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Hydrolysis of Electrophilic Olefins. I. Kinetic Studies on the Hydrolysis of *p*-Dimethylaminobenzylidene Derivatives of Active Methylene Compounds

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The dissociation constants (K_a) of the conjugate acids of the *p*-dimethylaminobenzylidene derivatives (I) of various active methylene compounds ($XYCH_2$) were determined. Alkaline hydrolysis of I was studied kinetically in 30% (v/v) ethanol at 25 °C. The rates of nucleophilic attack of a hydroxide ion on the carbon–carbon double bonds of I were linearly correlated with the corresponding pK_a values. Thus the pK_a values are suggested to be useful parameters to evaluate the relative activating ability of the X and Y groups to support the attack of nucleophiles on compounds of the type $XYC{=}CHAr$. In the hydrolysis of structurally similar compounds α-(substituted benzoyl)-*p*-dimethylaminocinnamonitriles, the rates of carbon-carbon bond fission of an uncharged addition intermediate and those of carbon-carbon double bond formation from a carbanion intermediate were also correlated with the dissociation constants (K_a^{AM}) of the corresponding substituted benzoylacetonitriles. The pH-rate profile and the relationship between rates and K_a (or K_a^{AM}) suggested that the carbon–carbon bond fission of the uncharged intermediate is the rate-determining step in the alkaline hydrolysis of I.

Keywords——*p*-dimethylaminobenzylidene derivative; active methylene; kinetics; nucleophilic addition; electrophilic olefin; linear free-energy relationship; dissociation constant; acidity function

As described previously,[1] a large excess of reagent, *p*-dimethylaminobenzaldehyde (DABA), was required for the colorimetric determination of 5-substituted 3-isoxazolecarboxylic acids because of the partial hydrolysis of the colored substances. Kinetic studies on the hydrolysis of the colored substances were started in connection with the mechanism of the color reaction.

Chemical reactivities[2] and spectral properties[3] of a large number of electrophilic olefins have been compared with their physiological activities. Studies on nucleophilic addition to carbon-carbon double bonds were reviewed by Patai and Rappoport.[4] Relative ability of activating groups X to support such a reaction at the double bonds in compounds $XCH{=}CH_2$ was correlated with Taft's σ_R substituent constants[5,6] or with the dissociation constants[6] of the corresponding carbon acids XCH_3. However, a significant correlation was not found between the rates of the reaction of $XYC{=}CHAr$ and the dissociation constants of $XYCH_2$.[6] Recently, the order of relative ability of the activating groups X and Y to support the attack of piperidine or morpholine on three electrophilic olefins $XYC{=}CHAr$ was compared with the order of ease of ionization of the corresponding carbon acids $XYCH_2$.[7]

The dissociation constants (K_a) of the conjugate acids of the *p*-dimethylaminobenzilidene derivatives (Ia—m) of 13 different active methylene compounds ($XYCH_2$) were determined as it appeared of interest to investigate the correlation of the relative activating ability of the X and Y groups with the corresponding pK_a values. In this paper, the kinetics and mechanism of the alkaline hydrolysis of Ia—i are presented, and it will be shown that the pK_a values are useful parameters to evaluate the relative ability of activating groups to support the attack of nucleophiles on activated electrophilic olefins.

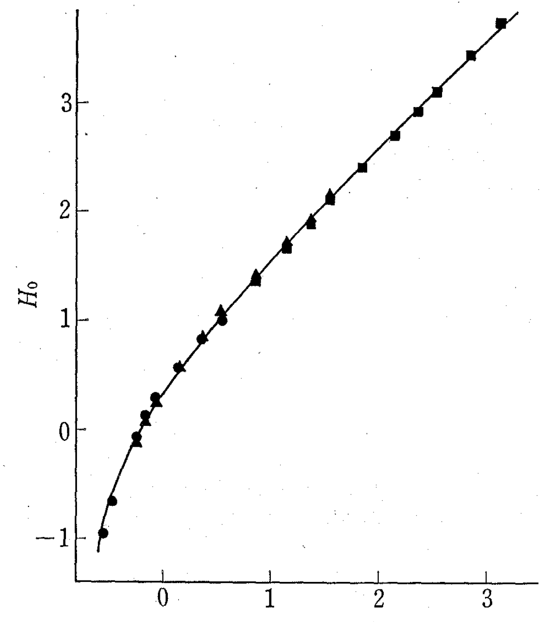


Fig. 1. H_0 Acidity Function of Hydrochloric Acid in 30% (v/v) Ethanol

o-Nitroaniline (●), *p*-nitroaniline (▲), *m*-nitroaniline (■).

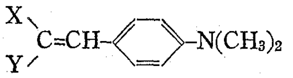
Results and Discussion

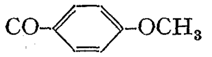
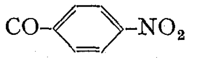
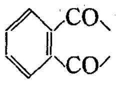
The pK_a values were determined by using the H_0 acidity function shown in Fig. 1 and the equilibrium ratio of concentrations of I to those of the corresponding conjugate acids, measured at the absorption maxima in 30% (v/v) ethanol. Table I shows the pK_a values, together with the absorption maxima and the melting points of I.

Pseudo first-order rate constants for the decrease of I (k_{DC}) and those for the formation of DABA (k_{FM}) were measured for the alkaline hydrolysis of Ia—i in 30% (v/v) ethanol at 25°C and ionic strength 0.7.

Two types of pH-rate profile (type A and B) were observed, as shown in Fig. 2. In the type A profile, k_{DC} was equal to k_{FM} within experimental error and showed first-order dependence on the activity of a hydroxide ion (a_{OH^-}). In the type B profile, k_{DC} was much larger than k_{FM} and was proportional to a_{OH^-}, while k_{FM} approached a limiting value with increase

TABLE I. pK_a Values, Absorption Maxima, and Melting Points of I



Compd. No.	X	Y	pK_a	λ_{max}, nm	mp, °C
Ia	CN	CN	0.65±0.06	442	178—179[a]
Ib	CN	$CONH_2$	1.64±0.04	426	197—198[b]
Ic	CN	$COCH_3$	1.08±0.05	450	108—109[c]
Id	CN	COPh	0.91±0.09	461	157—158[d]
Ie	CN		1.09±0.07	462	153—154
If	CN		0.60±0.11	476	233—235
Ig	$COCH_3$	$COCH_3$	2.65±0.03	405	104—105
Ih	$COCH_3$	COPh	2.43±0.03	408	182—184
Ii	H	NO_2	2.42±0.02	464	186—188[e]
Ij	CN	$CO_2C_2H_5$	1.19±0.05	436	127—128[f]
Ik			0.96±0.07	502	206—207[g]
Il	CH_3	NO_2	3.08±0.01	447	124—125[h]
Im	$CO_2C_2H_5$	$CO_2C_2H_5$	2.64±0.02	387	111—112[i]

a) Lit mp 178°C: L. Horner and K. Klüpfel, *Ann. Chem.*, **591**, 69 (1955).

b) Lit. mp 194—195°C: B.C. McKusick, R.E. Heckert, T.L. Cairns, D.D. Coffman, and H.F. Mower, *J. Am. Chem. Soc.*, **80**, 2806 (1958).

c) Lit. mp 108.0—108.5°C: see reference 1).

d) Lit. mp 162°C: H. Kauffmann, *Chem. Ber.*, **50**, 515 (1917).

e) Lit. mp 179.0—180.5°C: D.E. Worral and L. Cohen, *J. Am. Chem. Soc.*, **66**, 842 (1944).

f) Lit. mp 123.5—124.0°C: R. Merckx, *Bull. Soc. Chim. Belg.*, **58**, 460 (1949) [*C.A.*, **45**, 579*h* (1951)].

g) Lit. mp 199—200°C: see the reference given in *f*) above.

h) Lit. mp 123.4°C: O.M. Lerner, *Zhur. Priklad. Khim.*, **31**, 663 (1958) [*C.A.*, **52**, 18271*g* (1958)].

i) Lit. mp 111—112°C: M.V. Ionescu and O.G. Popescu, *Bull. Soc. Chim. Fr.*, **51**, 1215 (1932) [*C.A.*, **27**, 978 (1933)].

of pH. The compounds Ia, b, h (type A compounds) exhibit the type A profile and the others of Ia—i (type B compounds) exhibit the type B profile. Calmon *et al.*[8] reported a similar kinetic behavior to this type B profile and presented some evidence for the formation of a carbanion intermediate.

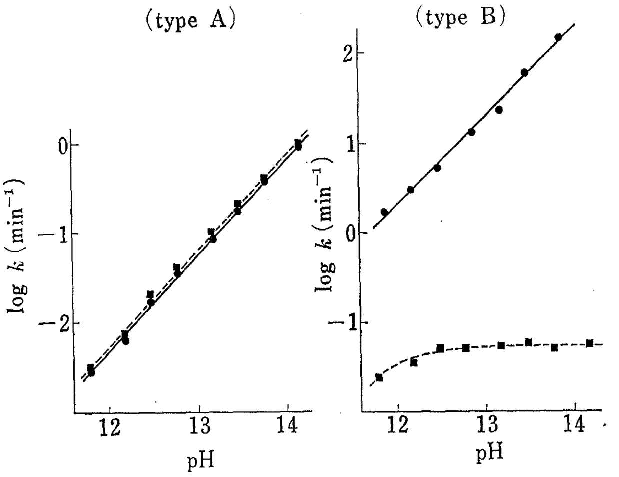


Fig. 2. Typical Examples for Two Types of pH-rate Profile for the Hydrolysis of I

Left: pH-rate profile for the hydrolysis of Ib (type A); Right: pH-rate profile for the hydrolysis of Id (type B). ●—●: k_{DC}, ■—■: k_{FM}.

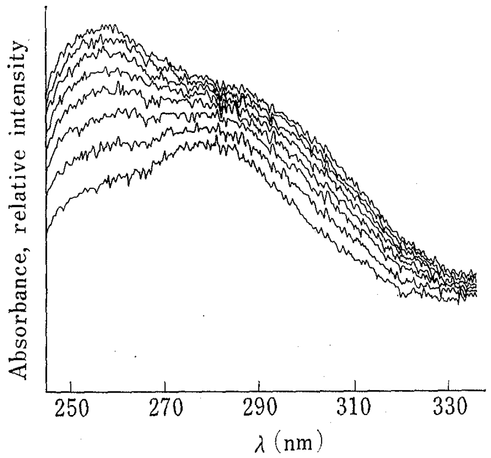


Fig. 3. Time Dependence of Rapid-scanning Absorption Spectra in the Hydrolysis of Id at pH 13

These spectra were obtained by subtracting the absorbance of the reagent blank from that of the reaction mixture at 0.43 s intervals. The intensity of the spectra increased with time (0—3.5 s).

In the initial step of the hydrolysis of Id at pH 13.17, the rate constant for the decrease of Id measured at 461 nm, λ_{max} of Id, was 24.5 min^{-1}, while that for the increase of the absorbance at 262 nm was 24.7 min^{-1}. After the initial faster decrease of Id, DABA was produced at a slower rate (k_{FM}=0.052 min^{-1} measured at 350 nm, λ_{max} of DABA), which was in accord with the rate for the decrease of the absorbance at 262 nm (k=0.055 min^{-1}). These results strongly suggest that an intermediate is accumulated in the initial step of the alkaline hydrolysis of Idand its absorption band appears at around 262 nm. Figure 3 shows the rapid-scanning absorption spectra obtained during the course of the initial faster reaction of Id. These spectra also exhibit the process of accumulation of the intermediate.

The kinetics of the alkaline hydrolysis of Ia—i suggests that the carbanion intermediate II is formed at first and is in rapid equilibrium with its protonated intermediate III. The next step is the rate-determining carbon-carbon bond fission of III.

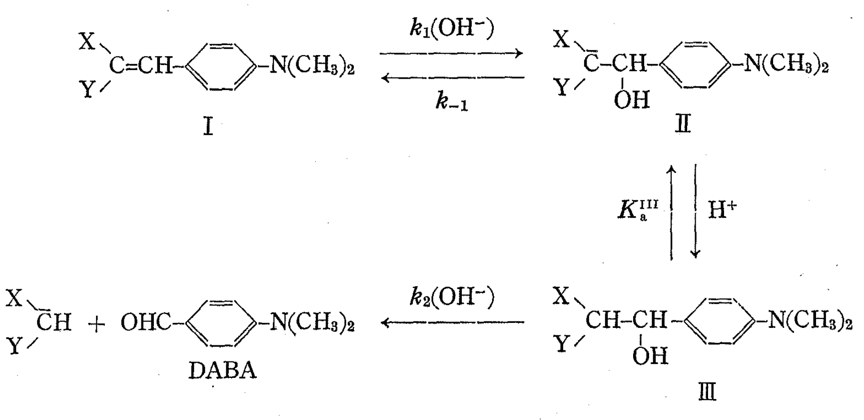


Chart 1

For the type A compounds, the rates of their disappearance were equal to those of the appearance of DABA, and no intermediate could be detected in the reaction mixtures. Thus, assuming that the intermediates II and III are in a steady state, k_{FM} is given by Eq. (1), where K_a^{III} is the dissociation constant of III and K_w is the ionic product of the water in the mixed solvent.

$$k_{FM} = \frac{k_1 k_2 K_w a_{OH^-}/K_a^{III}}{k_{-1}+k_2 K_w/K_a^{III}} \quad (1)$$

If $k_2K_w/K_a^{III} \gg k_{-1}$, Eq. (1) is reduced to Eq. (2).

$$k_{FM} = k_1 a_{OH^-} \quad (2)$$

As discussed later, this assumption appears to be incompatible with the results reported by Bernasconi *et al.*[7] and the linear relationships between rate parameters and the pK_a values. If $k_{-1} \gg k_2K_w/K_a^{III}$, Eq. (1) is reduced to Eq. (3), and this equation could account for the observed relationships.

$$k_{FM} = k_1 k_2 K_w a_{OH^-}/k_{-1}K_a^{III} \quad (3)$$

On hydrolysis of the type B compounds in strongly alkaline solution, an induction period was observed for the formation of DABA. Then, assuming that I, II, and III are in rapid equilibria, the following equations (4) and (5) can be derived where a_{H^+} is the activity of a hydronium ion.

$$k_{DC} = k_1 a_{OH^-} + k_{-1}K_a^{III}/(K_a^{III}+a_{H^+}) \quad (4)$$

$$k_{FM} = \frac{k_1 k_2 K_w a_{OH^-}/(K_a^{III}+a_{H^+})}{k_1 a_{OH^-}+k_{-1}K_a^{III}/(K_a^{III}+a_{H^+})} \quad (5)$$

The dissociation constant of an intermediate such as III is expected to be higher than that of the corresponding carbon acid ($XYCH_2$), as shown by Bernasconi and Leonarduzzi,[9] and Calmon *et al.*[8a] The dissociation constants (K_a^{AM}) of some of the active methylene compounds, $XYCH_2$, were measured in 30% (v/v) ethanol at 25°C. According to the above discussion, the K_a^{III} values for the hydrolysis intermediates, III, of the type B compounds are considered to be larger than a_{H^+} in the pH range studied (pH 10—14) from the pK_a^{AM} values listed in Table II.[10] Thus, equations (4) and (5) can be simplified to (6) and (7), respectively.

$$k_{DC} = k_1 a_{OH^-} + k_{-1} \quad (6)$$

$$k_{FM} = \frac{k_1 k_2 K_w a_{OH^-}/K_a^{III}}{k_1 a_{OH^-}+k_{-1}} \quad (7)$$

In strongly alkaline solution where $k_1 a_{OH^-} \gg k_{-1}$, equations (6) and (7) are reduced to (8) and (9), respectively.

$$k_{DC} = k_1 a_{OH^-} \quad (8)$$

$$k_{FM} = k_{limit} = k_2 K_w/K_a^{III} \quad (9)$$

Eq. (8) explains well the experimental result that k_{DC} is proportional to a_{OH^-} in strongly alkaline solution. Eq. (9) is also consistent with the result that k_{FM} approaches a limiting value, k_{limit}, with increase of pH. In weakly alkaline solution where $k_{-1} \gg k_1 a_{OH^-}$, Eq. (7) is also reduced to Eq. (3) described above. Accordingly, Eq. (7) should be applicable to the formation of DABA in the alkaline hydrolysis of all the compounds, Ia—i, A similar equation was derived for the hydrolysis of a series of 3-benzylideneacetylacetones.[8]

From Eq. (7), plots of a_{OH^-}/k_{FM} against a_{OH^-} should give a linear relationship, $a_{OH^-}/k_{FM} = pa_{OH^-}+q$, where the parameters p and q are defined by the following equations (10) and (11), respectively. From Eqs. (10) and (11), Eq, (12) can be derived, where K is the equilibrium constant for the attack of a hydroxide ion on the carbon-carbon double bond of I.

$$p = K_a^{III}/k_2K_w \tag{10}$$

$$q = k_{-1}K_a^{III}/k_1k_2K_w \tag{11}$$

$$p/q = k_1/k_{-1} = K \tag{12}$$

Substituting the k_1 value obtained from Eq. (8) into Eq. (12), k_{-1} can be calculated. Table II summarizes these rate parameters obtained above, together with the pK_a^{AM} values. The solid line in Fig. 4 is calculated according to Eq. (7) by the use of the parameters, p and $1/q$, listed in Table II for the alkaline hydrolysis of Ie as an example; the observed k_{FM} values fall on this line.

TABLE II. Rate Parameters for the Hydrolysis of I

Compd. No.	p (min)	$1/q$ (min^{-1} M^{-1})	k_1 (min^{-1} M^{-1})	k_{-1} (min^{-1})	log K (M^{-1})	pK_a^{AM}	(lit.)
Ia	Nearly 0	54.6					(11.19)[a]
Ib	Nearly 0	1.74					
Ic	3.13	29.1	487	5.35	1.96		
Id	18.3	24.4	555	1.25	2.65	7.96	(7.77)[b]
Ie	7.60	14.3	290	2.65	2.04	8.52	
If	169	84.8	1730	0.121	4.16	6.30	
Ig	13.8	0.381	2.12	0.406	0.72	9.13	(9.00)[a]
Ih	Nearly 0	0.0320				9.03	(9.40)[a]
Ii	141	14.7	75.5	0.0364	3.32		(10.21)[a]

a) R.G. Pearson and R.L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

b) V. Pihl, H. Siilbek, T. Tenno, A. Ranne, and A. Talvik, *Reacts. Sposobnost Org. Soedin., Tartu. Gos. Univ.*, **5**, 27 (1968) [*C.A.*, **69**, 100208*s* (1968)].

As shown in Fig. 5, plots of log k_1 against pK_a afford a good linear relationship with a slope of -1.42 ± 0.06 ($r=0.9974$, $n=5$), except for Ii. As discussed later, the relationship seems to reflect an early transition state for the process of the addition of a hydroxide ion; carbon-oxygen bond formation has made little progress in this transition state. As shown in Fig. 6, such a linear free-energy relationship can also be found between the pK_a values and the second-order rate constants (k)[11] for hydrolysis of the *p*-methoxybenzylidene derivatives of the active methylene compounds. These relationships indicate that the pK_a values are useful parameters to evaluate the relative ability of activating groups to support the attack of nucleophiles on activated electrophilic olefins. The upward deviation of Ii from the solid line in Fig. 5 may be due to reduced steric hindrance and/or less rehybridization[7,12] in the k_1 process.

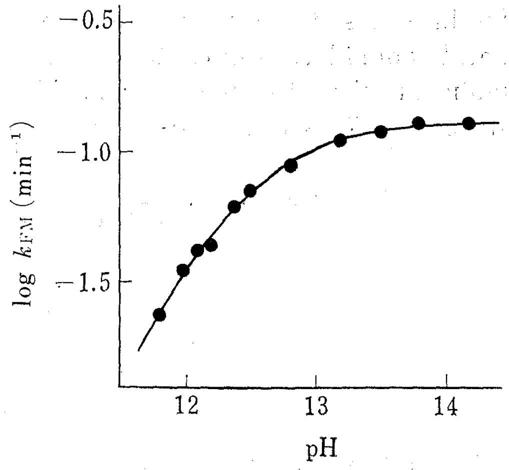


Fig. 4. Plots of log k_{FM} against pH for the Hydrolysis of Ie

The solid line is calculated from Eq. (7) by the use of the p and $1/q$ values listed in Table II.

If $k_2K_w/K_a^{III} \gg k_{-1}$ for the type A compounds, Eq, (1) is reduced to Eq. (2) as described above. The k_1 values for Ia, b, h calculated from Eq. (2) correspond to the $1/q$ values listed in Table II.[13] In a plot of these k_1 values against pK_a, all of the points show downward deviation (*ca.* 1.5 log units) from the solid line in Fig. 5. We cannot explain these deviations; it is unlikely that there are greater steric hindrance and greater rehybridization in the k_1 process for the type A compounds than for the type B compounds. Accordingly, the assumption, $k_2K_w/K_a^{III} \gg k_{-1}$, for the type A compounds may be invalid. On the other hand, the k_1 value

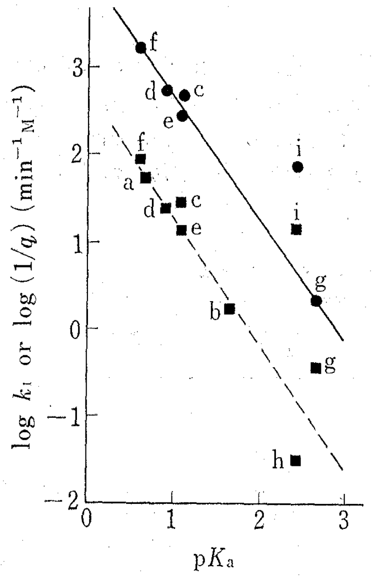


Fig. 5. Plots of log k_1 or log $(1/q)$ against pK_a

Symbols, a—i, represent the subscripts of I. ●——●: log k_1 *vs.* pK_a, ■——■: log $(1/q)$ *vs.* pK_a.

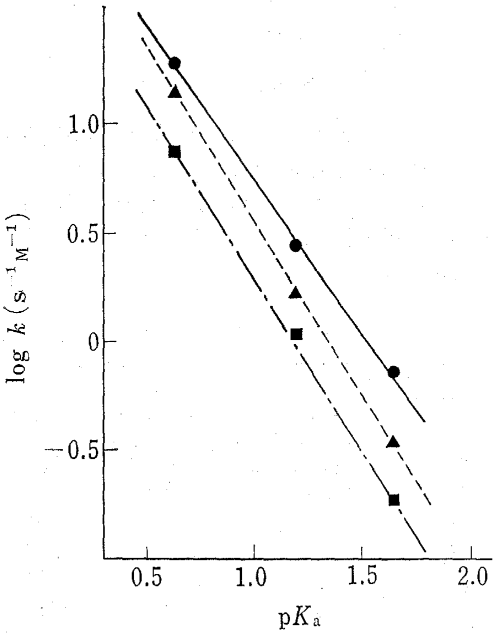
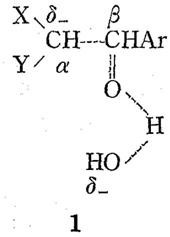


Fig. 6. Linear Relationship between Rate Constants and pK_a Values

The data used to determine the relationship were as follows: the second-order rate constants (k) for hydrolysis of the p-methoxybenzylidene derivatives of malononitrile, ethyl cyanoacetate, and cyanoacetamide measured at 48°C (●——●), 40°C (▲----▲), and 31°C (■--------■)[11]; the pK_a values of the corresponding conjugate acids of Ia,j,b presented in Table I.

for Ia is close to that for Ii calculated from Eq. (8). However, it seems improbable that Ia and Ii would have similar k_1 values, as it has been reported that the rate constants for nucleophilic addition of amines to benzylidenemalononitrile were much higher than those to β-nitrostyrene.[7] This again casts doubt on the validity of the above assumption.

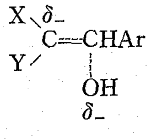
T.S. for the k_2 process:



$\mathrm{X(Y)\overset{\delta-}{\overset{\alpha}{C}}H\text{---}\overset{\beta}{C}H(Ar)\text{=}O\cdots H\cdots\overset{\delta-}{O}H}$

1

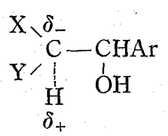
T.S. for the k_{-1} process:



$\mathrm{X(Y)\overset{\delta-}{C}{=}CH(Ar)\cdots\overset{\delta-}{O}H}$

2

T.S. for the process of deprotonation of III or protonation of II:



$\mathrm{X(Y)\overset{\delta-}{C}(\cdots\overset{\delta+}{H})\text{---}CH(Ar)OH}$

3

Chart 2

As shown in Fig. 5, plots of log $(1/q)$ against pK_a also gave a fair straight line with a slope of -1.45 ± 0.20 ($r=0.9451$, $n=8$), except for Ii. This linear correlation seems to indicate that Eq. (3), instead of Eq. (2), is reasonable for the type A compounds; the correlation covers not only the type B compounds but also the type A compounds.

Comparison of the slope of log k_1 *vs.* pK_a plots with that of log $(1/q)$ *vs.* pK_a plots shows that the effect of the activating groups on the term, $k_2/k_{-1}K_a^{\mathrm{III}}$, is very small. This indicates that the substituent effects of X and Y groups on the term, k_2/k_{-1}, are nearly identical with those on the K_a^{III} values. The reason for this identity is considered to be as follows. It is most likely that the substituent effects on the k_2 process are very similar to those on the deprotonation step of III as a negative charge is formed on the α-carbon of III in both transition states (**1** and **3**). On the other hand, there must be a comparable similarity between the effects on the k_{-1} process and those on the protonation step of

II, because the negative charge on the α-carbon of II is partially lost in both transition states (2 and 3).

Patai *et al.* found no significant correlation of the rates of nucleophilic attack on electrophilic olefins with the dissociation constants of the corresponding carbon acids.6) In our case, no correlation was observed between log k_1 and $\mathrm{p}K_a^{AM}$, as shown in Fig. 7. The reason for this is considered to be as follows: the k_1 process may be related to the deprotonation step of $XYCH_2$ as discussed by Bernasconi *et al.*,7) but not the protonation step of $XY\bar{C}H$.

Plots of log K, instead of log k_1, against $\mathrm{p}K_a^{AM}$ are expected to give a linear relationship as it is likely that the k_{-1} process is related to the protonation step of $XY\bar{C}H$. A fair straight line was observed between log K and $\mathrm{p}K_a^{AM}$ except for Ii as shown in Fig. 8 (r=0.9971, n=4).

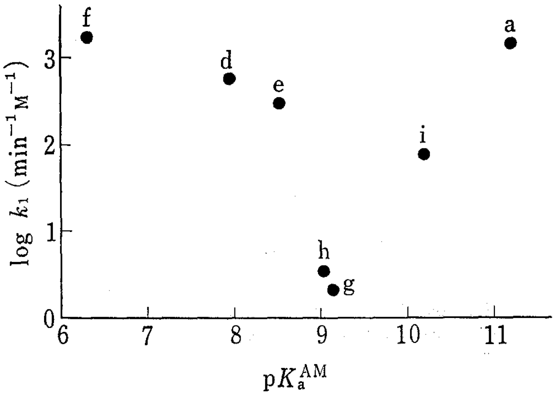


Fig. 7. Plots of log k_1 against $\mathrm{p}K_a{}^{AM}$

Symbols, a and d—i, represent the subscripts of I. The k_1 values used for Ia and Ih were estimated from the upper line in Fig. 5.

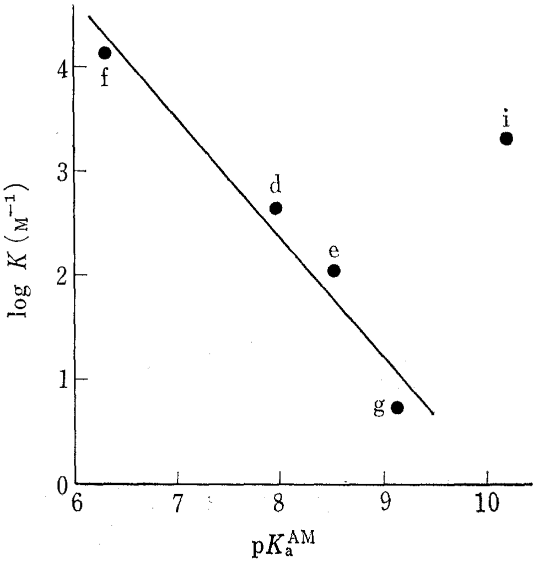


Fig. 8. Plots of log K against $\mathrm{p}K_a^{AM}$

Symbols, d—g and i, represent the subscripts of I.

Such a correlation can also be found between the dissociation constants of Meldrum's acid, 1,3-indanedione, and malononitrile, and the equilibrium constants14) for the addition of a hydroxide ion to their *p*-nitrobenzylidene derivatives (not shown).15)

However, no correlation was found between log K and $\mathrm{p}K_a$: the k_1 values are related to the $\mathrm{p}K_a$ values as described above, but the k_{-1} values may not be.

In structurally similar compounds, Id—f, plots of log k_{-1} and log $(1/p)$ against $\mathrm{p}K_a^{AM}$ gave two linear relationships with slopes of 0.61 (r=0.9999, n=3) and 0.60 (r=0.9994, n=3), respectively, as shown in Fig. 9. Assuming that $\mathrm{p}K_a^{AM}-\mathrm{p}K_a^{III}=$constant, a plot of log k_{-1} *vs.* $\mathrm{p}K_a^{AM}$ should show a linear correlation between log k_{-1} and $\mathrm{p}K_a^{III}$ with the slope of 0.61, and a plot of log $(1/p)$ *vs.* $\mathrm{p}K_a^{AM}$ should show a correlation between log k_2 and $\mathrm{p}K_a^{AM}$ with the slope of -0.40. These correlations indicate that the effects of activating groups on carbon-carbon double bond formation (k_{-1} process) and on carbon-carbon bond fission (k_2 process) are well correlated with the stability of the reacting carbanion (II) and the forming carbanion ($XY\bar{C}H$), respectively. It is interesting to note that the order of ease of carbon-carbon bond fission in the alkaline hydrolysis of carboxamides coincides with that of the stability of the forming carbanions.16)

As shown in Fig. 10, extended Brφnsted plots17) show two linear correlations for the k_1 and k_{-1} processes on hydrolysis of Id—f. Normalized α values,17b) $\alpha^n(k_1)$ and $\alpha^n(k_{-1})$, calculated from the slopes of the least-squares lines in Fig. 10 are 0.36 (r=0.9965, n=3) and -0.64 (r=0.9989, n=3), respectively. These values indicate an early transition state in the k_1 process as described above. The substituent effects of the benzoyl groups are in the direction

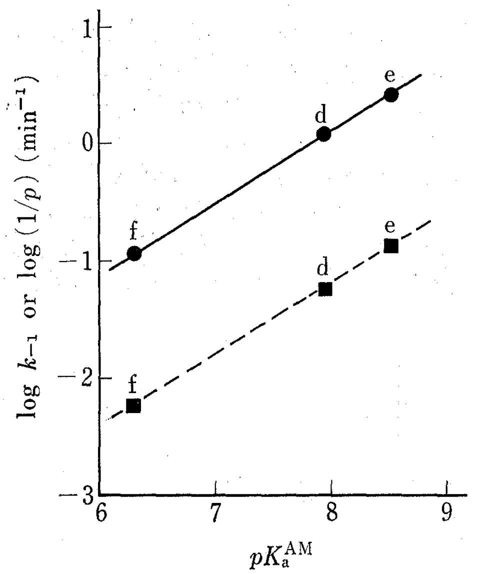


Fig. 9. Plots of log k_{-1} or log $(1/p)$ against pK_a^{AM}

Symbols, d—f, represent the subscripts of I.
●——●: log k_{-1} *vs.* p$K_a{}^{AM}$, ■----■: log $(1/p)$ *vs.* p$K_a{}^{AM}$.

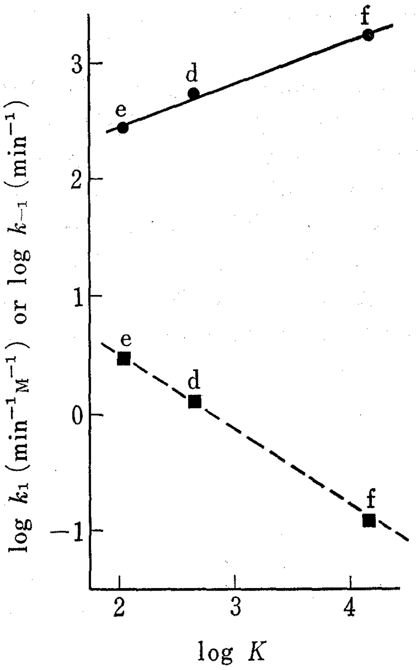


Fig. 10. Plots of log k_1 or log k_{1-1} against log K

Symbols, d—f, represent the subscripts of I.
●——●: log k_1 *vs.* log K, ■----■: log k_{-1} *vs.* log K.

to stabilize a negative charge on II and the transition state as positive ρ values were obtained from Hammett plots of log K and log k_1 against σ (not shown). Whether a partially positive or negative[17b)] charge is localized on the benzylic β-carbon at the transition state or not, a smaller substituent effect on the charge is expected, because the benzylic carbon is much farther away from the substituent on the benzoyl groups. Thus the value of $\alpha^n(k_1)$ would be a measure of negative charge formation on the α-carbon in the transition state.

In conclusion, the kinetic study presented in this paper suggests that the pK_a values are useful parameters to evaluate the relative ability of activating groups to support the attack of nucleophiles on activated electrophilic olefins such as I.

Experimental

Materials——Compounds (Ia—d, i—m) were prepared as described in the literature (see Table I). Compound Ie was prepared as follows; a mixture of *p*-methoxybenzoylacetonitrile (0.30 g), prepared by the method of Stepanov and Vul'fson,[18)] and *p*-dimethylaminobenzaldehyde (0.25 g) in ethanol (10 ml) was refluxed with one drop of piperidine for 10 min, and then the precipitate from the reaction mixture was recrystallized from ethanol. Yield, 90%. IR ν_{max}^{KBr} cm^{-1}: 2210 (CN), 1650 (C=O). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.46; H, 5.93; N, 9.28. Compound If was prepared without piperidine in a manner similar to that described above for Ie but with *p*-nitrobenzoylacetonitrile prepared from 5-(*p*-nitrophenyl)isoxazole by the method of Lynch and Shiu.[19)] The product was recrystallized from dichloromethane–ethanol. Yield, 61%. IR ν_{max}^{KBr} cm^{-1}: 2200 (CN), 1649 (C=O), 1347, 1519 (NO_2). *Anal.* Calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.41; H, 4.67; N, 13.29. Compound Ig was prepared as follows; a mixture of acetylacetone (0.5 g) and *p*-dimethylaminobenzaldehyde (0.7 g) in ethanol (15 ml) was allowed to stand in the presence of piperidine (0.3 g) at −20°C for 5 d, and then the precipitate from the reaction mixture was recrystallized from ethanol. Yield, 32%. IR ν_{max}^{KBr} cm^{-1}: 1640, 1704 (C=O). *Anal.* Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.75; H, 7.47; N, 6.06. Compound Ih was prepared in a manner similar to that described above for Ig but with benzoylacetone. Yield, 17%. IR ν_{max}^{KBr} cm^{-1}: 1638, 1670 (C=O). *Anal.* Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.71; H, 6.54; N, 4.75. *p*-Dimethylaminobenzaldehyde was purified by recrystallization. Thirteen active methylene compounds were purified by recrystallization or distillation. Nitroanilines (*o*-, *m*-, and *p*-) were purified by recrystallization from ethanol. Ethanol was purified by the method of Patai and Rappoport.[20] Glass-distilled water was used throughout. Other chemicals were of reagent-grade and were used without further purification.

Apparatus——Spectroscopic measurements were carried out with a Hitachi 356 dual-wavelength double-beam spectrophotometer equipped with a two-phenomena accessory and a thermostated cell holder. A Union rapid reaction analyzer, type RA-601, with a kinetic data processer system 71 was used to follow fast reactions. pH measurements were made using a Metrohm 436 potentiograph equipped with a glass-calomel electrode. The high performance liquid chromatography (HPLC) system consisted of a Shimadzu LC-3A solvent delivery pump, a Rheodyne 7125 sample injector, and a Shimadzu SPD-2A variable wavelength detector.

Determination of H_0 Acidity Function——The equilibrium ratios of three indicators (*o*-, *m*-, and *p*-nitroanilines) with their conjugate acids were measured spectrophotometrically in 30% (v/v) ethanol containing various concentrations of hydrochloric acid. H_0 values were obtained by the use of the equilibrium ratios and the acidity constants[21] of the conjugate acids.

Optical Measurements of Equilibrium Ratios——Aliquots (3.0 ml) of the stock solutions (ethanol) of the aniline indicators and Ia—m, prepared at appropriate concentrations, were pipetted into 10 ml volumetric flasks. Aqueous hydrochloric acid (7.0 ml) of various concentrations was added to the solutions. After the mixtures had been thermally equilibrated at 25°C, their absorption spectra were measured in the cell thermostated at 25°C. The concentrations of added hydrochloric acid were determined by titration with aqueous sodium hydroxide solution.

pK_a Determination——The pK_a values of the conjugate acids of I were determined by using the H_0 acidity function and the equilibrium ratios of I to the corresponding conjugate acids in 30% (v/v) ethanol at 25°C.

pK_a^{AM} Determination——The pK_a^{AM} values of some of the active methylene compounds were determined potentiometrically in 30% (v/v) ethanol at 25°C.

pH Determination——In 30% (v/v) ethanol, it is considered that $pH = \text{meter reading} - 0.10$[22] at 25°C. Determination of pH values more alkaline than 11.8 was made in 30% ethanol–aqueous sodium hydroxide solutions. The pH values in highly alkaline solutions containing more than 0.1 M NaOH were estimated from the relationship between pH and concentrations less than 0.1 M NaOH. The pK_w value of 14.47 in 30% ethanol, interpolated graphically from the values measured by Hepler *et al.*,[23] was also used for calculation of the activity of a hydroxide ion.

Product Analysis——A typical example is described. α-Benzoyl-*p*-dimethylaminocinnamonitrile (Id) was subjected to hydrolysis in 30% ethanol (pH 12.5) at 25°C. The initial concentration of Id in the mixture was 6.62×10^{-5} M. After 10 half-lives, the reaction mixture was subjected to HPLC to determine benzoylacetonitrile and DABA. The HPLC conditions were as follows: μ-Bondapak C_{18}; 4 × 300 mm column; pH 7.0 phosphate buffer (0.02 M)–acetonitrile (1: 1, v/v), 1 ml/min; at 254 nm. No peak other than those of the above two components could be detected. The yield was quantitative for both products.

Kinetic Measurements——Kinetic measurements in 30% ethanol were made spectrophotometrically in the cell thermostated at 25.0 ± 0.1°C by the stopped-flow method or by the two-phenomena method, which followed the appearance of DABA and the disappearance of I, unless otherwise specified. The absorption maximum of DABA was 350 nm in 30% ethanol and those of I are shown in Table I. The ionic strength of the reaction mixture was maintained at 0.7 with potassium chloride except at concentrations of the hydroxide ion of more than 0.7 M. The initial concentrations of I were in the range of 1×10^{-5} to 1×10^{-4} M. The reactions were initiated by the addition of 1.0 ml aliquots of stock solutions of I preequilibrated at 25°C in 30% ethanol to the cuvette thermostated previously at 25°C and containing 2.0 ml of 30% ethanol (aqueous buffer or aqueous sodium hydroxide). The observed pseudo first-order rate constants, k_{DC} and k_{FM}, were calculated from the least-squares plots of $\ln(A_t - A_\infty)$ and $\ln(A_\infty - A_t)$, respectively, against time. All runs were linear for at least 2 half-lives. The k_{DC} values for Ig were measured by the initial-rate method because of its slow disappearance.

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