Mechanism of the Fujiwara Reaction: Structural Investigation of Reaction Products from Benzotrichloride

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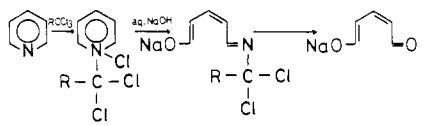
The mechanism of color development and the structures of chromophores of the Fujiwara reaction have been investigated by using benzotrichloride as a chromogenic reagent. Two products were isolated. NMR and mass spectroscopic investigation indicates that one of them is N^2-[(1*E*,3*E*)-1,3-butadienyl]-N^1-(1,3-butadienyl)benzamidine and that the other is *N*-[(1*E*,3*E*)-4-methanoyl-1,3-butadienyl]benzenecarboxamide. In alkaline media, the former develops an intense red color; the latter becomes yellow. The formation of these chromophores is explained by the hydrolytic scission of pyridine rings in the benzal dipyridinium cation intermediate.

The Fujiwara reaction[1] has been widely used for the colorimetric analysis of *gem*-polyhalogen compounds.[2-6] When a mixture of the *gem*-polyhalogen compound and pyridine is heated for a few minutes in a strongly alkaline medium, an intense red color (λ_{max} ca. 530 nm) develops. The absorption is strong enough to allow the detection of *gem*-polyhalogen compounds in concentrations as low as 1 μg.[5] The following mechanism (**1** → **2** → **3**) has been



1 **2** **3**

proposed.[7,8] The structure of the chromophore responsible for the red color has been assigned as **2**. It gradually turns almost colorless and yields glutaconaldehyde (**3**, λ_{max} ca. 360 nm)[9] as the final product.[5-8] However, it is quite unlikely that such a conjugated system as short as **2** has an absorption around 530 nm.

In order to investigate the mechanism further, we have isolated the products formed from benzotrichloride and determined their structures by means of NMR.

Experimental Section

Materials. Pyridine and benzotrichloride of analytical reagent grade (Wako Pure Chemical Industries Ltd.) were further purified by distillation and protected against light and moisture. Other chemicals of analytical reagent grade were used as supplied.

General Methods. UV and visible absorption spectra were measured on a UVIDEC-505 (JASCO) UV/vis spectrophotometer. ^{1}H NMR spectra were measured on Varian HA-100D (100 MHz) and Varian XL-200 (200 MHz) NMR spectrometers. The chemical shifts are given in parts per million from internal tetramethylsilane and are reported as δ values. Mass spectra were taken with JEOL-JMS-01SG (JEOL, Tokyo) spectrometer. High-resolution mass spectra were measured with JMS-2000 mass data analysis system. Column chromatography was carried out over silica gel (160 g of Wakogel C-200 packed in a 5-cm-i.d. glass column) with a solvent system of 1:1 benzene–ethyl acetate. The purity of the isolated compounds was checked by thin-layer chromatography (TLC) over silica gel (Merck, Kieselgel 60 F-254) with the same solvent system.

Isolation of Colored Products. Of the several spots detected by TLC, the species with R_f 0.44 (compound A) and 0.57 (compound B) were isolated by the following procedures.

Compound A. Benzotrichloride (6 mL) was mixed with 60 mL of pyridine and 60 mL of aqueous 20% sodium hydroxide. The mixture was stirred for 3 min at 100 °C and cooled to 0–5 °C. The pyridine layer was separated from the reaction mixture, and 5 N HCl was added until an oily substance precipitated. Excess benzotrichloride and benzoic acid formed as a byproduct were removed by extraction with 1:1 benzene–ethyl acetate. The aqueous layer was alkalized by adding 20% sodium hydroxide, diluted with 20 mL of water, and extracted with the same mixed solvent. The organic layer was washed with water and dried over sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in a small volume of 1:1 benzene–ethyl acetate and submitted to column chromatography. The fraction between 560 and 760 mL of eluate was collected. The evaporation of the solvent gave brownish red amorphous solid: mp (uncorrected) 143–145 °C; field desorption (FD) mass spectrum, *m/e* 280 (M^+).[10] Anal. Calcd for $C_{17}H_{16}N_2O_2 \cdot 2H_2O$: C, 64.54; H, 6.37; N, 8.85. Found: C, 63.85; H, 6.22; N, 8.51.

Compound B. Benzotrichloride (2 mL) was mixed with 20 mL of pyridine and 20 mL of aqueous 20% sodium hydroxide. The mixture was stirred for 10 min at 100 °C and cooled to 0–5 °C. The pyridine layer was separated, mixed with 30 mL of ethyl ether, and washed successively with 5 N HCl and water. The ether layer was separated and condensed by gradual evaporation of the solvent to give a syrup. When the syrup was rubbed with a glass rod, crystallization took place immediately. The precipitate was collected on a glass filter and washed with a small volume of benzene. Chromatographic separation was carried out with the same procedure as for compound A. The fraction between 220 and 520 mL of eluate was collected. The evaporation of the solvent gave yellowish white, fine, needlelike crystals: mp (uncorrected) 178 °C, FD mass spectrum, *m/e* 201 (M^+). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.66; H, 5.60; N, 6.80.

Methanolysis of Compound A (Compound A'). In order to obtain a reference material for the spectral assignment, we alcoholized the compound A by the following method.

The methanolic solution of compound A (15 mg/25 mL) was refluxed for 10 min, and the solvent was removed by evaporation. The resulting pale yellow substance was dissolved in 1:1 benzene–ethyl acetate and purified by column chromatography with

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(10) The sample was dried at 100 °C (5 mmHg).

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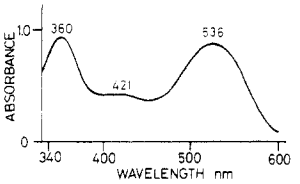


Figure 1. Absorption spectrum of the pyridine layer of the Fujiwara reaction solution prepared by heating for 3 min at 100 °C.

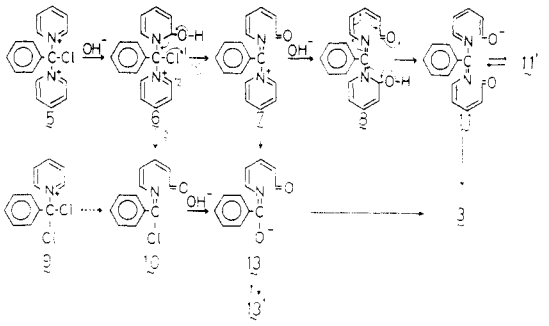


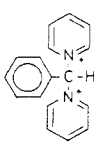
Figure 2. Chromophore-producing mechanism of the Fujiwara reaction. **11** is produced from **5** by the four-step reactions. **13** is formed from either **7** or **10**. **9** is shown as a possible precursor of **10**. Both the **11** and **13** chromophores turn into glutaconaldehyde **3**. The structural changes from **11** (red) to **11′** (yellow) and from **13** (yellow) to **13′** (colorless) are due to protonations.

the same solvent system. The fraction between 120 and 170 mL of eluate was collected. The evaporation of the solvent gave pale yellow oil, high-resolution mass spectrum calcd for $C_{13}H_{13}NO_2$ m/e 215.0947, found m/e 215.0950.

Results and Discussion

The pyridine layer of the Fujiwara reaction showed three absorption maxima at 360, 421, and 536 nm (Figure 1). The band at 360 nm is attributable to glutaconaldehyde.[9] A thin-layer chromatogram of the reaction solution exhibited ten distinctive spots. Among these, the spots at R_f 0.44 and 0.57 were clearly colored when sprayed with alcoholic KOH, the spot at R_f 0.44 (compound A) changed from yellow to intense red, which is responsible for the absorption band at 536 nm, and the spot at R_f 0.57 (compound B) which changed from colorless to yellow seems to be responsible for the band at 421 nm. The spots at R_f 0.92 and 0.39 are due to unchanged benzotrichloride and pyridine, respectively. The spots at R_f 0 and 0.20 were found to contain glutaconaldehyde and benzamide, respectively. The other spots seem unlikely to contribute to the color development. Thus, the structural investigations were conducted with respect to compounds A and B.

Molecular Structure of Compound A. It has been known that the reaction between benzal bromide and pyridine produces dipyridinium cation **4**, though this is not



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the Fujiwara reaction.[11,12] This fact strongly suggests that a similar intermediate, **5** (see Figure 2), may be involved in the Fujiwara reaction of benzotrichloride. If so, the compound **5** may be hydrolyzed by sodium hydroxide to produce **11** via the carbinol base **6**. The conjugated system of **11** is much longer than that of **2**, therefore promising to be responsible for the red color.

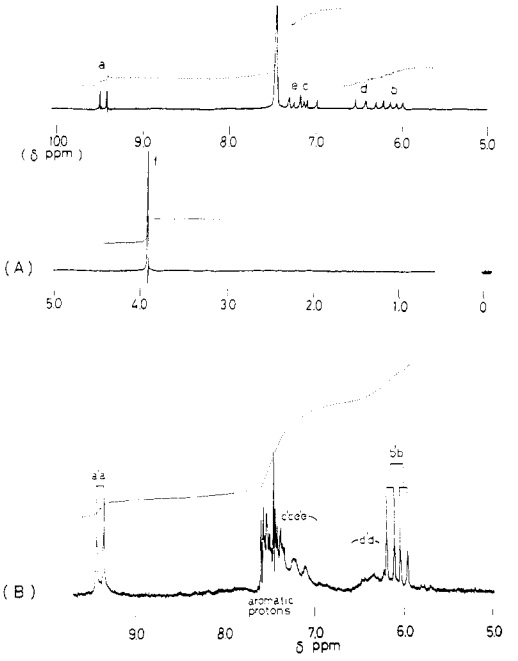


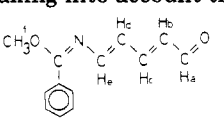
Figure 3. (A) ^{1}H NMR spectrum (100 MHz) of compound A′ (0.3 M solution in $CDCl_3$). (B) ^{1}H NMR spectrum (100 MHz) of compound A (0.04 M solution in 2:1 $CDCl_3$–CD_3OD).

Table I. Observed Chemical Shifts[a] and Spin-Spin Coupling Constants[b] of Compounds A′, A, and B

protons and coupling constants[g]	compd A′[c]	compd A[d,g]	compd B[e]
H_a (H_a')	9.47	9.36 (9.45)	9.48
H_b (H_b')	6.11	6.10 (6.10)	6.08
H_c (H_c')	7.13	7.34 (7.34)	7.27
H_d (H_d')	6.43	6.28 (6.43)	6.30
H_e (H_e')	7.25	7.21 (7.58)	7.65
phenyl	7.46	~7.6	~7.7
OCH_3	3.94		
NH		10.65	11.02[f]
$J_{H_aH_b}$	8.0	8.8	8.5
$J_{H_bH_c}$	15.0	15.0	15.0
$J_{H_cH_d}$	11.5	12.8	12.0
$J_{H_dH_e}$	13.0	13.6	14.0
J_{H_eNH}			10.0[f]

[a] In parts per million ± 0.01 ppm. [b] In hertz ± 0.2 Hz for A′ and B and ± 0.4 Hz for A. [c] In $CDCl_3$. [d] In Me_2SO-d_6; 200-MHz NMR spectrum. [e] In 2:1 $CDCl_3$–CD_3OD. [f] In Me_2SO-d_6. [g] The numbers in parentheses are for the protons in parentheses.

Figure 3 shows the ^{1}H NMR spectra of compound A and its methanolysis product (compound A′). The observed chemical shifts and spin–spin coupling constants are summarized in Table I. The NMR spectrum of the methanolysis product (Figure 3A) is much simpler in appearance than that of compound A (Figure 3B) and can be reasonably elucidated in accordance with the molecular structure of **12** by taking into account the chemical shifts,



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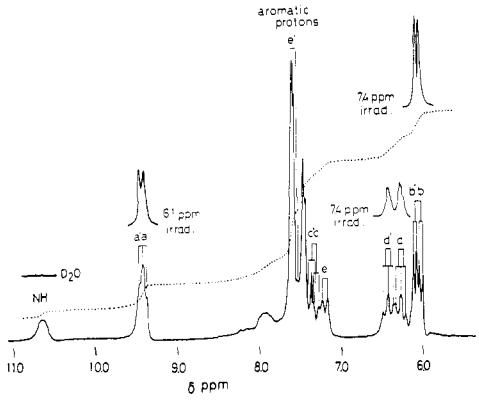

Figure 4. 200-MHz ^1H NMR spectrum of compound A (0.03 M solution in Me_2SO-d_6). The assignment for the signals aa', bb', ···, and ee' may be exchangeable in each pair. The lower field signals are tentatively assigned to protons on the chain conjugated with the benzene ring.

spin–spin coupling constants,[9,13] and integrated area. This structure is also supported by the high-resolution mass spectrum, since the most possible elemental composition is given as $C_{13}H_{13}NO_2$ (M^+: m/e 215; calcd, m/e 215.0947; found, m/e 215.0950). It is emphasized here that the structure of the methanolysis product, **12**, resembles **11** except that the N=CH···O^- moiety is replaced with the OCH_3 group.

The field-desorption mass spectrum of compound A indicated that the most possible molecular formula is $C_{17}H_{16}N_2O_2$ (M^+, m/e 280). This formula exactly meets **11** provided that the negative charge of **11** is neutralized by addition of one proton. The NMR spectrum of compound A (Figure 3B) shows the presence of an aldehydic proton (δ 9.36), aromatic protons (δ ~7.6), and olefinic protons (δ 7.1–6.0), suggesting structure **11** as a possible candidate. However, the olefinic signals locating in the region δ 7.5–6.3 are so broad and complicated that it seems difficult to make definite assignments. In the hope of overcoming this difficulty, we measured the 200-MHz ^1H NMR spectrum of compound A by use of dimethyl-d_6 sulfoxide instead of $CDCl_3$–CD_3OD (2:1) as a solvent. As shown in Figure 4 the spectrum indicates more resolved signals in the region δ 7.5–6.3 than in Figure 3B, but the whole feature looks quite dissimilar, especially with respect to the aldehydic proton at δ 9.4. It shows a collapsed triplet pattern, implying the presence of two slightly separated doublets. This means that there are two aldehydic protons located magnetically in somewhat different environments. This situation was more clearly observed by the spin-decoupling experiments. As shown in Figure 4, irradiation at δ 6.1 resulted in two singlet signals. One possible way to distinguish the two conjugated chains separated by a central quaternary carbon (structure **11'** in Scheme I) is to attach a proton at either of two nitrogen atoms. This idea also satisfies the requirement of the molecular formula mentioned above. If the structure of compound A is **11'**, then it might be expected that a signal of NH proton resonance would appear somewhere in the NMR spectrum. This was, in fact, observed as a broad signal at δ 10.65. Since this signal disappeared on addition of D_2O, it could then be assigned to the NH resonance. This result confirms the structure of compound A as **11'**. The assignments for the other resonances could also be ascertained by spin

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Scheme I

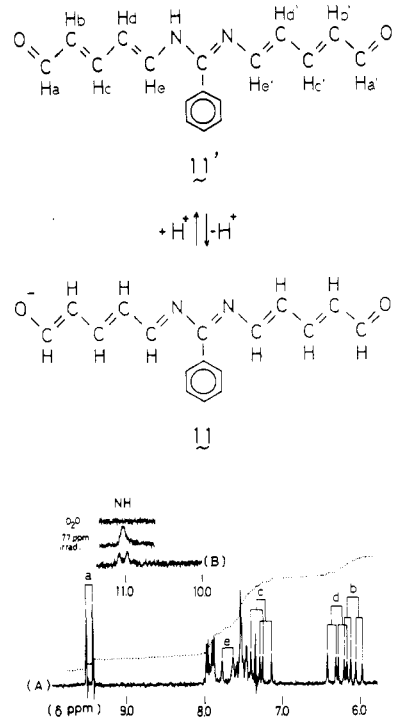


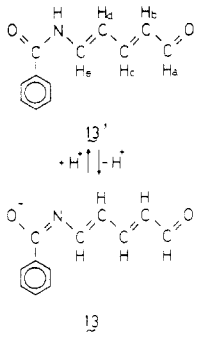
Figure 5. (A) ^1H NMR spectrum (100 MHz) of compound B (0.05 M in 2:1 $CDCl_3$–CD_3OD). (B) ^1H NMR spectrum (100 MHz) of compound B (0.04 M in Me_2SO-d_6).

decoupling experiments and are shown in Figure 4. The observed chemical shifts and spin–spin coupling constants are listed in Table I. The integrated area for the signals in the region δ 7.8–6.0 satisfies the number of protons expected from the structure **11'**. Thus, the structure of compound A is determined as **11'**, N^2-[(1*E*,3*E*)-1,3-butadienyl]-N^1-(1,3-butadienyl)benzamidine.

Development of an intense red color when compound A is dissolved in an alkaline medium may be due to deprotonation of the NH proton to give **11**, which results in a conjugated system which exists approximately twice as long as **11'** (see Scheme I). The presence of an exchangeable NH proton at one of the two nitrogens appears to be responsible for the broadening of resonances for the neighboring protons (i.e., H_d, H_d', and H_e shown in Figure 3B). In other words, the broadening of these resonances lends further support to the structure having the NH proton rather than, for example , the OH proton.

Molecular Structure of Compound B. Figure 5 shows the ^1H NMR spectrum of compound B. The spectrum indicates the presence of an aldehydic proton, aromatic protons, and olefinic protons. In dimethyl-d_6 sulfoxide solution, the NMR spectrum reveals the presence of an NH proton which is spin coupled to H_e (Figure 5B). These results suggest a structural resemblance to compound A (**11'**) and/or its methanolysis compound (**12**). The structure of compound B can be determined to be *N*-[(1*E*,3*E*)-4-methanoyl-1,3-butadienyl]benzenecarboxamide by taking into account the results of the field-desorption mass spectrum ($C_{12}H_{11}NO_2$, M^+, m/e 201) and the observed chemical shifts and spin–spin coupling constants[9,13] (Table I). This compound seems to be formed according to the process shown in Figure 2. Development of a yellow color in alkaline media may be due to the structural change from **13'** to **13** (see Scheme II), since this change enables the conjugated side chain to conjugate further with the benzene ring and therefore enhances the

Scheme II



extent of the conjugation. It is of interest here to point out that the λ_{max} values of **13** (423 nm) and **12** (420 nm) agree well with that of **11'** (421 nm), manifesting the mutual relevancy of molecular structures determined in this work.

Conclusion

N^2-[(1*E*,3*E*)-1,3-Butadienyl]-N^1-1,3-butadienylbenzamidine (**11'**) and *N*-[(1*E*,3*E*)-4-methanoyl-1,3-butadienyl]benzenecarboxamide (**13'**), but not **2**, have been found to be responsible for the red color in the Fujiwara reaction when benzotrichloride was used as a chromogenic reagent. In alkaline media, these compounds take the anionic forms **11** and **13** as a result of deprotonation of the NH group. Owing to these extended conjugated systems, they develop an intense red and yellow color, respectively. These compounds appear to be formed by the hydrolysis of a dipyridinium cation which results in ring breakage of the pyridine rings.

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Registry No. 11', 77965-69-6; 13', 77965-70-9; benzotrichloride, 98-07-7.

Reactivity of 2-Aminothiazole toward 2,4-Dinitrofluorobenzene. Products and Structures

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2-Aminothiazole and 4-methyl-2-aminothiazole act as bident nucleophiles toward 2,4-dinitrofluorobenzene (DNFB) in dimethyl sulfoxide. Product structures have been ascertained by ^{1}H NMR spectroscopy as well as by X-ray analysis. In the absence of steric hindrance, the "aza" nitrogen is a more effective nucleophile site than the exocyclic "amino" nitrogen of the 2-aminothiazoles.

2-Aminothiazole reacts as a nucleophile with either of its nitrogen atoms, the exocyclic nitrogen or the endocyclic nitrogen, depending upon the electrophilic center and the experimental conditions. For example, with alkyl halides,[1] in the absence of strong bases, the endocyclic nitrogen is the main nucleophile, while with acyl[2] and sulfonyl[3] halides the exocyclic nitrogen is the main nucleophile. In order to collect further information on this behavior and to test an example of nucleophilic attack on an aromatic sp^2 carbon, we have investigated the reactions of 2-aminothiazole, 4-methyl-2-aminothiazole and 2-(*sec*-butylamino)thiazole with 2,4-dinitrofluorobenzene (DNFB) in dimethyl sulfoxide. The structures of reaction products have been assigned by ^{1}H NMR spectroscopy and X-ray analysis.

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Results and Discussion

The reaction between 2-aminothiazole and DNFB, in equimolecular amounts or with a deficiency of DNFB, is complete in about 48 h in dimethyl sulfoxide at 25 °C. The major product of this reaction is an imino derivative, as ascertained by its ^{1}H NMR spectrum (see Table I[17]). In fact, the signals of the protons of the thiazole ring are in the same field range (H_4) or shifted to higher field (H_5)

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