Aromatic Nucleophilic Substitution. 9.[1] Kinetics of the Formation and Decomposition of Anionic σ Complexes in the Smiles Rearrangements of *N*-Acetyl-β-aminoethyl 2-X-4-Nitro-1-phenyl or *N*-Acetyl-β-aminoethyl 5-Nitro-2-pyridyl Ethers in Aqueous Dimethyl Sulfoxide

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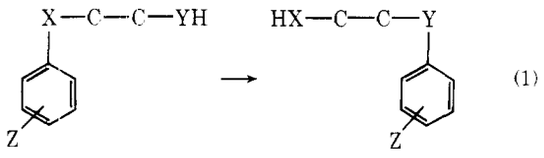
The kinetics of the base-catalyzed Smiles rearrangements of *N*-acetyl-β-aminoethyl 2-X-4-nitro-1-phenyl [X; NO_2 (**5**), Br (**8**), CN (**9**)] or *N*-acetyl-β-aminoethyl 4-nitro-2-pyridyl ether (**10**) in Me_2SO–H_2O have been studied. For all the substrates studied the anionic σ complexes were spectrophotometrically confirmed to intervene during the rearrangement process, and the rates of rearrangement were found to depend only on the decomposition process of the anionic σ complexes (independent of their formation process). The rate of rearrangement decreases in the order of **10** > **8** > **9** > **5**, and the rate of formation of the anionic σ complex decreases in the order of **5**, **9** > **10** > **8**.

Since the Smiles rearrangement was found by Henriques,[2] it has been developed by many workers, especially by Smiles.[3] The rearrangement is indicated as follows:

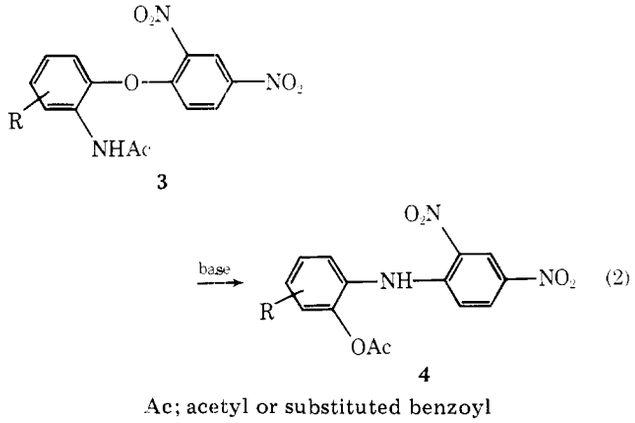


(1)

1 2

Z; activating group

Although the field has been recently reviewed,[4] there have been few studies on the detailed kinetics of rearrangements because of their mechanistic complexity.[5,6] McClement and Smiles[7] found that the base-catalyzed rearrangement of 2-hydroxy-2′-nitrodiphenyl sulfones to 2-sulfino-2′-nitrodiphenyl ethers is strongly accelerated by a 6-methyl group, which was interpreted to be attributable to its electronic effect, but Bunnett and Okamoto[6] reported that the rate of rearrangement of a 2-hydroxy-2′-nitrodiphenyl sulfone to a 2-(*o*-nitrophenoxy)benzenesulfinic acid is increased about 500 000-fold by the introduction of a methyl, chloro, or bromo substituent in the 6 position and that the origin of acceleration is not electronic but steric. Roberts and deWorms[8] carried out the Smiles rearrangement of 2-acylamidodiphenyl ethers **3** to 2-acyloxydiphenylamines **4** and concluded that the rate of rearrangement decreases with an increasing electron-attracting effect of the substituent in the phenyl or benzoyl group owing to the reduction in availability of the unshared electrons of an amido nitrogen (eq 2). Bernasconi et al.[9] have recently reported the kinetics of the base-catalyzed formation of the anionic σ complex from *N*-(β-hydroxy)ethyl-*N*-methyl-2,4-dinitroaniline and discussed the unusual (reverse) Smiles rearrangement.



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(2)

4

Ac; acetyl or substituted benzoyl

We have more recently carried out the base-catalyzed Smiles rearrangement of *N*-acetyl-β-aminoethyl 2,4-dinitrophenyl ether (**5**) to *N*-(β-acetyloxy)ethyl-2,4-dinitroaniline (**7**) in Me_2SO, where the Janovsky complex **6** was spectrophotometrically confirmed to intervene. The results suggested that the rearrangement takes place in two distinct stages and the kinetics in each stage could be spectrophotometrically followed.[10] Skarzewski and Skrowaczewska have recently reported the products in the reaction of various β-(*N*-acylamino)ethoxides or β-(amino)ethoxides with 2,4-dinitrofluorobenzene, which had resulted from an intramolecular Smiles rearrangement with the simultaneous migration of an acyl group from nitrogen to oxygen[11] as we already found in a similar phenomenon.[10] They could not, however, evidence the intervention of anionic σ complexes.

This paper reports the kinetics of the formation and decomposition of the anionic σ complexes in the base-catalyzed Smiles rearrangement of *N*-acetyl-β-aminoethyl nitrophenyl or nitropyridyl ethers and the effect of substituents in the 2 position of the phenyl group on the rate of rearrangement. On the basis of the kinetics, the decomposition of anionic σ complexes to products has been found to be rate determining in the rearrangement, which is interestingly independent of the formation of complexes and greatly contrasted with the results of the previous work.[6-8]

Results

Anionic σ Complexes in Base-Catalyzed Smiles Rearrangements of *N*-Acetyl-β-aminoethyl 2,4-Dinitro-1-phenyl (5), 2-Bromo-4-nitro-1-phenyl (8), 2-Cyano-4-nitro-1-phenyl (9), and 5-Nitro-2-pyridyl (10) Ethers in Me_2SO. The anionic σ complex [λ_{max} 347 (ε 14 300), 359 (ε 13 800), and 506 nm (ε 28 000)] formed in the tertiary-butanolic $KOC(CH_3)_3$-catalyzed rearrangement of **5** to **7** in Me_2SO was already described in the previous paper.[10] Figure 1 shows the spectral change when 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ is added to a Me_2SO solution of **8** (1.93×10^{-5} M). Curve d coincided in position and shape with the spectrum of **12** [λ_{max} 481 nm (ε 34 700)] obtained when excess tertiary-butanolic $KOC(CH_3)_3$ was added to a Me_2SO solution of *N*-(β-acetyloxy)ethyl-2-bromo-4-nitroaniline (**13**) under the same condition. Curve b can be attributed to the anionic σ complex **11**, because the stopped-flow method gave the same absorption spectrum as curve b when KOH was added to a Me_2SO–H_2O (96:4, v/v) solution of **8** (KOH 0.40×10^{-2} M; **8**

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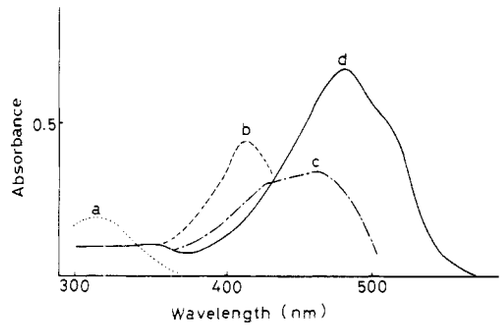
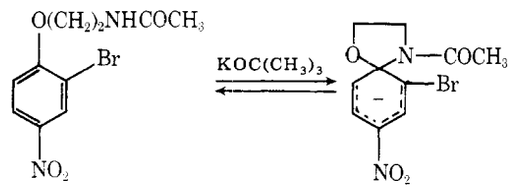
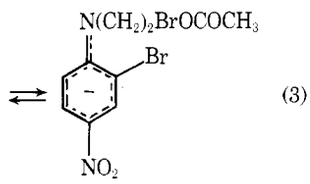


Figure 1. Absorption spectra relevant to the reaction of **8** with tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO at 25 °C. (a) **8** (1.93×10^{-5} M); b, c, and d monitered to the shorter wavelength region at 430, 500, and 600 nm, respectively, immediately after addition of 50 equiv of tertiary butanolic $KOC(CH_3)_3$ (chart speed 100 nm/1.67 min).

2.40×10^{-5} M) at the ionic strength (μ) of 0.1 ($KClO_4$) at 25 °C (Figure 2[12] and about the saponification of **12** refer to ref 16). Furthermore, the absorption spectrum of the anionic σ



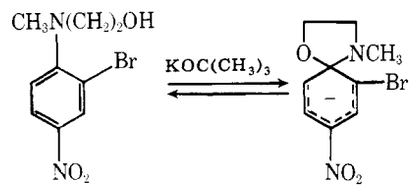
8 **11**



(3)

12

complex **15**, which is formed on addition of 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ to a Me_2SO solution of **14** and very



(4)

14 **15**

stable,[9,10] is similar in position and shape (λ_{max} 397 nm) to curve b. Hosoya et al.[13] already reported that the shape of absorption spectra of such complexes as **11** or **15** is little affected by the group attached to an amino nitrogen. These results, therefore, clearly indicate that curve b in Figure 1 is characteristic of the complex **11**.

The absorption spectra of the reaction of **9** (2.47×10^{-5} M) with 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO are shown in Figure 3, where curve b is attributed to the anionic σ complex **16** [λ_{max} 412 and 420 (sh) nm][9,10,13] and curve d to **17** [λ_{max} 475 nm (ϵ 30 600)]. These assignments were confirmed in a similar manner as with **8** (eq 4 and 6).

The reaction of **10** (2.68×10^{-5} M) with 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO gave only the spectrum of **22** [λ_{max} 461 nm (ϵ 28 400)] even at the faster chart speed, which is the same as that [λ_{max} 462 nm (ϵ 27 100)] obtained in the reaction of 2-[*N*-(β-acetyloxy)ethyl]amino-5-nitropyridine (**23**) with 50 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO. However, the stopped-flow method gave a similar spectrum

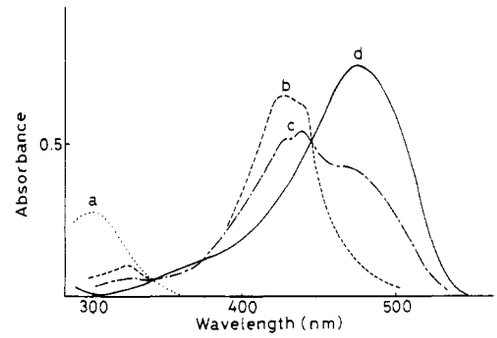
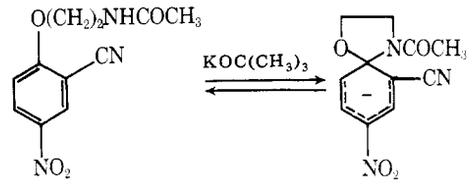
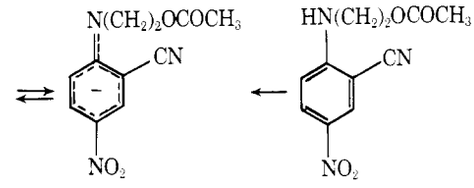


Figure 3. Absorption spectra relevant to the reaction of **9** with $KOC(CH_3)_3$ in Me_2SO at 25 °C: (a) **9** (2.47×10^{-5} M); b and c monitered to the shorter wavelength region at 500 and 600 nm, respectively, immediately after addition of 50 equiv of tertiary butanolic $KOC(CH_3)_3$ (chart speed 100 nm/1.67 min); (d) 5 min after addition of 50 equiv of tertiary butanolic $KOC(CH_3)_3$.

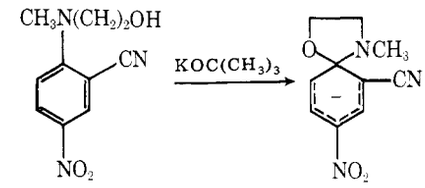


9 **16**



(5)

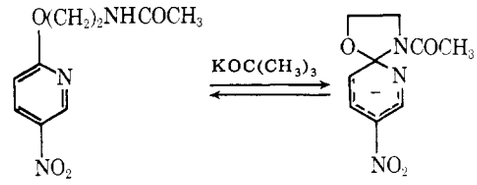
17 **18**



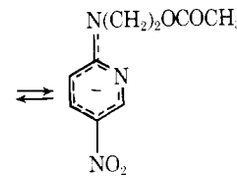
(6)

19 **20**

(λ_{max} 400 nm) to that [λ_{max} 406 nm (ϵ 20 900)] of the complex **25** formed in the reaction of 2-[*N*-(β-hydroxy)ethyl-*N*-



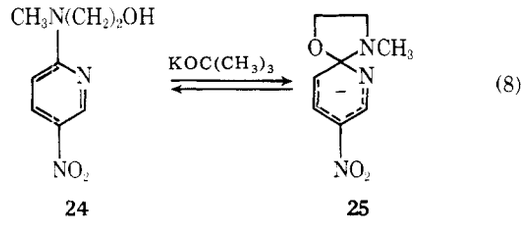
10 **21**



(7)

22

methyl]amino-5-nitropyridine (**24**) with 100 equiv of tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO under the same condition as with **10** (eq 8). These results indicate that **21** intervenes during the course of the reaction. From these results, we have found that the reaction of the substrate (**5**, **8–10**) with



24 25 (8)

$KOC(CH_3)_3$ in Me_2SO occurs in two observable stages: formation and decomposition of the anionic σ complex, the latter corresponding to the rearrangement.

Our observations will be shown later to be consistent with the mechanism of Scheme I, where hydroxide ion is used as a base.

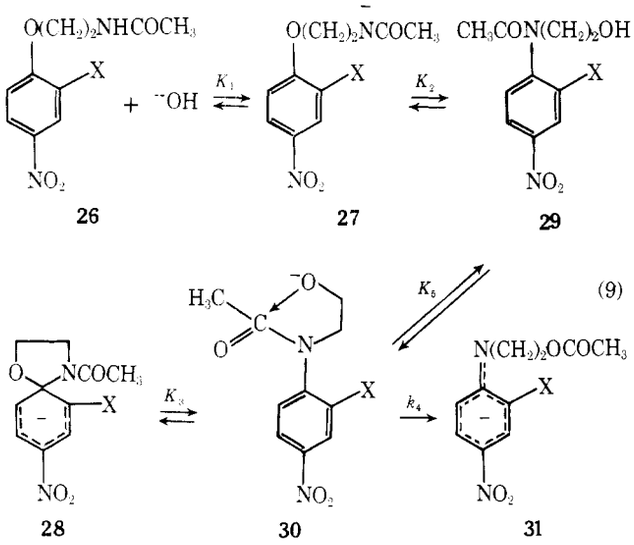
Rate Equations of Rearrangements. We rewrite Scheme I in a fashion more useful for quantitative discussions in Scheme II.

In Scheme II two rates are measurable (those of the formation and decomposition of **28**). Equations 10 and 13a pertain to proton abstraction equilibria which are rapidly established. Although **26**, an amide, functions as a weak acid,[14] the process (eq 10) occurs to some extent in strongly basic media as shown in the work of Hine and Hine[15] (in the case of 8 and **10**, [**27**]/[**26**] becomes 0.78 and 0.56, respectively, under the condition of $[^-OH] = 6 \times 10^{-3}$ M, based on the data as will be shown later). K_1K_2, therefore, is anticipated to be very large. K_5 can be resonably assumed to be very small. Under the present condition, therefore, the equilibria (eq 10 and 11, and 13a) lie almost entirely on **28** and **30**, respectively.

As will be shown later, the earlier stages (eq 10 and 11) are much faster than the later ones (eq 12 and 13), and, therefore, the earlier ones can be dealt with as equilibria in treatment of the kinetics of the later ones.

If the possibility that the substrate may be split among

Scheme I



Scheme II

$$26 + {}^-OH \underset{}{\overset{K_1}{\rightleftharpoons}} 27 \quad (10) \qquad 27 \underset{k_{-2}}{\overset{K_2}{\rightleftharpoons}} 28 \quad (11)$$

$$28 \overset{K_3}{\rightleftharpoons} 30 \quad (12) \qquad 30 \overset{K_5}{\rightleftharpoons} 29 \quad (13a)$$

$$30 \xrightarrow{k_4} 31 \quad (13b)$$

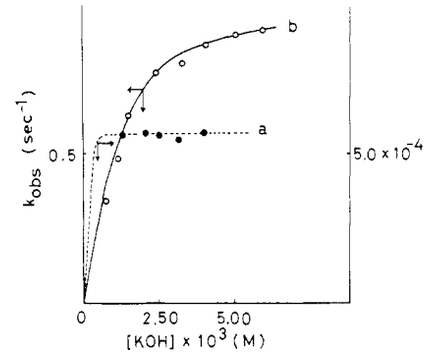


Figure 4. Relationship between k_{obsd} and [KOH] in the reactions of **5** (a, - - -) and **10** (b, —) with KOH in 96% Me_2SO at 25 °C: $[5]_0$ 3.0 × 10^{-5} M; $[10]_0$ 4.4 × 10^{-5} M; μ 0.1 ($KClO_4$).

27–30 is taken account of, for the rate of rearrangement the most general expression is as follows:

$$\text{rate} = k_{obsd}[26]_{st} = \frac{k_4K_1K_2K_3[^-OH][26]_{st}}{1 + K_1K_2K_3K_5 + (K_1 + K_1K_2 + K_1K_2K_3)[^-OH]} \quad (14)$$

Rearranging eq 14, one can derive

$$\frac{1}{k_{obsd}} = \frac{1 + K_1K_2K_3K_5}{k_4K_1K_2K_3[^-OH]} + \frac{1 + K_2 + K_2K_3}{k_4K_2K_3} \quad (15)$$

On the basis of plots of $1/k_{obsd}$ against $1/[^-OH]$, one can obtain $k_4K_1K_2K_3/(1 + K_1K_2K_3K_5)$ and $k_4K_2K_3/(1 + K_2 + K_2K_3)$ from slopes and intercepts. In the special case in which $(K_1 + K_1K_2 + K_1K_2K_3)[^-OH] \gg 1 + K_1K_2K_3K_5$, eq 14 simplifies to eq 16.

$$k_{obsd} = \frac{k_4K_2K_3}{1 + K_2 + K_2K_3} \quad (16)$$

Equation 16, therefore, indicates that the rate of rearrangement is zero-order in $[^-OH]$ under the above-described condition (Figure 4a). In the cases in which this condition is not fulfilled (Figure 4b), the curvilinear dependence of k_{obsd} on $[^-OH]$ will be found and consequently, k_{obsd} can be evaluated by the extrapolation of $1/[^-OH]$ to the intercept in the linear plot of $1/k_{obsd}$ against $1/[^-OH]$ (eq 15) (Figure 5[12]).

In all runs, the base (KOH) was in a large excess over the substrate concentration, which assures pseudo-first-order kinetics throughout.[16] Our data are summarized in Table I with activation parameters. In the case of 8 and **10** was found the curvilinear dependence of k_{obsd} on $[^-OH]$, and, consequently, the rate constants were obtained by use of inversion plots and found to be 3.58×10^{-2} and 1.10 s^{-1} for 8 and **10**, respectively (Figure 5[12]). Table I shows that the relative rate of rearrangement at 25 °C is 1, 62, 83, and 1900 for **5**, **8**, **9**, and **10**, respectively, and that it increases with decreasing electron-attracting effect of an ortho substituent, except for **10**. The order is reversed in the base-catalyzed rearrangement of 2-hydroxy-5-methyl-(2′-R-4′-nitro)diphenyl sulfone [R; NO_2 (very rapid) > C_6H_5CO > CO_2Na > H (very slow)] carried out by Galbraith and Smiles.[17] They concluded that their results were due to the easy formation of an anionic σ complex or a transition state by the electron-attracting effect of a 2′-R-group, even though it was not clear by way of which state the rearrangement proceeded. The result for **10** can be considered to be due to the absence of steric hindrance.

Thus, in our case it has been made clear that the rate of rearrangement increases, as an ortho substituent is less electron-attracting and less bulkier, which is different from the results of Bunnett and Okamoto,[6] too.

Rate Equations of Anionic σ Complex Formation (eq 10 and 11). In order to clarify whether the origin of the change

Table I. Kinetic Data Relevant to the Rearrangement

Substrate	Temp, °C	10^3 [KOH], M	k_{obsd}, s^{-1}	Rel rate	$\Delta H^{\ddagger}$, kcal·mol	$\Delta S^{\ddagger}$, e.u.
5[b]	20	6.0	3.28×10^{-4} [f]			
	25	1.2	5.84×10^{-4}			
		2.0	5.71×10^{-4}			
		2.4	5.76×10^{-4}	1	16.6	−18.1
		3.2	5.60×10^{-4}			
		4.0	5.94×10^{-4}			
	30	6.0	8.43×10^{-4} [f]			
	40	6.0	2.16×10^{-3} [f]			
8[c]	20	1.6	1.73×10^{-2}			
		2.4	1.83×10^{-2}			
		3.2	1.87×10^{-2}			
		4.0	1.96×10^{-2}			
		5.0	1.96×10^{-2}			
		6.0	2.00×10^{-2}			
	25	1.6	2.60×10^{-2}			
		2.4	2.98×10^{-2}			
		3.2	3.00×10^{-2}			
		4.0	3.06×10^{-2}	62	16.0	−11.5
		5.0	3.24×10^{-2}			
		6.0	3.27×10^{-2}			
	35	1.6	6.17×10^{-2}			
		2.4	6.76×10^{-2}			
		3.2	6.90×10^{-2}			
		4.0	7.30×10^{-2}			
		5.0	7.46×10^{-2}			
		6.0	8.06×10^{-2}			
9[d]	20	6.0	2.82×10^{-2} [f]			
	25	0.8	4.68×10^{-2}			
		1.6	4.83×10^{-2}			
		2.0	4.71×10^{-2}			
		2.8	4.93×10^{-2}	83	15.4	−13.1
		3.6	4.73×10^{-2}			
		4.0	4.72×10^{-2}			
	30	6.0	6.62×10^{-2} [f]			
	40	6.0	1.64×10^{-1} [f]			
10[e]	25	1.6	6.25×10^{-1}			
		2.4	7.69×10^{-1}			
		3.2	7.94×10^{-1}			
		4.0	8.55×10^{-1}	1900		
		5.0	8.93×10^{-1}			
		6.0	9.09×10^{-1}			
	35	1.6	1.27			
		2.4	1.60			
		3.2	1.75			
		4.0	2.06		16.6	−1.2
		5.0	2.05			
		6.0	2.07			
	45	1.6	2.50			
		2.4	3.40			
		3.2	3.82			
		4.0	4.24			
		5.0	4.27			
		6.0	4.60			

[a] Base KOH; μ 0.1 ($KClO_4$); solvent 96% Me_2SO (v/v). [b] $[5]_0$ 3.0×10^{-5} M. [c] $[8]_0$ 2.3×10^{-5} M. [d] $[9]_0$ 2.6×10^{-5} M. [e] $[10]_0$ 4.4×10^{-5} M; measured by means of a stopped-flow method. The accuracy of k_{obsd} is within ±0.25−. [f] All k_{obsd} are an average of at least triplicate measurements.

in the rate constant is electronic or steric, the kinetics of formation of anionic σ complexes were carried out under similar conditions to those in the measurements of the rates of rearrangement.

In the case of **5** and **9** the rates of formation of the anionic σ complexes were too fast to be followed by the stopped-flow spectrophotometric method, while in the case of **8** and **10** the stability of formed complexes was moderate enough for rates to be measured. From eq 10 and 11, the pseudo-first-order rate constant for the attainment of equilibrium is the sum of the first-order rate constants for the forward and reverse reactions. As a general rate expression, one can derive eq 17,

$$k_{\psi} = k_{-2} + \frac{k_2 K_1[^-OH]}{1 + K_1[^-OH]} \tag{17}$$

where k_2 and k_{-2} are the rate constants for the forward and reverse reactions of eq 11, respectively. Therefore, the plot of k_{ψ} against $[^-OH]$ would give a curvilinear dependence unless $K_1[^-OH] \gg 1$. This is the case with **8** and **10**, where k_{-2} could be obtained from the extrapolation of $[^-OH]$ to the intercept in the above-described plot (Figure 6[12]). Once k_{-2} is obtained, eq 18 could be easily derived. Therefore, from the slope and intercept in the plot of $1/(k_{\psi} - k_{-2})$ against $1/[^-OH]$ (eq 18), k_2 and K_1 could be evaluated (Figure 7[12]). Relevant data are summarized in Table II. K_1s in Table II is considered to be resonable from a consideration of the work of Hine and Hine.[14,15]

$$\frac{1}{k_{\psi} - k_{-2}} = \frac{1}{k_2} + \frac{1}{k_2 K_1[^-OH]} \tag{18}$$

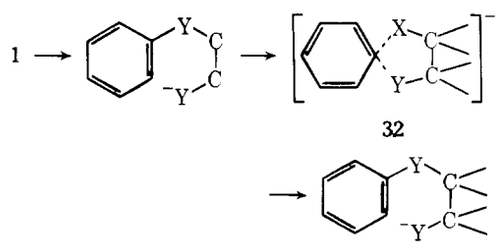
Discussion

Formation of Anionic σ Complexes. The difference between k_2s in Table II may result from the electron-attracting and stereoelectronic characters of pyridyl nitrogen. The values of K_1 are considered to be reasonable on the basis of the fact that a 2-Br group is a little more electron attracting than a pyridyl nitrogen from a consideration of the pK_as of 2-bromophenol[18] and 2-hydroxypyridine.[19] Although in the case of **5** and **9** k_2 and K_1 could not be obtained, K_1 and K_2 can be expected to be at least larger than 131 and 11, respectively, because the rates of formation of anionic σ complexes are too fast to be followed by a stopped-flow spectrophotometric method.

Rates of Rearrangement. As in both cases (**5** and **9**), K_2 is considered to be much larger than 1; therefore, one can approximate eq 16 as follows:

$$k_{obsd} = \frac{k_4 K_3}{1 + K_3} \tag{19}$$

Even in the case of **8** and **10**, K_2s are evaluated to be much larger than 1 as described in the preceding section, and, therefore, eq 19 still holds. Equation 19 indicates that the rate of rearrangement depends only on the decomposition of an anionic σ complex, independent of its formation. This result is very interesting, because all previous work put emphasis on the formation of the transition states **32** and **33**.[3,6,17] Several pathways are possible for the conversion of **1** to **2**; the nucleophilic function, YH, may be ionized with substitution proceeding via the transition state **32** (eq 20). On the other



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2 (20)

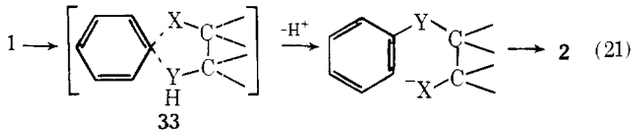
hand, prior ionization is not always required, and the rearrangement may proceed in a concerted fashion through the transition state **33** (eq 21). In certain systems the rearrangement proceeds through such a stabilized intermediate as **28**.[4a] If the rate of rearrangement, however, depends only on the decomposition process of a stabilized intermediate (anionic

Table II. Kinetic Data Relevant to the Formation of Anionic σ Complexes[a]

	k_2, s^{-1}	k_{-2}, s^{-1}	K_1, M	K_2	10^3 [KOH], M	k_Ψ
					0.8	(2.19 ± 0.10) × 10
					1.2	(2.76 ± 0.10) × 10
					1.6	(3.20 ± 0.10) × 10
8	1.18 × 10^2	1.10 × 10	1.31 × 10^2	1.07 × 10	2.4	4.03 ± 0.09) × 10
					3.2	(4.54 ± 0.16) × 10
					4.0	(5.10 ± 0.13) × 10
					5.0	(5.69 ± 0.15) × 10
					6.0	(5.83 ± 0.17) × 10
					0.8	(5.44 ± 0.31) × 10
					1.2	(7.46 ± 0.58) × 10
					1.6	(8.96 ± 0.35) × 10
10	5.99 × 10	1.20 × 10	9.33 × 10	4.60 × 10	2.4	(1.21 ± 0.10) × 10^2
					3.2	(1.57 ± 0.09) × 10^2
					4.0	(1.86 ± 0.04) × 10^2
					5.0	(2.00 ± 0.03) × 10^2
					6.0	(2.12 ± 0.01) × 10^2

[a] $[8]_0$ 2.4 × 10^{-5} M; $[10]_0$ 4.4 × 10^{-5} M; solvent 96% Me_2SO (v/v); base KOH; μ 0.1 ($KClO_4$); measurements at 416 (**8**) and 400 nm (**10**). k_Ψs represents average values of four or five determinations.

σ complex), the configuration of A or B would play an important role in the decomposition, because Table I indicates that the difference in rate constants would depend on the



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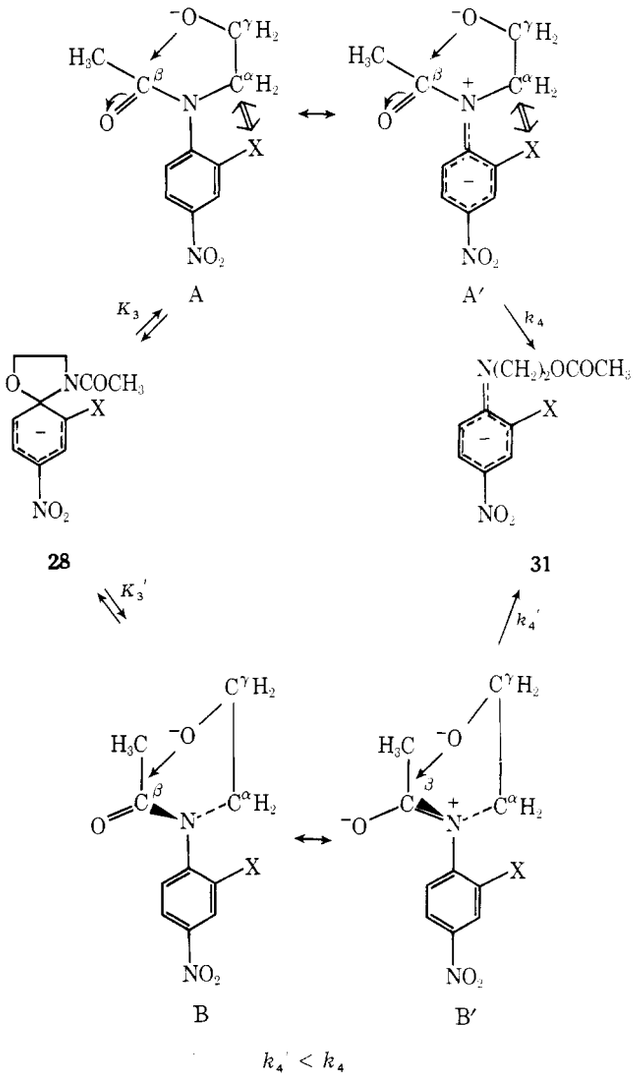
entropy of activation rather than on the enthalpy of activation. The conspicuous feature that the entropy of activation for **10** is much larger than those for other substrates indicates that the steric factor is very important in the rearrangement.

These results are clearly explained below. In **28** the five-membered heterocycle is perpendicular to the aromatic ring in the preferred configuration. In the case of **10**, the equilibrium (K_3) lies on configuration A, viz., K_3 is larger, in which the conjugation of the lone-pair electrons of the amino nitrogen with the pyridine ring is larger because of the coplanarity of the C^α–N–C^β group with the pyridine ring owing to the absence of the steric interference by an X group, and the free rotation of the N–C^α and C^α–C^γ bonds is possible (Scheme III). Therefore, in the transition state (k_4 stage) the rotation of the five-membered heterocycle about the C_1–N bond, which is formed by the attack of the oxyanion upon the carbonyl carbon, is considerably free. Furthermore, in configuration A the attack of the oxyanion is concerted with the

Scheme III. Interpretative Scheme Indicating the Influence of an Ortho Substituent



$k_4' < k_4$

polarization of carbonyl group because of the predominant resonance (A ↔ A′).

On the contrary, in the case of **5**, **9**, and **8**, the C^α–N–C^β group forms a certain angle with the benzene ring by the steric interference of an X group such that the hydrogen atom in the 6 position is put between the C^β=O and C^β–CH_3 bonds (configuration B); the lone-pair electrons of the amino nitrogen is conjugated with the aromatic ring to a lesser extent than in configuration A. With **5** the rotation of the N–C^α bond is completely inhibited and the free rotation of the C^α–C^γ bond is not possible, while with **9** and **8** the former rotation is not completely inhibited and the latter rotation is possible. These circumstances are reflected in the difference among the entropies (Table I). Furthermore, the attack of oxyanion on the carbonyl carbon is not completely concerted with the polarization of the carbonyl group owing to the partial resonance (B ↔ B′), viz., $k_4' < k_4$.

In conclusion, it is considered that the difference in the rate constant in the rearrangement would result mainly from the steric interference of 2-X group.

Experimental Section

Capillary melting points are uncorrected. NMR spectra were recorded with a Varian A-60D spectrometer according to the previous procedure.[20] Elemental analyses were performed at the Microanalytical Center of Gunma University. UV and visible spectra were measured with a Hitachi-124 UV–vis spectrophotometer. Molecular extinction coefficients and absorption maxima were determined in

Me_2SO. The reaction rates were followed conventionally and with a Union RA-1200 rapid-reaction analyzer (Union Giken Co., Ltd.). Chromatographic columns and TLC plates were prepared with Wako Gel C-200 (silica gel) and B-10 (silica gel), respectively.

***N*-Acetyl-β-aminoethyl 2,4-Dinitro-1-phenyl Ether (5).** The ether **5** was prepared according to the previous procedure.[10] The NMR and visible spectra of **5** and its spiro complex **6**, corresponding in structure to **11**, were described in the previous paper.[10] The preparation of *N*-(β-acetyloxy)ethyl-2,4-dinitroaniline (**7**) and its anion corresponding in structure to **11** and their NMR and visible spectra were already described.[10] The preparation of *N*-(β-hydroxy)ethyl-*N*-methyl-2,4-dinitroaniline and its spiro anionic σ complex corresponding in structure to **15** and **20**, respectively, were reported by Bernasconi et al.[9]

***N*-Acetyl-β-aminoethyl 2-Bromo-4-nitro-1-phenyl Ether (8).** 4-Nitrofluorobenzene (NFB), which is a yellowish oil [bp 95–97 °C/22 mm (lit.[21] 98–100 °C/18 mm)], was prepared according to the procedure of Olah et al.[21] in 68% (25 g) yield by the reaction of 25 g (0.260 mol) of commercial fluorobenzene with the mixed acid of 16 g of HNO_3 (*d* 1.41) and 56 g of concentrated H_2SO_4 at −10 °C. 2-Bromo-4-nitrofluorobenzene (BNFB) was obtained in a 64% yield (10 g) by brominating NFB according to the general procedure of Derbyshire and Waters:[22] white crystals, mp 57.5–58.5 °C (lit.[23] 58–59 °C). To a solution of 3.86 g (0.0375 mol) of *N*-acetylethanolamine (NAEA) in 100 mL of dioxane was added 0.975 g (0.025 g-atom) of potassium, and the mixture was refluxed until the potassium was completely dissolved. Upon cooling the mixture to room temperature, 5.0 g (0.023 mol) of BNFB was added and stirred for 30 min. Then, the mixture was poured onto ice water and extracted with chloroform. After the chloroform was distilled off, the residue was seperated on a chromatographic column (silica gel, benzene–acetone 10:3, v/v) and recrystallized from benzene–ligroin: yield 29% (2.0 g); mp 124.5–125.5 °C; UV λ_{max} 317 nm (ϵ 9.18 × 10^3).

Anal. Calcd for $C_{10}H_{11}BrN_2O_4$: C, 39.62; H, 3.66; N, 9.24. Found: C, 40.04; H, 3.73; N, 9.32.

***N*-Acetyl-β-aminoethyl 2-Cyano-4-nitro-1-phenyl Ether (9).** 2-Chloro-5-nitrobenzonitrile was obtained in a 75% yield [25 g, yellow oil, bp 119–122 °C/0.6 mm (lit.[24] 119–122 °C/0.6 mm)] by the reaction of 25 g (0.181 mol) of *o*-chlorobenzonitrile with 86 mL of fuming HNO_3 (*d* 1.5) according to the procedure of Wilshire.[24a] 2-Chloro-5-nitrobenzonitrile was also changed to 2-fluoro-5-nitrobenzonitrile (FNBN) in a 78% yield according to the procedure of Wilshire.[24a] **9** (pale-yellow crystals) was prepared from FNBN and NAEA in a 23% yield in a similar manner as with **6**: mp 132–133.5 °C; UV λ_{max} 303 nm (ϵ 1.14 × 10^4).

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.88; H, 4.53; N, 16.88.

***N*-Acetyl-β-aminoethyl 5-Nitro-2-pyridyl Ether (10).** 2-Aminopyridine was changed to 5-nitro-2-aminopyridine by use of a mixed acid of HNO_3 and H_2SO_4 in about 70% yield, which was further diazotized and hydrolyzed to 5-nitro-2-hydroxypyridine. 5-Nitro-2-hydroxypyridine was chlorinated to 5-nitro-2-chloropyridine with PCl_5 and $POCl_3$ according to the method of Phillips.[25] The yield including diazotization, hydrolysis, and chlorination was 27%. 5-Nitro-2-chloropyridine was fluorinated to 5-nitro-2-fluoropyridine [bp 86–87 °C/7 mm (lit.[26] 86–87 °C/7 mm)] in a 81% yield according to the procedure of Finger and Starr,[26] except for the reaction temperature of 120 °C and the reaction time of 8 h. **10** (white crystals) was prepared in a 36% yield in a similar manner as with **6**: mp 115–116 °C; UV λ_{max} 303 nm (ϵ 1.02 × 10^4).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.14; H, 4.91; N, 18.61.

***N*-(β-Acetyloxy)ethyl-2-bromo-4-nitroaniline (13).** After 3.27 mL of 0.450 N tertiary-butanolic $KOC(CH_3)_3$ (0.00147 mol) had been added to a solution of 0.495 g (0.00147 mol) of **8** in 50 mL of Me_2SO, the mixture was stirred for 1 h at room temperature, poured into 100 mL of water, neutralized with hydrochloric acid (1 N), extracted with chloroform, and dried over anhydrous Na_2SO_4. After evaporation of the chloroform, recrystallization from ethanol gave **13** quantitatively (0.490 mg): mp 99.5–100.5 °C; UV λ_{max} 386 nm (ϵ 1.81 × 10^4).

Anal. Calcd for $C_{10}H_{11}BrN_2O_4$: C, 39.62; H, 3.66; N, 9.24. Found: C, 39.95; H, 3.71; N, 9.28.

***N*-(β-Hydroxy)ethyl-*N*-methyl-2-bromo-4-nitroaniline (14).** After 1.5 g (0.0204 mol) of *N*-methylethanolamine (NMEA) had been added to a solution of 1.5 g (0.0076 mol) of BNFB in 20 mL of dioxane, the mixture was stirred at room temperature for 20 h, poured into 50 mL of water, neutralized with aqueous HCl (1 N), extracted with chloroform, and dried over anhydrous Na_2SO_4. Chromatographic seperation (silica gel–benzene) followed by evaporation of the benzene gave 1.17 g of reddish light brown oil **14** (61%): UV λ_{max} 390 nm (ϵ 4.64 × 10^3). Several attempts to induce recrystallization failed.

Anal. Calcd for $C_9H_{11}BrN_2O_3$: C, 39.29; H, 4.03; N, 10.18. Found: C, 38.80; H, 4.31; N, 9.69.

***N*-(β-Hydroxy)ethyl-*N*-methyl-2-cyano-4-nitroaniline (19).** After 3.08 g (0.041 mol) of NMEA had been added to a solution of 3.0 g (0.0164 mol) of 6-chloro-3-nitrobenzonitrile (CNBN) in 50 mL of Me_2SO, the mixture was stirred for 10 h at room temperature, poured onto ice water, and extracted with chloroform, and recrystallization from ethanol gave 2.0 g (55%) of **19** (yellow crystals): mp 107–109 °C; UV λ_{max} 388 nm (ϵ 1.76 × 10^4).

Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.12; H, 5.12; N, 19.28.

***N*-(β-Acetyloxy)ethyl-2-cyano-4-nitroaniline (18).** After 2.5 g (0.0409 mol) of ethanolamine had been added to a solution of 3 g (0.0164 mol) of CNBN in 50 mL of Me_2SO, the mixture was stirred for 3 h at room temperature, poured into water, and neutralized with aqueous HCl (1 N). The raw product [*N*-(β-hydroxy)ethyl-2-cyano-4-nitroaniline, 2.0 g] was submitted to the following procedure without further purification. After 1.8 g (0.0229 mol) of acetyl chloride was added dropwise to a solution of 1.6 g of *N*-(β-hydroxy)ethyl-2-cyano-4-nitroaniline at room temperature, the mixture was stirred for 30 min at 60 °C, cooled, and poured onto ice water. The formed crude crystals were extracted with benzene, dried over anhydrous Na_2SO_4, and separated through a column (silica gel–benzene). Evaporation of the benzene and recrystallization from ethanol gave 1 g (51%) of **18** (brownish light-yellow crystals): mp 125–126 °C; UV λ_{max} 372 nm (ϵ 1.69 × 10^4).

Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.90; H, 4.56; N, 16.90.

2-[*N*-(β-acetyloxy)ethyl]amino-5-nitropyridine (23). 5-Nitro-2-fluoropyridine was prepared according to the method described in the literature.[26] After 12.7 mL (0.00546 mol) of 0.430 N tertiary-butanolic $KOC(CH_3)_3$ was added dropwise to a solution of 1.23 g (0.00547 mol) of **10** in 50 mL of Me_2SO, the mixture was stirred 1 h, poured onto ice water, neutralized with aqueous HCl (1 N), extracted with chloroform, and dried over anhydrous Na_2SO_4. Evaporation of the chloroform and recrystallization from ethanol gave yellow crystals of **23** quantitatively: mp 124–125.5 °C; UV λ_{max} 369 nm (ϵ 1.77 × 10^4).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.10; H, 4.90; N, 18.57.

2-[*N*-(β-hydroxy)ethyl-*N*-methyl]amino-5-nitropyridine (24). After 1.18 g (0.0157 mol) of NMEA had been added to a solution of 1.0 g (0.00629 mol) of 5-nitro-2-chloropyridine, the mixture was stirred for 15 h at room temperature, poured onto ice water, extracted with chloroform, and dried over anhydrous Na_2SO_4. Evaporation of the chloroform and recrystallization from ethanol gave 0.80 g (65%) of **24** (yellow crystals): mp 88.5–90 °C; UV λ_{max} 387 nm (ϵ 2.03 × 10^4).

Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.51; N, 5.38; N, 21.12.

Kinetic Data. Kinetic measurements for the rearrangement were made using a Hitachi-124 UV–vis spectrophotometer, except with **10**. Rate constants were calculated by monitoring the decrease in absorbance at 506 nm (λ_{max} of the spiro complex) with **5** or the increase in absorbance at 481, 475, and 462 nm with **8**, **9**, and **10**, respectively, at which wavelengths the reactants were transparent. In any given solvent, in which the Me_2SO content is always 96%, the ionic strength was kept at 0.1 ($KClO_4$). Runs were set up so that KOH as a base was in large excess over the substrate.

Kinetic measurements for the rearrangement of **10** and the formation of the anionic σ complexes from **8** and **10** were made by means of a Union RA-1200 rapid-reaction analyzer.

Preparation of Anionic σ Complexes for NMR Measurements. A certain amount of a sample (ca. 10^{-4}–10^{-5} mol) was dissolved in a small amount of Me_2SO (ca. 0.25 mL) in a NMR tube. After 1.0 or 1.5 equiv of tertiary-butanolic $KOC(CH_3)_3$ (ca. 0.4 N) had been added in the solution through a microsyringe and shaken vigorously, the mixture was submitted to measurement. The NMR data are summarized in Table III.[12]

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Registry No.–**8**, 63989-43-5; **9**, 63989-50-4; **10**, 63989-49-1; **13**, 63989-48-0; **18**, 63989-47-9; **23**, 63989-46-8; **14**, 63989-45-7; **19**,

63989-44-6; **24**, 25948-15-6; **20**, 63988-97-6; **22**, 63988-99-8; **5**, 55759-61-0; **11**, 64011-18-3; **1**, 63989-41-3; **16**, 63988-98-7; **17**, 63989-42-4; NFB, 350-46-9; BNFB, 701-45-1; NAEA, 142-26-7; FNBN, 17417-09-3; 5-nitro-2-fluoropyridine, 456-24-6; NMEA, 109-83-1; CNBN, 16588-02-6; [*N*-(β-hydroxyethyl-2-cyano-4-nitroaniline, 63989-40-2; acetyl chloride, 75-36-5; 5-nitro-2-chloropyridine, 4548-45-2.

Supplementary Material Available. Table III and Figures 2, 5, 6, and 7 (6 pages). Ordering information is given on any current masthead page.

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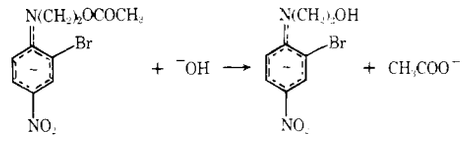

12 12a

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Crown–Cation Complex Effects. 8. Reactions of Crown Ether Activated *tert*-Butoxide Ion

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The effect of catalytic amounts of 18-crown-6 on tetrahydrofuran, *tert*-butyl alcohol, and benzene solutions of potassium *tert*-butoxide has been investigated. In each solvent, the enhanced nucleophilicity of *tert*-butoxide ion was manifested in its reaction with benzyl chloride; i.e., good yields of benzyl *tert*-butyl ether were obtained. In the latter solvent, 18-crown-6 served as phase-transfer agent as well as activator. *tert*-Butoxide ion was found to be most effective as a nucleophile in tetrahydrofuran solution, and, in general, the results of exemplary reactions indicated that nucleophilicity was enhanced more than basicity. Crown-activated *tert*-butoxide, for example, converts isatoic anhydride to *tert*-butyl anthranilate, benzaldehyde and diphenylmethane to benzhydryl phenyl ketone, and, in the presence of oxygen, fluorene directly to 2-carboxybiphenyl.

There has been interest for many years in solvent properties, particularly regarding their effect on the basicity and nucleophilicity of anionic reagents. The difference of 10^{11} in the rates of proton removal from carbon by alkoxide in methanol compared to dimethyl sulfoxide (Me_2SO) is an especially dramatic demonstration of such solvent effects.[1] Other studies conducted in the early 1960's demonstrated the value of *tert*-butoxide as a base, particularly in Me_2SO,[2,3] and it was at about this time that cation effects became clearly recognized.[4] A great deal is now known about the *tert*-butoxide ion[5] and, in general, about the chemistry of ion pairs.[6]

The ability of crown ethers to solvate cations has led to new studies of ion pairs both in the presence and absence of such ligands.[7] In general, in the presence of crown ether, aggregates of ion pairs are broken up and the anionic portion of the ligand separated or dissociated ion pair exhibits enhanced reactivity. This enhanced reactivity has manifested itself in decarboxylation reactions,[8] oxy-Cope rearrangements,[9] and elimination reactions.[10] We were particularly interested in the reactivity of potassium *tert*-butoxide (**1**) in the presence of crown ethers.[11] We felt that in such solvents as Me_2SO the enhanced basicity can be attributed, at least in part, to solvent assistance in carbanion formation.[12] In the presence of crown in a solvent such as tetrahydrofuran where solvent assistance is limited, the reactivity enhancement should be more apparent in the nucleophilic sense than in the basic sense. We have examined several reactions of *tert*-butoxide ion and have indeed found an enhancement of the nucleophilic behavior of this hindered base.

Results and Discussion

The chemistry of potassium *tert*-butoxide has been thoroughly reviewed.[5] This base has been utilized in a variety of media including *tert*-butyl alcohol, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, and benzene, although **1** is only sparingly soluble in the latter.[13] Benzyl chloride (**2**) has been used in the past as a substrate for studying nucleophile/base balance in systems where the anion behaved more as a base than as a nucleophile.[14] Utilization of this substrate

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