A Study on the Mechanism of the Dimerization of Quinazoline Compounds Catalyzed by Cyanide Ions

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It was shown that an intermediate, 4,4′(3*H*,3′*H*)-biquinazolinylidene (**2a**) was isolated in the formation process of 4,4′-biquinazolinyl (**3a**) which was obtained from the reaction of quinazoline (**1a**) with potassium cyanide, and **2a** was readily oxidized to **3a** by oxygen in air. The dimerization process was studied kinetically by NMR method. The result showed that the process was essentially similar to that of the benzoin condensation. The introduction of a methyl group into the C^2-position of **1a** resulted in a lowering of the reaction rate because the activation energy of 2-methylquinazoline (**1b**) dimerization became higher compared with that of **1a** dimerization.

It has been reported by Higashino et al.[1,2] that the chemical properties of the C^4-atom of quinazoline ring system are similar to those of carbonyl carbon. These properties were observed in the following reactions; i) the reaction of quinazoline(**1a**) with cyanide ions caused a dimerization,[1] ii) the benzoin-type condensation between quinazoline(**1a**) and aromatic aldehydes in the presence of cyanide ions resulted in the formation of α-aryl-4-quinazolinmethanol,[1] and iii) the benzilic acid-type rearrangement of aryl 4-quinazolinyl ketones proceeded in the presence of sodium hydroxide in dimethyl sulfoxide.[2]

Armarego and Willette[3] found that quinazoline (**1a**) reacted with cyanide ions to give 4,4′-biquinazolinyl(**3a**), and Higashino et al.[1] reported that this dimerization involved a benzoin-type condensation and oxidation. However, since an intermediate could not be isolated in the formation process of 4,4′-biquinazolinyl(**3a**), its mechanism is unknown. We studied its dimerization mechanism of quinazoline compounds in order to obtain useful information with respect to the carbonyl-like properties of the C^4-atom of quinazoline.

In this paper, we report that a benzoin-type condensation product, 4,4′(3*H*, 3′*H*)-biquinazolinylidene (**2a**), was isolated and the reaction process was investigated in detail by NMR technique.

Experimental

Infrared(IR) spectrum was recorded on a Jasco IRA-1 grating infrared spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were measured at 90 MHz and at 21 °C on a JEOL TNM-FX90QFT NMR spectrophotometer. Mass spectra were obtained on a JEOL JMS-D100 mass spectrometer. The samples were vaporized in a direct inlet system at 190 °C. Ultraviolet spectra were measured in dimethyl sulfoxide (DMSO) on a Shimadzu Recording Spectrophotometer UV-360.

Materials. Dimethyl sulfoxide and potassium cyanide were of the reagent grade. Dimethyl-d_6 sulfoxide was obtained from Merck.

Quinazoline(**1a**) was synthesized according to the method of Higashino.[4] After the crude **1a** was distilled under 15—20 mmHg (1 mmHg=133.322 Pa) and the fraction boiling at 115—125 °C was collected, it was twice passed through a column of alumina. The elution with benzene gave the pure compound, mp 48 °C, white needles. 2-Methylquinazoline(**1b**) was synthesied by the method described in the previous paper.[5] The crude **1b** was purified by the same manner as **1a** to give the pure compound, light yellow, needles, mp 41 °C.

4,4′(3*H*, 3′*H*)-Biquinazolinylidene (2a). A mixture of 3.8 mmol of **1a** and 7.7 mmol of KCN in 2 cm³ of DMSO was allowed to stand overnight under nitrogen atmosphere. The reaction mixture was poured into an ice-H_2O mixture. The separated crystals were collected and washed thoroughly with methanol and dried under reduced pressure. The crystals, mp 217—218 °C, were obtained as needles in a 70% yield. The compound **2a** had molecular formula, $C_{16}H_{12}N_4$ (*m/z*, 260(M^+)). The NMR spectrum was as follows; NMR (DMSO-d_6) $\delta(^1H)$=6.69—7.16 (8H, m), 8.73 (2H, d, J=8.0 Hz), and 6.3 (2H, bs). $\delta(^{13}C)$=113.2, 126.5, 138.0 (each s), 122.1, 127.0, 128.3, 129.0, 140.5 (each d). When **2a** was heated or allowed to stand overnight in air, it was readily oxidized to **3a**.

Oxidation of 2a with $K_3[Fe(CN)_6]$. A solution of 500 mg of $K_3[Fe(CN)_6]$ in 5 cm³ of H_2O was added to a mixture of 120 mg of **2a**, 10 cm³ of benzene and 1 cm³ of 50% NaOH, and the mixture was vigorously shaken for 1 h at room temperature. The benzene solution was dried over Na_2SO_4 and evaporation of the benzene gave **3a**.

2,2′-Dimethyl-4,4′(3*H*,3′*H*)-biquinazolinylidene (2b). The NMR data of **2b** in the reaction mixture were as follows; NMR (DMSO-d_6, 90 MHz) $\delta(^1H)$=2.60 (6H, s), 6.67—7.12 (6H, m) and 8.87 (2H, d, J=7.8 Hz). $\delta(^{13}C)$=112.8, 121.1, 125.9, 138.8 (each s), 121.6, 126.7, 128.8, 147.3 (each d), and 21.2 (q).

2,2′-Dimethyl-4,4′-biquinazolinyl (3b). The dimer, **3b**, mp 219 °C, was prepared by the same method described by Armarego and Willette.[3] The yield was 25%.

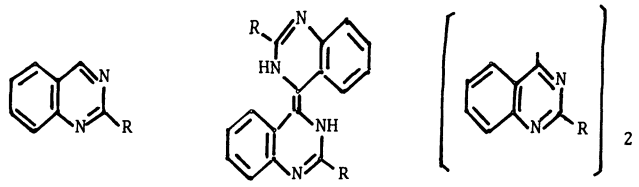
3,4-Dihydro-4-quinazolinecarbonitrile. 3,4-Dihydro-4-quinazolinecarbonitrile was synthesized according to the method of Higashino.[4]

Kinetics of Dimerization. The reaction mixture was made by mixing equal volumes (0.2 cm³) of KCN-DMSO-d_6 solution and DMSO-d_6 solution of quinazoline compound (**1**) in an NMR tube and air was replaced with N_2 after degassing. The concentrations of KCN and **1** in a mixture of 0.2 cm³ of KCN-DMSO-d_6 and 0.2 cm³ of **1**-DMSO-d_6 are represented as mol dm^{-3}. Temperature equilibration was done outside the NMR probe in a thermostat at a constant temperature±0.1 °C. These reactions were followed by integration of the signal of the hydrogen atom at C^4-position of **1a** or **1b**. The errors of integration of the hydrogen atom observed by using CH_2Cl_2

as the standard were ±1.2% for **1a** and ±2.6% for **1b**, respectively. Rate constants were calculated by a least-square computer.

Results and Discussion

Although Higashino et al.[1] assumed that 3,4-dihydro-4,4′-biquinazoline (**2′**) (Chart 2) was a formal benzoin-type condensation product for **1a**, **2′** could not be isolated. Furthermore, it is yet unknown whether the oxidation step is caused by oxygen in atmosphere or by **1a** which may act as the hydride ion acceptor to form a reduction product such as 3,4-dihydroquinazoline.

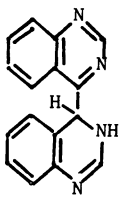


1a: R = -H
1b: R = -CH_3

2a: R = -H
2b: R = -CH_3

3a: R = -H
3b: R = -CH_3

Chart 1.



3,4-Dihydro-4,4′-biquinazoline (**2′**)

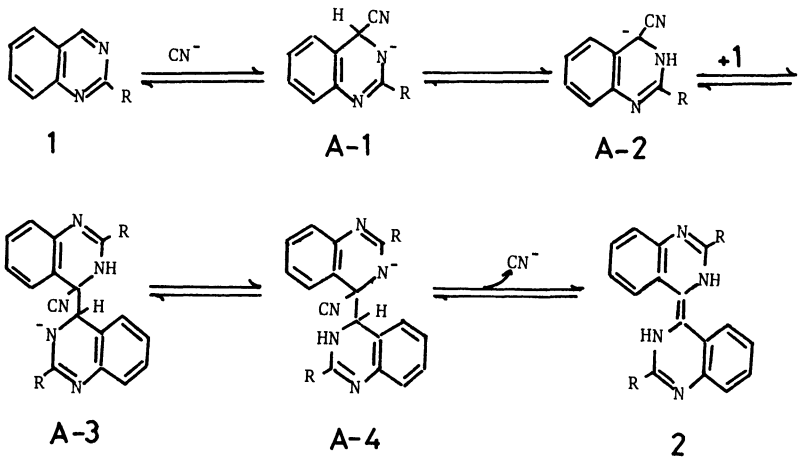
Chart 2.

When a dried dimethyl sulfoxide solution of **1a** containing potassium cyanide was allowed to stand under nitrogen atmosphere at room temperature, **2′** was not obtained, but the isomer, 4,4′(3*H*, 3′*H*)biquinazolinylidene (**2a**) was isolated. The structure of **2a** was elucidated by the spectra data (see Experimental) and the following chemical procedures. Compound **2a** was easily oxidized to **3a** not only with $K_3[Fe(CN)_6]$, but also by atmospheric oxygen at room temperature. The structure of **2a** was suggested as (*E*)-form as shown in Chart 1 on the basis of the following facts: (*E*)-Form corresponds to *trans*-stilbene and (*Z*)-form to *cis*-stilbene. Rizebos and Havinga[6] reported that *trans*-stilbene showed a longer wavelength shift of the absorption maximum (λ_{max} 295 nm, ε 27000) than *cis*-stilbene (λ_{max} 280 nm, ε 10500) because the hydrogen atoms at the ortho-positions of *cis*-stilbene interact mutually and the stilbene cannot exist in a coplanar structure either. On the other hand, Armarego and Willette[3] reported that the ultraviolet spectrum of 4,4′-biquinazolinyl(**3a**) is similar to that of **1a**, due to the restricted rotation about the 4,4′-bonds; the two halves of the molecule are not coplanar and the chromophores are not highly conjugated with one another. If the compound, **2a**, corresponds to (*Z*)-form, the hydrogen atoms at C^5-and $C^{5'}$-positions interact mutually and also it can hardly maintain a coplanar structure. However, the absorption maximum of **2a** in DMSO is at 414 nm (ε 9680), and is remarkably longer than that of **3a** (λ_{max} 320 nm, ε 7110 in DMSO). Therefore, this fact suggests that the double bonds of **2a** may be highly conjugated by maintaining a coplanar structure and it seems reasonable to assume that **2a** is in (*E*)-form.

Since the above result proved that the dimerization of **1a** in the presence of potassium cyanide gave **2a** which was oxidized to **3a**, the reaction process for the formation of **2** is assumed to be as shown in Scheme 1, which is similar to the benzoin condensation process: *N*-anion (**A-1**) formed by addition of cyanide ions to **1** would rearrange readily to carbanion (**A-2**) by a prototropic shift. Nucleophilic addition of **A-2** to quinazoline provides an intermediate *N*-anion, **A-3**, which rearranges readily to *N*-anion (**A-4**) and is finally converted to product **2** by rapid loss of CN^-. The process represented in Scheme 1 is also summarized as represented in Eqs. 1 and 2,

$$Q + C \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \textbf{A-2} \qquad (1)$$

$$\textbf{A-2} + Q \xrightarrow{k_2} P + C \qquad (2)$$



Scheme 1.

where [Q] refers to free quinazoline and C to free cyanide ions. **A-2** is the carbanion in Scheme 1, and P stands for product **2**. The presence of carbanion **A-2** is suggested from the following reasons: Hydrogen cyanide adds easily to quinazoline to produce 3,4-dihydro-4-quinazolinecarbonitrile. When 3,4-dihydro-4-quinazolinecarbonitrile in DMSO-d_6 was mixed with quinazoline and potassium hydroxide under nitrogen atmosphere in an NMR tube, the presence of **2a** was observed in the NMR diagram. This corresponds to the fact that α-hydroxyphenylacetonitrile was mixed with benzaldehyde and a base to give benzoin.[10]

Figure 1 shows the NMR diagram of the reaction mixture (0.4 cm^3) of **1a** (3.72×10^{-1} mol dm^{-3}) and KCN (4.55×10^{-2} mol dm^{-3}) in DMSO-d_6 at 25 min (A) and at 300 min (B) after mixing under nitrogen atmosphere, respectively. Since Fig. 1 shows only the presence of **1a** as the starting material and **2a** as the reaction product, it is possible to follow the reaction process kinetically by determing the time dependence of the signal of the hydrogen atom at C^4-position of quinazoline represented as * in Fig. 1. The rate constant may be derived, using a steady-state approximation in a similar manner as benzoin condensation.[7-10] That is to say, if $k_{-1}\gg k_2$, the following rate expression can be derived,

$$d[P]/dt = \frac{k_1k_2}{k_{-1}}[Q][C_0], \quad (3)$$

where [Q] refers to free quinazoline concentration and C_0 to cyanide ion concentration. The second order rate plots with respect to quinazoline are shown in Fig. 2. Although ^{1}H NMR method may be less accurate than other spectrophotometric methods, the second order plots were fairly linear ($r>0.98$) in all cases. This is in agreement with the result that benzoin condensation is kinetically second order in benzaldehyde.[7-10] Therefore, it suggests that the process of Eq. 2, that is, addition of carbanion, **A-2**, to the carbon at C^4-position of quinazoline is rate-determing, corresponding to the result that addition of carbanion, [ArC(CN)OH]$^-$, to the carbonyl carbon of benzaldehyde is rate-determining in benzoin condensation.[7-10] It seems also reasonable to consider that the chemical properties of C^4-atom of the quinazoline ring system are similar to those of carbonyl carbon.

Furthermore, the dimerization process of **1b** was investigated in order to clarify the effect of methyl group at C^2-position of **1** on the dimerization. When **1b** was allowed to react under the same experimental conditions as the quinazoline dimerization, only 2,2′-dimethyl-4,4′-biquinazolinyl(**3b**) was obtained. The intermediate, 2,2′-dimethyl-4,4′(3*H*,3′*H*)-biquinazolinylidene(**2b**) could not be isolated because it was readily oxidized, compared with **2a**. Figure 3 shows ^{1}H NMR spectra of the reaction mixture (0.4 cm^3) of **1b** (3.17×10^{-1} mol dm^{-3}) and KCN (5.3×10^{-2} mol dm^{-3}) in

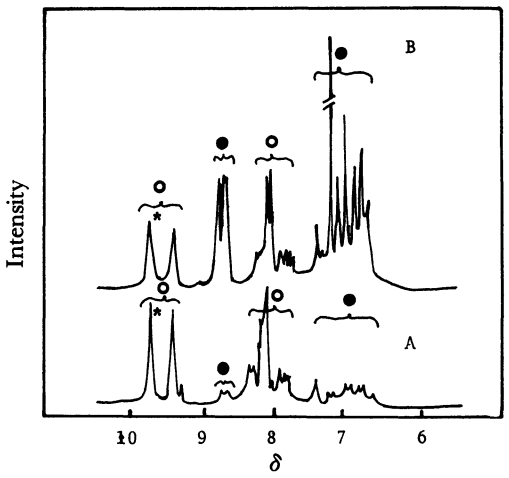


Fig. 1. ^{1}H NMR Spectra of the reaction mixture of quinazoline (**1a**) catalyzed by KCN in DMSO-d_6 at 21 °C.
○: **1a**, ●: **2a**, A: 25 min, B: 300 min.

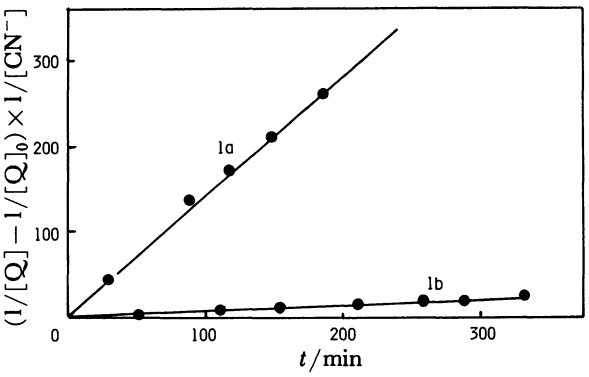


Fig. 2. Second order plots for the dimerization of quinazoline (**1a**) and 2-methylquinazoline (**1b**) at 25 °C.

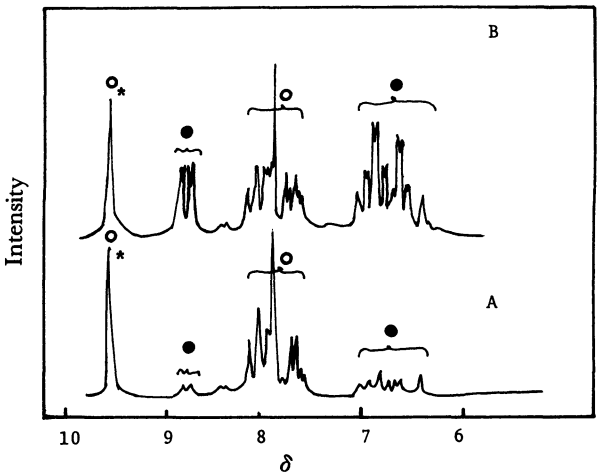


Fig. 3. ^{1}H NMR Spectra of the reaction mixture of 2-methylquinazoline (**1b**) catalyzed by KCN in DMSO-d_6 at 21 °C.
○: **1b**, ●: **2b**, A: 280 min, B: 1500 min.

Table 1. Kinetic and Thermodynamic Parameters for the Dimerization of **1**

Parameter	**1a**	**1b**
k/(mol dm^{-3})$^{-2}$ min^{-1} at 25 °C	1.20±0.09	7.18×10^{-2}±0.88×10^{-2}
ΔE^*/kJ mol^{-1}	1.02×10	2.39×10
ΔG^*/kJ mol^{-1} at 25 °C	5.71×10	6.42×10
ΔH^*/kJ mol^{-1}	5.24	1.90×10
ΔS^*/J mol^{-1} T^{-1}	−1.74×10^2	−1.52×10^2

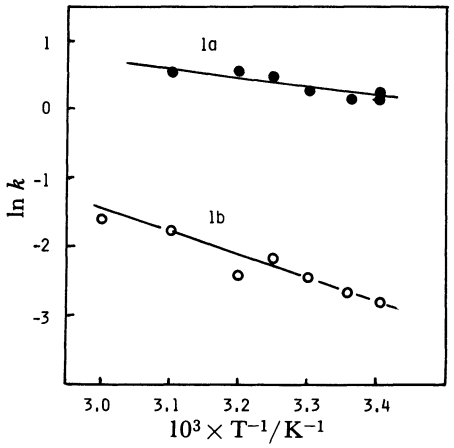


Fig. 4. Plots of ln k against T^{-1}.

DMSO-d_6 at 280 min (A) and at 1500 min (B) after mixing, respectively. Since the presence of **1b** and **2b** was observed by the NMR spectra shown in Fig. 3, the dimerization process of **1b** can be followed by ^{1}H NMR methods described above for the dimerization of **1a**. The rate was estimated by following the signal of hydrogen at C^4-position of **2b** represented as * in Fig. 3. Figure 2 shows second order rate plots for the **1b** dimerization, indicating that the rate of **1b** is lower than that of **1a**. Kinetic parameters were determined from the temperature-dependency of the rate constant, k. Plots of ln k vs. T^{-1} show an approximately linear relationship in the temperature ranges 20—45 °C for **1a** and 20—60 °C for **1b** (Fig. 4). Activation parameters, ΔE^*, ΔG^*, ΔH^*, and ΔS^* were determined (Table 1). The value of ΔE^* for the **1a** dimerization was smaller than that for the **1b** dimerization. In comparison with the parameters of benzoin condensation in methanol at 44—66 °C ($\Delta G^{\ddagger}_{298}$=94.1 kJ mol^{-1}, ΔH^*=41.8 kJ mol^{-1}, and ΔS^*=−75 J mol^{-1} T^{-1}), the values of ΔH^* and ΔG^* for both quinazolines were low. It is interesting because the reactivity of quinazoline compounds is suggested to be higher than that of benzaldehyde in regard to the benzoin condensation. Activation enthalpy, ΔH^*, for **1b** is much higher than that for **1a**, while ΔS^* at 25 °C is essentially the same. It is expected that the electrophilicity of the C^4-position of **1a** is higher than that of **1b** because electron density at the C^4-position of **1b** will increase due to the electron-donating effect of the methyl group. This expectation is compatible with the above result of activation parameters.

In conclusion, the present quantitative study verified that the dimerization process of **1** is essentially similar to the benzoin condensation process.

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