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Imidazole-Assisted Intramolecular Nucleophilic Attack of the Amide Oxygen at Ester Linkages in Aryl or Alkyl Esters of (*Z*)-α-(Acetylamino)cinnamic Acid

JUNGHUN SUH,[1] EUNKYEONG YANG, EUGENE OH, AND SEUNG SOO YOON

Department of Chemistry, Seoul National University, Seoul 151-742, Korea

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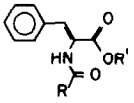
The intramolecular nucleophilic attack by the amide oxygen atoms of various aryl or alkyl esters of (*Z*)-α-(acetylamino)cinnamate leads to the cyclization of the esters producing (*Z*)-4-benzylidene-2-methyloxazolin-5-one. Kinetics of the cyclization reactions were measured in the presence and absence of imidazole (Im), *N*-methylimidazole (MeIm), or substituted pyridines. From the slopes of the plots of the logarithmic values of various rate constants against pK_{LG} values (pK_a of the leaving groups), β_{LG} values were calculated. The β_{LG} values indicate that the hydroxide-assisted cyclization involves rate-determining expulsion of the leaving phenols or alcohols. The Im-assisted reaction consisted of two paths: one involving the participation of Im only and the other involving that of Im together with hydroxide ion. When MeIm was added, only the reaction path involving MeIm was observed. The β_{LG} values for the reaction paths involving Im or MeIm were ca. 0 in the cyclization of the aryl esters, while they were quite large in the reaction of the alkyl esters. When pyridine bases were added, the cyclization reactions were not catalyzed. Based on these kinetic data, it is proposed that Im- or MeIm-assisted cyclization reactions involve the initial attack of Im or MeIm at the amide carbon followed by the attack of the oxyanion of the consequently formed tetrahedral intermediate at the ester carbon.

INTRODUCTION

Among various polar organic functional groups, the amide group is present most abundantly in the active sites of enzymes. In this regard, the possibility of participation of amide groups in enzyme catalysis has been suggested, and kinetic studies for the nucleophilic reactions of both the oxygen (*1*) and the nitrogen (*2*) atoms of amide groups have been performed with small organic compounds.

Previously, we reported very efficient intramolecular attack by the oxygen atom of the amide group at alkyl and aryl ester linkages (*3*). The intramolecular nucleophilicity of amide groups in aryl and alkyl esters **1a**, **1f**, **2a**, and **2b** was as high as or even higher than that of the carboxyl groups of the corresponding monoaryl or monoalkyl esters of phthalic acid derivatives:



[1] To whom correspondence should be addressed.

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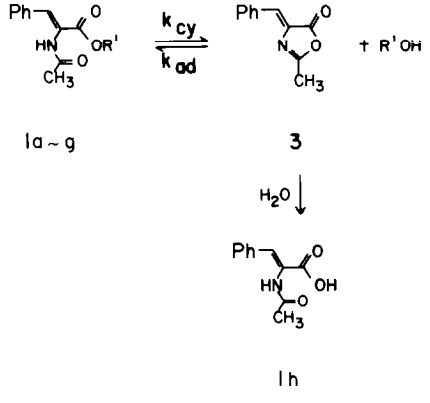
1a: R = CH_3, R′ = Ph
1b: R = CH_3, R′ = 3-Cl-Ph
1c: R = CH_3, R′ = 4-Cl-Ph
1d: R = CH_3, R′ = 4-CH_3Ph
1e: R = CH_3, R′ = CCl_3CH_2
1f: R = CH_3, R′ = CF_3CH_2
1g: R = CH_3, R′ = $CHCl_2CH_2$
1h: R = CH_3, R′ = H
2a: R = Ph, R′ = Ph
2b: R = Ph, R′ = CF_3CH_2

Highly efficient catalysis can be achieved by cooperation among several catalytic factors. If an amide group acts as a catalytic group of an enzyme, therefore, it would collaborate with other catalytic groups. In this article, we report kinetics of the cyclization (Eq. [1]) of the aryl and alkyl esters of **1h** leading to **3** measured in the presence of imidazole (Im),[2] the catalytic group of histidyl residues of enzymes, and related bases. In addition, the mechanism of the Im-assisted nucleophilic attack of the amide group is elucidated:



[1]

MATERIALS AND METHODS

Materials. Phenyl (Z)-α-(acetylamino)cinnamate (**1a**), *2,2,2-trifluororoethyl (Z)-α-(acetylamino)cinnamate* (**1f**), *(Z)-α-(acetylamino)cinnamic acid* (**1h**), *(Z)-4-benzylidene-2-methyloxazolin-5-one* (**3**): These compounds were prepared as described previously (*3*).

m-Chlorophenyl (Z)-α-(acetylamino)cinnamate (**1b**), *p-chlorophenyl (Z)-α-(acetylamino)cinnamate* (**1c**), *p-tolyl (Z)-α-(acetylamino)cinnamate* (**1d**), *2,2,2-trichloroethyl (Z)-α-(acetylamino)cinnamate* (**1e**), *2,2-dichloroethyl (Z)-α-(acetylamino)cinnamate* (**1g**): These compounds were prepared by reacting **3** with the corresponding phenol or alcohol at pH 7–10.5 and were recrystallized from ethanol according to the general procedures reported previously (*3*). **1b**: mp 134–136°C; ^{1}H NMR ($CDCl_3$) 2.15 (s, 3H, CH_3), 7.23–7.55 (m, 10H, aromatic and vinylic H): ir (KBr-disc) 1740 (ester C=O), 1660 (amide C=O); *Anal.* C, H, N. **1c**: mp 147–149°C; ^{1}H NMR ($CDCl_3$) 2.14 (s, 3H, CH_3), 7.17–7.55 (m, 10H, aromatic and vinylic H); ir (KBr-disc) 1740 (ester C=O), 1660 (amide C=O); *Anal.* C, H, N. **1d**: mp 127–129°C; ^{1}H NMR ($CDCl_3$) 2.12 (s, 3H, CH_3), 2.36 (s,

[2] Abbreviations used: Im, imidazole; MeIm, *N*-methylimidazole; Mes, 4-morpholineethanesulfonic acid; Hepes, *N*-(2-hydroxyethyl)-1-piperazineethanesulfonic acid.

3H, aromatic CH_3), 7.09–7.58 (m, 10H, aromatic and vinylic H); ir (KBr-disc) 1725 (ester C=O), 1640 (amide, C=O); *Anal.* C, H, N. **1e**: mp 136–137°C; ^{1}H NMR ($CDCl_3$) 2.13 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 6.70 (s, 1H, NH), 7.3–7.55 (m, 6H, aromatic and vinylic H); ir (KBr-disc) 1740 (ester C=O), 1670 (amide C=O); *Anal.* C, H, N. **1g**: mp 127–129°C; ^{1}H NMR ($CDCl_3$) 2.12 (s, 3H, CH_3), 4.60 (d, J = 6.4 Hz, 2H, CH_2), 5.90 (t, J = 6.4 Hz, 1H, $CHCl_2$), 6.83 (s, 1H, NH), 7.26–7.53 (m, 6H, aromatic and vinylic H); ir (KBr-disc) 1730 (ester C=O), 1670 (amide C=O); *Anal.* C, H, N.

Acetone, acetonitrile, phenol derivatives, ethanol derivatives, Im, *N*-methylimidazole, β-picoline, 4-aminopyridine, and *N,N*-dimethyl-4-aminopyridine were purified by distillation or recrystallization before being used in kinetic studies. Water was distilled, deionized, and then used in kinetic measurements.

Kinetic measurements. Reaction rates were measured with a Beckman Model 5260 uv/vis spectrophotometer. Temperature was maintained at 25 ± 0.1°C with a Lauda Brinkman T-2 circulator. pH measurements were performed with a Dongwoo DF-215 pH meter. Buffers used were Im (pH 6.4–8.1), *N*-methylimidazole (pH 6.5–8.3), 4-morpholineethanesulfonic acid (Mes; pH 5.5–6.7), *N*-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Hepes; pH 6.8–8.2), borate (pH 8.3–9.7), and sodium bicarbonate (pH 9.5–11.3). Ionic strength was maintained at 1.0 M with sodium chloride. Initially added concentrations (S_o) of substrates used in the rate measurements were 0.5–2 × 10^{-4} M. Kinetic measurements were performed in the presence of 9.1% (v/v) acetonitrile. The pH readings reported with kinetic results were measured in the presence of organic solvents as described previously (*4*).

RESULTS

Cyclization of 1a–g to form 3. The electronic spectrum of **3** manifests strong adsorbance at 330–370 nm, while **1a–h** do not absorb in this region. Kinetics of the formation of **3** due to cyclization of **1a–g** and breakdown of **3** due to its hydrolysis (*5*) were measured spectrophotometrically in this wavelength range. The formation of **3** was sufficiently faster (>20-fold) than the subsequent breakdown of **3** in the cyclization of **1a–d**. In this case, the pseudo-first-order rate constant (k_{cy}) for the cyclization (Eq. [1]) leading to **3** was calculated from the absorbance increase corresponding to the formation of **3**, as explained previously (*3*). For the reactions of **1e** and **1f**, the formation of **3** was not sufficiently faster than the breakdown step, and the biphasic absorbance (Abs) changes were analyzed according to Eq. [2] (*6*), in terms of the first-order rate constants for the first (k^1) and second (k^2) phases and the molar exctinction coefficient (ε^o) of 3:

$$\text{Abs} = k^1\varepsilon^o S_o(e^{-k^1t} - e^{-k^2t})/(k^2 - k^1). \qquad [2]$$

Since k^1 was not affected by the addition of R'OH (added concentrations, ~S_o), k_{cy} is much greater than k_{ad}[R'OH] (Eq. [1]) under the experimental conditions and, therefore, k^1 corresponds to k_{cy} (*3*).

The k_{cy} values measured at a given pH were not affected by 0.01–0.03 M buffers (Mes, Hepes, borate, or bicarbonate). The k_{cy} value thus obtained was propor-

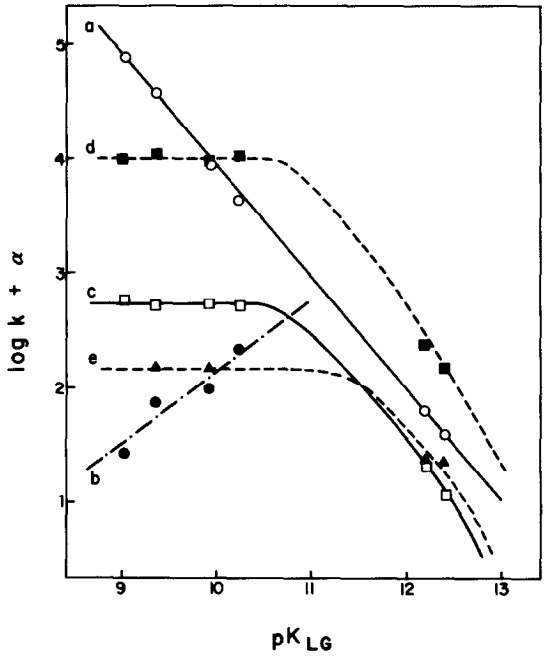


FIG. 1. Plots of the logarithmic values of various parameters against pK_{LG}. Line a (○), $k = k_{cy}^{OH}$ and $\alpha = 0$; line b (●), $k = K_{app}^{\circ}$ and $\alpha = 0$; line c (□), $k = (k_{cy}^{Im})_o$ and $\alpha = 5$; line d (■), $k = (k_{cy}^{Im})_{OH}$ and $\alpha = 0$; line e (▲), $k = (k_{cy}^{MeIm})_o$ and $\alpha = 5$. Standard deviations of the data points fall within the range indicated by the data symbols.

tional to $[OH^-]$ and the proportionality constants were assigned as k_{cy}^{OH} (*3*).[3] The values of k_{cy}^{OH} for the spontaneous cyclization of **1a–f** are summarized in Table 1 and plotted against pK_{LG} (pK_a of the leaving phenol or alcohol) in Fig. 1. The slope (β_{LG}) of the linear plot of log k_{cy}^{OH} against pK_{LG} obtained for **1a–f** is -0.97 ± 0.01.

When Im was added to the reaction mixture at a constant pH, k_{cy} manifested linear dependence on $[Im]_b$ (b denotes the the concentration of basic form of the added base)[4] as illustrated in Fig. 2. The slope of the plot of k_{cy} against $[Im]_b$ was taken as k_{cy}^{Im}. The k_{cy}^{Im} values thus calculated were linearly related to $[OH^-]$, as illustrated in Fig. 3. The intercept and the slope of the linear plot of k_{cy}^{Im} against $[OH^-]$ are denoted $(k_{cy}^{Im})_o$ and $(k_{cy}^{Im})_{OH}$, respectively. The rate data measured in the presence of Im, therefore, are expressed by

$$k_{cy} = k_{cy}^{OH}[OH^-] + k_{cy}^{Im}[Im]_b$$
$$= k_{cy}^{OH}[OH^-] + (k_{cy}^{Im})_o[Im]_b + (k_{cy}^{Im})_{OH}[Im]_b[OH^-]. \quad [3]$$

[3] The values of K_w in the reaction medium containing 9.1% (v/v) acetonitrile was assumed as 1×10^{-14} M^{-2} in the calculation of $[OH^-]$. The inaccuracy (*3*) in K_w results in the error of the estimated values of k_{cy}^{OH} or $(k_{cy}^{Im})_{OH}$. However, the respective β_{LG} values are unaffected.

[4] $[Im]_b$ and $[MeIm]_b$ were calculated with pK_a values of 7.25 and 7.29, respectively, as measured under the experimental conditions.

TABLE 1

Values of Kinetic Parameters for Cyclization of 1a–f[a]

Compound	pK_{LG}	k_{cy}^{OH} (M^{-1} s^{-1})	K_{app}^{o} (M^{-1})	$(k_{cy}^{Im})_o$ (10^{-3} M^{-1} s^{-1})	$(k_{cy}^{Im})_{OH}$ (10^{4} M^{-1} s^{-1})	$(k_{cy}^{MeIm})_o$ (10^{-3} M^{-1} s^{-1})
1a	9.92	9400	100	5.50	1.02	1.52
1b	9.03	77800	27.5	5.61	1.02	
1c	9.35	39100	75.0	5.34	1.10	1.60
1d	10.25	4560	215	5.41	1.07	
1e	12.20	63.1	[b]	0.204	0.0246	0.225
1f	12.40	40.1	[b]	0.118	0.0153	0.224

[a] Measured at 25°C and ionic strength 1.0 M in the presence of 9.1% (v/v) acetonitrile.
[b] These values were not obtained since they were too large to measure accurately.

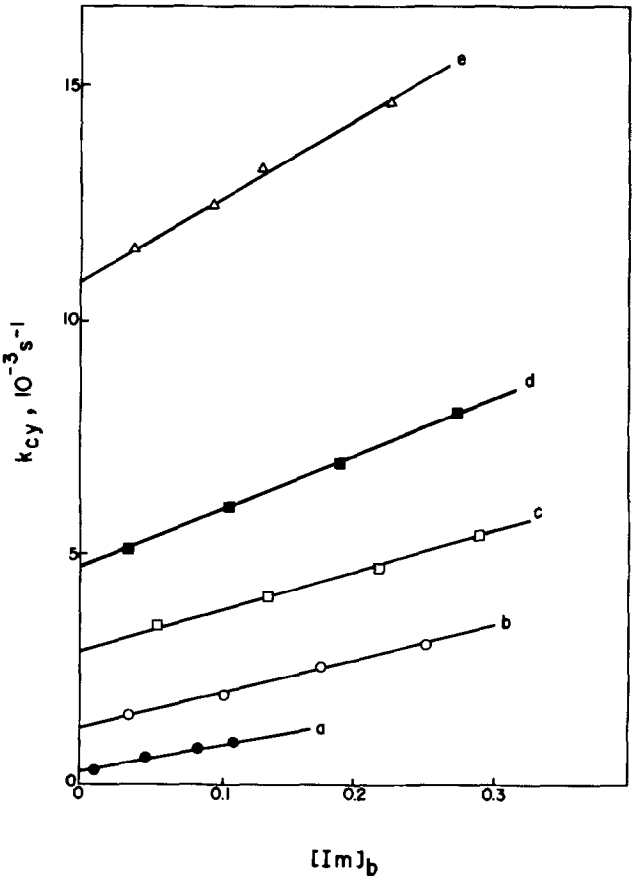


FIG. 2. Plots of k_{cy} against $[Im]_b$ at pH 6.44 (a), 7.06 (b), 7.52 (c), 7.77 (d), and 8.03 (e) for 1a.

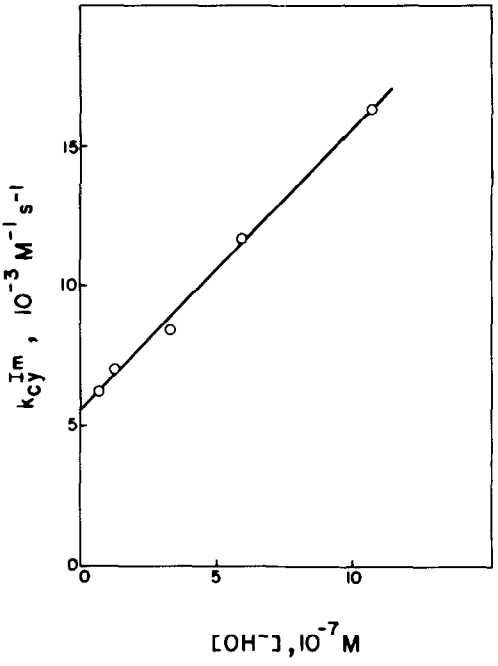


FIG. 3. Plot of k_{cy}^{Im} against [OH⁻] for **1a**.

The values of $(k_{cy}^{Im})_o$ or $(k_{cy}^{Im})_{OH}$ are summarized in Table 1 and plotted against pK_{LG} in Fig. 1.[5]

Kinetics of the cyclization of **1a**, **1c**, **1e**, and **1f** were also investigated in the presence of *N*-methylimidazole (MeIm). The values of k_{cy} depended linearly on $[MeIm]_b$.[4] The reaction path involving both MeIm and hydroxide ion, however, was not observed. The rate data observed in the presence of MeIm conform to Eq. [4] and the values of $(k_{cy}^{MeIm})_o$ estimated from the kinetic data are summarized in Table 1[5]:

$$k_{cy} = k_{cy}^{OH}[OH^-] + (k_{cy}^{MeIm})_o[MeIm]_b. \quad [4]$$

Kinetics of the cyclization of **1a** and **1e** were also investigated in the presence of β-picoline at pH 7.3 or in the presence of 4-aminopyridine (NH_2Py) or 4-*N*,*N*-dimethylaminopyridine (NMe_2Py) at pH 8.3–9.3.[6] No rate increase due to the added pyridine derivatives (up to 0.7 M) was observed.

[5] In the presence of Im or MeIm, the accumulation of **3** was much faster than the subsequent breakdown process in the reaction of **1a–d**, whereas **3** accumulated in considerably less than quantitative amounts in the reactions of **1e** and **1f** because the formation of **3** was not sufficiently faster than the breakdown step. For **1g**, **3** accumulated in very small amounts in the presence or absence of Im or MeIm, and rate constants were not measurable. Thus, the values of $(k_{cy}^{Im})_o$, $(k_{cy}^{Im})_{OH}$, or $(k_{cy}^{MeIm})_o$ for **1g** (pK_{LG} = 12.90) is markedly smaller than those of **1f**.

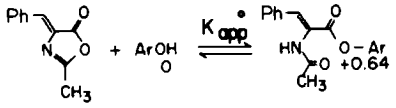
[6] The pK_a values of β-picoline, NH_2Py, and MMe_2Py are 5.68, 9.11, and 9.52, respectively, in water (*7*).

Addition of phenol derivatives to 3 to form 1a–d. The formation constant (K_{app}) for **1**a–d from **3** and phenol derivatives were measured at several pHs as indicated previously (*3*). The K_{app} value decreases as the phenol derivative is ionized. From the pH dependence of K_{app}, the limiting value (K^{o}_{app}) of the formation constant is estimated. The K^{o}_{app} value represents the formation constant when the phenol derivative is fully protonated (Eq. [1]) (*3*). The values of K^{o}_{app} are summarized in Table 1 and the dependence of log K^{o}_{app} on pK_{LG} is illustrated in Fig. 1, from which the β_{LG} value of 0.64 ± 0.14 is obtained.

DISCUSSION

Values of β_{LG} are obtained from the plots of logarithmic values of various kinetic parameters (k^{OH}_{cy}, $(k^{Im}_{cy})_o$, $(k^{Im}_{cy})_{OH}$, and $(k^{MeIm}_{cy})_o$) against pK_{LG}. The β_{LG} value may be taken as the difference in the effective charges on the leaving atom between the rate-determining transition state and the ground state for the reaction path represented by the respective kinetic parameter (*8*).

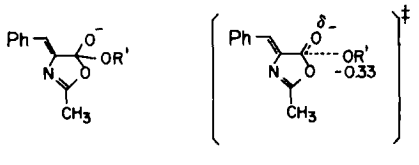
The β_{LG} value of 0.64 ± 0.14 obtained for the plot of log K^{o}_{app} against pK_{LG} indicates that the leaving oxygen atom contains an effective positive charge of 0.64 ± 0.14 in the ester substrates (Eq. [5]), when the effective change on the oxygen atoms of phenols is taken as 0:



[5]

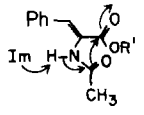
This agrees with the positive charges (ca. 0.7) (*8*) assigned on the phenol oxygen atoms of aryl carboxylates. This positive effective charge is attributable to the resonance of the ester linkage and the electron-withdrawing inductive effects of the acyl moiety (*8*).

The β_{LG} of −0.97 ± 0.01 for k^{OH}_{cy} in turn reveals that the aryl oxygen atom in the transition state contains an effective charge of −0.33 ± 0.14. The nucleophilic attack of amide oxygen atoms at acyl centers is proposed to proceed through the formation of tetrahedral intermediates (*1*). Accordingly, hydroxide-assisted cyclization of esters of **1**h would involve the formation of tetrahedral intermediate A. The β_{LG} values for K^{o}_{app} and k^{OH}_{cy} suggest that the leaving phenols or alcohols are



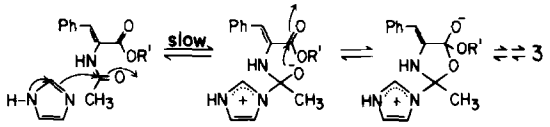
considerably expelled in the rate-determining transition state (B) for hydroxide-assisted cyclization of **1a–f**.[7]

The Im-assisted cyclization of both the aryl and the alkyl esters of **1h** occurs through two reaction paths: one involving Im only and the other involving both Im and hydroxide ion. The possibility that Im participates as a general base (C) can be excluded on the ground that even stronger nitrogen bases such as NMe_2Py or NH_2Py do not raise the reaction rate.[8]



C

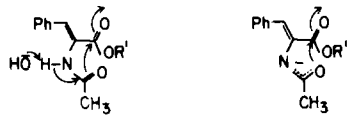
The rate constants ($(k_{cy}^{Im})_o$ and $(k_{cy}^{Im})_{OH}$) for the two paths involving Im are independent of pK_{LG} when only aryl ester substrates **1a–d** are considered. This indicates that the bond between the amide oxygen atom and the ester carbon atom is formed to an insignificant extent in the rate-determining transition state for the aryl esters. The kinetic data observed for the Im-assigned paths are best explained in terms of Eq. [6], which includes a tetrahedral intermediate formed by the attack of Im at the amide group:[9]



[6]

D E F

[7] Since the breakdown of intermediate A is rate-determining in the hydroxide ion-assisted cyclization of **1a–f**, whether L or M operates (*1*) cannot be differentiated:



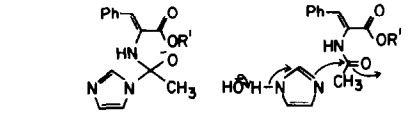
L M

[8] It is possible that Im attacks the ester linkage to activate the acyl group, prior to the nucleophilic attack by the amide oxygen at the ester carbon. In this case, the overall rate for the Im-assisted cyclization cannot be faster than the attack of Im at the ester linkage. The rate of the release of phenolate ion from the attack of Im at phenyl (*E*)-cinnamate was 40–80 times slower than that at **1a** at pH 7.5 and 8.0. In view of the Hammett σ value ($0 \sim 0.2$) (*9*) for the acetylamino group, the attack of Im at the ester linkage of phenyl (*E*)-cinnamate would be similar to that of **1a**. The possibility of initial attack of Im at the ester carbon of **1a** prior to the cyclization step, therefore, can be excluded. In the presence of Im (0.6 M) at pH 8.5, 2,2,2-trifluoroethyl (*E*)-cinnamate was unchanged for 1 day, indicating that Im does not attack directly at the ester linkage in the Im-assisted cyclization of **1f**.

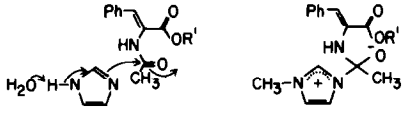
[9] It has been reported (*10*) that oxyanions of tetrahedral intermediates produced by the addition of nucleophiles to aldehydes or ketones can act as intramolecular nucleophiles toward ester linkages. These reactions, therefore, can be cited as analogs of the present reaction (Eq. [6]), except that they

The independence of $(k_{cy}^{Im})_o$ and $(k_{cy}^{Im})_{OH}$ on pK_{LG} further suggests that the rate-determining step is the attack of Im at the amide carbon for **1a–d** and that the attack of Im is not concerted with the attack of the amide oxygen atom at the ester carbon atom.

The lack of catalysis by pyridine derivatives in the cyclization reaction indicates the importance of the stabilization of the positive charge (E) developed on the nucleophile nitrogen atom by the additional nitrogen atom in the Im. The positive charge on the imidazole ring in the tetrahedral intermediate is removed when hydroxide ion participates together with Im (the $(k_{cy}^{Im})_{OH}$ path) to produce G (H, or deprotonation of F by hydroxide ion). This positive charge might be also removed (I) in the $(k_{cy}^{Im})_o$ path if water molecule acts as a general base. This possibility (I), however, does not appear very likely since $(k_{cy}^{MeIm})_o$ is comparable to $(k_{cy}^{Im})_o$. In the MeIm-assisted reaction, intermediate J should contain a positive charge on the remote nitrogen atom of the MeIm ring. The dependence on pK_{LG} of $\log(k_{cy}^{MeIm})_o$ resembles that of $\log(k_{cy}^{Im})_o$, further supporting that MeIm-assisted and Im-assisted reactions involve similar mechanisms.

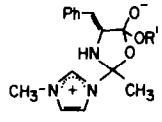


G H



I J

For alkyl esters, the values of $\log (k_{cy}^{Im})_o$, $\log (k_{cy}^{Im})_{OH}$, or $\log (k_{cy}^{MeIm})_o$ decrease considerably as pK_{LG} is raised (Fig. 1). Although the exact β_{LG} value is not estimated,[5] it appears that the leaving oxygen atom acquires a significant amount of negative charge in the transition state. The rate-determining step, therefore, seems to be the breakdown of oxazolinone intermediates E, G, or K. Thus, the decrease in the leaving ability of the leaving groups of **1a–f** is accompanied by the change in the rate-determining step in Im- or MeIm-assisted cyclization.



K

involve carbonyl groups of aldehydes or ketones, whereas the present reaction involves that of an amide. Addition reactions at the carbonyl groups of aldehydes and ketones often produce stable tetrahedral species. The tetrahedral species derived from aldehydes or ketones would be, therefore, much more stable than those (e.g., E, G, J) formed by addition to the carbonyl groups of amides.

The kinetic data obtained for Im-assisted cyclization of **1**a–g suggest that very basic alkoxide anions may be displaced by the amide group as fast as substituted phenolate anions if the leaving ability of the oxyanion nucleophile produced by the addition of Im to the amide group is sufficiently suppressed. In **1**a–g, the leaving ability of the oxyanion nucleophile would depend on the conformational stability of oxazolinone rings of E, G, and K as well as the basicity of the amide anion. In enzymes, the nucleophilicity of an amide oxygen toward ester linkages can be considerably enhanced by collaboration with the imidazolyl side chain of a histidyl residue, if the geometry involving the three groups and their microenvironment is suitably provided.

ACKNOWLEDGMENT

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