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Mechanism of the Ullmann Condensation. I.*1 Kinetic and Thermodynamic Studies

Tran Dinh TUONG and Mitsuhiko HIDA

Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo

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Kinetic studies of the Ullmann condensation of an aryl halide, sodium 1-amino-4-bromoanthraquinone-2-sulfonate and an amine, aniline, were undertaken. Cupric copper was used as the catalyst. The reaction was found to be first order in monomeric aryl halide and first order in amine, and to depend hyperbolically on the concentration of the catalyst. It was shown by ESR measurements that the copper catalyst exists largely as cupric species. The experimental results were discussed mechanistically.

A large number of patents and papers have been written on the condensation reaction of aryl halides with amines or phenoxides in the presence of a copper catalyst. This reaction is known as the Ullmann condensation reaction[1] and has been an important tool in, for example, the synthesis of dyes, drugs and compounds of biochemical interest. On the other hand, the reaction has been classified as an unknown mechanism[2,3] since the mechanism has not yet been well established in spite of the efforts of several investigators.[4-10]

Particularly it is noticeable that little information is availahle as to what the real catalytic species is. Mechanistic studies are difficult for the following reasons:

a) The reaction must often be carried out under vigorous conditions, *i.e.*, at temperatures higher than 150°C and sometimes under high pressure.

b) Since homogeneous systems are rarely obtained, kinetic studies are hampered.

Because the mechanism is not yet known in detail, the improvement of this industrially important reaction has been attempted[11-14] empirically rather than from the theoretical point of view. Thus, in order to use this reaction in synthetic chemistry more efficiently, more investigations must be undertaken in connection with the mechanism of this reaction. This necessity prompted the present study. The preliminary results will be reported in this paper.

Results and Discussion

A kinetic study was made of the condensation of sodium 1-amino-4-bromoanthraquinone-2-sulfonate (I) with aniline in an aqueous buffer solution. Cupric sulfate was selected as the catalyst because of its large solubility in water and because of the weak coordinating ability of the sulfate ion to the metal ion. The reaction is known to proceed under comparatively mild conditions.[15,16]

When aniline was used in large excess compared with I, a homogeneous system could be attained and kinetic measurements with a good reproducibility were possible.

Reaction Products. Paper chromatography revealed that the reaction products were bromamic

*1 Presented in part at the Annual Meetings of the Chemical Society of Japan, March, 1968 (Osaka), and April, 1969 (Tokyo).

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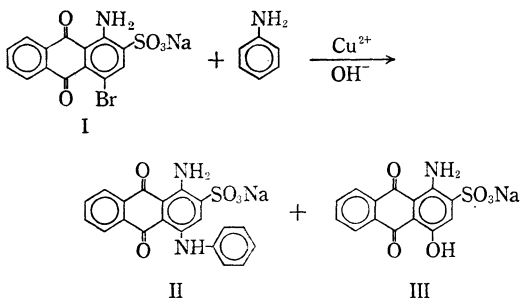

I

II III

acid (I), sodium 1-amino-4-anilinoanthraquinone-2-sulfonate (II), and sodium 1-amino-4-hydroxyanthraquinone-2-sulfonate (III).

Their amounts were determined spectrophotometrically.

Compared with the main product, II, III was found to be formed in a negligibly small quantity (less than 3% of the total concentration) and so it was neglected in the calculation of the reaction rates. This by-product was also formed in the reaction carried out in the absence of aniline, but it was not produced by treating II in an alkaline solution. These facts show without doubt that III was the condensation product of I with the alkaline aqueous solvent. Other side reactions, such as dehalogenation and biaryl formation which are known often to accompany the Ullmann condensation reaction,[17] were not observed.

Kinetics. As is shown in Fig. 1, the initial rate, v_0, was not proportional to the concentration of I.

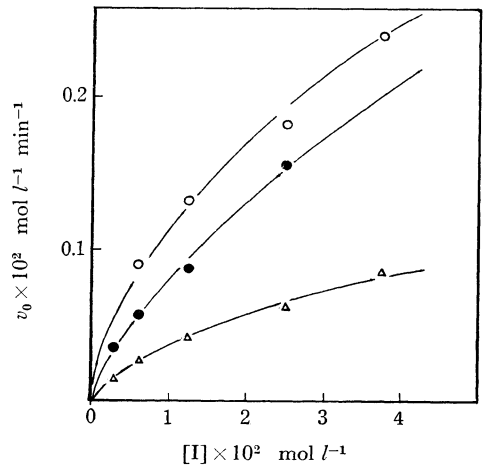

Fig. 1. Dependence of the initial rate on the concentration of I.
pH=9.94, T=343°K
$[PhNH_2]_0$=0.30 mol l^{-1}
$[Cu^{2+}]_0$=2.5×10^{-4} mol l^{-1} (△)
12.5×10^{-4} mol l^{-1} (●)
50.0×10^{-4} mol l^{-1} (○)

These results can be understood as follows.

The spectrum of bromamic acid (I) in an aqueous solution was observed to change bathochromically and hypochromically with an increase in the concentration. This fact suggests that I aggregates in an aqueous solution. The degree of aggregation and the aggregation constant at 70°C and at pH 9.94 were found to be 2 and about 200 respectively by the maximum slope method.[18] Thus, the monomeric and dimeric species are equilibrated in the reaction system. If the initial rate is assumed to be proportional to the concentrations of the monomer and the dimer (c_1 and c_2), the initial rate may be expressed by Eq. (1):

$$v_0 = k_1 c_1 + k_2 c_2 \quad (1)$$

where k_1 and k_2 are rate constants associated with the monomer and the dimer respectively.

If the analytical amount of I is denoted as c_0, we have:

$$c_0 = c_1 + 2c_2 \quad (2)$$

By combining Eq. (1) with Eq. (2), we obtain Eq. (3):

$$v_0 = \left(k_1 - \frac{k_2}{2}\right)c_1 + \frac{k_2}{2} c_0 \quad (3)$$

Therefore,

$$\frac{v_0}{c_0} = \left(k_1 - \frac{k_2}{2}\right)f_1 + \frac{k_2}{2} \quad (4)$$

where f_1 is the fraction of the monomer.

The concentration, c_1, of the monomeric species

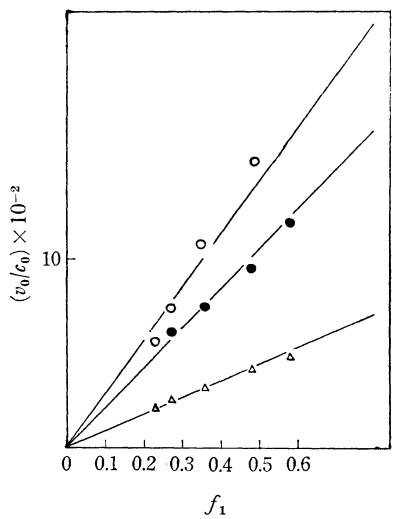

Fig. 2. Linear relationsnip between v_0/c_0 and the monomer fraction f_1.
pH=9.94, T=343°K
$[PhNH_2]_0$=0.30 mol l^{-1}
$[Cu^{2+}]_0$=2.5×10^{-4} mol l^{-1} (△)
12.5×10^{-4} mol l^{-1} (●)
50.0×10^{-4} mol l^{-1} (○)

17) R. G. R. Bacon and H. A. O. Hill, *Quart. Rev.*, **19**, 95 (1965).

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is obtained by solving Eq. (5):

$$400c_1^2 + c_1 - c_0 = 0 \quad (5)$$

Figure 2 shows the linear plot of v_0/c_0 against f_1. The values of k_1 and k_2 can be determined from the slope ($=k_1-k_2/2$) and the intercept ($=k_2/2$) of the straight lines.

These results suggest that only the monomeric species was active and that the reaction was first order with respect to the monomer of I.

The unimolecularity of the aryl halide in the Ullmann condensation reaction has been reported by several workers.[9,10]

Figure 3, where the initial rate is plotted against the initial concentration of aniline, shows that the first order can be assigned to the amine.

The rate law is, therefore, given by:

$$\text{rate} = k_0 f_1 c_0[\text{PhNH}_2] = k_{app} c_0[\text{PhNH}_2] \quad (6)$$

where k_{app} is a function of the reaction conditions (pH, temperature and the atmosphere) and of the concentration of the copper ion.

The dependence of the apparent rate constant, k_{app}, on the concentration of the catalyst is shown by the data tabulated in Table 1. The experimental data can be satisfied by the following three relations:

a) $$k_{app} = k[\text{Cu}^{2+}]^m \quad (7)$$

where k and m are constants.

The value of m varied over the range from 0.48 to 0.70, according to the conditions of the reaction (pH and temperature). The fact that the value of m varied around 0.50 is interesting, but attempts to devise mechanisms which could fit the above relation were unsuccessful.

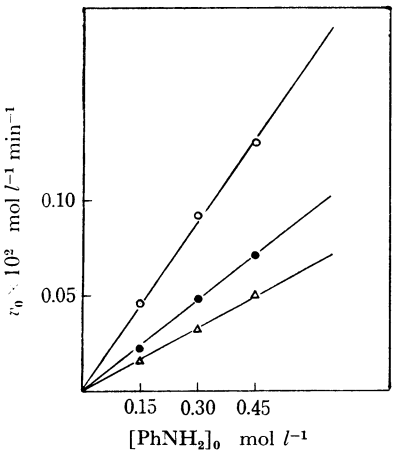

Fig. 3. Linear relationship between the initial rate and the concentration of aniline.
pH=9.94, T=343°K
$[I]_0=1.25\times10^{-2}$ mole l^{-1}
$[Cu^{2+}]_0=2.50\times10^{-4}$ mol l^{-1} (△)
5.00×10^{-4} mol l^{-1} (●)
100.00×10^{-4} mol l^{-1} (○)

Table 1.[a] Dependence of the apparent rate constant k_{app} on the catalyst concentration

No	pH	T, °K	$Cu^{2+}\times10^4$ mol l^{-1}	$k_{app}\times10^2$, l mol^{-1} min^{-1}
1	9.46	343	2.62	3.23
2	9.46	343	5.81	4.68
3	9.46	343	8.32	5.61
4	9.46	343	12.87	7.07
5	9.46	243	16.64	7.53
6	9.94	343	2.50	8.46
7	9.94	343	2.80	9.22
8	9.94	343	5.02	15.74
9	9.94	343	8.12	19.58
10	9.94	343	12.50	24.96
11	9.94	343	50.00	28.72
12	10.57	343	2.74	9.06
13	10.57	343	5.54	13.67
14	10.57	343	8.11	16.90
15	10.57	343	12.88	17.82
16	9.94	333	2.72	5.76
17	9.94	333	5.50	9.91
18	9.94	333	8.29	12.29
19	9.94	333	13.08	13.98
20	9.94	353	2.72	14.21
21	9.94	353	5.35	22.89
22	9.94	353	8.17	31.72
23	9.94	353	12.84	36.86
24	9.94	363	2.69	18.05
25	9.94	363	5.54	32.33
26	9.94	363	8.22	42.55
27	9.94	363	12.77	46.69

a) Experiments under nitrogen atmosphere, $[I]_0=1.25\times10^{-2}$ mol l^{-1}, $[PhNH_2]_0=0.30$ mol l^{-1}.

b) $$k_{app} = k\frac{[\text{Cu}^{2+}]}{[\text{Cu}^{2+}]+\alpha} \quad (8)$$

where k and α are constants, their values depending on the pH and the temperature.

The energies and entropies associated with k and α were found to be as follows:

$$\Delta E^{\neq}(k) = 12.37 \text{ kcal}\cdot\text{mol}^{-1}$$
$$\Delta S^{\neq}(k) = -19.80 \text{ eu } (T=343°\text{K})$$
$$\Delta E^{\neq}(\alpha) = 4.12 \text{ kcal}\cdot\text{mol}^{-1}$$
$$\Delta S^{\neq}(\alpha) = -60.30 \text{ eu } (T=343°\text{K})$$

This hyperbolic relation could be derived from the following mechanism (I is denoted as ArBr):

$$\text{Cu}^{2+} \overset{K_1}{\rightleftharpoons} \text{Cu}^{+} \quad (9)$$

$$\text{Cu}^{+} + \text{ArBr} \overset{K_2}{\rightleftharpoons} \text{Cu}^{+}\cdot\text{BrAr} \quad (10)$$

$$\text{Cu}^{2+} + \text{Cu}^{+} \overset{K_3}{\rightleftharpoons} \text{Cu}^{2+}\cdot\text{Cu}^{+} \quad (11)$$

$$Cu^{+}\cdot BrAr + PhNH_2 + OH^- \xrightarrow{k} Cu^+ + ArNHPh + Br^- + (ArOH) \quad (12)$$

If the values of both K_2 and K_3 are sufficiently small, we can derive Eq. (13) from Eqs. (9)—(12):

$$\text{rate} = (kK_1K_2/2K_3)[ArBr][PhNH_2][Cu^{2+}]/([Cu^{2+}]+K_1+1/2K_3) \quad (13)$$

Equation (13) is identical with Eq. (8) provided that:

$$k_0 = kK_1K_2/2K_3$$

and

$$\alpha = K_1 + 1/2K_3$$

In proposing this mechanism, an equilibrium between cuprous and cupric species, the activity of cuprous[19] copper and the deactivating effect of the cupric ion were postulated.

c) The dependence of the reaction rates on the catalyst concentration could also be interpreted on the assumption of the formation of clusters. Thus, the catalyst is assumed to exist in the reaction system as a monomer and as a cluster of the n-th degree, so that:

$$n\text{Cu} \overset{K}{\rightleftharpoons} \text{Cu}_n \quad (14)$$

By designating the initial concentration of the catalyst as $[Cu^{2+}]_0$, we obtain Eq. (15):

$$[Cu^{2+}]_0 = [Cu] + n[Cu_n] \quad (15)$$

Further, it is assumed that the apparent rate constant, k_{app} $(=k_0f_1)$, can be written as follows:

$$k_{app} = k_1[Cu] + n\bar{k}_n[Cu_n] \quad (16)$$

where k_1 is the rate constant of the reaction of the monomeric species and where $\bar{k}_n$ $(=k_n/n)$ is the rate constant of the clusters (per molecule).

By combining Eq. (15) with Eq. (16), we get Eq. (17):

$$k_1[Cu^{2+}]_0 - k_{app} = n(k_1-\bar{k}_n)Cu_n \quad (17)$$

and:

$$k_{app} - \bar{k}_n[Cu^{2+}]_0 = (k_1-\bar{k}_n)[Cu] \quad (18)$$

By inserting Eq. (18) into Eq. (14):

$$\frac{k_1[Cu^{2+}]_0 - k_{app}}{n(k_1-\bar{k}_n)} = \frac{K}{(k_1-\bar{k}_n)^n}(k_{app}-\bar{k}_n[Cu^{2+}]_0)^n \quad (19)$$

or

$$\log (k_1[Cu^{2+}]_0-k_{app}) = n \log (k_{app}-\bar{k}_n[Cu^{2+}]_0) + \log \frac{nK}{(k_1-\bar{k}_n)^{n-1}} \quad (19')$$

where K is the equilibrium constant.

19) The addition of reducing agents, such as $NaHSO_3$, $SnCl_2$, $FeSO_4$, $TiCl_3$, *etc.*, to the reaction system, was observed to enhance markedly the reaction rate. Detailed results will be reported and discussed in a later paper of the series.

If the cluster is assumed to be inactive, we can rewrite Eq. (19′) as Eq. (20):

$$\log (k_1[Cu^{2+}]_0-k_{app}) = n \log k_{app} + \log \frac{nK}{k_1^{n-1}} \quad (20)$$

The value of k_1 is given by Eq. (21):

$$k_1 = \lim_{[Cu^{2+}]_0 \to 0} \frac{dk_{app}}{d[Cu^{2+}]_0} \quad (21)$$

The value of k_1 was determined graphically from the slope of the tangent of the plot of k_{app} *vs.* $[Cu^{2+}]_0$ at $[Cu^{2+}]_0=0$, and then $\log (k_1[Cu^{2+}]_0-k_{app})$ was plotted against $\log k_{app}$ (Fig. 4). The values of n and K were determined from the slope and the intercept; their values are summarized in Table 2. It was found that n was independent of the reaction conditions and that it has a constant value of 3.

The activation parameters associated with k_1 were determined from the Arrhenius plot:

$$\Delta E^{\ddagger}(k_1) = 9.91 \text{ kcal}\cdot\text{mol}^{-1}$$

$$\Delta S^{\ddagger}(k_2) = -18.33 \text{ eu } (T=343^{\circ}\text{K})$$

The apparent energy of activation associated with k_{app} was also determined to be 9.14 kcal mol^{-1}. As is shown in Fig. 5, the apparent energy of activation is independent of the concentration of the cupric ion. Since:

$$k_{app} = k_1f_1F_1[Cu^{2+}]_0$$

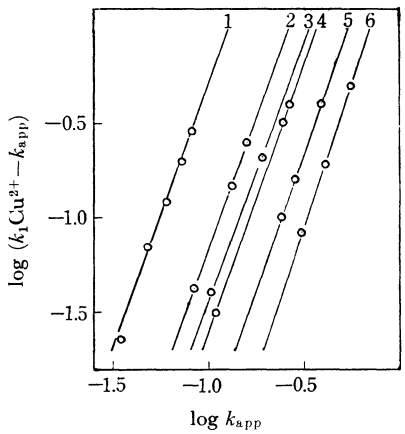

Fig. 4. Linear relationship between $\log(k_1Cu^{2+} - k_{app})$ and $\log k_{app}$.

	1	2	3	4	5	6
pH	9.46	9.94	10.57	9.94	9.94	9.94
T°K	343	343	343	333	353	363

Table 2
The aggregation of copper catalyst

pH	T°K	$k_1\times10^{-2}$	n	$k\times10^{-6}$
9.46	343	1.85	3	5.85
9.94	343	4.05	3	1.70
10.57	343	4.75	3	3.60
9.94	333	2.40	3	8.39
9.94	353	5.75	3	5.65
9.94	363	8.00	3	8.53

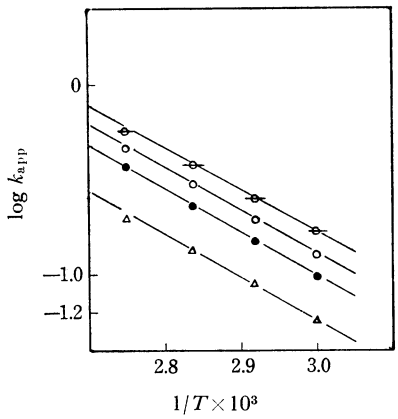

Fig. 5. Arrhenius plots.
pH=9.94, $[I]_0=1.25\times10^{-2}$ mole l^{-1}
$[PhNH_2]_0=0.30$ mole l^{-1}
$[Cu^{2+}]_0=2.5\times10^{-4}$ mol l^{-1} (△)
5.0×10^{-4} mol l^{-1} (●)
8.1×10^{-4} mol l^{-1} (○)
13.0×10^{-4} mol l^{-1} (-⊖-)

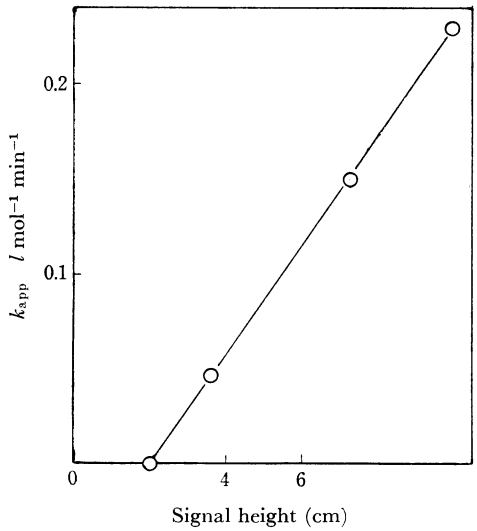

Fig. 6. Linear relationship between the apparent rate constant k_{app} and ESR absorption intensity.

where F_1 is the fraction of the monomeric catalyst, the apparent enthalpy of activation, H_{app}, is given by Eq. (22):

$$\Delta H^{\neq}_{app} = \Delta H^{\neq}_0 + \frac{1-f_1}{2-f_1}\Delta H_1 + \frac{1-F_1}{3-2F_1}\Delta H_2 \quad (22)$$

In Eq. (22), the enthalpy of activation for k_1 and the enthalpies of the aggregation of bromamic acid and the catalyst are designated as $\Delta H_0^{\neq}$, ΔH_1 and ΔH_2 respectively.

The second and third terms are negligibly small, compared with the first term. Therefore, the apparent energy of activation is near to $\Delta E^{\neq}(k_1)$ and independent of the concentration of the catalyst.

In order to obtain more information as to the nature of the catalyst species in the reaction solution, we examined the ESR spectra of the reaction system.[20] The results showed that the catalyst exists mostly in the divalent form, and a good proportionality was observed between the apparent rate constant, k_{app}, and the intensity (height) of the signal (Fig. 6). The intercept on the abcissa axis corresponds to the absorption due to the solvent water.

The kinetic data and the results of ESR measurements can be correlated if we assume that the copper clusters are inactive towards both the reaction and the electron-spin-resonance absorption. The monomeric cupric species can thus be postulated to be responsible for the promotion of the condensation reaction, but the possibility that this species exhibits the catalytic activity only after being reduced to a lower oxidation state[19] cannot be excluded.

Further studies are in progress to elucidate the nature of the "true" catalytic species and to obtain more information as to the elementary processes of the reaction.

20) Detailed results will be reported later. The authors are indebted to Dr. K. Hirasawa of The University of Tokyo for ESR measurements and helpful discussions.

Experimental

Materials. Commercial sodium 1-amino-4-bromoanthraquinone-2-sulfonate (I) was purified by repeatedly salting out with sodium acetate until the absorbance became constant. The purity was confirmed by paper chromatography (R_f=0.72), by elemental analysis (Found: N, 3.51%. Calcd: 3.47%), and by the conversion into its salts (*p*-toluidine salt : mp(corr) 241—241.2°C, Found: N, 5.82%. Calcd: 5.67%. *S*-benzylthiuronium salt: mp (corr) 202.9—203.4°C, Found: N, 7.64. Calcd: 7.66%). The visible spectrum shows a maximum at 485 mμ.[21]

Sodium 1-amino-4-anilinoanthraquinone-2-sulfonate (II) was synthesized by the reaction of I with aniline. Purification was carried out by salting out with sodium chloride. R_f=0.86. Found: N, 6.69%. Calcd 6.73%. λ_{max}=604 mμ.[21]

Sodium 1-amino-4-hydroxyanthraquinone-2-sulfonate (III) was obtained from the reaction of I and boric acid in 4% oleum, in yield of 85% (based on I). R_f=0.66. Found: N, 4.11%. Calcd: 4.54%. λ_{max}=540 mμ[21]

G.R. aniline was used after having been distilled under reduced pressure in the presence of zinc powder.

The cupric sulfate (pentahydrate) was of a reagent grade. The copper content was determined by iodometry.

The solvent was prepared by combining aqueous solutions of sodium carbonate (0.2M) and borax (0.15M) at an appropriate volumetric ratio.

21) T. Tokumitsu, M. Okamoto and T. Hayashi, *Kogyo Kagaku Zasshi*, **67**, 201 (1964).

Analytical Procedures. Paper chromatography was accomplished on Toyo Paper No. 5 at room temperature, using the *n*-BuOH - EtOH - 2% aqueous ammonia (6 : 2 : 3) solution as the solvent.[22]

The concentrations of the reaction products were determined by the usual spectrometrical method, in which the absorbances at 485, 540, and 604 mμ were used.

It was also confirmed that copper salts did not influence the spectrum of the reaction mixture.

Apparatus and Operation. Experiments were carried out in an apparatus devised to shut out the air. The nitrogen was purified of contaminating oxygen by passing it through pyrogallol.

A typical kinetic measurement was as follows:

Aniline, bromamic acid (I) and the solvent were mixed in a flask. A nitrogen stream was then introduced and allowed to bubble into the solution at room temperature for 2.5 hr. The solution was subsequently brought to the reaction temperature and the catalyst (in an aqueous solution) was added with the help of a syringe. This instant was taken to be time 0.

At 3-min intervals, 0.05-cc portions of the reaction solution were taken out with the micropipette, diluted in 50 or 25 cc of water, and subjected to spectroscopic measurements.

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22) T. Tokumitsu, M. Okamoto and T. Hayashi, *Kogyo Kagaku Zasshi*, **67**, 197 (1964).