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Aromatic Nucleophilic Substitution. X.[1] Confirmation of the Anionic σ Complex in the Base-catalyzed Smiles Rearrangement of 2-(Acetylamino)ethyl 2,4-Dinitrophenyl Ether in Dimethyl Sulfoxide

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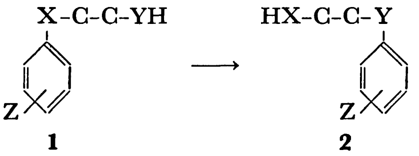
2,4-Dinitrofluorobenzene reacts with 2-(acetylamino)ethanol in dioxane in the presence of sodium to give 2-(acetylamino)ethanol 2,4-dinitrophenyl ether (**7**), *N*-(2-acetoxyethyl)-2,4-dinitroaniline (**8**), which is considered to be a Smiles rearranged product of **7**, and *N*-(2-hydroxyethyl)-2,4-dinitroaniline (**9**), a hydrolysis product of **8**. Furthermore, **7** undergoes a Smiles rearrangement in DMSO in the presence of $NaOCH_3$ or $KOC(CH_3)_3$, giving **8** and **9**. Spiro Janovsky complex was spectrometrically confirmed to exist during the course of rearrangement.

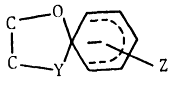
The Smiles rearrangement is known as a typical intramolecular aromatic nucleophilic substitution reaction:



Z: activating group

It is well established that aromatic nucleophilic substitution reactions proceed *via* Bunnett's intermediate mechanism.[2] The Smiles rearrangement is considered to be a good model for studying the mechanism of aromatic nucleophilic substitution reactions.

Although several pathways are possible for the conversion of **1** into **2**, the intermediate (**3**) (spiro Meisenheimer or Janovsky complex, hereinafter referred to as σ complex) might be confirmed spectrometrically or isolated in certain systems in which an aromatic ring is much activated by nitro, cyano, or other electron-attracting group. This has been recently reviewed in detail.[3] Kleb[4] reported the rearrangement of 2-(methylamino)ethyl 4-nitrophenyl ether to *N*-(2-hydroxyethyl)-*N*-methyl-4-nitroaniline, in which the reaction proceeds very rapidly, no cyclic intermediate being detected.



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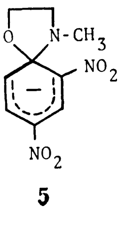
Bernasconi *et al.*[5] reported the base-catalyzed reverse Smiles rearrangement of *N*-methyl-*N*-(2-hydroxyethyl)-2,4-dinitroaniline (**4**), in which the formation of the spiro σ complex (**5**) was confirmed by absorption and NMR spectra. Skarzewski and Skrowaczeska[6] recently carried out the Smiles rearrangement of 2,4-dinitrofluorobenzene (**6**) with 2-(acetylamino)ethoxides and 2-aminoethoxides, but they did not confirm the intervention of σ complexes such as **5**.



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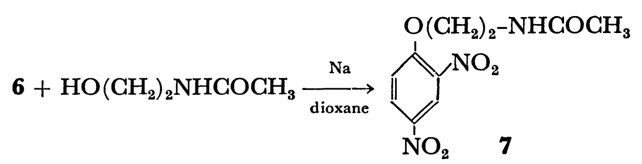
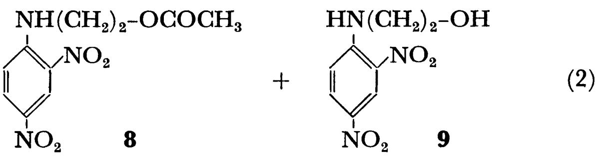
In order to study the reaction of 2-(acetylamino)ethyl 2,4-dinitrophenyl ether (**7**) with bases, we attempted to synthesize **7** by the following reaction. However, a mixture of **8** and **9** was obtained in a larger amount than **7**. **8** and **9** were formed from the base-catalyzed Smiles rearrangement of **7**.





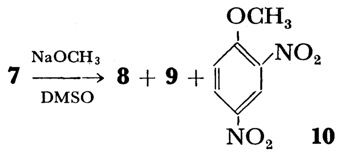
We wish to report the reaction path of the base-catalyzed Smiles rearrangement of **7** and the spectrometrical confirmation of an anionic σ complex during the course of rearrangement.

Results and Discussion

*Reaction of 2,4-Dinitrofluorobenzene (**6**) with 2-(Acetylamino)ethanol (AAE).* Treatment of **6** with AAE in the presence of metallic sodium (equivalent to **6**) in dioxane gave **7**, *N*-(2-acetoxyethyl)-2,4-dinitroaniline (**8**), and *N*-(2-hydroxyethyl)-2,4-dinitroaniline (**9**) in 14, 9, and 37% yields, respectively (see Experimental). **6** has a tendency to react with an oxide ion rather than an acetamido group.[7] The hydroxyl hydrogen of AAE is more acidic than the amide hydrogen.[8]

Thus AAE is expected to react with metallic sodium to give 2-(acetylamino)ethoxide ion, **7** being the main product. Compounds **8** and **9** can be considered to be formed *via* the Smiles rearrangement of **7**. The results prompted us to carry out the Smiles rearrangement of **7** under alkaline conditions.

*Reaction of 2-(Acetylamino)ethyl 2,4-Dinitrophenyl Ether (**7**) with $NaOCH_3$ or $KOC(CH_3)_3$.* Treatment of a solution of **7** in DMSO with an equimolar amount of $NaOCH_3$ at room temperature for 1 h gave **8** and **9** in 54 and 23% yields, respectively, and a small amount of **10** as shown in the following. No reaction took



$$7 \xrightarrow[\text{DMSO}]{\text{NaOCH}_3} 8 + 9 + 10 \qquad (3)$$

place in the absence of $NaOCH_3$. This indicates that **8** in Eq. 2 is formed from **7** *via* the Smiles rearrangement and **8** partly decomposes into **9** with $NaOCH_3$.[9]

In order to obtain closer insight into the decomposition of **8** to **9**, **8** was treated under similar alkaline conditions. Treatment of **8** in DMSO with an equimolar amount of $NaOCH_3$ followed by neutralization with an aqueous HCl solution gave **9** in 89% yield. On the other hand, treatment of **7** in DMSO with an equimolar amount of $KOC(CH_3)_3$ followed by neutralization with an aqueous HCl solution gave **8** in 78% yield and a trace amount of **9**. Thus the formation of a larger amount of **9** in the case of $NaOCH_3$ than in the case of $KOC(CH_3)_3$ indicates that methoxide ion attacks **8** at the acetyl group more easily than *t*-butoxide ion due to the former being less bulky.

Visible and NMR Spectra Relevant to the Reactions of 2-(Acetoxylamino)ethyl 2,4-Dinitrophenyl Ether (7) and N-*(2-Acetoxyethyl)-2,4-dinitroaniline (8) with* $NaOCH_3$ *or* $KOC(CH_3)_3$. In order to study the detailed reaction path of the Smiles rearrangement of **7**, the absorption and NMR spectra relevant to the reactions of **7** and **8** with $NaOCH_3$ or $KOC(CH_3)_3$ in DMSO were measured.

Immediately after the addition of 50 equivalents of $NaOCH_3$, a solution of **7** (9.15×10^{-8} mol) in 3 ml of DMSO turned red [λ_{max} 346 (ε 14300), 359 (ε 13800), and 506 nm (ε 28000), Fig. 1b], indicating the formation of a complex. Curve b (Fig. 1) is similar in shape to that of **5** [λ_{max} 347 (ε 12400), 358 (sh), and 501 nm (ε 22800), aqueous 80% DMSO].[10] It turned into curve d [λ_{max} 432 and 490 nm (sh)] after 8 h. Similar spectral changes were obtained for the molar ratios 100 and 1000.

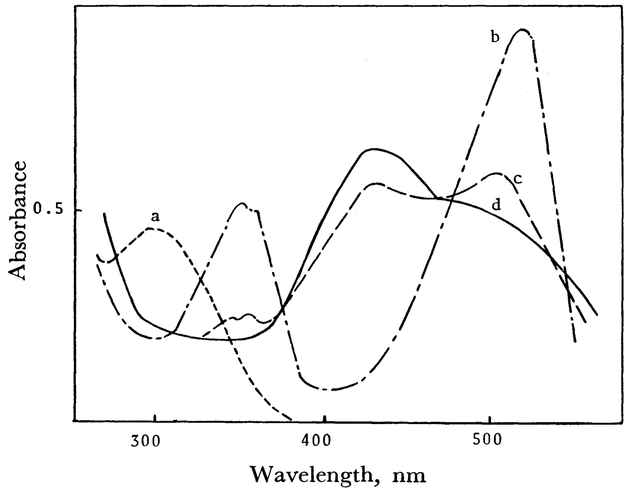


Fig. 1. Visible spectra relevent to the reaction of **7** (9.15×10^{-8} mol) with $NaOCH_3$ (molar ratio 1 : 50) in DMSO at 25 °C; curve a (----), **7** before the addition of $NaOCH_3$; curves b (——), c (——), and d (——) *ca.* 0, 4, 8 h after the addition of $NaOCH_3$, respectively.

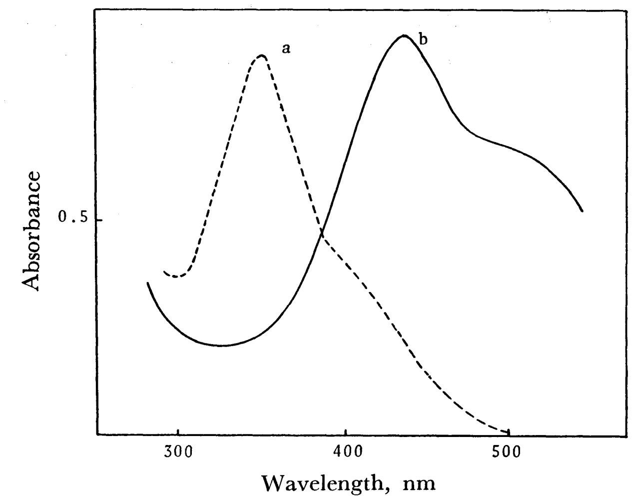
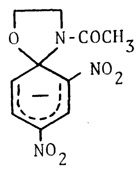


Fig. 2. Visible spectra relevant to the reaction of **8** (1.26×10^{-7} mol) with $NaOCH_3$ (molar ratio 1 : 50) in DMSO at 25 °C; curve a (----) **8** before addition of $NaOCH_3$; curve b (——) immediately after the addition of $NaOCH_3$.



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A solution of **8** (1.26×10^{-7} mol, Fig. 2a) in 3 ml of DMSO immediately turned red [λ_{max} 432 (ε 21000) and 490 nm (sh, ε 15700), Fig. 2b] after the addition of 50 equivalents of $NaOCH_3$. Curve b (Fig. 2) is similar in shape to curve d (Fig. 1). Thus, curve d can be attributed to the anilide ion of **8**. Hosoya *et al.*[11] concluded by MO calculation that curve b is attributable to the σ complex (**11**).

In order to examine the reversible conversion between **7** and **11**, the visible spectral changes were measured when $NaOCH_3$ and HCl (aqueous solution) were successively added. On addition of 50 equivalents of $NaOCH_3$ (0.165 M, 27.8 μl), a solution of **7** (9.15×10^{-8} mol) in 3 ml of DMSO immediately turned red to give the same spectrum as that of curve b in Fig. 1. On subsequent addition of 100 equivalents of HCl (1.00 M, 9.2 μl), the solution immediately turned yellow to give the same spectrum as that of curve a (Fig. 1). When 150 equivalents of $NaOCH_3$ (1.65 M, 8.2 μl) were added thereto, **11** was immediately formed again. The results indicate that a reversible conversion between **7** and **11** exists and the life of **11** is relatively long.

The NMR spectra of the reaction system of **7** or **8** with $KOC(CH_3)_3$ were measured, since NMR measurements are known to be useful for the confirmation of anionic σ complexes.[12] Immediately after the addition of an equimolar amount of $KOC(CH_3)_3$, the red solution gave the spectrum (b) (sweep time 500 Hz/50 s), H^A resonance peak disappearing and H_3, H_5, and H_6

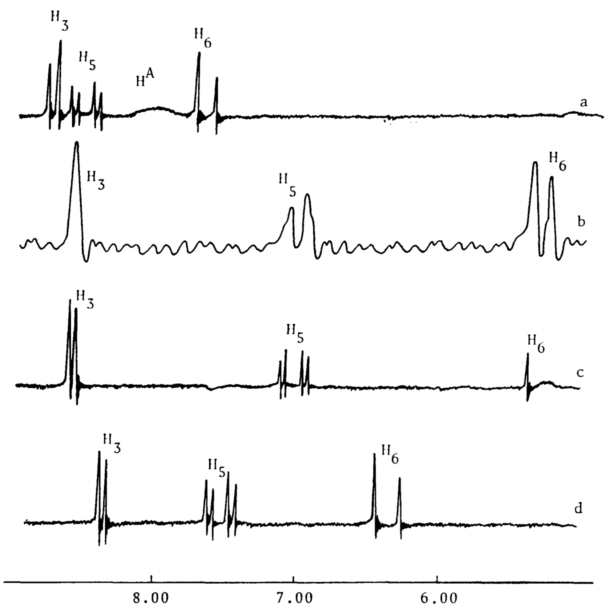
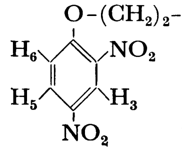


Fig. 3. NMR spectra of the reaction of **7** with $KOC(CH_3)_3$ in DMSO-d_6: a **7** before addition of $KOC(CH_3)_3$; b and c immediately after the addition of $KOC(CH_3)_3$, measured at the faster and normal sweep velocity; d several min after additon of $KOC(CH_3)_3$.



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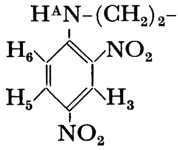

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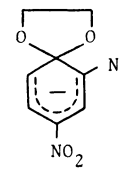
resonance peaks shifting upfield. The upfield shifts are typical of a negatively charged 2,4-dinitrobenzene or 1,1-disubstituted 2,4-dinitrophenyl anionic σ complex such as **5**, **11**, **12**, **16**, or **17**.[13] The chemical shifts of aromatic protons of other similar stable σ complexes are given in Table 1 for comparison. The results show that spectrum (b), where poor resolution is due to the fast sweep time (Fig. 3b), is attributable to **11**. Spectrum (c) measured at the normal sweep time immediately after the addition of $KOC(CH_3)_3$, is similar to spectrum (b), although the H_6 resonance peak collapsed a little in shape owing to the proceeding reaction. A few minutes after addition of $KOC(CH_3)_3$, spectrum (c) turned into spectrum (d) attributable to the anilide ion of **8** formed by the abstraction of H^A, since the same spectrum was obtained when **8** was treated with an equimolar amount of $KOC(CH_3)_3$ in DMSO.

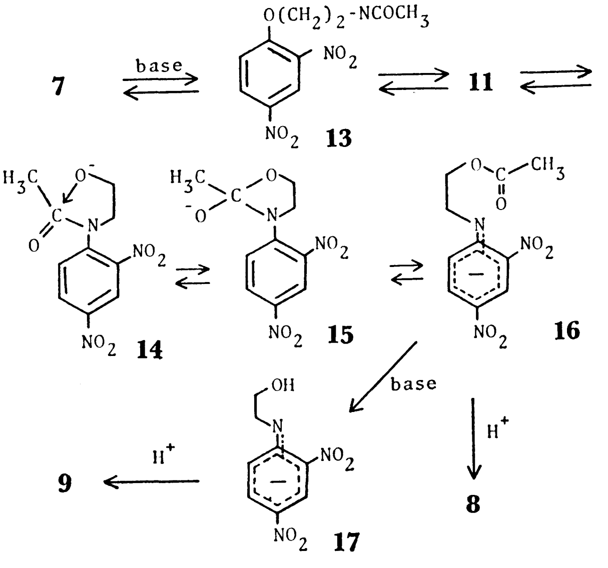
Table 1. Chemical shifts of anionic σ complexes

	5	12[a)]	11
H_3	8.50(d)	8.52(d)	8.57(d)
H_5	6.88(dd)	6.90(dd)	7.00(dd)
H_6	5.13(d)	5.36(d)	5.33(dd)

a) **12**: [13]



All the results are in line with the following scheme:[12] **7** functions as an acid in strongly basic media[14] to produce the amide ion (**13**) and then **11**. In **11** the C_1–O bond is more easily cleaved than the C_1–N bond as seen in ordinary aromatic nucleophilic substitution.[15] The intramolecular attack of the oxide ion (**14**) on the carbonyl carbon gives **15** and then **16**. A less bulkier alkoxide ion such as CH_3O^- reacts with **16** at the carbonyl carbon to give **17**.



Scheme.

In the normal Smiles rearrangement our case is the first example in which the anionic σ complex was detected.

Experimental

Melting points were uncorrected. NMR spectra were recorded with a Varian A-60D spectrometer. Elemental analyses were performed at the Microanalytical Center of Gunma University. Visible spectra were measured with a Hitachi-124 UV-VIS spectrophotometer. All the reagents were purified by recrystallization or by ditillation.

2-(Acetylamino)ethyl 2,4-Dinitrophenyl Ether (7). After 0.60 g (0.030 mol) of metallic sodium had been added to a stirred solution of 4.64 g (0.045 mol) of 2-(acetylamino)-ethanol (AAE) in 50 ml of dioxane, the mixture was refluxed for 5 h so that sodium was completely dissolved. After a solution of 5.6 g (0.030 mol) of 2,4-dinitrofluorobenzene (**6**) in 30 ml of dioxane had been added dropwise under stirring, the mixture was stirred at 30 °C for 4 h. The mixture was then poured into 200 ml of ice–water and extracted with chloroform. After the organic layer had been dried over anhydrous Na_2SO_4, the solvent was evaporated to give crude products, which were separated by column chromatography (silica gel, benzene–acetone) and recrystallized from benzene or benzene–ligroin, mp 105—105.5 °C, λ_{max} 298 nm (ε 11300) (**7**), 131—132 °C, λ_{max} 358 (ε 17400) and 410 nm (sh) (**8**), and 91—92 °C, λ_{max} 362 (ε 17700) and 390 nm (sh) (**9**). Yield 14% (**7**), 9% (**8**), and 37% (**9**). Found: C, 44.33; H, 4.04%

for **7**; C, 44.42; H, 4.02% for **8**. Calcd for $C_{10}H_{11}N_3O_6$ (**7** and **8**): C, 44.61; H, 4.12%. Found: C, 44.01; H, 3.89%. Calcd for $C_8H_9N_3O_5$ (**9**): C, 44.29; H, 3.99%.

Reaction of 7 with Sodium Methoxide. (a) To a solution of 0.692 g (2.57×10^{-3} mol) of **7** in 10 ml of DMSO was added 0.68 ml (2.57×10^{-3} mol) of methanolic $NaOCH_3$ (3.78 M) at room temperature under stirring, and the mixture was stirred for 1 h. After 2.57 ml of 2.00 M HCl solution had been added under stirring, the mixture was poured into 100 ml of water, extracted with chloroform, and dried over anhydrous Na_2SO_4. The solvent was evaporated to give crude products, which were separated by column chromatography (silica gel, benzene) and recrystallized from benzene or benzene–ligroin. **8** and **9** were obtained in 82% yield and in a small amount, respectively. (b) To a stirred solution of 0.708 g (2.63×10^{-3} mol) of **7** in 3 ml of DMSO was added at room temperature 2.44 ml (2.64×10^{-3} mol) of methanolic $NaOCH_3$ (1.08 M). After the mixture had been stirred for 1 h, 5.26 ml of 1.00 M HCl aqueous solution was added. The mixture was treated according to procedure (a). **8**, **9**, and **10** were obtained in 54 and 23% yields and in a small amount, respectively.

Reaction of 7 with Potassium t-Butoxide. To a stirred solution of 0.778 g (2.89×10^{-3} mol) of **7** in 10 ml of DMSO was added at room temperature 2.37 ml (2.89×10^{-3} mol) of *t*-butyl alcoholic $KOC(CH_3)_3$ (1.22 M). After the mixture had been stirred for 1 h, 2.89 ml of 2.00 M HCl solution was added. The mixture was then treated according to procedure (a). **8** and **9** were obtained in 78% yield and in a small amount, respectively.

Reaction of 8 with Sodium Methoxide. To a stirred solution of 0.341 g (1.27×10^{-3} mol) of **8** in 10 ml of DMSO was added at room temperature 0.62 ml (1.27×10^{-3} mol) of methanolic $NaOCH_3$ (2.05 M). After the mixture had been stirred for 30 min and 2.53 ml of 1.00 M HCl solution added, the mixture was treated according to procedure (a). **9** was obtained in 89% yield.

Reaction of 8 with Hydrochloric Acid. To a stirred solution of 0.309 g (1.15×10^{-3} mol) of **8** in 10 ml of DMSO was added 2.30 ml (2.30×10^{-3} mol) of 1.00 M HCl aqueous solution at room temperature. After stirring for 30 min at room temperature, the mixture was poured into 100 ml of water, filtered, dried, and purified. **8** was quantitatively recovered.

NMR Measurement. About 35 mg of a sample was dissolved in *ca.* 0.25 ml of DMSO in NMR tube. After an equimolar amount of alkoxide had been added to the solution through a microsyringe and shaken vigorously, the mixture was subjected to measurement.

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