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Predominant role of basicity of leaving group in α-effect for nucleophilic ester cleavage

Yasuo Nomura,[a,b] Takayasu Kubozono,[b] Makoto Hidaka,[b] Mineko Horibe,[b] Naoki Mizushima,[b] Nobuyuki Yamamoto,[b] Toshio Takahashi,[b] and Makoto Komiyama[a,*]

[a] *Research Center for Advanced Science and Technology, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan*
[b] *Lion Corporation, 13-12, Hirai 7-chome, Edogawa-ku, Tokyo 132-0035, Japan*

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Abstract

It has been found that α-effects in nucleophilic reactions, unexpectedly large nucleophilicity due to adjacent unpaired electrons, are strongly dependent on the structure of substrate. The nucleophilic cleavages of 4-nitrobenzoate esters and 4-methylbenzoate esters by HOO^- have been systematically investigated in detail. When the leaving groups of substrates are sufficiently good (aryl, 2,2,2-trifluoroethyl, and 2,2-dichloroethyl esters), α-effect is evident. However, this effect drastically decreases as the leaving group gets poorer, and is only marginal for the cleavages of 2-fluoroethyl and methyl esters. In the nucleophilic cleavages by salicylaldoxime and acetohydroxamic acid, α-effect is also notable only for the esters having good leaving groups. These enormous dependences of α-effects on the substrate-structure have been interpreted in terms of the difference in the position of transition-state in the reaction coordinate.

Keywords: α-Effect; Nucleophilic ester cleavage; 4-Nitrobenzoate ester; 4-Methylbenzoate ester; Hydroperoxide ion; Hydroxyl ion; Rate constant; Substrate-structure; Transition-state; Reaction coordinate

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[*] Corresponding author. Fax: +81-3-5452-5209.
E-mail address: komiyama@mkomi.rcast.u-tokyo.ac.jp (M. Komiyama).

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1. Introduction

Design of highly active nucleophilic agents is one of the keys for further developments of chemistry and biochemistry, and so-called "α-effect" has been widely employed there as the leading principle [1–4]. This interesting and significant proposal in nucleophilic reactions says that "compounds which contain an electronegative atom with a free electron pair adjacent to the nucleophilic atom display an unusually high nucleophilic reactivity" [1]. One of the most comprehensive and conclusive data supporting this hypothesis was presented by Jencks and Carriuolo [5] in the nucleophilic cleavages of 4-nitrophenyl acetate. Although the nucleophilicity of most of nucleophiles monotonously increased with increasing pK_a (as expected from Brønsted law), the points for hydroperoxide ion, hydrazine, hydroxylamine and others, which have adjacent unpaired electrons, significantly deviated from this relationship in positive direction. For certain nucleophiles, the deviation was as large as 10^3- to 10^4-fold. Similar unusual rate enhancements assignable to α-effect were reported by Bruice et al. [6] for the cleavage of phenyl acetate. Strong and concrete evidence for "α-effect" was provided. This effect is also significant in biological systems. For example, hydroxylamine and hydrazine attack nucleobases in DNA far more efficiently than does ammonia, resulting in the transformation of DNA to non-natural form [7].

Although many attempts have been made to rationalize α-effects in terms of physicochemical factors (e.g., polarizability, hydrogen bonding, single electron transfer character, and others), mechanistic details have not yet been sufficiently clear [1–6,8–10]. Furthermore, it is uncertain if these effects are widely applicable to variety of reactions involving non-activated substrates or not (because of experimental convenience, previous evidence for these effects was obtained only on the cleavages of highly active aryl esters). In order to design highly active nucleophilic reactions by using this effect, these points must be more clarified. Here we report the results of systematic studies on nucleophilic cleavages of 4-nitro- and 4-methylbenzoate esters bearing various (both aryl and alkyl) leaving groups. As "α-effect" nucleophiles, hydrogen peroxide and others are used. It will be shown that α-effect is dominant only in the cleavages of the substrates having good leaving groups and marginal for the cleavages of common alkyl esters. The role of the acyl portions of esters is also investigated. The origin of these remarkable substrate dependences of α-effect is discussed.

2. Materials and methods

2.1. Materials

Most of the ester substrates were prepared from the acid chloride and the alcohol, and were sufficiently characterized by ^{1}H NMR. The choline esters were obtained by methylating the corresponding *N*,*N*-dimethylaminoethyl esters with dimethyl sulfate [11]. Hydrogen peroxide was purchased from Mitsubishi Gas Company, INC and used without further purification. The concentration of H_2O_2 therein was determined by the titration with permanganate. The water used for the kinetic analysis was purified by a Millipore Milli-XQ system, and has the specific resistance greater than $18.3\,\mathrm{M\Omega\,cm^{-1}}$. All other reagents were commercially obtained.

2.2. Kinetic analysis of ester cleavage

The reactions were initiated by adding stock solutions of esters (either in acetonitrile or in water), and carried out at 30 °C in $0.05\,\mathrm{mol\,dm^{-3}}$ carbonate buffer (for the reactions at pH 9.0) or $0.05\,\mathrm{mol\,dm^{-3}}$ phosphate buffer (pH 6.0, 7.0, and 8.0). Ionic strength was maintained at $0.1\,\mathrm{mol\,dm^{-3}}$ by using NaCl. The substrate concentration was $0.5\,\mathrm{mmol\,dm^{-3}}$, and the concentration of hydrogen peroxide was varied in 5–$400\,\mathrm{mmol\,dm^{-3}}$. With appropriate intervals, some portions of the reaction mixtures were taken out and analyzed by the reversed-phase HPLC equipped with an RP-C18 column (Cica-Merck LiChroCART 125-4). The peaks were assigned by coinjection with authentic samples. By using the absorbance at 260 nm, the amounts of ester, acid, and alcohol (only for the aryl esters) were determined. In all the reactions, the disappearance of ester satisfactorily showed pseudo-first-order kinetics. The peracids ($R_1C(O)OOH$), formed by the nucleophilic attack of HOO^- towards the carbonyl carbon atom of $R_1C(O)OR_2$, were rapidly digested to the acids under the conditions employed and not much accumulated.

The kinetic behaviors of ester cleavages are summarized as follows:

(1) In the absence of hydrogen peroxide, the apparent first-order rate constant k_{obs} for the disappearance of ester was proportional to $[HO^-]$.

(2) At constant pH, k_{obs} increased in proportional to $[HOOH]_0$.

(3) The slope of linear plot between k_{obs} and the equilibrium concentrations of HOO^- in the mixtures was constant irrespective of pH. Here, $[HOO^-]$ was calculated by using pK_a of HOOH (11.6) [12]. On the basis of these results, k_{obs} is expressed by Eq. (1):

$$k_{obs} = k_1[HOO^-] + k_2[OH^-] + k_3, \tag{1}$$

where k_1 and k_2 are the second-order rate constants for the nucleophilic cleavages of ester by HOO^- and HO^-, respectively, and k_3 is the first-order rate constant for the water reaction. Buffer catalysis is negligibly small in the present reactions, as confirmed by control experiments. The rate constants for the ester cleavages by other nucleophiles were determined in the same way.

3. Results and discussion

3.1. Hydrogen peroxide for nucleophilic cleavages of 4-nitro- and 4-methylbenzoate esters having various leaving groups

When hydrogen peroxide was added to aqueous solutions of aryl and alkyl esters of 4-nitrobenzoate and 4-methylbenzoate in Table 1, the cleavages of these esters were significantly accelerated with respect to the reactions in its absence. The pseudo-first-order rate constants were proportional to the concentration of hydrogen

Table 1
Structures of esters used and the pK_a of conjugate acids of their leaving groups

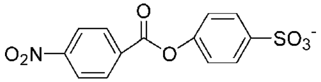
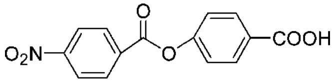
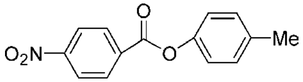
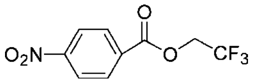
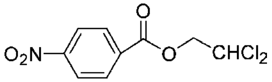
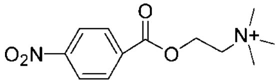
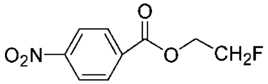
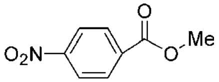
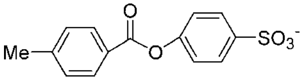
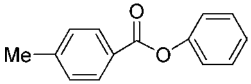
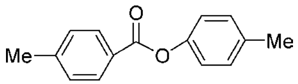
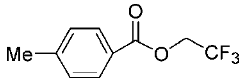
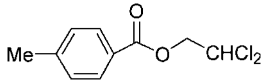
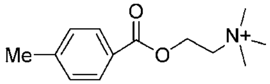
		pK_a[a]
4-Nitrobenzoate esters Aryl esters (1)		8.66
(2)		9.46
(3)		10.3
Alkyl esters (4)		12.4
(5)		12.9
(6)		13.2
(7)		14.4
(8)		15.5
4-Methylbenzoate esters Aryl esters (9)		8.66
(10)		9.90
(11)		10.3

Table 1 (*continued*)

		pK_a[a]
Alkyl esters (12)		12.4
(13)		12.9
(14)		13.2

[a] Ref. [12].

peroxide. Furthermore, the logarithm of rate linearly increased with the pH of solution, and the slope of this straight line was unity. Apparently, the ester cleavages by hydrogen peroxide proceed with HOO^- as the nucleophilic species (the pK_a of HOOH is 11.6) [12,13]. All the second-order rate constants k_1 for the ester cleavage by HOO^- are listed in Table 2. The rate constants k_2 for alkaline hydrolysis of these esters, determined by the pH dependence of hydrolysis rate in the absence of hydrogen peroxide, are also presented.

As shown in Fig. 1A, the k_1 for the cleavages of aryl esters of 4-nitrobenzoate by HOO^- (the open circles) monotonously decreases with increasing pK_a of the conjugate acid of leaving group. On the other hand, the k_1 values for the cleavages of alkyl esters by HOO^- (the closed circles) fit another straight line, which is much steeper than that for the aryl esters (the slopes are −0.8 and −1.5, respectively: see Table 3).

Table 2
Second-order rate constants k_1 and k_2 (in $s^{-1}\,mol^{-1}\,dm^3$) for the cleavage of various benzoate esters by HOO^- (k_1) and by HO^- (k_2)

Ester	k_1 ($s^{-1}\,mol^{-1}\,dm^3$)	k_2 ($s^{-1}\,mol^{-1}\,dm^3$)
(1)	14,000	25
(2)	1700	8
(3)	800	6
(4)	600	45
(5)	80	15
(6)	8	9
(7)	0.2	9
(8)	0.02	3
(9)	200	0.2
(10)	30	0.6
(11)	10	0.08
(12)	20	1.8
(13)	0.6	0.2
(14)	0.4	1.6

(The structures of esters are presented in Table 1 in text.)

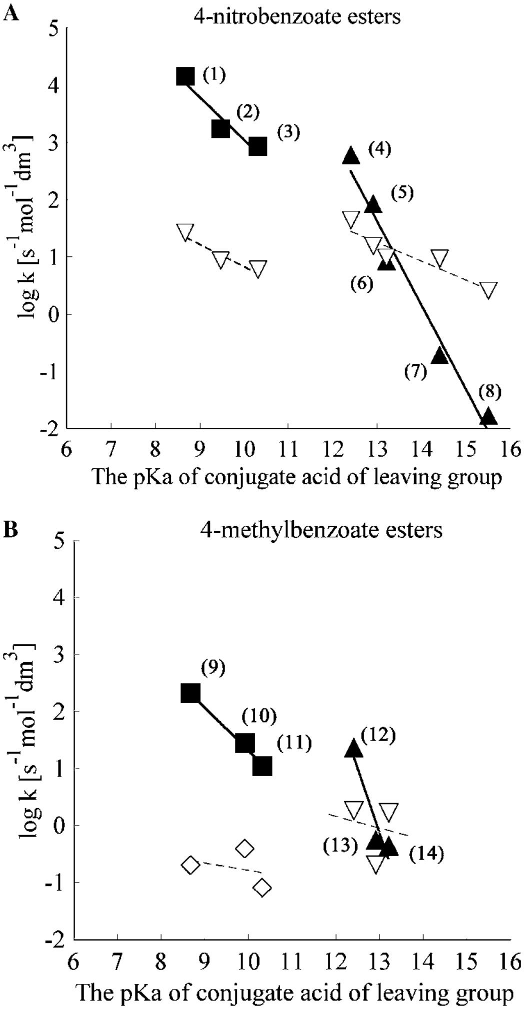


Fig. 1. Plots of the second-order rate constants k_1 at 30 °C for the HOO^--induced cleavages of (A) 4-nitrobenzoate esters and (B) 4-methylbenzoate esters as the function of pK_a of conjugate acid of leaving group. The rate constants k_2 for alkaline hydrolysis of these esters are also presented: cleavage of aryl esters by HOO^- (filled squares); cleavage of alkyl esters by HOO^- (filled triangles); cleavage of aryl esters by HO^- (open diamonds); cleavage of alkyl esters by HO^- (open down triangles).

Table 3
Slopes of the plots between the logarithm of rate constants (k_1 or k_2) and the pK_a of conjugate acid of leaving group for the aryl and alkyl esters of 4-nitro- and 4-methylbenzoate

Substituent in the acyl portion	log k_1		log k_2	
	Aryl	Alkyl	Aryl	Alkyl
Nitro	−0.8 ± 0.1	−1.5 ± 0.1	−0.4 ± 0.1	−0.3 ± 0.05
Methyl	−0.8 ± 0.3	−2.3 ± 0.3	−0.1 ± 0.3	−0.2 ± 0.7

The rate constants k_2 for alkaline hydrolysis of these esters also provide two lines for each of the aryl esters (the open squares) and the alkyl esters (the closed squares). Both of these two lines are rather flat, compared with the lines for the HOO^- reactions. For the cleavage of 4-methylbenzoate esters by HOO^- (Fig. 1B), the k_1 values are 10^1- to 10^2-fold smaller than those for 4-nitrobenzoate esters, as expected from the electron-donating activity of its 4-methyl substituent. However, the relationship between the k_1 and the pK_a is similar to that for the cleavages of 4-nitrobenzoate esters, and the points for the aryl and the alkyl esters fit two different straight lines. The line for the alkyl esters is far steeper than that for the aryl esters. The k_2 values also provide rather flat two lines. The slopes of all of these lines are similar to the values for the 4-nitrobenzoate esters (Table 3).

3.2. *Dependence of the magnitude of α-effect on substrate-structure in the nucleophilic ester cleavage by HOO^-*

The ratio of the rate constant k_1 for the nucleophilic cleavage of an ester by HOO^- to the corresponding value k_2 for the cleavage by HO^- was taken as a measure of the α-effect of HOO^-. This ratio directly reflects the effect of leaving group on the magnitude of α-effect. The difference in the electrophilicity of the carbonyl carbon atom of esters, due to either electron-donation or electron-withdrawal by the alcohol residue, is satisfactorily compensated in these k_1/k_2 ratios. In Fig. 2, these ratios are plotted against the pK_a of leaving group for both the 4-nitrobenzoate esters and 4-methylbenzoate esters [12]. The open circles are for the cleavages of the aryl esters of 4-nitrobenzoate, and the open squares are for the aryl 4-methylbenzoates. For all of these aryl esters, the k_1/k_2 ratios are 10^2 or greater, confirming the substantial α-effects of HOO^-. These results are consistent with the previous findings on the cleavages of 4-nitrophenyl acetate and phenyl acetate [5,6].

The k_1/k_2 ratio gradually decreases with increasing pK_a of leaving group. However, this change is modest (the slope $= -0.5$). Note that the magnitude of α-effect of HOO^- in these reactions should be still greater than the k_1/k_2 ratio, since HOO^- having a smaller basicity is intrinsically less nucleophilic than is HO^-. The pK_a of HOOH (11.6) is by 4.1 U smaller than that of H_2O (15.7), and thus the intrinsic nucleophilicity of HOO^- (in the absence of α-effect) should be 10^2- to 10^3-fold smaller than that of HO^-, as estimated from the Brønsted law [14]. Accordingly, the magnitude of α-effect in these reactions should be as large as 10^4- to 10^5-fold [15]. In the cleavages of 2,2,2-trifluoroethyl esters of both 4-nitrobenzoate and 4-methybenzoate (the closed circles and the closed squares numbered as (4) and (12), respectively, in Fig. 2), the k_1 is 14-fold greater than the k_2. For these alkyl esters having a rather good leaving group ($pK_a = 12.4$), the α-effect is also notable. This α-effect has been further confirmed by the Brønsted plot in Fig. 3 for the nucleophilic cleavage of 2,2,2-trifluoroethyl 4-nitrobenzoate by various nucleophiles. The point for HOO^- notably deviates in positive direction from the straight line for "non-α-effect" nucleophiles (glycine, piperidine, and HO^-).

Quite significantly, in Fig. 2, the k_1/k_2 ratio for the cleavages of alkyl esters drastically decreases as the leaving group becomes poorer (the closed circles for

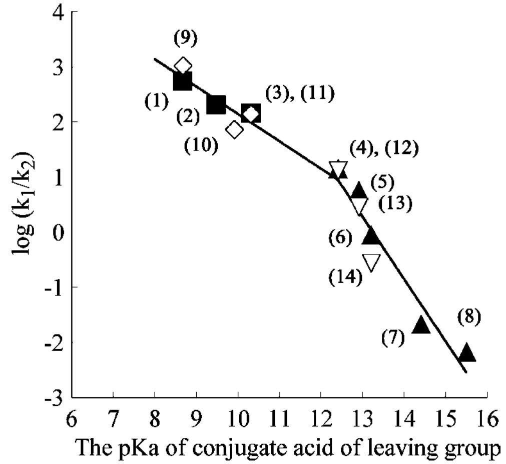


Fig. 2. Plots of k_1/k_2 ratios as the function of pK_a of conjugate acid of leaving group for the cleavage of aryl 4-nitrobenzoates (filled squares), alkyl 4-nitrobenzoates (filled triangles), aryl 4-methylbenzoates (open diamonds), and alkyl 4-methylbenzoate esters (open down triangles).

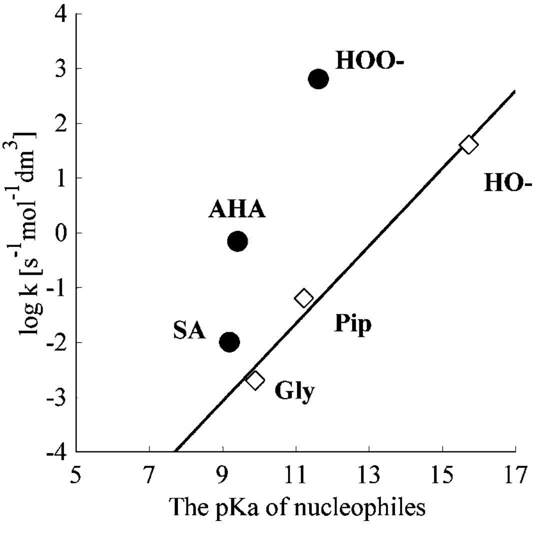


Fig. 3. Plots of second-order rate constants at 30 ° C for nucleophilic cleavage of 2,2,2-trifluoroethyl 4-nitrobenzoate. Gly, glycine; SA, salicylaldoxime; Pip, piperidine; AHA, acetohydroxamic acid.

the 4-nitrobenzoates and the closed squares for the 4-methylbenzoates). The slope is −1.1 and far steeper than the corresponding slope for the aryl esters. For the choline esters (pK_a of leaving group = 13.2), the rate constants k_1 for the HOO$^-$ reactions and k_2 for the HO$^-$ reactions are comparable with each other. With the 2-monofluoroethyl ester (pK_a = 14.4) and the methyl ester (pK_a = 15.5), the k_1 is even smaller than the k_2 by factors of 45 and 150, respectively. For these two substrates having very poor leaving groups, the α-effect is, if any, marginal. These arguments hold, even when the difference in pK_a between HOOH and H_2O is taken into consideration. Apparently, the α-effect in the nucleophilic cleavages by HOO^- is explicit only when the substrates have good leaving groups.

It is noteworthy that the k_1/k_2 values for the cleavages of 4-nitrobenzoate esters and 4-methylbenzoate esters fit the same line (for both the alkyl esters and the aryl esters). The acyl portions of esters show no significant effects on the magnitude of the present α-effects. Even when the electrophilicity of the carbonyl carbon atom is altered by the electronic effects of acyl portion, this factor is satisfactorily normalized in the k_1/k_2 ratios as described above.

3.3. α-Effects in the ester cleavages by various nucleophiles

The k_2 values for the nucleophilic cleavage of 2,2,2-trifluoroethyl 4-nitrobenzoate by salicylaldoxime and acetohydroxamic acid (p$K_a = 9.2$ and 9.4, respectively) are 0.01 and $0.7\,s^{-1}\,mol^{-1}\,dm^3$. As depicted in Fig. 3, these values notably deviate in positive direction from the straight line for "non-α-effect" nucleophiles. The α-effect is evident here. However, the deviations for these two nucleophiles are rather small, compared with that for HOO^- [16]. Thus, the rate constants for these two nucleophiles are 4.5×10^3- and 6.4×10^1-fold smaller than the corresponding k_2 values for alkaline hydrolysis, whereas the cleavage of the same ester by HOO^- is 14 times as fast as alkaline hydrolysis. It is strongly indicated that "α-effect" nucleophiles having smaller pK_a require still better leaving group in the substrate in order to show sufficient α-effect. These arguments are further supported by the fact that, in the cleavage of 4-nitrophenyl acetate (having a very good leaving group), both salicylaldoxime and acetohydroxamic acid are 5- to 10-fold more active than HO^- and the α-effects are so remarkable [6]. This is in marked contrast with the results in the cleavage of 2,2,2-trifluoroethyl 4-nitrobenzoate (vide ante). Predominant importance of leaving group for efficient α-effect has been further substantiated.

3.4. Origin of remarkable dependence of α-effect on substrate-structure

The essential role of leaving group in α-effect is associated with the difference in the position of rate-determining transition-state in the course of the reaction-coordinate. As was concretely evidenced by Jencks [1], Jencks and Fersht [17], Bender [2], Bruice and Benkovic [3], and others (and also as indicated by the Hammond postulate) [18], the position of transition-state gradually moves to the end of reaction coordinate as the leaving group becomes poorer. When the leaving group is good, the transition-state exists in the early stage of reaction (the solid line in Fig. 4A) and a bond between the nucleophilic center and the carbonyl carbon atom is only partially formed there. The rate of overall reaction is mostly governed by the efficiency of attack by the nucleophile towards the substrate. Under these conditions, "α-effects" are evident, since the transition-state is stabilized by: (i) the overlap of the non-bonding electron pair of neighboring atom to the nucleophilic center and/or (ii) the orbital hybridization among the carbonyl carbon atom, the nucleophile center atom, and

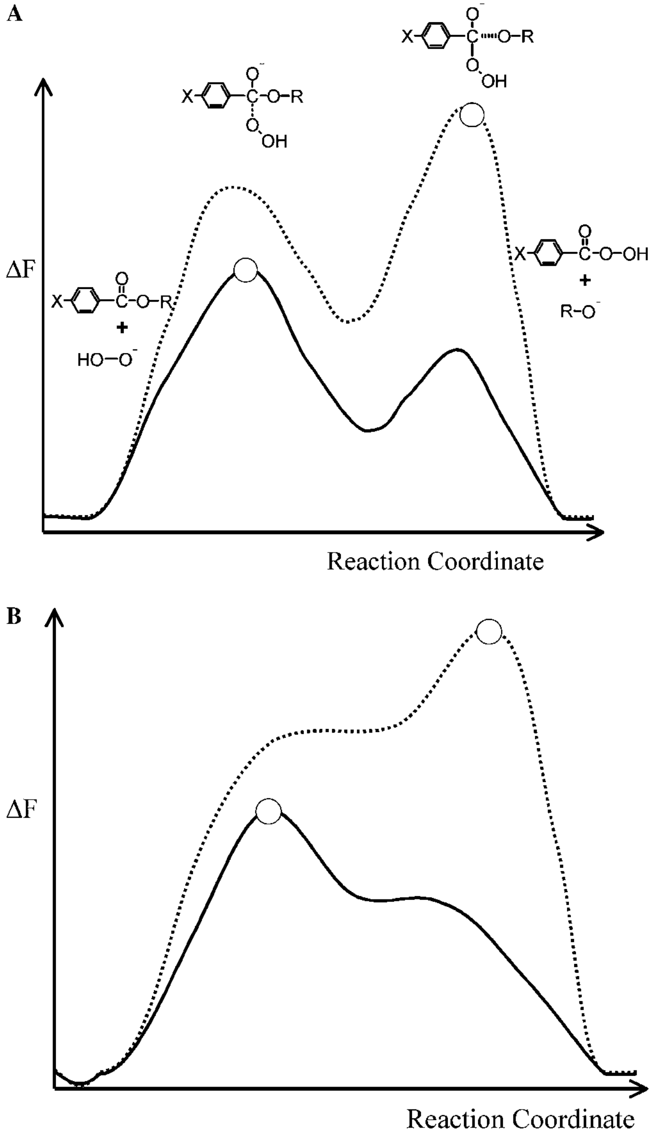


Fig. 4. Transition-state diagram (A) for reaction with a tetrahedral intermediate and (B) for the reactions with no intermediate. Good leaving group (solid line), poor leaving group (dashed line), rate-limiting transition-state (open circle).

the α-position atom bearing lone-pair electrons [1–4]. Consistently, the k_1 value is not much dependent on the pK_a of leaving group in the cleavages of aryl esters of both 4-nitrobenzoate (Fig. 1A) and 4-methylbenzoate (Fig. 1B). Furthermore, in Fig. 2, the k_1/k_2 values for the alkyl esters having rather good leaving groups (e.g., the trifluoroethyl esters (the number 4 and 12) and dichloroethyl esters (number 5 and 13)) almost fit the straight lines for the aryl esters. This result further confirms the critical role of the basicity of leaving group in determining the magnitude of α-effect.

With the reactions involving a poor leaving group (the methyl esters and monofluoroethyl esters), however, the removal of leaving group from the carbonyl carbon atom is rate-limiting (the dashed line in Fig. 4A) and a tetrahedral intermediate is formed in pre-equilibrium. The reaction rate is mostly governed by the basicity of leaving group, and the plot of $\log k_1$ vs. pK_a is accordingly steep (the closed circles in Figs. 1A and B). Under these conditions, the pre-equilibrium concentration of the tetrahedral intermediate is little affected by the "α-effects" in nucleophiles. Even though the pre-equilibrium formation of this intermediate is accelerated by the lone-pair electrons in the α-position, the backward reaction is also accelerated in the same magnitude. Consistently, the rate constants for the cleavages of methyl esters and monofluoroethyl esters by HO^- (k_2) are even larger than those by HOO^- (k_1), reflecting directly the difference in intrinsic nucleophilicity between HO^- and HOO^-.

The substituent in the acyl portion of substrate (benzoates in this study) alters the electrophilicity of the carbonyl carbon and thus affects the nucleophilic attack by HOO^- and HO^- (and other nucleophiles) in a similar extent to each other. As the result, the magnitude of α-effect is almost independent of the structure of acyl group.

We have argued above the origin of α-effects simply in terms of a stepwise reaction. However, there is also a possibility that the reactions are concerted ones without very stable tetrahedral intermediates. It is not very clear at present, which is really the case. However, the arguments on the origin of α-effects are unchanged in either of the cases.

Acknowledgments

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(b) E.P. Serjeant, B. Dempsey, IUPAC Chemical Data Series, 23, 1979 (2,2,2-trifluoroethanol, 2,2-dichloroethanol, and methanol);
(c) Kirk-Othmer Encyclopedia of Chemical Technology, fourth ed., Wiley-Interscience, New York, 11 (1994) 521 (2-fluoroethanol);
(d) J.T. Edsell, J. Wyman, Biophysical Chemistry, Academic Press Inc, New York, 1958 (glycine);
(e) H.K. Hall Jr., J. Am. Chem. Soc. 79 (1957) 5441–5444 (piperidine);
(f) A.L. Green, B. Saville, J. Chem. Soc. (1956) 3887–3892 (salicylaldoxime);
(g) W.M. Wise, W.W. Breandt, J. Am. Chem. Soc. 77 (1955) 1058–1059 (acetohydroxamic acid);
(h) P.J. Pearce, R.J.J. Simkins, Can. J. Chem. 46 (1968) 241–248 (4-methylphenol);
(i) R.L. Hinman, J. Org. Chem. 23 (1958) 1587–1588 (hydrazine). The pK_a of choline was evaluated by using Hammett relationship in D.D. Perrin, B. Dempsey, E.P. Serjeant, pK_a Prediction for Organic Acids and Bases, Chapman and Hall, London, 1981. The pK_a values for all other nucleophiles are from Kagaku Binran II-317, ed. by Chemical Society of Japan, Maruzen, Japan, 1993.

[13] For the nucleophilic cleavages of aryl esters, there should exist small amounts of peracids in the mixtures. However, they were rapidly cleaved and not detected by the HPLC. In this study, the rate constants were determined by using the amount of ester left unchanged in the mixtures. Thus this factor causes no effect on the present kinetic studies.

[14] When the slopes in the plot of log k_1 vs. pK_a are 0.5 and 0.7, respectively, the correction factors should be 1.1×10^2 and 7.4×10^2. The slope of this plot for the cleavage of 4-nitrophenyl acetate is 0.68 [5], and the plot in Fig. 3 in text gave a similar value.

[15] Still more precise evaluation of the magnitudes of α-effects was quite difficult, since steric hindrance was not negligible in nucleophilic reactions and this factor also induced some deviation in the Brønsted plots (see [2]).

[16] The cleavage of 2,2,2-trifluoroethyl 4-nitrobenzoate by hydrazine as "α-effect" nucleophile (p$K_a = 8.1$) was also examined. However, it was too poorly active, compared with the cleavages by water, to measure the catalytic constant precisely. It was concluded that this nucleophile having small pK_a value exhibits no significant α-effect.

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