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"Naked" Hydrogencarbonate Ion as a Bifunctional Catalyst toward Amide Substrates.[1] Nucleophilic Ion Pairs. 9

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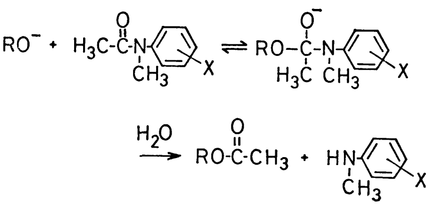
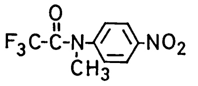
The cleavage of amide substrates(*p*-nitro-*N*-methyltrifluoroacetanilide and *p*-nitro-*N*-methyldichloroacetanilide) with anionic nucleophiles was studied at 30 °C in aprotic (acetonitrile and *N,N*-dimethylformamide) and protic(ethanol) media. Hydrogencarbonate ion acted as catalyst much more efficiently in the aprotic solvents (about 10^3 fold) than expected from its aqueous pK_a, but in ethanol, its reactivity was close to those of simple nucleophiles (*p*-cyanophenolate anion and *N*-hydroxysuccinimide anion) that possess analogous pK_a values in water. The reaction rate in the aprotic solvents was sensitive to small amounts of water. The kinetic isotope effect showed that proton transfer was involved (at least partially) in the rate-determining step. Thus, hydrogencarbonate ion behaves in aprotic media as a nucleophilic-general acid catalyst for the amide cleavage. The biochemical implication with regard to the action of biotin was discussed.

The catalytic hydrolysis of amide substrates has been of special concern as model systems of hydrolytic enzymes. Amide groups are generally very stable toward nucleophiles, so that investigation has been limited to the alkaline hydrolysis of amide substrates containing strongly electron-attracting groups.[2—5] In the previous publications of this series, we reported that the cleavage of amide linkages which was virtually impossible in aqueous systems did take place in very dry aprotic solvents with tetraalkylammonium hydroxamate ion pairs.[6,7] The rate augmentation observed reached 10^8—10^9 fold in comparison with that in the aqueous system. We proposed, on the basis of several pieces of evidence, that the amide cleavage is achieved due to (i) enhanced nucleophilicity of the hydroxamate anion(or probably oxide anions in general: RO^-) which is desolvated in aprotic solvents[8,9] and (ii) efficient proton transfer from poorly solvated water molecules to the tetrahedral intermediate.[6,7] Particularly, the second factor is characteristic of the amide cleavage, since it requires proton sources to avoid the formation of energetically-unfavorable amine anions.[10] Obviously, these are opposing factors: that is, factor (i) arises from enhanced basicity(nucleophilicity) of oxide anions and factor (ii) is related to the enhanced reactivity of water molecules as proton source. Thus, the combination of these two factors in a single reaction medium is not easy.

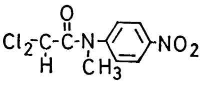


(1)

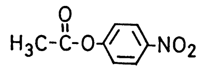
However, a tautomer which combines within a molecule structural characteristics of acid(s) (proton source) and base(s) (oxide anions) may serve as an efficient catalyst for the amide cleavage. Tautomeric catalysts have been extensively employed as bifunctional catalysts in mutarotation and acyl transfer reactions.[11] However, they cannot be applied directly to the amide cleavage, because their nucleophilic reactivities are not sufficiently large. Therefore, we adopted potassium hydrogencarbonate ($HCO_3^-K^+$) as a bifunctional catalyst which has an oxide anion group ($pK_a=6.37$ in H_2O)[12] as well as a dissociable OH group. As monofunctional nucleophiles, potassium *p*-cyanophenolate(*p*-$CNC_6H_4O^-K^+$: $pK_a=7.95$ in H_2O)[12] and potassium salt of *N*-hydroxysuccinimide(SIO^-K^+: $pK_a=6.0$ in H_2O)[13] were employed. These salts were solubilized in desired solvents with 10 times excess perhydrodibenzo-18-crown-6. Substrates employed are recorded below with their abbreviations.



F_3-PNMA



Cl_2-PNMA



PNPA

Experimental

Materials. Equimolar amounts of *p*-cyanophenol and potassium hydroxide were mixed in methanol and the solvent was evaporated. The residue was recrystallized from acetonitrile and methanol to give monohydrate of potassium *p*-cyanophenolate. The potassium salt of *N*-hydroxysuccinimide was prepared in the same way. *p*-Nitro-*N*-methyltrifluoroacetanilide (F_3-PNMA) was prepared by Dr. T. Sakamoto in these laboratories from *p*-nitro-*N*-methylaniline and trifluoroacetic anhydride, mp 129—131 °C (lit,[14] 126.5—131 °C). *p*-Nitro-*N*-methyldichloroacetanilide (Cl_2-PNMA) was obtained from dichloroacetyl chloride and *p*-nitro-*N*-methylaniline in the presence of triethylamine in benzene. Recrystallization from benzene–hexane gave slightly yellow powders; mp 131—133 °C, Found: C, 41.38; H, 3.10; N, 10.59%. Calcd for $C_9H_8N_2O_3Cl_2$: C, 41.05; H, 3.07; N, 10.65%. The purification of solvents was described previously.[7]

Kinetics. The potassium salts were dissolved in desired solvents with 10 times excess perhydrodibenzo-18-crown-6 by sonication (1.5 h). All kinetic measurements were carried out at 30±0.1 °C in modified Thunberg cuvettes. The details of the procedure have been described elsewhere.[8,9] The progress of the reaction was monitored spectrophotometrically by following the increase in the absorption of *p*-nitro-*N*-methylaniline or that of *p*-nitrophenolate: 401 nm for PNPA and 390 nm for F_3-PNMA and Cl_2-PNMA. Since excess nucleophiles were present in all the cases, pseudo

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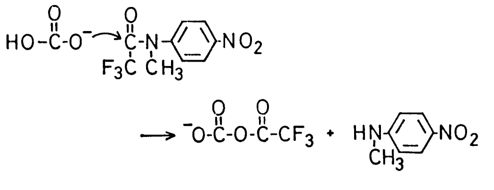
first-order behavior was observed. The water content of the reaction medium was evaluated immediately after the reaction, using a coulometric Karl-Fisher apparatus (Hiranuma Aquacounter AQ-1). The water concentration listed is the average of two to three determinations (relative error, less than 10%).

Product Analysis. A mixture of potassium hydrogencarbonate (3.9×10^{-3} M) (1 M=1 mol dm^{-3}), perhydrodibenzo-18-crown-6 (3.9×10^{-2} M), F_3-PNMA (7.0×10^{-3} M), and aniline (1.0×10^{-2} M) in acetonitrile was refluxed for 3 h, and evaporated to dryness *in vacuo*. The residue taken in methanol was subjected to high-speed liquid chromatography (Hitachi type 635 instrument; solvent, methanol; column, Hitachi gel 3010; wavelength, 254 nm). The following peaks appeared in this order and were identified by comparison with authentic samples: trifluoroacetanilide, aniline, substrate, and *p*-nitro-*N*-methylaniline. The peak height of trifluoroacetanilide was almost the same as that of aniline.

On the other hand, trifluoroacetanilide was not detected in the reaction of aniline and trifluoroacetic acid (7.0×10^{-3} M) under the comparable reaction conditions. Salt formation occurred immediately after mixing as confirmed by UV spectroscopy.

Results

Nucleophilic vs. *General Base Attack of Hydrogencarbonate.* In order to assess whether HCO_3^- acts as a nucleophile or as a general base, the semi-quantitative product analysis was performed with a high-speed liquid chromatograph.



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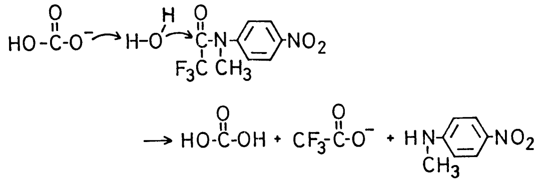
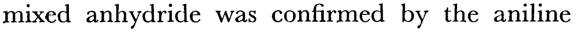


(3)

If HCO_3^- acts as a general base, it directly produces trifluoroacetate and *p*-nitro-*N*-methylaniline (Eq. 2). On the other hand, the nucleophilic reaction would give a mixed acid anhydride, $^-OCOOCOCF_3$ (Eq. 3), which then, decomposes rapidly to trifluoroacetate and hydrogencarbonate. The intermediacy of the mixed anhydride was confirmed by the aniline trapping experiment (Eq. 4) described in Experimental. It was confirmed in separate experiments that the trapping product, trifluoroacetanilide, was not formed directly by the reaction of aniline with F_3-PNMA substrate or with trifluoroacetic acid. The possibility that trifluoroacetanilide is formed *via* a mechanism related to the general base mechanism of Eq. 3 (Eq. 5) may be denied by the following argument. Provided that Eq. 5 is the predominant path, added aniline should accelerate the reaction. In Fig. 1, the second-order rate constant(k_2) for the reaction of HCO_3^- and F_3-PNMA is plotted as a function of added aniline. Since aniline retards the reaction, Eq. 5 is not likely to occur.



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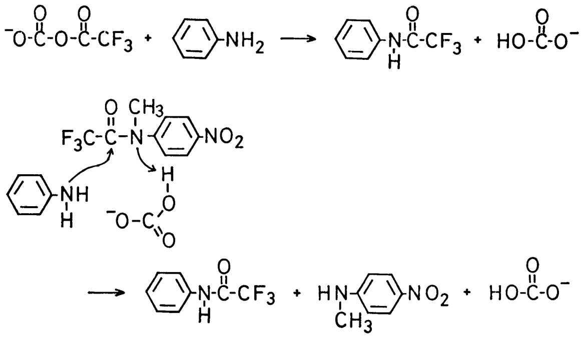

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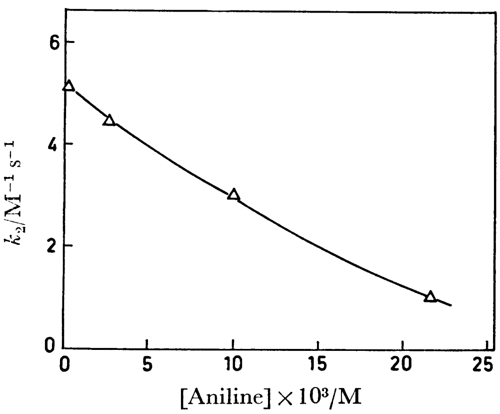


Fig. 1. Second-order rate constants for the reaction of HCO_3^- and F_3-PNMA in acetonitrile ($[H_2O]=4\pm1$ mM), plotted as a function of added aniline. $[HCO_3^-]=1.28\times10^{-3}$ M, $[F_3\text{-PNMA}]=4.87\times10^{-5}$ M.

The presence of trifluoroacetanilide in the product of the aniline experiment, together with the rate-retarding effect of aniline, clearly indicates that the amide cleavage proceeds *via* direct attack of hydrogencarbonate ion on the amide substrate.

Absorption Spectra of Nucleophilic Anions. Prior to the kinetic examination, the relative absorbance of nucleophilic anions was measured as a function of water concentration in order to obtain reliable information on prototropic equilibria. *p*-Cyanophenol (*p*-CNC_6H_4OH) in very dry acetonitrile ($[H_2O]=11.7$ mM) possesses the absorption maximum at 243 nm with $\varepsilon=18400$, and the spectrum was not affected by added perhydrodibenzo-18-crown-6 (10 times excess). On the other hand, the absorption maximum of *p*-$CNC_6H_4O^-K^+$ solubilized in acetonitrile with 10 times excess of perhydrodibenzo-18-crown-6 appeared at 294 nm ($\varepsilon=19800$), which can be clearly differentiated from that of *p*-CNC_6H_4OH. The absorbance decreased only slightly with increasing water concentrations, the relative absorbance at $[H_2O]=999$ mM being 86% of the original value in very dry acetonitrile. At this water concentration a weak shoulder was observed at 243 nm which is ascribable to the absorption of *p*-CNC_6H_4OH. The relative amount of the neutral species calculated with $\varepsilon=18400$ was 12%, which is in good accord with the decrease of *p*-$CNC_6H_4O^-K^+$ ($\approx14\%$) within the experimental error. Therefore, the increase in the water concentration causes a small shift in the prototropic equilib-

TABLE 1. SECOND-ORDER RATE CONSTANTS FOR THE CLEAVAGE OF AMIDE AND ESTER SUBSTRATES[a)]

Solvent[b)]	Nucleophile	k_2/M^{-1} s^{-1}		
		F_3-PNMA	Cl_2-PNMA	PNPA
DMF	HCO_3^-	59	3.7	19
DMF	p-$CNC_6H_4O^-$	1.3	0.51	26
DMF	SI-O$^-$ [d)]	1.6	—	*ca.* 10^3
Acetonitrile	HCO_3^-	0.37—3.9[c)]	0.048—0.15[c)]	46
Acetonitrile	p-$CNC_6H_4O^-$	0.035	0.0033	22
Acetonitrile	SI-O$^-$ [d)]	0.0030—0.032[c)]	—	400
Ethanol	HCO_3^-	1.5	0.16	0.38
Ethanol	p-$CNC_6H_4O^-$	1.1	0.085	0.32

a) [nucleophile] = (0.4—20) × 10^{-4} M, [substrate] = (5—20) × 10^{-5} M, [perhydrodibenzo-18-crown-6] = 10 × [nucleophile salt]. b) [H_2O]: 6.2—9.2 mM in DMF, 4.9—7.0 mM in acetonitrile, 100±15 mM in ethanol. c) The probable range of k_2 estimated from the non-linear plots. d) Potassium salt of *N*-hydroxysuccinimide.

rium between p-$CNC_6H_4O^-K^+$ and p-CNC_6H_4OH.

The absorption spectra of SI-O$^-$K$^+$ were somewhat more complicated. SI-O$^-$K$^+$ solubilized in very dry acetonitrile ([H_2O] = 14.1 mM) with 10 times perhydrodibenzo-18-crown-6 gave rise to two absorption maxima at 278 nm (ε 2320) and 294 nm (ε=2360). The absorption peak at 278 nm gradually increased upon addition of water and the peak at 294 nm disappeared almost completely at [H_2O] > 200 mM. However, the increase in the absorption of *N*-hydroxysuccinimide (ε=*ca.* 7000 at 210 nm (shoulder)) was not detected. This means that the spectral change cannot be ascribed to the prototropic equilibrium. Conceivably, added water may affect the nature of the ion pair which is reflected in the absorption spectrum.

Unfortunately, HCO_3^- ion does not have an absorption maximum in the UV region suitable to study the prototropic equilibrium. We thus measured the IR spectrum of $HCO_3^-K^+$ solubilized in acetonitrile with 10 times perhydrodibenzo-18-crown-6. The $\nu_{C=O}$ absorption band of the carboxylate group appeared at 1632 cm^{-1} which is comparable to that of solid $KHCO_3$ (KBr disc, $\nu_{C=O}$ 1628 cm^{-1}). The absorption peak hardly changed even in acetonitrile containing 1000 mM of water.

It is assumed from the above experimental data that the shift of prototropic equilibria due to small quantities of added water is not extensive, as compared with dramatic rate retardations observed (see below). Although a clear, quantitative analysis of prototropy was possible only in the p-CNC_6H_4OH system, the similarity in the aqueous pK_a values[12,13)] suggests that the prototropic equilibria for SI-O$^-$ and HCO_3^- would not differ greatly from that for p-$CNC_6H_4O^-$.

Estimation of Rate Constants. In the presence of excess nucleophile, the formation of *p*-nitro-*N*-methylaniline from the amide substrates gave good first-order plots for up to 70% reaction, so that the reactions are first-order in substrates. The pseudo first-order rate constants(k_{obsd}) thus determined were plotted against the concentration of nucleophile. As shown in Fig. 2, plots of k_{obsd} *vs.* [nucleophile(hydrogencarbonate)] were not always linear. The second-order rate constants(k_2) were calculated as k_{obsd}/[nucleophile] and listed in Table 1. In the case of the non-linear plots, the probable range of k_2 is given.

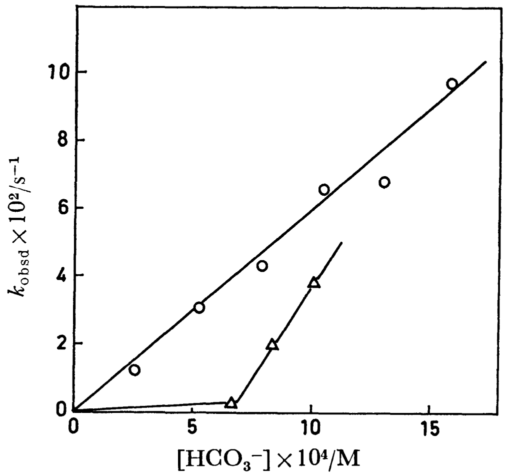


Fig. 2. Pseudo-first-order rate constants for the reaction of HCO_3^- and F_3-PNMA in DMF(○) and acetonitrile(△) plotted as a function of [HCO_3^-]. [F_3-PNMA] = 8.80 × 10^{-5} M. Water concentrations are recorded in Table 1.

In accordance to close pK_a values in aqueous solution, the second-order rate constants for the reaction of PNPA with HCO_3^- and p-$CNC_6H_4O^-$ are not much different in three solvents employed (two times difference at the largest). The much higher reactivity of SI-O$^-$ toward PNPA may be attributed to the so-called α-effect. It is known that the nucleophilic attack is wholly rate-determining in water for phenyl esters with good leaving groups such as *p*-nitrophenolate.[10)] Whether or not this holds true in aprotic solvents is not clear at the moment. However, the relative reactivity of the nucleophiles used shows approximately parallel tendencies between the aqueous and aprotic media (Table 1).

Interestingly, HCO_3^- acted as the most efficient catalyst toward amide substrates: for example, the reaction of HCO_3^- and F_3-PNMA in DMF was faster by factors of 37—45 than the corresponding reactions with p-$CNC_6H_4O^-$ and SI-O$^-$. On the other hand, the rate difference between HCO_3^- and p-$CNC_6H_4O^-$ was very small in ethanol (protic solvent).

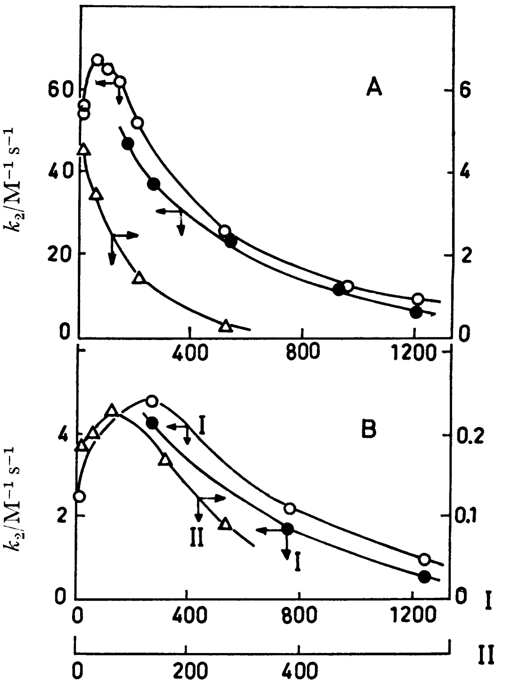


Fig. 3. Second-order rate constants for F_3-PNMA cleavage plotted as a function of [H_2O] or [D_2O]. (A) HCO_3^-+F_3-PNMA: ○; H_2O in DMF, ●; D_2O in DMF, △; H_2O in acetonitrile. (B) p-$CNC_6H_4O^-$+F_3-PNMA: symbols used stand for the same as above.

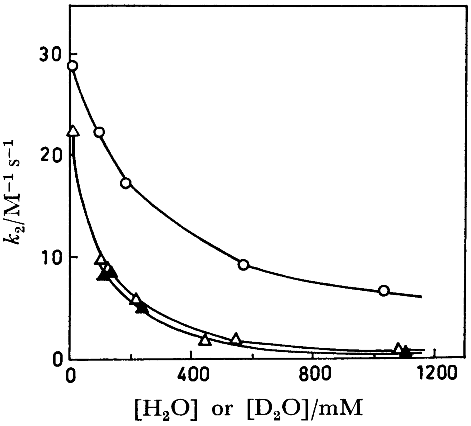


Fig. 4. Second-order rate constants for PNPA cleavage plotted as a function of [H_2O] or [D_2O]. ○: H_2O for p-$CNC_6H_4O^-$+PNPA in DMF, △: H_2O for HCO_3^-+PNPA in acetonitrile, ▲: D_2O for HCO_3^-+PNPA in acetonitrile.

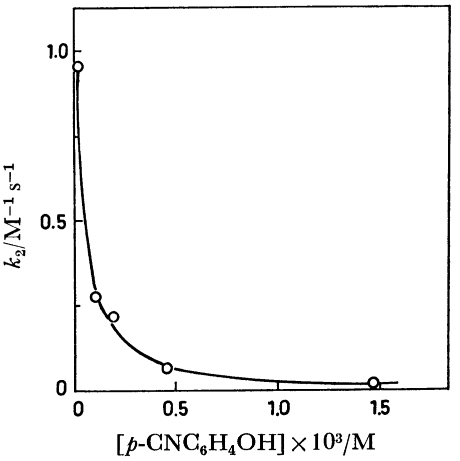


Fig. 5. Second-order rate constants for the reaction of p-$CNC_6H_4O^-$ and F_3-PNPA in DMF ([H_2O]= 4±2 mM) plotted as a function of added p-CNC_6H_4-OH. [p-$CNC_6H_4O^-$]=1.61×10^{-3} M, [F_3-PNMA]= 2.51×10^{-5} M.

Influence of Small Amounts of Water on Reaction Rates. The experiments described above were performed at almost constant water concentrations, which are recorded in the caption for Figures or in the footnote for Tables. Followingly, we determined the second-order rate constant as a function of water concentration in the respective reaction media. The results are illustrated in Figs. 3 and 4. It is clear that the rates are sensitive to small amounts of water. The rate constants are almost meaningless without accurate indication of the water concentration. In some of the amide cleavage(HCO_3^-+F_3-PNMA in DMF, p-$CNC_6H_4O^-$+F_3-PNMA in DMF, and p-$CNC_6H_4O^-$+F_3-PNMA in acetonitrile), rate maxima were observed at about 100—300 mM H_2O. On the other hand, F_3-PNMA cleavage by HCO_3^- in acetonitrile (Fig. 3A) and the nucleophilic reaction of HCO_3^- and p-$CNC_6H_4O^-$ toward PNPA (Fig. 4) did not provide such rate maxima. Thus, the phenomenon seems to be confined to the amide cleavage, but is not limited to the catalysis by HCO_3^-.

Water may suppress the reaction by neutralizing p-$CNC_6H_4O^-$ ion or by reducing reactivity of p-$CNC_6H_4O^-$ due to solvation.[7-9] If added water produces p-CNC_6H_4OH which then act as general acid in the amide cleavage, a rate maximum could arise from the cooperative action of p-$CNC_6H_4O^-$ and p-CNC_6H_4OH.

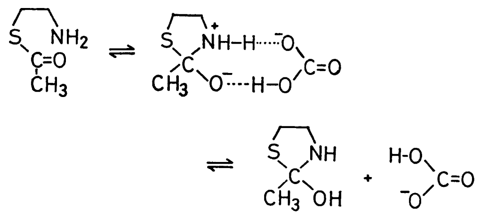
Figure 5 shows the second-order rate constant at the constant water concentration plotted against the concentration of added p-CNC_6H_4OH. The reaction rate diminished with increasing p-CNC_6H_4OH concentration, contrary to the expectation. p-CNC_6H_4OH quenches the reactivity of p-$CNC_6H_4O^-$ probably due to the hydrogen-bonded solvation, instead of assisting the reaction as general acid. Therefore, it appears that only the intramolecular proton in the tetrahedral intermediate of HCO_3^- and amide substrates is capable of acting as effective proton source (see Eqs. 7 and 8).

Kinetic Isotope Effects. If the rate-determining step involves proton transfer to the tetrahedral intermediate, the reaction will be retarded by replacing H_2O with D_2O. Figures 3 and 4 indicate that at the same water concentration the rate constants in the D_2O-containing medium are smaller than those in the H_2O-containing medium: $k_{2,H_2O}/k_{2,D_2O}=1.3\pm0.2$ for HCO_3^-+F_3-PNMA, 1.2±0.1 for p-$CNC_6H_4O^-$+F_3-PNMA, and 1.10±0.06 for HCO_3^-+PNPA. Since the acyl transfer reaction with PNPA is considered not to be general acid catalyzed,[10] the isotope effect of 1.1 may be associated with the simple nucleophilic step. The $k_{2,H_2O}/k_{2,D_2O}$ value for the F_3-PNMA is somewhat greater than this, and suggests the involvement of general acid catalysis.

The kinetic isotope effect was also assessed for the reaction in ethanol-*d*. The rate constants were relatively insensitive to the water concentration (or D_2O concentration in ethanol-*d*). Though the relative error of 10—20% must be assumed, the magnitude of $k_{2,EtOH}/k_{2,EtOD}$ for $HCO_3^- + F_3$-PNMA and $HCO_3^- +$ Cl_2-PNMA (2.2 and 1.6, respectively) is greater than that for PNPA (1.1—1.5).

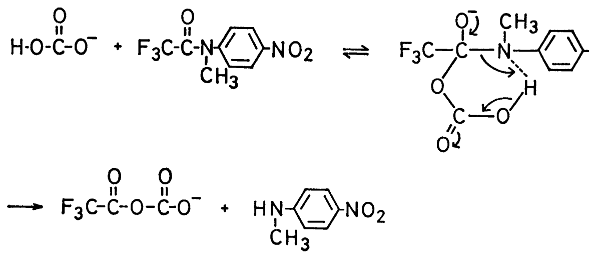
Discussion

Polyvalent inorganic salts have been considered to act as bifunctional catalyst, since they can accept and release proton simultaneously.[11] Cunningham and Schmir[15] and Barnett and Jencks[16] reported that intramolecular aminolysis is accelerated by hydrogencarbonate ion. The kinetic examination established that HCO_3^- partitions the zwitterionic tetrahedral intermediate in favor of the products. For example, the rate constant for hydrogencarbonate-catalyzed intramolecular aminolysis of *S*-(2-aminoethyl)thioacetate exhibits positive deviation of two orders of magnitude.[16] Thus, it is concluded that HCO_3^- interacts with the tetrahedral intermediate in a cyclic manner to accelerate its decomposition (Eq. 6).



(6)

A similar acceleration of the breakdown of the tetrahedral intermediate by HCO_3^- was reported for the alkaline hydrolysis of trifluoroacetanilide,[4] but not for that of *p*-nitrotrifluoroacetanilide.[5] However, HCO_3^- by itself cannot cleave the amide substrate in an aqueous system. Since the nucleophilicity of anions is drastically enhanced in aprotic solvents,[7,17] HCO_3^- in aprotic solvents can act as a bifunctional catalyst toward amide substrates. The product analysis strongly indicates that HCO_3^- in acetonitrile directly attacks the amide group of F_3-PNMA. The rate data suggest that the OH group of HCO_3^- acts as general acid during the breakdown of the tetrahedral intermediate. The most reasonable reaction scheme would be the following.



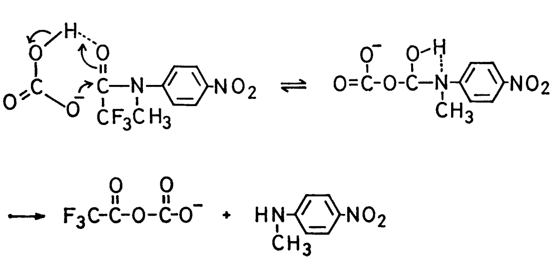
(7)

Table 2. Relative reaction rates and efficiency parameters for amide cleavage[a)]

Solvent		F_3-PNMA	Cl_2-PNMA	PNPA
DMF	$k_{rel,CNC_6H_4O^-}$	45	7.3	0.73
	$k_{rel,SI-O^-}$	37	—	0.019
	$r_{CNC_6H_4O^-}$	62	10	1.0
	r_{SI-O^-}	*ca.* 1900	—	1.0
Acetonitrile	$k_{rel,CNC_6H_4O^-}$	11—110	15—45	2.1
	$k_{rel,SI-O^-}$	120	—	0.12
	$r_{CNC_6H_4O^-}$	5.2—52	7.1—21	1.0
	$r_{rel,SI-O^-}$	*ca.* 1000	—	1.0
Ethanol	$k_{rel,CNC_6H_4O^-}$	1.4	1.9	1.2
	$r_{CNC_6H_4O^-}$	1.2	1.6	1.0

a) $k_{rel} = k_2$ for HCO_3^-/k_2, $r = k_{rel}$ for amide/k_{rel} for PNPA. For detail see text (Eqs. 9, 10, and 11).

However, the bifunctional attack of hydrogencarbonate ion followed by efficient proton transfer (Eq. 8), if it occur, would not be differentiated kinetically.



(8)

In Table 2, we summarize relative reaction rates (k_{rel}) and efficiency parameters (r) for the amide cleavage. The r value given by Eq. 11 stands for a measure

$$k_{rel,CNC_6H_4O^-} = \frac{k_2 \text{ for } HCO_3^-}{k_2 \text{ for } p\text{-}CNC_6H_4O^-} \quad (9)$$

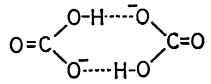
$$k_{rel,SI-O^-} = \frac{k_2 \text{ for } HCO_3^-}{k_2 \text{ for SI-O}^-} \quad (10)$$

$$r = \frac{k_{rel} \text{ for a substrate}}{k_{rel} \text{ for PNPA}} \quad (11)$$

of relative efficiency of HCO_3^- catalysis for amide cleavage *versus* PNPA cleavage. The r value for PNPA is, of course, equal to unity. The data of Table 2 substantiates that (i) r-values in DMF and acetonitrile are always much greater than unity and r_{SI-O^-} amounts to 10^3; in contrast, (ii) r-values in ethanol are almost equal to unity. Therefore, in the present system, the general acid catalysis by the hydroxyl group of HCO^-_3 is effective only in aprotic solvents. Proton transfer from hydrogencarbonate hydroxyl group may not be particularly favorable in ethanol due to its hydrogen bonding with the solvent and/or due to proton transfer from solvent ethanol. In addition, SI-O$^-$ (highly nucleophilic toward PNPA) is not effective in the amide cleavage, which again points to the importance of proton transfer.

As shown in Figs. 4 and 5, the isotope effect for the amide cleavage is greater than that for PNPA cleavage. The corresponding data in organic media are scarce. Breslow and McClure[18] gave $k_{H_2O}/k_{D_2O} =$ 1.47—2.27 for the general-acid catalyzed cleavage of maleamic acid in acetonitrile containing 1 M H_2O. Schowen *et al.*[19] also reported that, in the basic methanolysis of amide substrates, $k_{2,\mathrm{EtOH}}/k_{2,\mathrm{EtOD}}$ approaches 2.0 when proton transfer becomes involved in the rate-limiting step. The isotope effects observed in the present study for the amide cleavage are: $k_{2,\mathrm{H_2O}}/k_{2,\mathrm{D_2O}}=1.3$ (for F_3-PNMA) and $k_{2,\mathrm{EtOH}}/k_{2,\mathrm{EtOD}}=1.6$—2.2. These data are comparable to those observed for other general acid catalyses, and proton transfer is supposedly involved (at least partially) in the rate-limiting step in the present case.

The dependence of rate constants on the nucleophile and water concentrations is complicated. Among conceivable factors, (1) added water lowers the nucleophilicity of HCO_3^- and p-$CNC_6H_4O^-$ [5,6,8] and (2) added water changes the aggregation structure of the nucleophilic ion pairs, tightness of ion pairs, *etc.* The rate maximum observed is not amenable to simple interpretation. The non-linear dependence on nucleophile concentrations may reflect a similar phenomenon. In particular, HCO_3^- ion pairs may exhibit a strong association tendency in aprotic solvents as shown below.



(12)

Finally, we would like to point out the analogy of the hydrogencarbonate catalysis with the action of biotin. Mg-ATP and HCO_3^- are believed to form mixed acid anhydride, which (in a stepwise manner or in a concerted manner) reacts with enzyme-bound biotin.[20] The present study would suggest that the efficiency of HCO_3^- as acyl-group (or probably phosphate-group) acceptor can be enhanced in the aprotic environment. We could prepare mixed acid anhydride from HCO_3^- and F_3-PNMA, but trifluoroacetyl group, not hydrogencarbonate, was transfered to aniline.

In conclusion, the present study substantiates that HCO_3^- in aprotic media acts as a proper nucleophilic-general acid catalyst in the cleavage of amide substrates.

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