The Catalytic Life of $CdBr_2$–KBr and Its Affect on the Rate of Indole Formation from Aniline and Ethylene Glycol

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In the liquid-phase synthesis of indole from aniline and ethylene glycol (EG), a $CdBr_2$–KBr catalyst gave a high yield of indole. In recycling experiments using the catalyst in an autoclave, the yield of indole remained stable and the inorganic components of the catalysts did not suffer degeneration. The time course of the reaction under high pressure and high temperature was evaluated using a newly devised autoclave. The rate of formation of indole was determined to be proportional to the concentrations of both EG and the catalyst. Based on these findings for the reaction over $CdBr_2$–3KBr, it is clear that this catalyst provides a simple and low-cost catalytic process for the formation of indole.

Indole is used industrially for amino acid drips and as a raw material for producing indigo dye and perfume. It is also an important raw material that is used in the production of tryptophan (an amino acid).

There are various methods that have been used to produce indole. Previous main methods are characterized by one or two best catalysts. In the synthesis from o-ethylaniline, a yield of indole of 50.7% was gained over TiO_2 catalyst at 660—680 °C.[1] Over Cr–Cu–K/carbon, the yield was 44.8% at 640 °C and in a decompression system of 10 mmHg (1 mmHg=133.322 Pa).[2] A merit of the o-ethylaniline method is that indole can be obtained in a high concentration in a one-step process in a fixed bed and flow-type reactor. However, o-ethylaniline is expensive, and the yields of the process are low. In the synthesis from o-aminostyrene, indole was formed in a yield of 74.0% over $[PdCl_2(CH_3CN)_2]$–LiCl.[3] In the synthesis by hydrogenation of 2-(o-aminophenyl)ethanol a high yield of 90.0% was gained over Cu–Cr at 250 °C.[4] However, the costs of o-aminostyrene and 2-(o-aminophenyl)ethanol profitable are high and have to be lowered by inovations of syntheses of these materials for industrial production of indole. In the case of direct synthesis from aniline and acetaldehyde, the raw materials are inexpensive. The maximum yield is, however, very low, 18.0% at 700 °C.[5] Styrene and ammonia are very cheap as raw materials. This method provided indole in a yield of only 18.4% over Cr–Cu–K catalyst at 670 °C and at an 8 mol/mol ratio (ammonia:styrene).[6] In the synthesis from phenylhydrazine and paraldehyde (the Fischer method), γ-Al_2O_3 is an active catalyst at 240—400 °C and a yield of about 60% is reliably obtained.[7] However, phenylhydrazine is also expensive. Thus, previous methods cannot provide a low-cost process of indole production on an industrial scale.

On the other hand, catalytic synthesis of indole from aniline and ethylene glycol (EG) has the potential to produce inexpensive indole.[8—11] We have found that in liquid phase reactions, PbI_2–KI,[10,12] PbI_2–SrI_2,[12] PbI_2–BaI_2,[12] and $CdBr_2$–KBr[11,13] provide indole in high yields. However, according to the results of recycling experiments, PbI_2–KI suffered a slight decrease in the yield after the first cycle, but from the second cycle on, the yield was maintained.[12] To investigate the life of binary catalysts of Cd(II) (e.g., $CdBr_2$–KBr), the catalysts were recycled in a batch mode in an autoclave. We also evaluated various methods for recovery of the catalyst. Here we report encouraging results for the recycling of $CdBr_2$–KBr catalysts, including chemical analysis of the catalysts. Furthermore, we also investigated the rates of indole formation over $CdBr_2$–KBr using a newly constructed autoclave that is large in size and which has a suction pipe for sampling of the reaction liquids. By using this new system, we were able to directly analyze the time course of the reaction.

Experimental

The liquid-phase catalytic reactions, including recycling experiments, were conducted in a Hastelloy-lined autoclave containing the catalyst, aniline, and EG at a content of 50 to 80 ml under a pressure of 15 to 70 $kg\,cm^{-2}$. After the reaction, the autoclave was cooled to room temperature and the composition of the gas and liquid components were analyzed by gas chromatography (GC). A GC column (fused silica/OV-1 capilary column) was used for analyzing the condensed products. Two GC columns (molecular sieve 13X and PORAPAK QS) were used for analyzing (1) H_2, CO,

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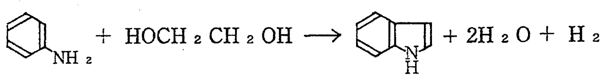
and CH_4 and (2) CO_2, C_2H_4, and C_2H_6, respectively, in the uncondensed gas. In order to determine the rates of the reaction over $CdBr_2$–KBr, a 1000-ml Hastelloy-lined autoclave with a suction pipe was constructed and used for sampling of the reaction liquid under pressure. Aniline and EG (Wako pure chemical, high grade) were used as raw materials, and $CdBr_2$ was used as a catalyst after dehydration of commercial $CdBr_2 \cdot 4H_2O$.

Results and Discussion

The direct synthesis of indole from aniline and ethylene glycol is comprised of dehydration and dehydrogenation.



(1)

In the gas–solid phase reactions, many metal oxides were tested as catalysts, but the yields of indole were very low. When mixed oxides or halides were used as catalysts, the yields were significantly higher than those of oxides of the same metals in most cases. We found that PbI_2, $CdBr_2$, and CdI_2 exhibited relatively high yields.[12]

Moreover, we found a drastic increase in the yield when KI was added to PbI_2 in a liquid phase reaction.[12] We also tried additions of KX to CdX_2 (X: halogen). Table 1 shows the catalytic activities of cadmium compounds and CdX_2–KX in the liquid phase. When using cadmium compounds alone, cadmium halides except CdF_2 exhibited relatively high selectivities and reaction rates, while the other cadmium compounds had low rates of indole formation. $CdBr_2$ provided the highest yield of indole. We found that for the bromide and iodide forms of the catalysts, positive effects were produced by addition of KX to CdX_2, while for the chloride and fluoride forms, addition of KX caused a decrease in the reaction rate. With addition of 1—2 mol/mol of KBr to $CdBr_2$, the yield did not increase much. With 3 mol/mol of KBr, the yield increased markedly. We discovered that a yield of 76.0% was obtained using $CdBr_2$–3KBr. Additions of other metal bromides, for example $NaBr_2$ or $SrBr_2$, to $CdBr_2$ did not cause significant increases in the yield. Thus, $CdBr_2$–3KBr exhibited a specific effect on the formation of indole.

Table 1. Catalytic Activity of Cadmium Compounds and CdX_2–KX (X: Halogen) in Liquid Phase

Catalyst[a)] (mole ratio)	Time h	EG conv. %	Indole select. %
CdI_2–KI (1–1)	1.5	99.8	63.9
(1–3)	1.5	99.6	67.5
$CdBr_2$–KBr (1–1)	1.4	99.5	66.6
(1–2)	1.2	99.6	67.7
(1–3)	1.2	99.8	76.2
(1–4)	1.9	99.5	71.2
$CdCl_2$–KCl (1–1)	2.1	98.9	49.4
(1–3)	1.5	67.7	62.5
CdF_2–KF (1–3)	3.6	4.9	10.2
CdI_2	1.5	97.5	54.6
$CdBr_2$	1.8	99.2	62.6
$CdCl_2$	1.8	99.2	51.9
CdF_2	3.3	12.5	55.2
$CdSO_4$	5.2	13.5	40.0
$Cd(OAc)_2$	3.6	65.9	4.1
CdS	1.8	53.9	28.2

a) Mole ratio: EG/Cd=4.9, aniline/EG=10, Temp=330 °C, H_2=15 kg cm^{-2}.

Recycling tests using the $CdBr_2$–3KBr catalyst were done to determine the catalytic life. The reactions used an aniline/EG mole ratio of 5 and a reaction temperature of 300 °C. The yield under these conditions was about 70%, just under the maximum yield. Figure 1 shows the results of recycling tests of $CdBr_2$–3KBr using two methods for treatment of the catalyst. After the reaction, all of the contents were removed from the autoclave and transferred to a flask by using either methanol or carbon tetrachloride. The catalyst was obtained as a reside by evaporating the volatile components from the flask (≦10 mmHg, ≦250 °C). The residue was physically scraped from the flask and transferred back to the autoclave. Fresh aniline and EG were introduced into the autoclave and the air in the autoclave was replaced by an inactive gas (N_2). The reaction was then repeated.

For CCl_4 treatment, the first to the third reactions lead to a decrease in the yield of indole. For MeOH treatment, the first to the ninth reactions had a stable yield. Figure 2 shows the behavior of the reaction rates of the two treatments. For CCl_4 treatment, the reaction time increased about 290% from the first to the third reactions. For MeOH treatment, the reaction

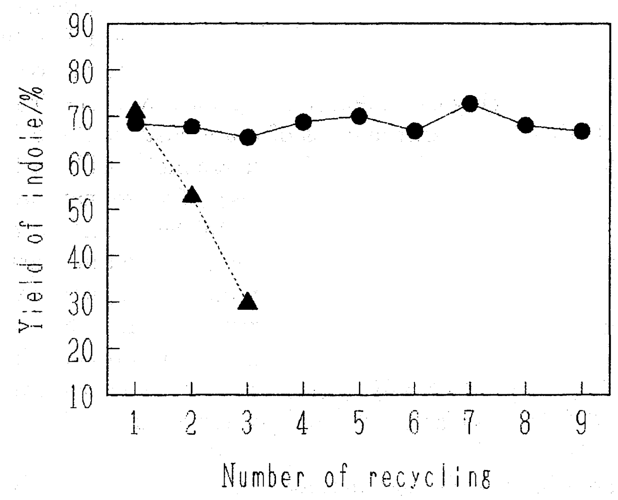


Fig. 1. Behavior of the yield in the recycling of $CdBr_2$–3KBr. Treatment of recovery of the catalyst: CCl_4 (▲), MeOH (●). Mole ratio: aniline/EG=5, EG/$CdBr_2$=4.9, 300 °C, N_2=5 kg cm^{-2}.

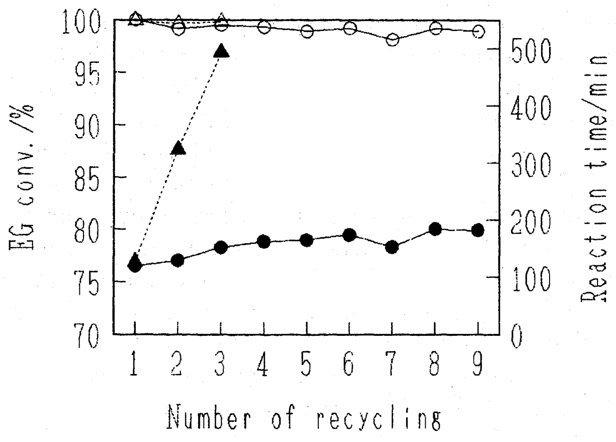


Fig. 2. Behavior of reaction velocity in the recycling. CCl_4 treatment: time (▲), conv. (△), MeOH treatment: time (●), conv. (○).

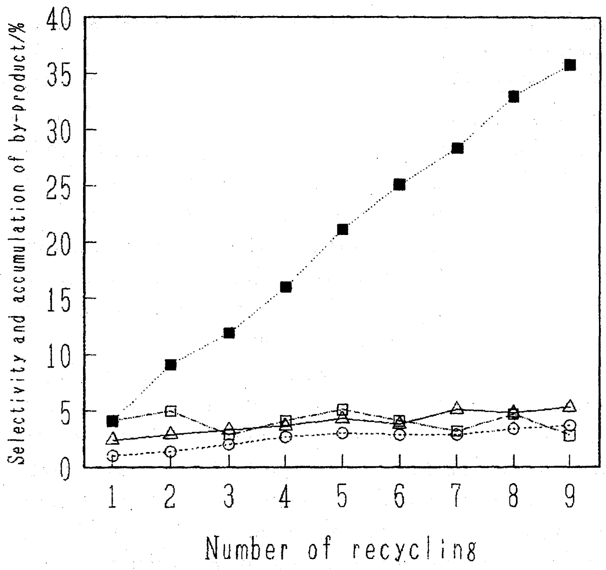


Fig. 3. Behavior of by-products in the recycling by MeOH treatment. Accumulation of by-products (■). Selectivity: indoline (○), by-products with high bp (□), 4-methylquinoline and *p*-ethylaniline (△).

time increased about 50% from the first to the ninth reactions. These results indicate that a small amount of contamination by CCl_4 adversely affects indole formation. Table 2 shows the results of elemental analyses of the catalyst recycled nine times using MeOH treatment. Figure 3 shows the behavior of by-product formation when using MeOH treatment. From the first to the ninth cycles, the formation of indoline, *p*-ethylaniline, and 4-methylquinoline increased slightly, while the formation of by-products such as oligomers remained almost the same. The total accumulation of by-products detected by GC increased remarkably. The efficiency of by-products removal by evaporation is different as follows: indoline (100%), *p*-ethylaniline (100%), 4-methylquinoline (81%), and oligomers (4%). Therefore, the concentration in the autoclave of by-products with high boiling points such as oligomers increases with each recycling step. The slight decrease of the reaction rate may be due to this increase in the concentration of low volatility by-products. As shown in Table 2, after nine recyclings, the recovered catalyst contained a stoichiometric quantity of Br.

The catalyst residue recovered after evaporation of the reaction content was divided into A and B samples. Sample A consisted of the chloroform-insoluble substances that remained in the residue and sample B was obtained from the chloroform-soluble substances. Most of the catalyst was included in sample A, which contained Cd and K in a ratio of 1 : 3 and organic ingredients for which the composition was different from that of aniline. These organic components are thought to include accumulated by-products. Sample B contained a small amount of $CdBr_2$ and a large percentage of organic compounds. The recovery percentages of $CdBr_2$

Table 2. Elementary Analysis of Catalyst Recycled Nine Times[a)]

	Mole ratio						Composition of
	Cd	K	Br	N	C	H	[Cd+K+Br+N+C+H]
Sample A[b)] 17.86 g	1.00	3.05	5.14	0.61	5.35	4.15	96.5%
Sample B[c)] 4.17 g	1.00	0.00	1.96	14.3	167	131	88.3%
Recovery of $CdBr_2$	91.6%			Recovery of KBr	88.9%		
per reaction	99.0%			per reaction	98.7%		

a) First reaction: $CdBr_2$=7.249 g, KBr=9.507 g. Aniline : EG : $CdBr_2$: KBr=24.5 : 4.9 : 1 : 3 (mole ratio). 300 °C, N_2=5 kg cm^{-2}. b) $CHCl_3$-insoluble residue. c) $CHCl_3$-soluble residue (washed with CCl_4–$CHCl_3$ (v/v 3 : 2)).

and KBr were both about 90%. This indicates that the averaged percent recovery for each recycle step is about 99%, which is a reasonable value considering the losses due to scrapping the residue from the flask. It is concluded that in the recycling of $CdBr_2$–3KBr, there is no elimination of Br from $CdBr_2$. We verified that nine recyclings of the catalyst provided a constant yield. This positive result clearly indicates that the cost of the catalyst will be much smaller than that of the raw materials and that a catalytic process for the formation of indole can be realistically accomplished.

The rate of indole formation over $CdBr_2$–3KBr was investigated to determine the conditions that would be necessary for an industrial process and to determine the reaction mechanism. A 1000-ml Hastelloy-lined autoclave equipped with a suction pipe was constructed. The instrument for sampling the reaction liquid under high pressure and high temperature consists of a suction pipe, a pipe-shaped cell with a volume of about 4 ml, and an outlet. The three portions are divided by two valves. The end of the suction pipe was put into the reaction liquid. When the value of the suction pipe was opened, a small portion of the reaction liquid was pushed into the cell by the pressure in the autoclave. When the value was shut and the outlet valve was opened, about 4 ml of the liquid in the cell was pushed out by the vapor pressure of the hot liquid. Thus, sampling of the reaction liquid during the reaction is not difficult to do when using such an autoclave. The liquid was sampled at different times and analyzed by GC. Figure 4 shows a typical time course for the reaction. The concentration of EG decreased exponentially with time and the concentration of indole increased without an induction period. One of the by-products, *N*-(2-hydroxyethyl)aniline (HEA), formed with a clear induction period. It seems that free HEA itself is not an intermediate in the formation of indole. The slope of the tangential lines of the indole curve was plotted against the concentration of EG as shown in Fig. 5. The relation between the rate of indole formation and the concentration of EG was linear. The slope of the linear line was constant with varying initial concentration of EG. Thus, the rate of indole formation revealed a first-order dependency on EG concentration. Figures 6 and 7 show the dependency on the concentration of the catalyst. Every [indole]–[EG] plot was linear, and the slope of each plot was almost proportional to the concentration of the catalyst. The rate of indole formation also had a first-order dependency on the concentration of $CdBr_2$–3KBr. Figure 8 shows Arrhenius plots of the reaction. Figure 9 shows the effect of H_2O addition on indole formation under the same conditions as those used for the reaction shown in Fig. 1. When water at a 2—10 mol/mol ratio ($H_2O:CdBr_2$) was added, the yield of indole decreased slightly and at a 10 mol/mol ratio, the maximum decrease in the yield was observed. In the initial period of the reaction, the rate of indole formation decreased slightly with increasing amount of added water. The relation between the amount of water added and the decrease in the rate of indole formation was not linear but sigmoid.

After the reaction, 79% of the $CdBr_2$ was precipitated as a $[CdBr_2(aniline)_2]$ complex as determined by X-ray diffraction, infrared spectroscopy, and elemental analysis. By conducting the reactions in a glass autoclave, we were able to observe almost complete dissolution of the two catalysts, ($CdBr_2$–3KBr and $[CdBr_2(aniline)_2]$–3KBr) up to a temperature of

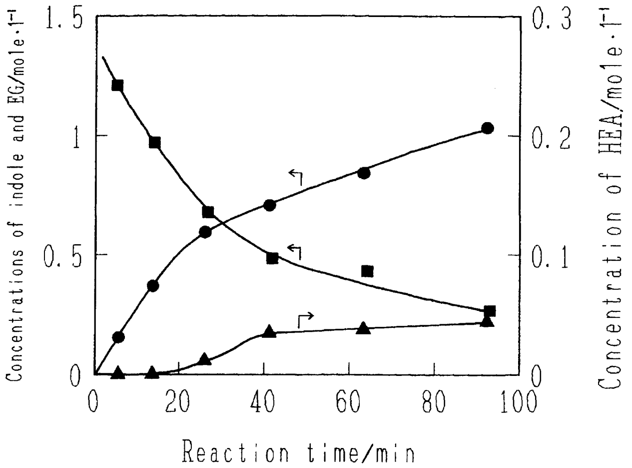


Fig. 4. Time courses of the concentrations of indole, EG and HEA. Indole: ●, EG: ■, HEA: ▲. Aniline:EG:$CdBr_2$:KBr=25:5:1:3 (mole ratio). 285 °C, N_2=5 kg cm^{-2}.

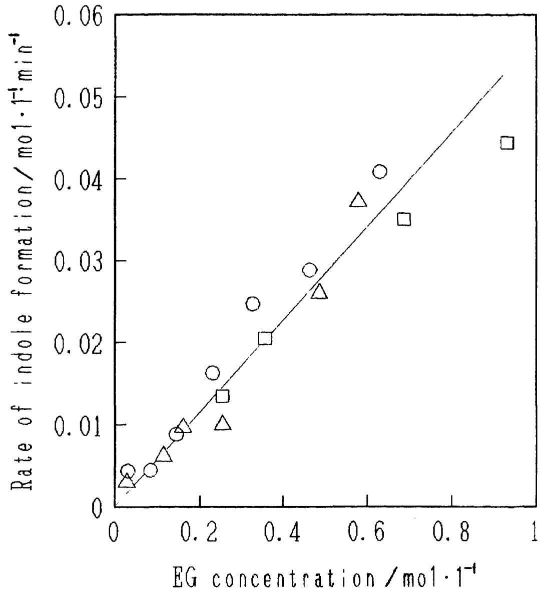


Fig. 5. Relation between the rate of indole formation and EG concentration. Mole ratio of EG/$CdBr_2$: 3 (○), 5 (□), 7 (△). Mole ratio of aniline/$CdBr_2$=25, KBr/$CdBr_2$=3, $[CdBr_2]$=0.37 mol dm^{-3}, 300 °C, N_2=5 kg cm^{-2}. Reaction time: 82 min (○), 115 min (□), 136 min (△).

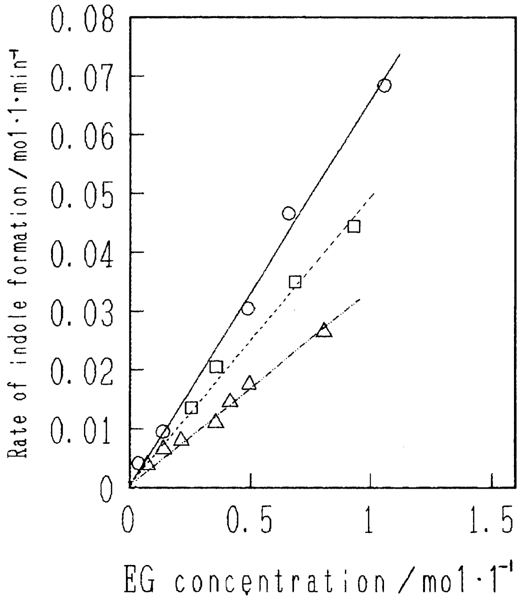


Fig. 6. Effect of the concentration of $CdBr_2$–3KBr on indole formation. Mole ratio of aniline/$CdBr_2$: 15 (○), 25 (□), 45 (△). EG/$CdBr_2$=5 (mol/mol), 300 °C, N_2=5 kg cm^{-2}. Reaction time: 110 min (○), 115 min (□), 130 min (△).

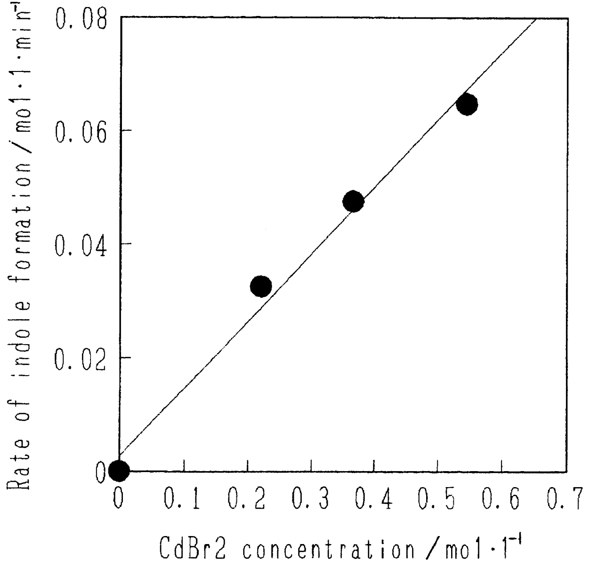


Fig. 7. Relation between the rate of indole formation and the concentration of $CdBr_2$–3KBr. The reaction conditions are the same as Fig. 6.

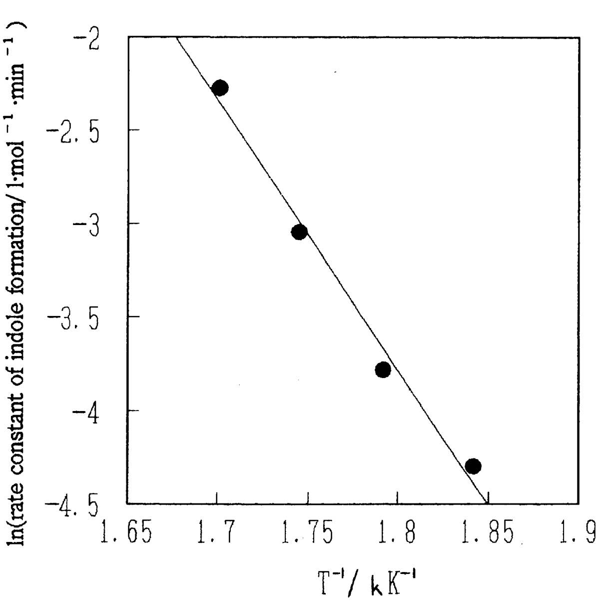


Fig. 8. Arrhenius plot of indole formation. Aniline : EG : $CdBr_2$: KBr = 25 : 5 : 1 : 3. N_2=5 kg cm^{-2}. Reaction time: 201 min (270 °C), 120 min (285 °C), 115 min (300 °C), 77 min (315 °C).

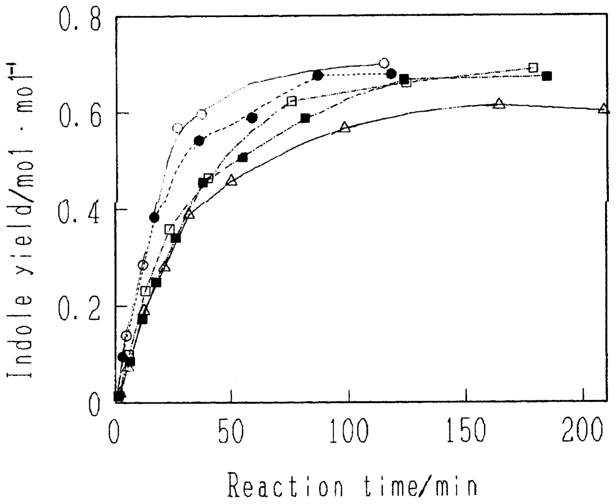
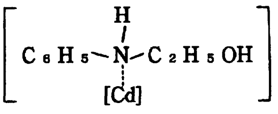


Fig. 9. Effect of an addition of H_2O. Mole ratio: H_2O/Cd=0 (○), 2.0 (●), 3.5 (□), 5.3 (■), 10.1 (△), aniline/EG = 5, EG/$CdBr_2$ = 5, KBr/$CdBr_2$ = 3.300 °C, N_2=5 kg cm^{-2}.

250 °C (the temperature at which the pressure is near the pressure limit of the glass autoclave). $CdBr_2$ and [$CdBr_2$(aniline)$_2$] completely dissolved up to a temperature of 200 °C. Dissolution of KBr at a 3 mol/mol ratio (KBr : $CdBr_2$) was incomplete under 200 °C, and the majority of KBr dissolved at 250 °C. The $CdBr_2$–KBr catalyst is thought to form a complex in a dissolved state during the reaction because CdX_2 (X=I, Br, Cl) forms [CdX_2(aniline)$_2$] complex with aniline.[14—16]

As shown in Table 1, CdI_2, $CdBr_2$, and $CdCl_2$ yielded much higher rates than other cadmium compounds. Therefore, this type of complex is a key substance for indole formation. According to observation of the thermal decomposition of the complexes, [$CdCl_2$(aniline)$_2$] yields the intermediate products $CdCl_2 \cdot 4/3C_6H_5NH_2$ and $CdCl_2 \cdot 1/2C_6H_5NH_2$, while [$CdBr_2$(aniline)$_2$] loses two molecules of aniline simultaneously at a decomposition temperature of 190 °C.[15] Thus, during the reaction with $CdBr_2$–KBr at 300—330 °C, coordination and desorption of an aniline molecule to Cd(II) should occur with a high frequency. From our research, we obtained the following equation for the rate of indole formation, r.



$$\left[C_6H_5-\overset{\displaystyle H}{\underset{\displaystyle [Cd]}{N}}-C_2H_5OH \right]$$

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Chart 1.

$$r = k[\mathrm{EG}][\mathrm{CdBr_2}],$$
$$k = 3.8 \times 10^9 \exp\left[-E/RT\right]\ \mathrm{dm^3\,mol^{-1}\,min^{-1}}$$
$$E = 28.6\ \mathrm{kcal\,mol^{-1}}$$

The reaction mechanism is thought to involve a coordinative attack of EG on an aniline complex of Cd(II). The bond formation between aniline and EG is the rate-determining step. We propose an HEA complex of Cd(II) (**1**) as an intermediate in the formation of iodole (Chart 1). Intramolecular cyclization of HEA in the complex would rapidly proceed over Cd(II) and lead to the formation of indole. Once HEA desorbs from Cd(II) in **1**, coordination of aniline from the solvent to Cd(II) would quickly take place and inhibit the N-coordination of the free HEA. Thus, free HEA is not a direct intermediate.

In this paper, the catalytic life and the rate of indole formation over the active catalyst $CdBr_2$–3KBr was clarified. Our results indicate that this catalyst can provide a simple and low-cost (perhaps the best to date) procedure for the production of indole on an industrial scale.

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