

## PHOTOCATALYTIC ISOQUINOLINE PRODUCTION AND N-ALKYLATION BY PLATINIZED TITANIUM(IV) OXIDE PARTICLES SUSPENDED IN ALCOHOLIC SOLUTION OF PHENETHYLAMINES

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(Received 29 October 1994, accepted 18 December 1994)

**Abstract** – Photocatalytic ( $\lambda_{ex} > 300$  nm) reaction at room temperature by platinumized titanium (IV) oxide particles produced 1-methyl-1,2,3,4-tetrahydroisoquinolines (MIQ's)<sup>†</sup> from phenethylamines in aqueous ethanol suspension under deaerated atmosphere. Among the phenethylamines, dopamine (2-(3,4-dihydroxyphenyl) ethylamine) showed the highest reactivity to give MIQ almost selectively under the neutralized conditions. The other phenethylamines gave predominantly N-alkylated and N,N-dialkylated products in the methanol or ethanol solutions. The reaction mechanism includes a Schiff base intermediate to undergo either nucleophilic attack leading to MIQ or reduction to N-alkylated products.

### INTRODUCTION

Isoquinolines constitute one of the basic groups of naturally occurring alkaloids.<sup>1</sup> For their chemical synthesis is usually applied Pictet-Spengler reaction consisting of two steps; condensation of phenethylamines with aldehydes into Schiff bases followed by acid-catalyzed ring closure into a six-membered isoquinoline structure.<sup>2</sup> The reaction, generally, requires both use of organic solvents, such as benzene, and operation at their boiling temperature. Furthermore, preparation of rather unstable aldehydes is necessary.

Semiconductor photocatalytic reaction is based on the reduction and oxidation by photoexcited electrons ( $e^-$ ) and positive holes ( $h^+$ ), respectively, at the semiconductor-solution interface.<sup>3</sup> As one of most superior characteristics of the photocatalytic reaction, it proceeds at ambient temperature and pressure, in contrast to general catalytic reactions. We have shown that photoirradiation onto a suspension of semiconductor particles, e.g., titanium (IV) oxide ( $TiO_2$ ) or cadmium sulfide (CdS), in aqueous solutions

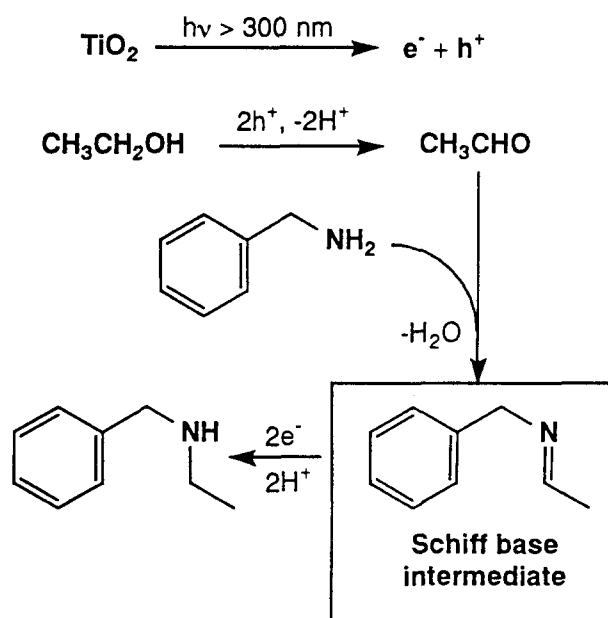
and/or organic solvents induces various types of redox-related reactions of organic molecules and they are applicable to organic syntheses.<sup>4</sup> For example, we obtained L-pipecolic acid (piperidine-2-carboxylic acid, PCA), a naturally occurring but not proteinogenic cyclic imino acid, stereoselectively from L-lysine and/or its derivatives through photocatalytic deaminocyclization by suspended platinumized titanium (IV) oxide particles.<sup>5,6</sup> As far as we know, this is a unique procedure of one-step catalytic process of L-PCA production from a rather cheap starting material, L-lysine. The room temperature and ambient pressure operation, which is also in this case, is the superior characteristics as well as that this photocatalytic process requires no addition of materials other than the substrate, photocatalyst and solvent.

We have reported that various amines and ammonia undergo N-alkylation by the semiconductor-induced photocatalytic reaction in alcoholic solutions,<sup>7,8</sup> e.g., N-ethyl and/or N,N-diethylbenzylamine is obtained in an ethanolic solution of benzylamine with suspended platinumized  $TiO_2$  photocatalyst, as Scheme 1 shows.

This photocatalytic reaction involves a Schiff bases intermediate (e.g., N-ethylidenebenzylamine in Scheme 1), which is same as the Pictet-Spengler reaction. Here we show a trial for utilization of the Schiff base intermediates, generated by the room-temperature photocatalytic reaction in alcoholic suspension, to the production of isoquinolines from phenethylamines. We focused on the reaction conditions, i.e., catalysts, solvents, or additives, for selec-

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<sup>†</sup> Abbreviations: MIQ, 1-methyl-1,2,3,4-tetrahydroisoquinoline; PCA, pipecolic acid; PEA, phenethylamine; TRA, tyramine, 2-(4-hydroxyphenyl) ethylamine; DPA, dopamine, 2-(3,4-dihydroxyphenyl) ethylamine; DMA, 2-(3,4-dimethoxyphenyl) ethylamine; MS, mass spectroscopy; EI, electron impact; CI, chemical ionization; IQ, isoquinoline; TMS, trimethylsilyl.



Scheme 1. Mechanism of the photocatalytic N-alkylation (ethylation) of benzylamine in ethanol suspension of platinized  $\text{TiO}_2$  particles.

tive cyclization into isoquinolines rather than N-alkylated products.

## MATERIALS AND METHODS

**Materials.** Commercial  $\text{TiO}_2$  powders (Degussa P-25 and Merck) were used mainly. They were platinized by impregnation from chloroplatinic acid followed by heat-treatment under continuous hydrogen ( $\text{H}_2$ ) stream. As a result, 2 wt% of platinum (Pt) was loaded. The detailed description of this platinization procedure was reported elsewhere.<sup>6,9</sup> Phenethylamines, phenethylamine (PEA), 2-(4-hydroxyphenyl)ethylamine (tyramine, TRA; hydrochloride), 2-(3,4-dihydroxyphenyl)ethylamine (dopamine, DPA; hydrochloride), and 2-(3,4-dimethoxyphenyl)ethylamine (DMA), were of best available grade and supplied from Wako Pure Chemicals or Nacalai Tesque. Authentic sample of an isoquinoline, 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, was supplied from Aldrich as hydrobromide. Analytical grade alcohols (methanol and ethanol) were used as received. Ion-exchanged water prepared with a Corning Mega Pure System MP-190 ( $> 16 \text{ M}\Omega \text{ cm}$ ) was used throughout this study.

**Photoirradiation and product analyses.** A suspension of catalyst (50 mg) in an alcoholic or aqueous alcoholic solution (5.0 mL) of phenethylamine (50  $\mu\text{mol}$ ) was placed in a test tube (18 mm  $\times$  180 mm, transparent for the light of wavelength  $> 300 \text{ nm}$ ) and was purged by argon (Ar). The tube was sealed with a rubber septum and irradiated with a 400 W mercury arc (Eiko-sha) at 298 K ( $\pm 0.5^\circ$ ) under magnetic stirring (1000 rpm). After the irradiation, products in the gas phase were analyzed by gas

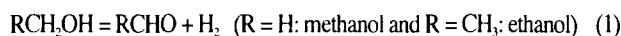
chromatography (GC)<sup>6</sup> and those in the liquid phase by high performance liquid chromatography (HPLC) with a Shimadzu LC6A equipped with a reversed phase column (Nacalai Cosmosil 5C18-AR, 4.6 mm  $\times$  250 mm) and an ultraviolet absorption detector. GC/MS analyses were performed with a Shimadzu QP-1000EX equipped with a fused silica capillary (Shimadzu CBP-M25-025). Supernatant solution was evaporated to dryness, treated with N-methyl-N-trimethylsilyltrifluoroacetamide (Pierce) in a sealed glass tube under nitrogen ( $\text{N}_2$ ), and injected to GC-MS. MS patterns of GC fractions were recorded in both electron impact (EI, 70 eV) and chemical ionization (CI, with isobutane) modes.

## RESULTS AND DISCUSSION

Table 1 shows representative results of photocatalytic reaction of phenethylamines in methanol or ethanol by suspended platinized  $\text{TiO}_2$  ( $\text{TiO}_2\text{-Pt}$ ) particles.

Cadmium sulfide ( $\text{CdS}$ ) powders loaded with Pt or its oxide ( $\text{PtO}_2$ ) were also used but showed lesser photocatalytic activity (data not shown). Hydrogen evolution was commonly observed along with formation of aldehydes, formaldehyde from methanol and acetaldehyde from ethanol. Dark reaction with photocatalyst or photoreaction without photocatalyst gave apparently no  $\text{H}_2$ , indicating that the process is *photocatalytic*.

The molar amount of aldehyde was not measured (formaldehyde was analyzed qualitatively by colorimetric method<sup>10</sup> and acetaldehyde by GC)<sup>11</sup> but it is expected that equimolar amount of  $\text{H}_2$  and aldehyde formed according to the stoichiometry:



as previously reported.<sup>7,10,11</sup> In methanol suspensions, PEA was less reactive with both  $\text{TiO}_2\text{-Pt}$  photocatalysts even though large amount ( $> 6$  times of amine in feed) of aldehyde might exist in the reaction mixtures; formation of neither corresponding isoquinoline, 1,2,3,4-tetrahydroisoquinoline, nor N-alkylated product, N-methylphenethylamine, could be observed. However, addition of small amount (20 vol%) of water improved the yield of N-methyl derivative of PEA to be almost selective. Recent report by Shibata and co-workers has shown the similar effect of water on the  $\text{TiO}_2\text{-Pt}$  photocatalyzed methylation of aniline.<sup>12</sup> This is (at least for the present results) attributable to inhibition of acetal formation via condensation of formaldehyde and methanol to result in the increase of effective concentration of formaldehyde. Aldehydes tend to form acetal in the presence of acid.<sup>11</sup> The present photocatalysts show acidic property, which may be caused by the remaining hydrochloride as a by-product in the platinization procedure. Therefore,

Table 1 Photocatalytic reaction of amine/alcohol solutions by suspended TiO<sub>2</sub>-Pt particles.<sup>a</sup>

run	amine <sup>b</sup>	catalyst <sup>c</sup>	alcohol	additive	irrad. (/h)	conv. <sup>d</sup> (/%)	H <sub>2</sub> (/μmol)	IQ <sup>e</sup> (/%)	NAL <sup>f</sup> (/%)
1	PEA	M	methanol	none	12	26	313	ND	ND
2	PEA	P	methanol	HCl	6	0	576	ND	ND
3	PEA	P	methanol	none	6	10	431	ND	ND
4	PEA	P	+20%water	none	12	100	1781	ND	90
5	PEA	M	ethanol	HCl	6	100	116	ND <sup>g</sup>	D <sup>g</sup>
6	PEA	M	ethanol	none	6	100	216	ND <sup>g</sup>	ND <sup>g</sup>
7	TRA+HCl	M	+20%water	none	24	49	176	ND <sup>g</sup>	D <sup>g</sup>
8	TRA+HCl	M	+20%water	NaOH	24	100	381	D <sup>g</sup>	D <sup>g</sup>
9	DPA+HCl	M	ethanol	none	24	31	8	1	30 <sup>g</sup>
10	DPA+HCl	M	+20%water	none	24	0	6	ND	trace
11	DPA+HCl	M	+20%water	NaOH	24	87	40	66	trace
12	DPA+HCl	P	ethanol	none	24	0	598	ND	trace
13	DPA+HCl	P	+20%water	none	12	87	123	4	49 <sup>h</sup>
14	DPA+HCl	P	+20%water	NaOH	24	39	5	16	ND

<sup>a</sup>Catalyst 50 mg was suspended in an alcoholic solution (5.0 mL) of amines (50 μmol) with or without additives (equimolar to the phenethylamine) and irradiated (at > 300 nm) under argon with vigorous magnetic stirring. <sup>b</sup>PEA: phenethylamine, TRA: tyramine, and DPA: dopamine. <sup>c</sup>P: Degussa (Nippon Aerosil) P-25 and M: Merck (anatase), loaded with 2 wt% of Pt. <sup>d</sup>Conversion of starting amines. <sup>e</sup>Corresponding 1,2,3,4-tetrahydroisoquinolines. D: detected, ND: not detected. <sup>f</sup>N-Alkylated product. <sup>g</sup>Confirmed by GC-MS. <sup>h</sup>Estimated by HPLC on the assumption that N-alkylated product has absorption coefficient same as the phenethylamine at the detection wavelength.

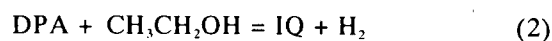
formaldehyde undergoes condensation into the acetal and the added water may hydrolyze it.

On the contrary, PEA was converted almost completely in the ethanol system in the absence of water, even though we detected the predominant formation of acetal, 1,1-diethoxyethane, by GC also in this case.<sup>11</sup> In the presence of hydrochloric acid (HCl, equimolar to PEA) formation of N,N-diethyl derivatives of PEA was confirmed by GC-MS; MW = 177, CI: 178 (M+1)<sup>+</sup>, EI: 105 (M<sup>+</sup> - (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>N), 91 (M<sup>+</sup> - (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NCH<sub>2</sub>), 86 (M<sup>+</sup> - benzyl), 77 (M<sup>+</sup> - (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>), and 58 (C<sub>2</sub>H<sub>5</sub>NH<sup>+</sup>=CH<sub>2</sub>). No such GC peak was obtained in the absence of HCl, while an N-ethyl-substituted dimeric product, ethyl-diphenethylamine, was detected; MW = 253, CI: 254 (M+1)<sup>+</sup>, EI: 162 (M<sup>+</sup> - benzyl), 105 (M<sup>+</sup> - (C<sub>2</sub>H<sub>5</sub>)NCH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>), 91 (CH<sub>2</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub><sup>+</sup>), and 58 (C<sub>2</sub>H<sub>5</sub>NH<sup>+</sup>=CH<sub>2</sub>). These facts show that PEA as well as solvent, ethanol, undergoes photocatalytic oxidation into a Schiff base followed by reduction to yield diphenethylamine. Thus, negligible formation of isoquinoline from PEA could be seen.

Substitution of aromatic-ring hydrogen(s) in PEA with hydroxyl group(s) changed the reaction mode as shown in Table 1. Both tyramine (TRA) and dopamine (DPA) gave corresponding isoquinoline derivatives (IQ's) as well as N-ethyl and N,N-diethyl compounds; for TRA in the presence of sodium hydroxide (NaOH), di-TMS-IQ MW = 307, CI: 308 (M+1)<sup>+</sup>, N-ethyl-di-TMS derivative MW = 309, CI: 310 (M+1)<sup>+</sup>, EI: 130 ((C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>N(TMS)CH<sub>2</sub>)<sup>+</sup>, N,N-diethyl-TMS derivative MW = 265, CI: 266 (M+1)<sup>+</sup>, EI: 86 ((C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NCH<sub>2</sub>)<sup>+</sup>, for DPA in the presence of

NaOH, tri-TMS-IQ MW = 395, CI: 396 (M+1)<sup>+</sup>, EI: 380 (M<sup>+</sup> - CH<sub>3</sub>). The formation of 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, salsolinol,<sup>13-6</sup> was confirmed by comparison with the authentic sample. For these IQ formations, it is necessary to add water to ethanol, as also seen for the PEA system, and to neutralize HCl included in the starting material by the addition of NaOH. The latter effect is discussed in the following section. Regarding the catalyst, Merck anatase TiO<sub>2</sub> showed relatively higher activity for the IQ formation than P-25 TiO<sub>2</sub>. As the results, the best yield of IQ could be obtained by TiO<sub>2</sub>(Merck)-Pt particles suspended in mixture of ethanol and water with sodium hydroxide.

Figure 1 shows the effect of NaOH on the DPA conversion and the yield of IQ and H<sub>2</sub>. With the increase in added NaOH, both the conversion and the IQ yield increased drastically. The highest conversion and yield were obtained by the addition of NaOH corresponding to ca. 80 mol% of starting DPA; almost quantitative conversion and selective formation of IQ were seen and the IQ yield decreased a little by further addition of NaOH. It is clear from this figure that almost equimolar amount of H<sub>2</sub> and IQ formed in the presence of NaOH, following a stoichiometry,



to yield IQ (salsolinol). As an extension, DMA was also used as a starting material to synthesize 6,7-dimethoxyisoquinoline derivative. GC-MS analysis

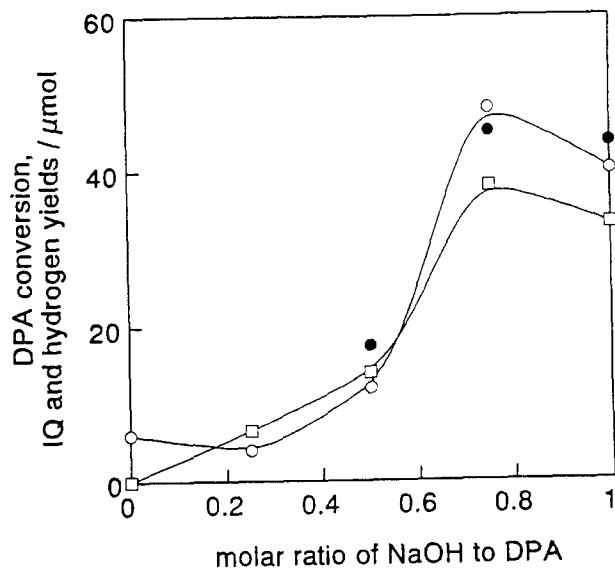
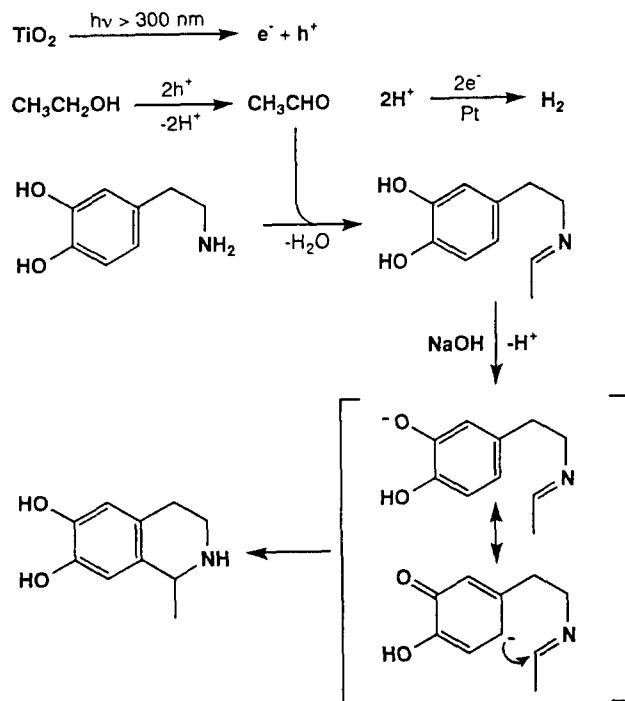


Figure 1. DPA conversion (closed circle) and yield of IQ (square) and hydrogen (open circle) as a function of molar ratio of added NaOH to DPA. DPA (50  $\mu\text{mol}$  in feed) in aqueous ethanol (20 vol% water) with or without NaOH was irradiated for 12 h.

of dried-up reaction mixture from DMA/ethanol/ $\text{TiO}_2$ (Merck)-Pt system showed the formation of small amount of the expected product, 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (salsolidine);<sup>17-19</sup> TMS-derivative, MW = 279, CI: 280 (M+1)<sup>+</sup>. However, the reproducibility for the detection of such compound was rather poor; the GC peak was seldom found. This behavior was contrastive to the DPA system and suggests the importance of hydroxyl group, not methoxy group, in the *para* position of the ring closure site. The less selective IQ formation from TRA, as shown above, also supports this. We could not confirm further the effect of *para* substituent because of lack of commercial reagent of 2-(3-hydroxyphenyl) ethylamine, having a hydroxyl group at the *para* position.

Scheme 2 for the photocatalytic production of IQ from DPA is based on the results described above. First,  $\text{TiO}_2$  absorbs the light of energy larger than its bandgap (*ca.* 3.1 eV, 400 nm) to result in the formation of  $e^-$  and  $h^+$ . The  $h^+$  oxidizes ethanol adsorbed on the  $\text{TiO}_2$  surface to give acetaldehyde. Simultaneously,  $e^-$  moves to the deposited Pt site to evolve  $\text{H}_2$ . The aldehyde is condensed with DPA into a Schiff base. Because of the acidic function of 3-hydroxy group and resulting resonance structure, ring closure by nucleophilic attack to imine carbon may occur before reduction of the imine moiety with photoexcited electrons (or hydrogen atom on Pt surface) into N-alkylated products.



Scheme 2. Proposed reaction mechanism for the photocatalytic production of 1-methyl-1,2,3,4-tetrahydroisoquinoline from dopamine in aqueous ethanol by platinumized  $\text{TiO}_2$  catalyst.

## CONCLUSION

Photocatalytic reaction of phenethylamines by platinumized  $\text{TiO}_2$  suspended in alcohol or aqueous alcohol solutions was investigated. Among the phenethylamines, dopamine in ethanol was converted selectively into 1-methyl-1,2,3,4-tetrahydroisoquinoline (salsolinol) in the presence of NaOH to neutralize hydrochloride of the substrate. The proposed mechanism involves a Schiff base as a reaction intermediate to undergo, not reduction by photoexcited electron into an N-ethyl derivative, but intramolecular nucleophilic attack by phenyl anion to salsolinol. From these results, we can expect the extensive possibility of utilization of the Schiff bases produced through photocatalytic reaction toward the syntheses of naturally occurring materials. Research along this line is now in progress.

*Acknowledgments* — We thank Mr. Shota Morimoto (Kyoto University) for his help and discussion of GC-MS analyses. Parts of photocatalysts were prepared by Mr. Yosuke Goto and Mr. Masami Kozawa (Kyoto University). This research is supported partly by a Grant-in-Aid on Priority-Area-Research "Photoreaction Dynamics" from the Ministry of Education, Science and Culture of Japan (No. 06239235).

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