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Aromatic Nucleophilic Substitution. XVIII.[1] Kinetics of Reactions of 2-(Acetylamino)ethyl 2,6-Dinitrophenyl Ether and *N*-Acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline with Sodium Isopropoxide

Shizen Sekiguchi,* Motohiko Hirai, and Noboru Tomoto†
Department of Synthetic Chemistry, Gunma University, Kiryu, Gunma 376
† *Department of Industrial Chemistry, Miyazaki University, 1-1-1 Kirishima, Miyazaki, Miyazaki 880*

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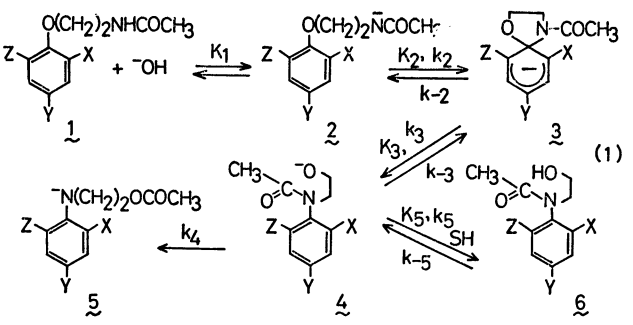
The kinetics of the reactions of 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (Smiles rearrangement) and *N*-acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline with sodium isopropoxide in the DMSO-2-propanol mixture (20 : 80 v/v) was studied. Both reactions were found to rapidly produce the same spiro anionic σ complex, giving *N*-(2-acetoxyethyl)-2,6-dinitroaniline. Although the rates for formation of the complex were different in both reactions, the rates for rearrangement were the same.

Previously we reported the OH⁻-catalyzed Smiles rearrangement of 2-(acetylamino)ethyl 2-X-4-nitrophenyl ether (**1a** X=Y=NO_2, Z=H; **1b** X=Br, Y=NO_2, Z=H; **1c** X=CN, Y=NO_2, Z=H), where the process **1**$\rightleftarrows$**2**$\rightleftarrows$**3** was very fast and the one **3**$\rightleftarrows$**4**$\rightarrow$**5** relatively slow (Scheme 1).[2–5]



Scheme 1.

Hence, the former process (hereafter called Stage 1) can be followed by stopped-flow technique, whereas the latter (hereafter called Stage II) can be done by usual spectrophotometry.

As shown in previous work,[1] no information on the K_3 and K_5 processes was obtained in the kinetics of rearrangement of **1**.[3,5]

Although the kinetics of the reaction of **6** with bases should give such detailed information, the synthesis of **6a**, **6b**, and **6c** has been unsuccessful. More recently *N*-acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline [**6d** (X=Z=NO_2; Y=H)] has been synthesized.[1]

As the UV-VIS and NMR time-dependent spectra of the base-catalyzed rearrangements of 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (**1d**, X=Z=NO_2, Y=H) and **6d** showed the reaction path shown in Scheme 1,[1] this paper reports the kinetics of the reactions of **1d** and **6d** with $NaOCH(CH_3)_2$ in the DMSO–2-propanol mixture (20:80 v/v) in order to elucidate the detailed reaction processes.

Results

*Stage I. Rearrangement of 2-(Acetylamino)ethyl 2,6-Dinitrophenyl Ether (**1d**)*: In carrying out the kinetic measurement of Stage I, one can neglect Stage II reaction. Accordingly, in the presence of excess $NaOCH(CH_3)_2$ the apparent first-order rate constant (k_ψ^0) for formation of **3d** is expressed in Eq. 2. If $K_1[NaOCH(CH_3)_2] \ll 1$, Eq. 3 is derived. Table 1

$$k_\psi^0 = k_{-2} + \frac{k_2K_1[NaOCH(CH_3)_2]}{1+K_1[NaOCH(CH_3)_2]} \tag{2}$$

$$k_\psi^0 = k_{-2} + k_2K_1[NaOCH(CH_3)_2] \tag{3}$$

shows the dependence of k_ψ^0 on $[NaOCH(CH_3)_2]$, which is illustrated in Fig. 1. The results in Fig. 1 are compatible with Eq. 3. As a result, the k_{-2} and k_2K_1 values can be estimated from the intercept and slope in the linear plots, respectively (Table 3).

Table 1. Rate constants for formation and decomposition of spiro anionic σ complex formed from 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (**1d**) and sodium isopropoxide in the DMSO–2-propanol mixture (20:89 v/v)[a)]

Temp / °C	$10^3[NaOCH(CH_3)_2]$ / M	k_ψ^0 [b)] / s^{-1}
15	1.77	0.490±0.081
	3.54	0.851±0.023
	5.90	1.91 ±0.04
	8.85	2.50 ±0.05
	11.8	3.80 ±0.13
	18.9	5.99 ±0.11
25	2.63	1.61 ±0.01
	5.25	3.82 ±0.07
	7.88	6.36 ±0.42
	10.5	8.16 ±0.09
	15.8	13.8 ±0.2
	20.3	15.0 ±0.4
	24.6	18.7 ±0.8
35	2.63	3.07 ±0.18
	5.25	7.70 ±0.2
	7.88	11.8 ±0.5
	9.40	14.0 ±0.6
	10.5	16.0 ±0.6
	15.8	22.6 ±0.8
	18.9	27.1 ±1.4

a) $[\mathbf{1d}]_0$ 3.67×10^{-5} M (≡mol dm^{-3}); μ 0.04 M ($NaClO_4$). b) Measured at 580 nm (λ_{max} for **3d**) with a stopped-flow method.

Rearrangement of N-*Acetyl*-N-*(2-hydroxyethyl)-2,6-dinitroaniline (**6d**)*: In the reaction of **6d** with $NaOCH(CH_3)_2$ the fast process **6d**$\rightleftarrows$**4d**$\rightleftarrows$**3d** occurs first, followed by the comparatively slow one **3d**$\rightleftarrows$**4d**$\rightleftarrows$**5d**.[1] Accordingly the similar kinetic procedure applies aptly

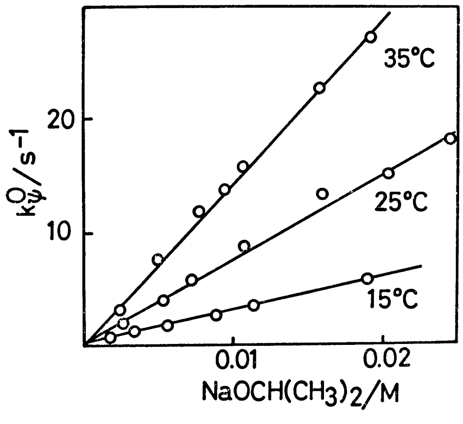


Fig. 1. Relationship between k^{o}_{ψ} and $[\mathrm{NaOCH(CH_3)_2}]$ in the reaction of 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (**1d**) with $\mathrm{NaOCH(CH_3)_2}$ in the DMSO-2-propanol mixture (20:80 v/v) [μ 0.04 M ($\mathrm{NaClO_4}$)].

Table 2. Rate constants for formation and decomposition of spiro anionic σ complex formed from *N*-acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline (**6d**) in the DMSO-2-propanol mixture (20:80 v/v)[a)]

Temp / °C	$10^3[\mathrm{NaOCH(CH_3)_2}]$ / M	k^{N}_{ψ} [b)] / s^{-1}
20	4.40	293± 7
	6.75	444±11
	9.38	695±17
	11.3	844±21
	15.2	1204±30
	20.2	1514±38
	27.4	1947±49
	33.0	2393±84
30	4.30	630±19
	5.50	841±25
	6.75	931±28
	9.38	1468±51
	10.8	1559±55
	12.9	1896±76
	17.2	2399±84
40	4.30	1063±43
	6.75	1627±65
	9.38	2175±87
	10.8	2479±109

a) $[\mathbf{6d}]_0$ 3.71×10^{-5} M; μ 0.04 M ($\mathrm{NaClO_4}$). b) Measured at 580 nm ($\lambda_{\max}$ for **3d**) with a stopped-flow method.

Table 3. Temperature dependence of k_2K_1, k_{-2}, K_1K_2, $k_{-3}K_5^{-1}$, k_3, and $K_5^{-1}K_3^{-1}$ for formation and decomposition or spiro anionic σ complexes formed from 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (**1d**) or *N*-acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline (**6d**) and sodium isopropoxide in the DMSO-2-propanol mixture (20:80 v/v)[a)]

Temp / °C	k_2K / $\mathrm{M^{-1}\,s^{-1}}$	k_{-2} / $\mathrm{s^{-1}}$	$10^3\,K_1K_2$ [b)] / $\mathrm{M^{-1}}$
		1d	
15	326±17	—	—
25	774±43	0.12±3.86	6.4
35	1460±90	0.60±1.31	2.4
	$10^{-4}\,k_{-3}\,K_5^{-1}$ / $\mathrm{M^{-1}\,s^{-1}}$	k_3 / $\mathrm{s^{-1}}$	$10^{-3}\,K_5^{-1}\,K_3^{-1}$ [b)] / $\mathrm{M^{-1}}$
		6d	
15	5.66±0.06	7.86±4.43	7.2
20	7.10±0.12	25.8±13.2	2.8
30	13.6±0.2	62.8±10.7	2.2
40	11.8±0.1	135±40	—

a) $[\mathbf{1d}]_0$ 3.67×10^{-5} M; $[\mathbf{6d}]_0$ 3.71×10^{-5} M; μ 0.04 M ($\mathrm{NaClO_4}$). b) Calculated from $K_1K_2=k_2K_1/k_{-2}$ and $K_3^{-1}K_5^{-1}=k_{-3}K_5^{-1}/k_3$ by using the mean values, respectively.

in this case, too. As a result, the following expression can be derived as to the apparent first-order rate constant (k^{N}_{ψ}) for formation of **3d** in the presence of excess $\mathrm{NaOCH(CH_3)_2}$ (note the relationship between the directions of reactions and rate or equilibrium constants).

$$k^{\mathrm{N}}_{\psi} = k_3 + \frac{\dfrac{k_{-3}}{K_5}[\mathrm{NaOCH(CH_3)_2}]}{1+\dfrac{1}{K_5}[\mathrm{NaOCH(CH_3)_2}]} \tag{4}$$

Therefore, the plot of k^{N}_{ψ} against $[\mathrm{NaOCH(CH_3)_2}]$ would show the curvilinear dependence asymptotically approaching the fixed value unless $[\mathrm{NaOCH(CH_3)_2}]/K_5\gg1$. If $[\mathrm{NaOCH(CH_3)_2}]/K_5\ll1$, however, the linear dependence should be obtained (Eq. 5). Table 2

$$k^{\mathrm{N}}_{\psi} = k_3 + \frac{k_{-3}}{K_5}[\mathrm{NaOCH(CH_3)_2}] \tag{5}$$

shows the linear dependence of k^{N}_{ψ} on $[\mathrm{NaOCH(CH_3)_2}]$ (not shown), giving the k_3 and k_{-3}/K_5 values from the intercept and slope in the linear plots (Table 3).

Table 3 shows the temperature dependence of k_2K_1, k_{-2}, $k_{-3}K_5^{-1}$, k_3, $K_3^{-1}K_5^{-1}$ for formation and decomposition of **3d**. Comparison of k_{-2} with k_3 shows that **3d** proceeds to **4d** faster than reverts to **2d**, which is compatible with the fact that alkoxyl groups of activated aromatics are easily displaced with amines.[6–8)]

*Stage II. Rearrangement of 2-(Acetylamino)ethyl 2,6-Dinitrophenyl Ether (**1d**)*: In treatment of the kinetics of Stage II, Stage I reaction can be regarded as a fast mobile equilibrium lying almost entirely on the right (Table 3). Accordingly, as to the rate of Stage II reaction ($k^{\mathrm{o}}_{\mathrm{obsd}}$ apparent first-order rate constant for rearrangement of **1d**) the following expression is obtained in the presence of excess $\mathrm{NaOCH(CH_3)_2}$, provided that the k_4 stage is rate-determining and the K_5 and K_3 stages are fast mobile equilibria (Table 4).

$$k^{\mathrm{o}}_{\mathrm{obsd}} = \frac{k_4K_1K_2K_3[\mathrm{NaOCH(CH_3)_2}]}{\left(\begin{array}{l}1+K_1K_2K_3K_5+(K_1+K_1K_2\\ \qquad +K_1K_2K_3)[\mathrm{NaOCH(CH_3)_2}]\end{array}\right)} \tag{6}$$

Although the relationship between $k^{\mathrm{o}}_{\mathrm{obsd}}$ and $[\mathrm{NaOCH(CH_3)_2}]$ is curvilinear (asymptotically approaching the fixed value), Eq. 7 would hold, if $(K_1+K_1K_2+K_1K_2K_3)\times[\mathrm{NaOCH(CH_3)_2}]\gg1+K_1K_2K_3K_5$. Therefore, $k^{\mathrm{o}}_{\mathrm{obsd}}$ is independent of $[\mathrm{NaOCH(CH_3)_2}]$ (Fig. 2). The re-

Table 4. Rate constants for rearrangement of 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (**1d**) in the DMSO-2-propanol mixture (20:80 v/v)[a]

Temp °C	10^3[NaOCH(CH$_3$)$_2$] M	$10^4 k^{\mathrm{O}}_{\mathrm{obsd}}$[b] s^{-1}
20	3.42	1.30
	5.13	1.31
	6.84	1.13
	19.5	1.17
	34.2	1.11
	39.0	1.13
30	4.20	4.16
	5.13	3.91
	8.40	4.08
	12.6	3.90
	19.3	4.09
40	3.42	10.7
	5.13	11.8
	6.84	11.4
	19.3	10.5
	34.3	11.0

a) [**1d**]$_0$ 5.88×10^{-5} M; μ 0.04 M (NaClO$_4$). b) Estimated limit of error $\pm1.5\%$; measured at 580 nm ($\lambda_{\max}$ for **3d**).

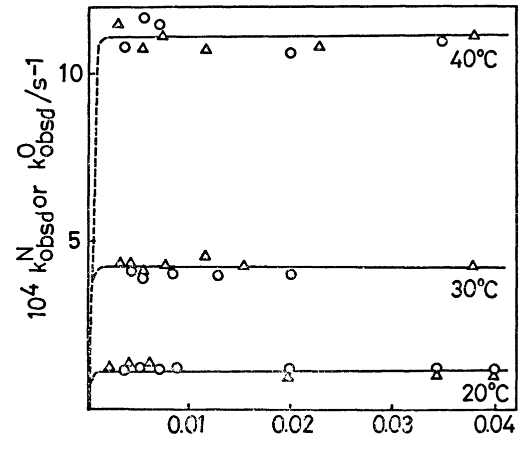


Fig. 2. Relationship between $k^{\mathrm{O}}_{\mathrm{obsd}}$ or $k^{\mathrm{N}}_{\mathrm{obsd}}$ and [NaOCH(CH$_3$)$_2$] in the reaction of 2-(acetylamino)ethyl 2,6-dinitrophenyl ether (**1d**) or *N*-acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline (**6d**) with NaOCH(CH$_3$)$_2$ in the DMSO-2-propanol mixture (20:80 v/v) [μ 0.04 M (NaClO$_4$)]: ○ $k^{\mathrm{O}}_{\mathrm{obsd}}$; △ $k^{\mathrm{N}}_{\mathrm{obsd}}$.

sults in Table 4 are compatible with Eq. 7.

$$k^{\mathrm{O}}_{\mathrm{obsd}} = \frac{k_4K_2K_3}{1+K_2+K_2K_3} \tag{7}$$

Rearrangement of N-*Acetyl*-N-*(2-hydroxyethyl)-2,6-dinitroaniline (**6d**)*: In the rearrangement of **6d**, the process **6d**$\rightleftarrows$**4d**$\rightleftarrows$**3d** is very fast, and the one **3d**$\rightleftarrows$**4d**$\rightarrow$**5d** relatively slow.[1] Therefore, in the kinetics of Stage II the K_3 and K_5 stages can be regarded as fast mobile equilibria. Accordingly, as to the rate of Stage II ($k^{\mathrm{N}}_{\mathrm{obsd}}$ apparent first-order rate constant for rearrangement of **6d**) Eq. 8 is obtained in the presence of excess

Table 5. Rate constants for rearrangement of *N*-acetyl-*N*-(2-hydroxyethyl)-2,6-dinitroaniline [**6d**] in the DMSO-2-propanol mixture (20:80 v/v)[a]

Temp °C	10^3[NaOCH(CH$_3$)$_2$] M	$10^4 k^{\mathrm{N}}_{\mathrm{obsd}}$[b] s^{-1}
20	1.78	1.46
	3.56	1.46
	5.34	1.42
	8.90	1.40
	19.7	1.13
	34.3	1.12
	39.0	1.12
30	3.68	4.46
	3.80	4.40
	5.52	4.05
	7.60	4.30
	11.4	4.72
	15.2	4.30
	38.6	4.14
40	2.97	11.6
	5.57	10.7
	7.00	11.1
	11.4	10.7
	22.8	10.8
	38.6	11.3

a) [**6d**]$_0$ 1.32×10^{-5} M; μ 0.04 M (NaClO$_4$). b) Estimated limit of error $\pm1.5\%$; measured at 580 nm ($\lambda_{\max}$ for **3d**).

$$k^{\mathrm{N}}_{\mathrm{obsd}} = \frac{\dfrac{k_4}{K_5}[\mathrm{NaOCH(CH_3)_2}]}{1+\dfrac{1}{K_5}\left(1+\dfrac{1}{K_3}\right)[\mathrm{NaOCH(CH_3)_2}]} \tag{8}$$

NaOCH(CH$_3$)$_2$, indicating the curvilinear dependence of $k^{\mathrm{N}}_{\mathrm{obsd}}$ on [NaOCH(CH$_3$)$_2$] (asymptotically approaching the fixed value). Under the condition $1/K_5(1+1/K_3)[\mathrm{NaOCH(CH_3)_2}]\gg1$, Eq. 9 is obtained, indicating that $k^{\mathrm{N}}_{\mathrm{obsd}}$ is independent of [NaOCH(CH$_3$)$_2$]. Equation 9 is compatible with the results in Table 5.

$$k^{\mathrm{N}}_{\mathrm{obsd}} = \frac{k_4K_3}{1+K_3} \tag{9}$$

Most interestingly the $k^{\mathrm{N}}_{\mathrm{obsd}}$ values are nearly equal to the $k^{\mathrm{O}}_{\mathrm{obsd}}$ ones at each [NaOCH(CH$_3$)$_2$] (Fig. 2), which shows that either **1d** or **6d** is catalyzed with [NaOCH(CH$_3$)$_2$] to substantially change into **3d** at first, and then undergoes the rearrangement, giving **5d**.

Discussion

Stage I. With **1d** and **6d** the k_2, K_1, k_{-3}, and K_5 values can not be estimated separately from Eqs. 3 and 5. With **6d**, however, the k_3, k_{-3}, and K_5 values at 15 °C could be determined as follows: when the rate measurement was carried out at higher [NaOCH(CH$_3$)$_2$], the relationship between k^{N}_{φ} and [NaOCH(CH$_3$)$_2$] was found to be curvilinear (asymptotically approaching the fixed value), in which the different ionic strengths did not affect the rate (Fig. 3). The result is compatible with Eq. 4. If the k_3 value (7.86 s^{-1}) can be obtained by extrapolation of [NaOCH(CH$_3$)$_2$]$\rightarrow$0 in Eq. 4, one can derive the following

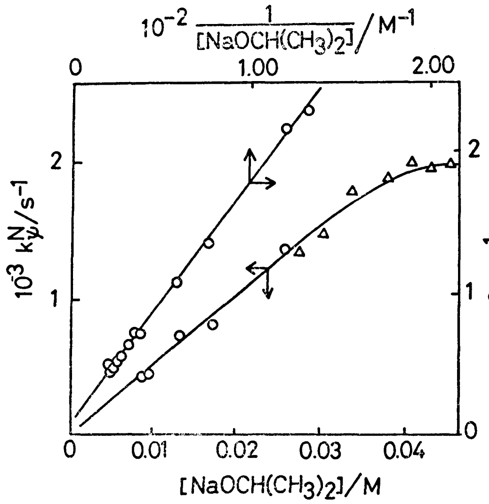


Fig. 3. Relationships between k_ψ^N and $[NaOCH(CH_3)_2]$ and between $1/(k_\psi^N-7.86)$ between $1/[NaOCH(CH_3)_2]$ in the reaction of *N*-acetyl-*N*-(2-hydroxyethyl-2,6-dinitroaniline (**6d**) with $NaOCH(CH_3)_2$ in the DMSO-2-propanol mixture (80:20 v/v at 15 °C): ○ at $\mu = 0.04$ M ($NaClO_4$); △ at $\mu = 0.05$ M ($NaClO_4$); $[\mathbf{6d}]_0$ 3.71×10^{-5} M.

equation (Eq. 10) by substituting this value into Eq.

$$\frac{1}{k_\psi^N-7.86} = \frac{1}{k_{-3}} + \frac{K_5}{k_{-3}[NaOCH(CH_3)_2]} \tag{10}$$

4 and rearranging. Thus, k_{-3} and K_5 can be obtained from the slope and intercept in the plot of $1/(k_\psi^N-7.86)$ against $[NaOCH(CH_3)_2]$. The k_{-3}, K_5^{-1} (equilibrium constant for **6d**$\rightleftarrows$**4d**), and K_3^{-1} (equilibrium constant for **4d**$\rightleftarrows$**3d**) values were found to be 1.82×10^4 s^{-1}, 3.1 M^{-1}, and 2.3×10^3, respectively (all the values are average ones). As a result, the $K_3^{-1}K_5^{-1}$ value is calculated by using these values to be $7.1_3\times10^3$ M^{-1}, which is fairly in agreement with the value (7.2×10^3 M^{-1}) shown in Table 3. Furthermore, the K_5 value (0.32 M) is considered to be reasonable, compared with those by Hine and Hine[9] and Bowden,[10] although the solvents used are different. From these values, the equilibrium **3d**$\rightleftarrows$**4d** lies almost on the side of **3d**, indicating that such anionic σ complexes as **3d** having activating substituents at 2- and 6-positions are extermely stable.[2-5,11,12] The equilibrium **6d**$\rightleftarrows$**4d** was reasonably found to lie almost on the side of **4d**. Therefore, in the rearrangement of **1d**, the K_5 stage is considered to scarcely contribute to the process.

With **1d** such results as shown in Fig. 3 were not obtained. The K_1, k_2, and k_{-2} values, however, can be estimated with some accuracy. In a previous work on the rearrangement of 2-(acetylamino)ethyl 2-X-4-nitrophenyl ether (**1**),[3] those values were determined (for **1b**, k_2 1.18×10^2 s^{-1}, k_{-2} 1.10×10 s^{-1}, K_1 1.31×10^2 M^{-1}:; for the pyridyl derivative,[3] k_2 5.99×10^2 s^{-1}, k_{-2} 1.20×10 s^{-1}, K_1 9.33×10 M^{-1}).

2,6-Dinitrophenyl group is expected to be inferior in electron-withdrawing character to 2-X-4-nitrophenyl one owing to the steric hindrance. Accordingly the k_2 value is expected to be at least two orders or one in magnitude. Anyhow, the k_2 value is clearly smaller than the k_{-3} one, indicating that an alkoxide ion is superior in nucleophilicity to an acetamide ion, in which the negative charge on the nigrogen is reduced by the resonance effect of an acetyl group.

Stage II. Tables 4 and 5 interestingly show that k_{obsd}^O and k_{obsd}^N are almost the same within the experimental error.

The reason for this equality is as follows: the K_2 value is rationally expected to be far larger than one, based on the above discussion. Then, Eq. 7 is reduced to Eq. 11. As a result, k_{obsd}^O is equal to k_{obsd}^N (Eq. 9).

$$k_{obsd}^O = \frac{k_4K_3}{1+K_3}(=k_{obsd}^N) \tag{11}$$

In conclusion, almost **1d** or **6d** is base-catalyzed to change into **3d** (K_1K_2 and $K_3^{-1}K_5^{-1}$ in Table 3), which, then, slowly rearranges to **5d** at the same rate as if the process **1d**$\rightleftarrows$**2d**$\rightleftarrows$**3d** were irreversible.[7]

At the end, one remark should be added: since there are two isomers ([*Z*] and [*E*]) for **6d**,[1] the equilibrium and rate constants might be the results from the composite effect of each isomer. The above-mentioned discussion, however, would not be affected by this fact.

Experimental

Meterials. The compounds (**1d** and **6d**) were prepared according to the methods described in the literature.[1]

Rate Measurement. As regards the kinetics of formation and decomposition of the spiro anionic σ complex (**3d**), the transmittance of complex was measured in order to estimate the apparent pseudo-first-order rate constants (k_ψ^O and k_ψ^N) with a thermostatted Union RA-1300 Stopped-Flow Analyzer (Union Giken). The kinetic measurements for decomposition of the complex (rearrangement (k_{obsd}^O and k_{obsd}^N) were made on a thermostatted Hitachi Model 200-10 Spectrophotometer for following the decrease in the absorbance due to **3d**.

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