane, the less substituted imidazoles, which are better hydrated, would require more unfavourable entropies of activation which may be offset by slightly more favourable enthalpies of activation. The activation parameters in Table 2 are in line with this reasoning. Water molecules that participate in the transition state act as favourably for a cationic species developed from the substrate, keeping a positively charged 2-substituted imidazolium ion at a distance.

Substituent Effects.—The second-order rate constants of 2-substituted imidazoles at 30 °C decrease with increasing bulkiness of the substituents (Table 1). The value of k_{imH^+} for 2-t-butylimidazole which has the most bulkyl substituent in the series is only five times as small as that for the parent imidazole. A similar sort of a small rate decrease has been observed for general base catalysis by 2-substituted imidazole.[11] It can be said that steric hindrance is less important in general catalysis.

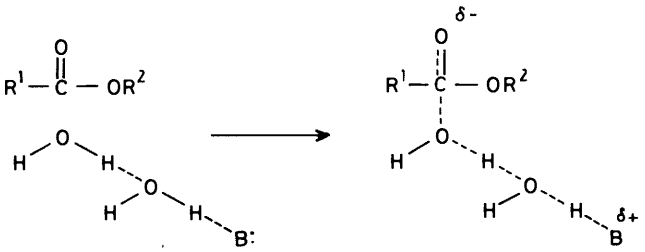
To evaluate the steric effect of the substituents, log ($k_{imH^+}/k_{imH^+}^{\circ}$), where $k_{imH^+}^{\circ}$ is the second-order rate constant for the patent imidazole, is plotted against Taft steric constant parameter, E_s,[23] as shown in Figure 3. Hydroxyalkyl groups are tentatively plotted on the same scale as the corresponding alkyl groups although the oxygen atom has its own bulk. The slope of the plot represents the susceptibility of the steric effects on the reaction and it is estimated to be 0.22 ± 0.03 (standard error). The susceptibilities of steric effect in general base[11] and nucleophilic catalysis[10] have been found to be 0.26 and 1.3, respectively. The small susceptibility implies that the rate-determining proton transfer from an acid to the substrate is indirect. A mechanism represented by Scheme 2 shows that at least one solvent water molecule intervenes between an imidazolium ion and the orthoester, stabilises the transition state by separating the charge-developing species, and facilitates proton transfer through the hydrogen bond formed. In fact,



Scheme 2.

many proton-transfer reactions in hydrolytic solvents have been known to proceed with participation of solvent water molecules.[24]

General Catalysis and Solvent Molecules.—General acid catalysis is depicted without water molecules, as in Scheme 1. However, it should correctly be shown as in Scheme 2. While general acid catalysis requires at least one solvent molecule, what is the requirement for base catalysis? According to the principle of microscopic reversibility of a chemical reaction, general base catalysis in one direction should be general acid catalysis in the opposite direction. In so far as general acid catalysis entails a water molecule, general base catalysis also requires one water molecule. For ester hydrolysis with base, for example, we could suggest it should be expressed as in Scheme 3,



Scheme 3.

although general acid-catalysed decomposition of a tetrahedral intermediate into an ester is not found.

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