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Kinetics and mechanism of large rate enhancement in an acidic aqueous cleavage of the tertiary amide bond of *N*-(2-methoxyphenyl)-*N*′-morpholinophthalamide (**1**)

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ABSTRACT

The rate of conversion of **1** to *N*-(2-methoxyphenyl)phthalimide (**2**) within [HCl] range 5.0×10^{-3}–1.0 M at 1.0 M ionic strength (by NaCl) reveals the presence of both uncatalyzed and specific acid-catalyzed kinetic terms in the rate law. Intramolecular carboxamide group-assisted cleavage of amide bond of **1** reveals rate enhancement of much larger than 10^6-fold compared to the expected rate of analogous intermolecular reaction.

1. Introduction

The classical paper of Shafer and Morawetz revealed more than 10^6-fold rate enhancement in the specific base-catalyzed carboxamide group-assisted cleavage of amide bond of phthalamide and *N*,*N*′-dimethylphthalamide in aqueous solvent [1]. Since the huge rate enhancements due to intramolecularity of reactions bear a striking resemblance to enzyme-catalyzed reactions [2] a surge of interest in this area of research can be seen in the literature [2d,2e,3]. Almost all such and closely related studies involve cyclization coupled with only hydroxide ion and general base catalysis [4]. A search of literature reveals only one report on intramolecular aminolysis of amides where the cyclization of 2-aminomethylbenzamide to phthalimidine has been also studied within the pH 5 to 5 M HCl [5]. But the kinetic data analysis for data obtained within the pH 5 to 5 M HCl was complicated due to the presence of rather more basic 2-aminomethyl group in the substrate containing the amide group. Cohen and Lipowitz [6] reported acid-catalyzed hydrolysis of *o*-benzamido-*N*,*N*-dicyclohexylbenzamide where neighboring amide group assistance turned out to be $>10^4$-fold. These authors followed a synthetic approach and consequently a quantitative estimation of neighboring amide group assistance as well as fine details of mechanism remained unclear. Nearly 10^4- to 10^{14}-fold rate enhancement has been reported in the intramolecular carboxyl group–assisted cleavage of amide bond at pH $\leqslant$ 3 [7]. The aim of the present study was to explore quantitatively the probable rate enhancement in the intramolecular amide group-assisted cleavage of another neighboring amide bond of **1** at pH < 3. The observed results and their probable explanation(s) are described in this manuscript.

2. Experimental

2.1. Materials

Synthesis of *N*-(2-methoxyphenyl)phthalimide (**2**) is described elsewhere [8]. Synthesis of *N*-(2-methoxyphenyl)-*N*′-morpholinophthalamide (**1**), *N*-benzoylmorpholine (**3**), kinetic measurements and product identification are described in Supplementary Data (SD). Stock solutions of **1** (0.025 M) and **3** (0.01 M) were prepared in acetonitrile.

3. Results and discussion

3.1. Aqueous cleavage of **1** at different [HCl] and 35 °C

The rate of aqueous cleavage of **1** was studied within [HCl] range 5.0×10^{-3}–1.0 M at constant ionic strength of 1.0 M (by NaCl). It is noteworthy that light precipitates appeared into the reaction mixtures after reaction time $t \geqslant 4.7$ h (i.e. $\geqslant \sim 1$ halflife) at $\leqslant$0.05 M HCl. But this kinetic problem is solved as described in the 'Kinetic Measurements' in Supplementary Data (SD). Similar observations were obtained into the reaction mixture for acid-catalyzed hydrolysis of **2** under similar conditions [8].

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Pseudo-first-order rate constants (k_{obs}) at different [HCl] fit to the following empirical equation

$$k_{obs} = \frac{k_0 + k_c K[HCl]}{1 + K[HCl]} \quad (1)$$

where k_0, k_c and K represent empirical constants. The nonlinear least-squares calculated values of k_0, k_c and K are summarized in Table 1. The extent of the reliability of observed data fit to Eq. (1) is evident from the plot of Fig. 1 where solid line is drawn through the least-squares calculated data points. The absolute percent residual errors {ARE = 100 × $|(k_{obsi} - k_{calcdi})/k_{obsi}|$} where k_{obsi} and k_{calcdi} represent respective observed and calculated values of pseudo-first-order rate constants at the ith value of [HCl]} are ⩽2% at ⩾0.01 M HCl while ARE = 5–6% at 5.0×10^{-3} M HCl.

The standard deviation (=36%) associated with k_0 is significantly large and consequently a skeptic might think that k_0 is not significantly different from zero. Although the standard deviation is large (36%), perhaps it is not too large to believe that k_0 is different from zero for the following calculated results. (i) The contributions of k_0 compared to $k_cK[H^+]$ in the numerator of Eq. (1) are 62, 45, 14, 8 and 4% at 0.005, 0.01, 0.05, 0.1 and 0.2 M HCl, respectively. (ii) The attempt to calculate k_c and K from Eq. (1) with $k_0 = 0$ resulted in systematic positive ARE as 59, 42, 13, 3 and < 1% at the respective 0.005, 0.01, 0.05, 0.1 and >0.1 M HCl. But the values of ARE at the corresponding values of [HCl], turned out to be −6, −2, 2, −1 and < 1% when the data treatment with Eq. (1) involved k_0, k_c and K as three unknown parameters. The results described above as (i) and (ii) demonstrate that k_0 cannot be neglected compared to $k_cK[H^+]$ within the [HCl] range of present study.

The downward curvature of the plot of Fig. 1 does not seem to be visible to the naked eye. So a few kinetic runs were carried out within 2.0–5.0 M HCl in the absence of NaCl (i.e. ionic strength was not kept constant) and the k_{obs} values, under such conditions, showed upward curvature (Fig. 2) which could be ascribed to the ionic strength effect. Thus, a few kinetic runs were also carried out at constant ionic strength (5.0 M by NaCl) and within [HCl] range 2.0–5.0 M. An attempt to carry out the kinetic run at 1.0 M HCl and 5.0 M ionic strength (by NaCl) was unsuccessful because the reaction mixture became turbid at $t > \sim 300$ s. The values of k_{obs} within [HCl] range 2.0–5.0 M HCl at 5.0 M ionic strength were treated with Eq. (1) considering k_0 as known parameter and the nonlinear least-squares calculated values of k_c and K are shown in Table 1, where $k_0 = 2.19 \times 10^{-5}$ s^{-1}. The data fit appears satisfactory as evident from Fig. 2.

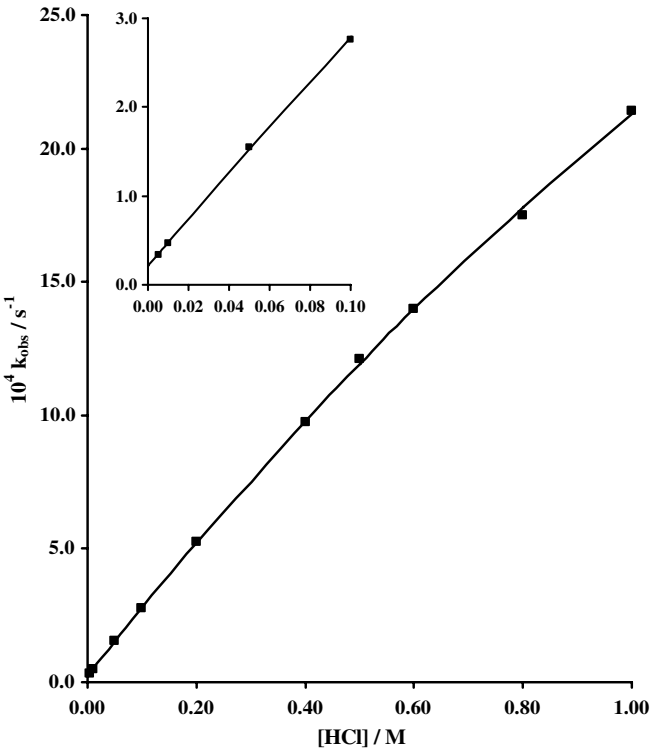


Fig. 1. The plot showing the dependence of pseudo-first-order rate constants, k_{obs}, upon [HCl] for acidic hydrolysis of **1** at 2.0×10^{-4} M **1**, 1.0 M ionic strength (by NaCl) and 35 °C. The solid line is drawn through the least-squares calculated data points using Eq. (1).

Unlike NaCl, the use of NaBr to maintain the constant ionic strength at 5.0 M did not produce turbidity problem into the reaction mixture at ⩽1.0 M HCl. Thus, a few kinetic runs were also carried out within [HCl] range 0.2–5.0 M. The values of k_{obs} obtained under such conditions, as shown graphically in Fig. 2, were found to fit to Eq. (1) and the nonlinear least-squares calculated values of k_0, k_c and K are shown in Table 1. Negative value of k_0 with standard deviations of more than 600% merely indicates that the contribution of k_0 compared to $k_c K[HCl]$ in the numerator of Eq. (1) is insignificant and hence a relatively more reliable values of k_c and K were obtained from Eq. (1) by considering $k_0 = 21.9 \times 10^{-6}$ s^{-1} obtained at 1.0 M ionic strength. Such calculated values of k_c and K are also summarized in Table 1.

Table 1
Values of k_0, k_c and K calculated from Eq. (2) for the aqueous cleavage of **1** and **3**[a]

Amide	μ[b] (M)	Temp (°C)	10^7 k_0 (s^{-1})	10^4 k_c (s^{-1})	10^2 K (M^{-1})	pK_a[c]	[HCl] range (M)	# of runs
1	1.0	35	219 ± 78[d]	104 ± 9[d]	25.3 ± 2.8[d]	−0.60 (−0.75)[e]	0.005–1.0	10
	5.0	35	219	262 ± 17	33.3 ± 4.7	−0.48	2.0–5.0	4
	5.0[f]	35	−740 ± 4640	227 ± 11	46.9 ± 6.8	−0.33	0.2–5.0	8
			219	229 ± 7	45.7 ± 3.3	−0.34	0.2–5.0	8
3	1.0[b]	65	0.36 ± 3.54	0.165 ± 0.060	66.7 ± 39.7	−0.18	0.05–1.0	6
		65	0	0.161 ± 0.036	69.8 ± 23.5	−0.16	0.05–1.0	6
		35[g]	0	2.81×10^{-3}				
Benzamide[h]	6.0[i]	25	0	$(8.34 \pm 0.28) \times 10^{-3}$	81.0 ± 9.7	−0.09	1.0–6.0	6

[a] [$\mathbf{1}_0$] = 2.0×10^{-4} M, λ = 290 nm, aqueous reaction mixture for each kinetic run contained 0.8% v/v CH_3CN. [$\mathbf{3}_0$] = 1.3×10^{-4} M, λ = 230 nm, aqueous reaction mixture for each kinetic run contained 1.3% v/v CH_3CN.
[b] Ionic strength was maintained by NaCl.
[c] pK_a = log K.
[d] Error limits are standard deviations.
[e] Thermodynamic pK_a (=concentration pK_a + log γ where activity coefficient γ = 0.70 at 1.0 M ionic strength).
[f] Ionic strength was kept constant by NaBr.
[g] The value of k_c at 35 °C was estimated from k_c value at 65 °C using Eyring equation.
[h] The observed data (k_{obs} versus [HCl]) were obtained from Ref. [9].
[i] Ionic strength was kept constant by LiCl.

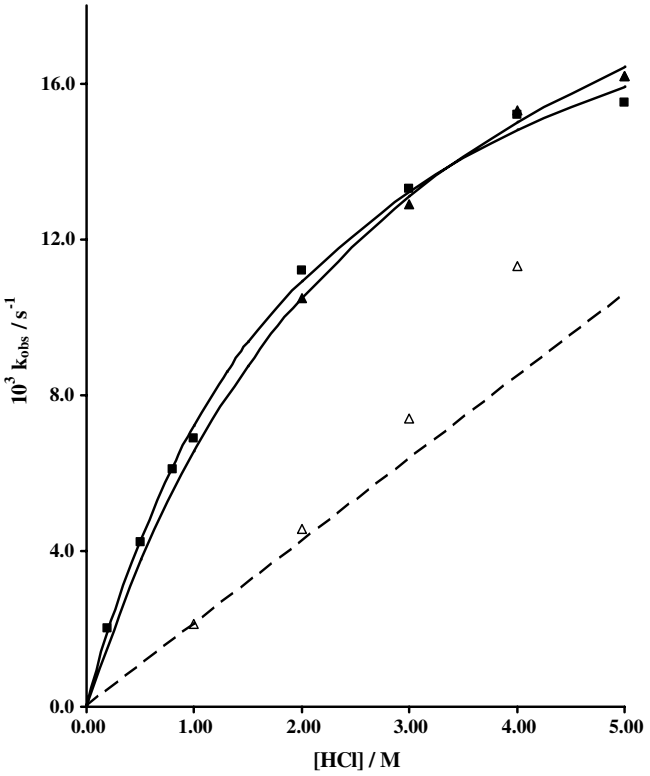


Fig. 2. The plots showing the dependence of pseudo-first-order rate constants, k_{obs}, upon [HCl] for aqueous cleavage of **1** at 2.0×10^{-4} M **1**, 5.0 M ionic strength (by NaBr (■) and by NaCl (▲)) and 35 °C. The solid lines are drawn through the least-squares calculated data points using Eq. (1). The symbol (Δ) represents k_{obs} obtained in the absence of NaCl, i.e. ionic strength was not kept constant in these kinetic runs.

It may be noted that the values of k_{obs}, obtained within [HCl] range 2.0–5.0 M 5.0 M ionic strength, vary by < 7% in the presence of NaCl and NaBr. However, the observed data fit to Eq. (1) at 5.0 M ionic strength by NaCl is considered to be less reliable compared to that at 5.0 M ionic strength by NaBr because of the lack of k_{obs} value at ⩽1.0 M HCl in the presence of NaCl.

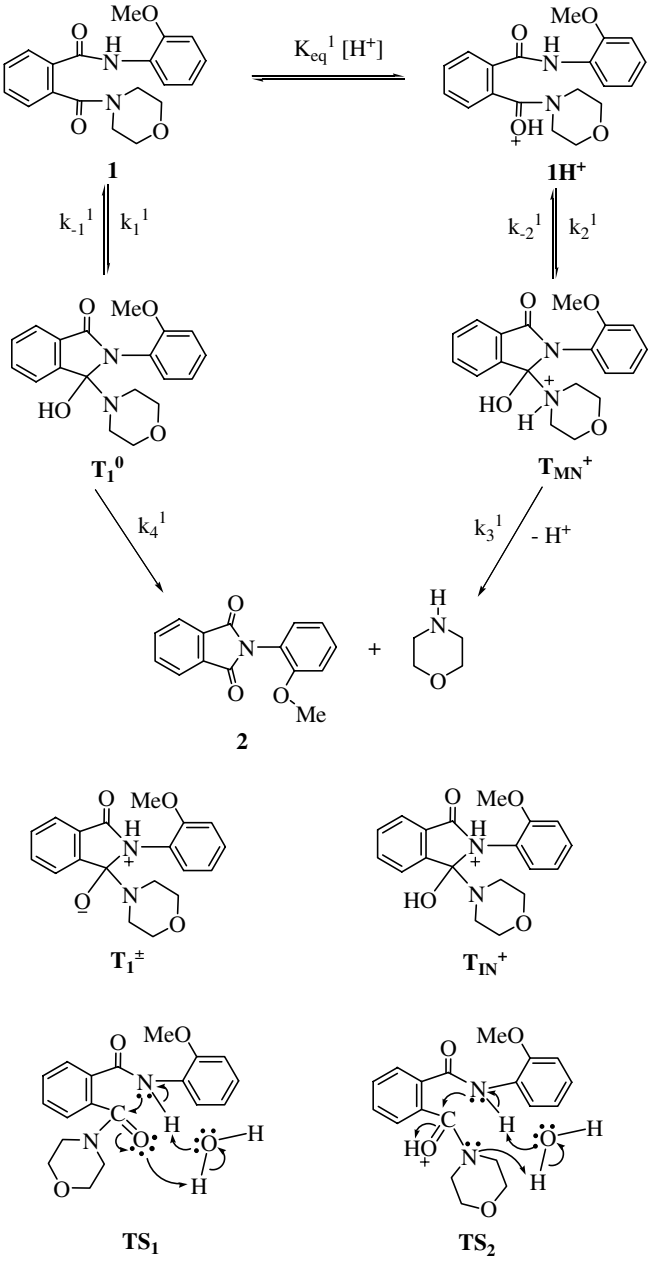
3.2. Aqueous cleavage of N-benzoylmorpholine (**3**) at different [HCl] and 65 °C

Rate of specific acid-catalyzed hydrolysis of **3** was studied within [HCl] range 0.05–1.0 M at 1.0 M ionic strength (by NaCl). Pseudo-first-order rate constants (k_{obs}), as shown graphically in Fig. I (Supplementary Data, SD), showed reasonably good fit to Eq. (1). The nonlinear least-squares calculated values of k_0, k_c and K are summarized in Table 1. The calculated value of k_0 is associated with extremely high (∼10-fold) standard deviation (Table 1) which shows insignificant contribution of k_0 compared to $k_c K$[HCl] in Eq. (1) and consequently the calculated value of k_0 is unreliable. Thus, the values of k_c and K were also calculated from Eq. (1) with $k_0 = 0$ and such calculated values of k_c and K are shown in Table 1. It is evident from Table 1 that the values of k_c and K remained almost unchanged with change in k_0 value from 0.0 to $3.6 \times 10^{-8}\ s^{-1}$. The k_0-step could not be detected in the specific acid-catalyzed hydrolysis of various amides [9,10]. The value of k_{obs} ($=1.39 \times 10^{-8}\ s^{-1}$) at 0.1 M HCl and 1.0 M ionic strength may be compared with $k_{obs} = 1.7 \times 10^{-9}\ s^{-1}$ obtained for hydrolysis of *N*,*N*-dimethylbenzamide at 0.12 M HCl and 0.12 M ionic strength and 35 °C [9]. The value of pseudo-first-order rate constant (k_0) for neutral uncatalyzed hydrolysis of formamide is $6 \times 10^{-10}\ s^{-1}$ (at 35 °C) [11].

The values of k_{obs}, obtained for hydrolysis of benzamide within [HCl] range 1.0–6.0 M at 25 °C and constant ionic strength 6.0 M (by LiCl) [9], were found to fit reasonably well to Eq. (1) with $k_0 = 0$ and the nonlinear least-squares calculated values of k_c and K are shown in Table 1. The effects of [HCl] on k_{obs} for hydrolysis of benzamide and *N*,*N*-dimethylbenzamide reveal ∼3-fold larger value of k_{obs} for benzamide than that for *N*,*N*-dimethylbenzamide under similar experimental conditions [9].

Unlike the mechanisms of thoroughly studied highly efficient hydroxide ion-catalyzed intramolecular carboxamide group-assisted cleavage of amide bonds, the mechanisms of rarely studied specific acid (hydronium ion)-catalyzed such reactions are not well explored. However, a plausible mechanism of such a reaction as described in the present manuscript may be shown by Scheme 1 where the protonation of **1** in an acidic medium is shown by an equilibrium process with equilibrium constant K^1_{eq}.

In Scheme 1, if the expected immediate intramolecular addition product, $T_1^{\pm}$ and T_{IN}^{+} in respective k_1^1-step and k_2^1-step are too unsta-



Scheme 1. Structures $T_1^{\pm}, T_{IN}^{+}, TS_1, TS_2$.

ble to exist for a period of longer than 10^{-13} s [12], then the formation of T_1^0 and T_{MN}^+ are expected to occur through transition states TS_1 and TS_2, respectively. The fact that the pK_a of conjugate acid of leaving group is larger in k_4^1-step than that in k_{-1}^1-step and also the release of five-membered ring strain in k_{-1}^1-step make $k_{-1}^1 \gg k_4^1$ and this inequality leads to k_4^1-step as the rate-determining step. The pK_a of conjugate acid of leaving group in k_3^1-step is significantly smaller than that in k_{-2}^1-step which in turn imply that $k_3^1 \gg k_{-2}^1$. But the release of five-membered ring strain in k_{-2}^1-step makes $k_{-2}^1 \gg k_3^1$. Thus, the combined effects of relative pK_a of conjugate acids of leaving groups in k_3^1-step and k_{-2}^1-step as well as release of five-membered ring strain in only k_{-2}^1-step would dictate whether k_3^1-step or k_2^1-step is the rate-determining step. The observed rate law: rate = k_{obs} [**1**]$_T$ and Scheme 1 can lead to Eq. (2)

$$k_{obs} = \frac{k_4^1 K_1^1 + k_3^1 K_2^1 K_{eq}^1 [H^+]}{1 + K_{eq}^1 [H^+]} \quad (2)$$

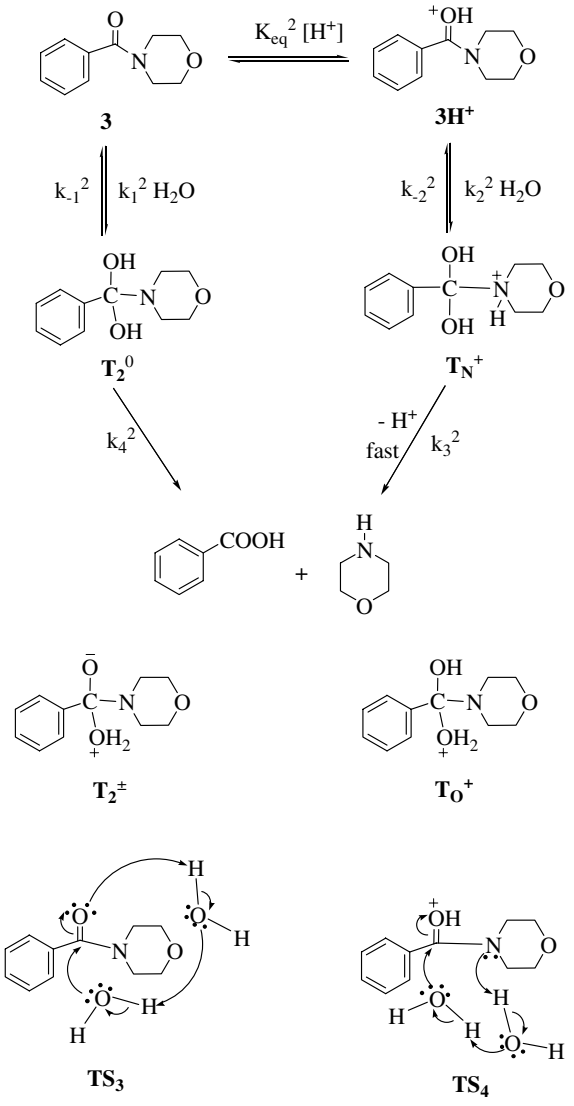
where $K_1^1 = k_1^1/k_{-1}^1$, and $K_2^1 = k_2^1/k_{-2}^1$. Eq. (2) is similar to Eq. (1) with $k_0 = k_4^1 K_1^1$, $k_c = k_3^1 K_2^1$ and $K = K_{eq}^1$. Thus, the ratio k_c/k_0 (≈ 500) shows that specific acid-catalytic factor is ~500-fold in the cyclization of **1** to **2**.

One of the reviewers has raised an interesting point that whether the amide group acts as a nitrogen nucleophile through the enol form—which is the only species with a lone pair of electrons on N available to act as a nucleophile, or not.[1] It is well known that C—N bond in an amide is neither a pure single bond nor a pure double bond. The nucleophilicity of the amide nitrogen is essentially governed by its basicity. The reported pK_a values of MeC≡NH$^+$, Me$_2$C=NHMe$^+$ and MeNH$_3^+$ are −10.1, 5.5 and 10.7, respectively [13]. The values of $\sigma_p^{COMe} = 0.50$, $\sigma_m^{COMe} = 0.38$, $\sigma_p^{COPh} = 0.44$, $\sigma_m^{COPh} = 0.36$, $\sigma_{COMe}^- = 0.82$ and σ_R^- (COMe) = 0.32 [14]. In view of these findings, it seems difficult to believe that the amide nitrogen is a stronger base in pure enol form (where lone pair of electrons of N exist in sp^2 orbital) than in pure keto form (where sp^3 orbital contains lone pair of electrons of the amide N). Although the kinetic data of the present study are not sufficient to rule out completely the possibility of the sp^2 nitrogen of the enol form of the amide acting as the nucleophile in the conversion of **1** to **2**, the mechanism shown in Scheme 1 is considered to be more appropriate for the following reasons: (i) experimental and theoretical evidence for enol formation in the aqueous solutions of primary and secondary amides are lacking (at least to the best of our literature search) and (ii) the enol form of the amide group has not been considered in any closely related studies [7g,15,16].

The specific acid-catalyzed hydrolysis of amides has been extensively studied [17]. In view of these extensive experimental studies and a recent theoretical study [18], a plausible reaction mechanism for hydrolysis of **3** in an acidic aqueous solution is shown in Scheme 2 where the catalytic reaction involves k_2^2-step as the rate-determining step [17–19]. In Scheme 2, if the immediate intermolecular addition intermediates $T_2^\pm$ and T_O^+ in respective k_1^2-step and k_2^2-step become too unstable to exist as intermediates, then the formation of T_2^0 and T_N^+ involves transition states TS_3 and TS_4, respectively. The pK_a of conjugate acid of leaving group is significantly larger in k_4^2-step than that in k_{-1}^2-step and consequently $k_{-1}^2 \gg k_4^2$ which leads to k_4^2-step as the rate-determining step. Similarly, the pK_a of conjugate acid of leaving group is larger in k_{-2}^2-step than that in k_3^2-step and this leads to $k_3^2 \gg k_{-2}^2$ which in turn reveals k_2^2-step as the rate-determining step. The observed rate law: rate = k_{obs} [**3**]$_T$ and Scheme 2 give Eq. (3)

$$k_{obs} = \frac{k_1^2 [H_2O] + k_2^2 [H_2O] K_{eq}^2 [H^+]}{1 + K_{eq}^2 [H^+]} \quad (3)$$

[1] We thank the reviewer for suggesting this point.



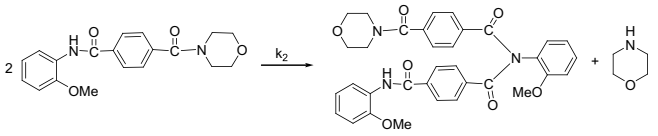
Scheme 2. Structures $T_2^\pm, T_O^+, TS_3, TS_4$.

where k_1^2 and k_2^2 represent second-order rate constants for uncatalyzed and specific acid-catalyzed hydrolysis of **3**. Empirical Eq. (1) is similar to Eq. (3) with $k_0 = k_1^2$ [H$_2$O], $k_c = k_2^2$ [H$_2$O] and $K = K_{eq}^2$.

It is evident from Schemes 1 and 2 that $K_{eq}^1 = 1/K_a^{1H+}$ and $K_{eq}^2 = 1/K_a^{3H+}$ where K_a represents concentration ionization constant. The calculated values of $K(= K_{eq}^1$ or $K_{eq}^2)$ were used to calculate K_a for **1**H$^+$ and **3**H$^+$ which are summarized in Table 1. The value of thermodynamic pK_a (= −1.17) for protonated *N*,*N*-dimethylbenzamide, determined spectrophotometrically in the absence of an inert salt [9], may be compared with concentration pK_a (= −0.60) for **1**H$^+$. The value of concentration K_a for **1**H$^+$ is ~3-fold larger than that for **3**H$^+$ at 1.0 M ionic strength (Table 1) which could be partly attributed to steric hindrance due to 2-CONHC$_6$H$_4$OMe-2′ group in **1**H$^+$ [14]. The value of K_a for **1**H$^+$ at 1.0 M ionic strength is ~1.3- to 1.8-fold larger than that at 5.0 M ionic strength (Table 1). Similarly, the calculated concentration K_a (=1.23 M) value for benzamide at 6.0 M ionic strength (by LiCl), calculated from kinetic data of Ref. [20], is ~28- to 117-fold smaller than thermodynamic K_a (=34, 55, 62 and 144 M) obtained spectrophotometrically in the absence of an inert salt [9]. Various reports show that the values of pK_a of O-protonated amide groups vary in the range of 0 to −3 [21].

In order to assess the rate enhancement due to intramolecularity of the reaction as displayed by Scheme 1, one requires the value

of second-order rate constant (k_2) for the bimolecular reaction (Eq. (4)) carried out under the experimental condition of present study.



4 5 (4)

But the formation of product **5** from **4** is apparently impossible for the reason that the rate of hydrolysis of **4** should be much faster than that of imide (**5**) formation from **4** under the present experimental conditions. This speculation is based upon, at least, following two reasons. (i) Although the basicity of amide nitrogen of **4** may not be significantly different from that of H_2O in terms of pK_b values, the nucleophilic site of **4** is more sterically hindered than that of H_2O. (ii) The concentration of H_2O is $\sim 2.7 \times 10^5$-fold larger than that of **4**. Thus, an underestimated value of rate enhancement of 2×10^6-fold due to intramolecular carboxamide group-assisted cleavage of the amide bond in **1** may be obtained by comparing the value of k_c for $\mathbf{1}H^+$ and $k_c/[H_2O]$ for $\mathbf{3}H^+$ (Table 1). It is perhaps noteworthy that the value of k_0 ($=2.19 \times 10^{-5}\ s^{-1}$) and the effective molarity ($=2 \times 10^6$ M) due to intramolecularity in the acidic aqueous cleavage of **1** may give $k_0/[H_2O]$ as $1.1 \times 10^{-11}\ M^{-1}\ s^{-1}$ ($=2.19 \times 10^{-5}\ s^{-1}/2 \times 10^6$ M) for **3** provided k_c/k_0 value remained same for the aqueous cleavage of both **1** and **3**. Thus, the estimated value of $k_0 = 6 \times 10^{-10}\ s^{-1}$ for uncatalyzed hydrolysis of **3** is similar to the corresponding reported k_0 value for uncatalyzed hydrolysis of formamide [11].

4. Conclusions

Perhaps this is the first report which reveals the rate enhancement of much more than 10^6-fold due to intramolecular carboxamide group assistance in the cleavage of the amide bond in mild acidic aqueous solution. Intermolecular specific acid catalytic component is ~500-fold. The present finding predicts an efficient conversion of phthalamide, *N*-substituted, *N*,*N*′-disubstituted and *N*,*N*,*N*′-trisubstituted phthalamides to the corresponding phthalimide and *N*-substituted phthalimides under mild acidic pH. The finding of large rate enhancement in the intramolecular amide nitrogen-assisted cleavage of an amide bond under neutral/mild acidic pH reveals the possibility that the acidic hydrolysis of a peptide can be assisted by a neighboring amide group, which could be relevant to the action of numerous enzymes.

Acknowledgments

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Appendix A. Supplementary data

Fig. I, Experimental details for synthesis of **1**, **3**, kinetic measurements, product identification and NMR spectra for **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bioorg.2008.03.003.

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