the precipitate in MeOH (18 ml.) was added dropwise a 0.5*M* sodium methoxide solution (6.70 ml.) at room temperature under nitrogen. After being stirred for 12 min., the mixture was neutralized with AcOH, concentrated below 40° ***in vacuo*** and diluted with water to give a precipitate (0.87 g.). This was dissolved in $CHCl_3$ and chromatographed over silica gel (34.7 g.). Fractions eluted with $CHCl_3$ (100 ml.) and with $CHCl_3$-acetone (9:1, 300 ml.) were discarded. From the subsequent fractions eluted with $CHCl_3$-acetone (9:1, 100 ml.; 1:1, 200 ml.) was obtained a product which was crystallized from hexane-AcOEt to give XI (0.45 g.). Recrystallization from the same solvent mixture gave an analytical sample, m.p. 200~202°(sintered at 190°), $[\alpha]_D$ +194.2°(c=1.24, EtOH). UV λ_{max} mμ (ε): 256 (10510); inflexion 225 (7810). IR ν_{max} cm^{-1}: 3450, 1710, 1628, 1575, 1511, 1118, 1096, 1055, 1043, 1006, 897, 861. *Anal.* Calcd. for $C_{21}H_{28}O_5N_2$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.90; H, 7.03; N, 7.17.

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Masaichiro Masui and Hidenobu Ohmori: Method for Obtaining the Rate Constant of a Reversible Reaction.

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When a homogeneous chemical reaction is followed by the change of some physical property, a pseudo-first-order kinetic treatment is usually applied because of its mathematical simplicity, and the apparent rate constant is generally calculated by a graphical method. Roseveare,[1] however, pointed out that in a reaction in which the rate is represented by the equation, $dx/dt=k(a-x)\pm k'(b-x)$, where a and b are constants, a straight line is obtainable by an ordinary first-order plot of $\ln(a-x)$ *vs.* time, or by Guggenheim's plot. Thus, when the above methods are applicable, it must be ascertained whether there is any contribution from the second term.

Further, we recognized that the above treatments for a reaction expressed by a rate expression, $-dx/dt=k(a-x)-k'x^2$, also gave an almost linear plot from which an approximate rate constant k was obtainable.

In a reversible reaction (1),

$$\mathrm{X} \overset{k}{\rightleftarrows} \mathrm{Y}+\mathrm{Z} \tag{1}$$

the forward rate constant, k, can be obtained from eq. (2)

$$\ln\frac{x_0^2-xx_e}{x_0(x-x_e)}=k\left(\frac{x_0+x_e}{x_0-x_e}\right)t \tag{2}$$

where x expresses the concentration of X at time t and the subscripts 0 and e refer to the initial and equilibrium concentrations, respectively.[2] The concentration of Y and Z are zero when $t=0$. When β represents the amount of some physical property of X at time t, which is proportional to the concentration, $\beta=ax$ where a is a proportionality constant. Thus eq. (2) becomes

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1) W. E. Roseveare: J. Am. Chem. Soc., **53**, 1651 (1931).

2) A. Frost, R.G. Pearson: "Kinetics and Mechanisms," 2nd Ed. p. 187. John Wiley & Sons, Inc., London.

$$\ln \frac{\beta_0^2-\beta\beta_e}{\beta_0(\beta-\beta_e)}=k\left(\frac{\beta_0+\beta_e}{\beta_0-\beta_e}\right)t. \tag{3}$$

It follows that

$$\ln(\beta-\beta_e)=\ln \frac{\beta_0^2-\beta_e^2}{\beta_0 \exp(krt)+\beta_e} \tag{4}$$

where $r=\dfrac{\beta_0+\beta_e}{\beta_0-\beta_e}$.

When $\beta_0 \exp(krt) \gg \beta_e$, eq. (4) can be simplified to

$$\ln(\beta-\beta_e)=\ln(\beta_0^2-\beta_e^2)/\beta_0-krt, \tag{5}$$

so that by plotting $\ln(\beta-\beta_e)$ against time t a straight line with a slope equal to S_1 is obtained,

$$S_1=-kr=-k(\beta_0+\beta_e)/(\beta_0-\beta_e). \tag{6}$$

When $t \geqq 0$, eq. (4) would follow a curve like that of A shown in Fig. 1, in which the scales are arbitrary.

As seen from (4) and (5), at the upper limit of t curve A approaches line B to infinity; that is line B in Fig. 1 is an asymptote of curve A.

Differentiation of eq. (4) yields

$$-\frac{d\ln(\beta-\beta_e)}{dt}=\frac{d\ln(\beta_0 \exp(krt)+\beta_e)}{dt}=\frac{\beta_0 kr \exp(krt)}{\beta_0 \exp(krt)+\beta_e}. \tag{7}$$

Then the slope, S_2, of line C in Fig. 1, the tangent of curve A at $t=0$, is

$$S_2=-\beta_0 kr/(\beta_0+\beta_e)=-\beta_0 k/(\beta_0-\beta_e). \tag{8}$$

Therefore, the slope S of a line made by combining the point at $t=0$ and any other point on curve A, is

$$-\beta_0 k/(\beta_0-\beta_e)=S_2>S>S_1=-(\beta_0+\beta_e)k/(\beta_0-\beta_e). \tag{9}$$

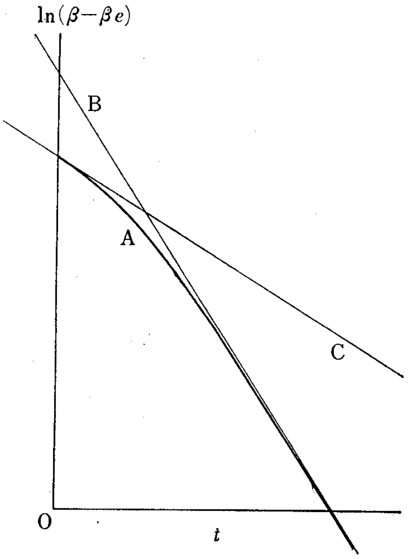

Fig. 1. Schematic Curve for Eq. (4)

Curve A represents a plot of $\ln(\beta-\beta_e)$ against time, line B is the asymptote of curve A for $t=\infty$, and line C is the tangent of curve A at $t=0$.

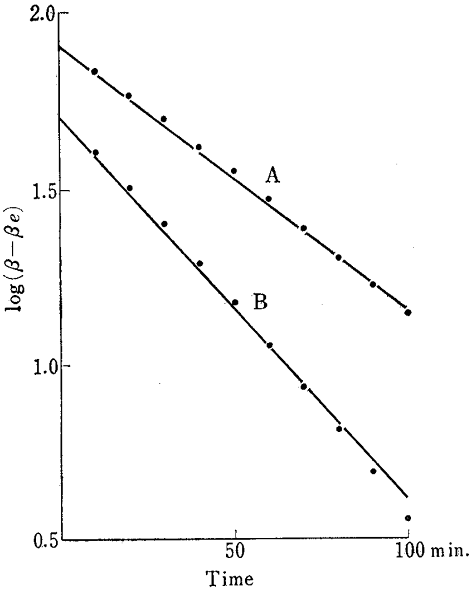

Fig. 2. Pseudo-first-order Plots for Reversible Reactions like Eq. (1) with $\beta_e=\beta_0/3$ (A) and $\beta_e=\beta_0/2$ (B)

When over 90% of the reaction has occurred, $\beta_0 \exp(krt) \gg \beta_e$ is mostly satisfied, and hence eq. (5) may be realized. Under ordinary experimental conditions, however, it is not possible to get a rate constant from the data obtained in such a region, because of the large experimental error relative to the amount of change in the concentration.

On the other hand, when the proportion of β_e to β_0 becomes smaller, the range of S in eq. (9) becomes narrower, or the plot of $\ln(\beta-\beta_e)$ *vs.* time t becomes a better fit of a straight line. For example, when $\beta_e \leqq \beta_0/3$, an almost straight line with a deviation which is well within the limits of experimental error is obtained. In such a case, the forward rate constant k can be estimated approximately by dividing the slope S of the line by $-(2\beta_0+\beta_e)/2(\beta_0-\beta_e)$, the arithmetic mean of S_1 and S_2 in eq. (9). The deviation of the approximate value obtained when $\beta_e=\beta_0/3$ from the correct value calculated from eq. (3) is not more than 100/7%.*[2] In Fig. 2, two hypothetical runs with $\beta_e=\beta_0/2$ and $\beta_e=\beta_0/3$ are illustrated. The rate constants calculated by using the above procedure and the straight line drawn through the point at $t=0$ and that at 80% completion of the reaction are found to be $9.77 \times 10^{-3}\ \text{min}^{-1}$ and $9.92 \times 10^{-3}\ \text{min}^{-1}$ for $\beta_e=\beta_0/3$ and $\beta_e=\beta_0/2$, respectively, whereas the true rate constant is assumed to be $10.00 \times 10^{-3}\ \text{min}^{-1}$ in each case.*[3]

The experimental data for the hydrolysis of Girard hydrazones in aqueous solution were treated by the present method and, in Table I, the rate constants obtained for benzaldehyde and phenylacetaldehyde Girard hydrazone are compared with those calculated by using the ordinary treatment involving eq. (3).

Table I. Forward Pseudo-first-order Rate Constants obtained by the Present Method and eq. (3) for the Hydrolysis of Benzaldehyde and Phenylacetaldehyde Girard Hydrazone at 25° in Various Buffer Solutions containing 2% Ethanol

$\text{R-CH=N}\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{N}^+(\text{CH}_3)_3\text{Cl}^-$

R	pH	$k_{\text{obs.}}\ (\text{min}^{-1}) \times 10^3$ by the present treatment	$k_{\text{obs.}}\ (\text{min}^{-1}) \times 10^3$ from eq. (3)	β_e/β_0
C_6H_5	1.96	42.6	43.7	0.21
	4.00	2.28	2.21	0.30
$C_6H_5CH_2$	3.91	283	294	0.24
	5.45	24.7	24.2	0.20
	7.60	3.40	3.56	0.13
	7.97	3.99	4.01	0.14
	8.54	5.60	5.68	0.15
	8.96	7.31	7.33	0.16
	9.39	14.6	14.9	0.21
	10.00	20.8	20.1	0.30
	10.50	15.1	15.6	0.37

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*[2] When accurate values of β_0 and β_e are obtained, it is apparent from eq. (9) and Fig. 1 that the largest error in the rate constant resulting from the above treatment is $-S\left(\frac{2(\beta_0-\beta_e)}{2\beta_0+\beta_e}-\frac{\beta_0-\beta_e}{\beta_0+\beta_e}\right)$ or $-S\left(\frac{\beta_0-\beta_e}{\beta_0}-\frac{2(\beta_0-\beta_e)}{2\beta_0+\beta_e}\right)$; and the true rate constants are $-S(\beta_0-\beta_e)/(\beta_0+\beta_e)$ and $-S(\beta_0-\beta_e)/\beta_0$, respectively. If $\beta_e=\beta_0/a$, where a is a constant, the largest errors are $-S(a-1)/(a+1)(2a+1)$ and $-S(a-1)/a(2a+1)$, respectively, and the relative error is $100/(2a+1)$% of the true value in either case.

*[3] Although the value for $\beta_e=\beta_0/2$ unexpectedly became closer to the true value, the degree of error may generally be greater than that for $\beta_e=\beta_0/3$, because of the larger curvature. The increased curvature also increased the inaccuracy in estimating a value extrapolated to zero time.

In the case of the hydrolysis of *p*-chlorobenzaldehyde Girard hydrazone excellent linear plots of $\log(\beta-\beta_e)$ *vs.* t were obtained at pH 1.03, 1.53 and 2.01. The apparent pseudo-first-order rate constants, $k_{obs.}$, directly estimated from the slopes of the straight lines are listed in Table II. In spite of the good linearity and the reasonable assumption, deduced by analogy with the case of benzaldehyde Girard hydrazone,[3] that the reaction should depend on the first power of the hydronium ion concentration, these values are not strictly first-order with respect to the hydronium ion concentration.[*4] However, the values of $k_{obs.corr.}$ obtained by dividing the values of $k_{obs.}$ by $(2\beta_0+\beta_e)/2(\beta_0-\beta_e)$ which are listed in the third column of Table II show much better first-order dependence on the hydronium ion concentration : the values of β_e are measured directly and those of β_0 are estimated by extrapolation to zero time.

Table II. Forward Pseudo-first-order Rate Constants, $k_{obs.}$ obtained directly from the Plots of $\log(\beta-\beta_e)$ *vs.* Time and $k_{obs.corr.}$ obtained by Correcting $k_{obs.}$ by the Present Method, for the Hydrolysis of *p*-Chlorobenzaldehyde Girard Hydrazone at 25° in HCl-KCl Buffer Solutions containing 2% Ethanol

pH	$k_{obs.}$ (min^{-1}) $\times 10^2$	$k_{obs.corr.}$ (min^{-1}) $\times 10^2$	β_e/β_0
1.03	28.5	26.9	0.04
1.53	9.57	8.05	0.11
2.01	3.83	2.70	0.22

When a reversible reaction, such as that represented in eq. (1), is followed by some physical property, the rate constant can be obtained from eq. (2) or eq. (3) without estimating the extrapolated value of β_0, provided that the physical property is proportional to the concentration of the species followed and the proportionality constant is accessible. The proportionality constant, however, may vary with experimental conditions such as the pH of the reaction mixture, the solvent and the temperature. When the reaction is to be followed by the change in X, the foward rate constant k is, therefore, calculated, in general, from the initial part of the reaction or from eq. (3) using an estimated value of β_0.

However, if the reaction is faster, the error of the measurement at the beginning of the reaction increases; moreover, since the uncertainty of the value of β_0 in such a case is probably very large, it seems unlikely that the general method would give a better result than the present method. We believe that the present method involving much less arithmetical work than in that involving eq. (3) is to be recommended for studies in which many runs must be made.

As in the case of *p*-chlorobenzaldehyde Girard hydrazone, a plot of $\log(\beta-\beta_e)$ *vs.* time may sometimes gives a very good straight line though a reversible process of the type shown in eq. (1) is actually operative. In this case the rate constant k calculated from the slope of the line is always too large. Therefore, it is necessary to correct the value by the present method, or to estimate k by the usual method, represented in eq. (3). When a plot is made according to Guggenheim's method, the same procedure must be carried out.

[*4] This is not due to the occurrence of over all general acid catalysis, since the reaction were carried out in HCl-KCl systems.

3) M. Masui, H. Ohmori : unpublished data.

Experimental

Girard hydrazones were prepared as described previously.[4] Other materials were of reagent grade unless otherwise specified. Kinetic measurements were made polarographically at 25±0.1° as described previously with a Yokogawa Polarograph, type POL-11.[5] pH values were measured by a Tōadempa, model HM-5A, pH meter with a glass-saturated calomel electrode.

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UDC 547.751.07

Yoshio Ban, Takeshi Oishi, Yoshiko Kishio, and Ikuo Iijima :

The Fischer Indole Synthesis with Formic Acid. I. A Convenient Synthesis of 4a-Ethyl-9-formyl-1,2,3,4,4a,9a-hexahydro-9*H*-carbazole.

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Various procedures including thermal cyclizations are available for the Fischer indole synthesis.[1] Formic acid has been sometimes used as an effective catalyst for this reaction as well as acetic acid or propionic acid.[2]

It seems, however, not to be known in the literature that anhydrous (98∼100%) formic acid has been used for indolization of 2-alkylcyclohexanone arylhydrazone (for instance, I). In this reaction with the other catalysts, there produces a mixture of indolenine and indole (as are exemplified by Ⅲ and Ⅳ, respectively), the relative quantities of which have been found to be dependent upon the catalyst used.[3,4]

In connection with the synthetic studies on aspidosperma alkaloids,[5] it became necessary for us to effect the smooth Fischer indolization of 2-substituted cyclohexanone arylhydrazone with the more predominant formation of indolenine rather than indole.

Thus, as a preliminary, a solution of the phenylhydrazone (I, 1 mole eq.), freshly prepared from 2-ethylcyclohexanone and without purification,[2a] in 98∼100% formic acid (5 mole eq.) was refluxed for 45 min., during which time evolution of carbon dioxide was observed. The resulting mixture was separated into two portions, the neutral and the basic, in the usual manner. The neutral material was purified twice by chromatography on alumina and the elution with *n*-hexane-benzene (3:1) yielded a main fraction of pale red oil (63.7% yield), which was unexpectedly identified, by comparison of ultraviolet and infrared spectra, with the N-formylindoline (Ⅱ), the entitled compound, prepared from

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