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## Computer–Aided Synthesis of Dimerized Eugenol

Seiichiro Fujisawa,<sup>1</sup> Mariko Ishihara,<sup>1</sup> and Ichiro Yokoe<sup>2</sup>

<sup>1</sup> Meikai University School of Dentistry, 1–1 Keyakidai, Sakado, Saitama, 350–0283 Japan

<sup>2</sup> Josai University, School of Pharmaceutical Science, 1–1 Keyakidai, Sakado, Saitama, 350–0283  
Japan

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## Computer–Aided Synthesis of Dimerized Eugenol<sup>#</sup>

Seiichiro Fujisawa,<sup>1,\*</sup> Mariko Ishihara,<sup>1</sup> and Ichiro Yokoe<sup>2</sup>

<sup>1</sup> Meikai University School of Dentistry, 1–1 Keyakidai, Sakado, Saitama, 350–0283 Japan

<sup>2</sup> Josai University, School of Pharmaceutical Science, 1–1 Keyakidai, Sakado, Saitama, 350–0283 Japan

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### Abstract

**Motivation.** Eugenol, an antioxidant is used as a fragrance, a flavoring agent, and in dental materials. As an adverse effect, eugenol causes allergic contact dermatitis, possibly due to its prooxidant activity and the formation of eugenol–quinone methide (compound **1**). We recently reported that dimer of eugenol, dehydrodieugenol A (compound **2**) showed the less cytotoxicity and greater antiinflammatory activity than parent eugenols. Therefore, we examined high–yielding methods of producing dimers of eugenol.

**Method.** Dimerization of eugenol was carried out in CuCl(OH)/trimethylenediamine (TMEDA) in dichloromethane in air at 20° C. Dimerization reaction pathway of eugenols was evaluated from a PM3 semiempirical calculation.

**Results.** The simplicity and excellent yield of approximately 79% made it the method of choice for preparing this compound, **2**. In contrast, compound **3**, dehydrodieugenol B was not synthesized from eugenols. The experimental result was supported by the PM3 calculation, which suggested that compound **3** could be synthesized from eugenols with six–coordinating metals, but not with four–coordinating metals such as copper.

**Conclusions.** Dehydrodieugenol (**2**) was synthesized from eugenols in approximately 79% yield. This dimerization reaction pathway was estimated by the PM3 calculation.

**Keywords.** Eugenol dimer; dehydrodieugenol A; dehydrodieugenol B; PM3.

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## 1 INTRODUCTION

Eugenol (4–allyl–2–methoxyphenol) is a phenol derivative which is used not only in combination with zinc oxide as a pulp capping agents, temporary filling, and root canal sealer in dentistry, but also as a fragrant and flavoring agents in a variety of cosmetics and food products [1]. The joint FAO/WHO committee on food additives has permitted an acceptable daily intake of eugenol of 2.5 mg/kg body weight for humans [2]. It is considered non–carcinogenic and no–mutagenic and is generally recognized as safe by the Food and Drug Administrations [3]. However, eugenol causes allergic contact dermatitis [4,5], possibly because it can react directly with proteins

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\* Correspondence author; phone: +81492861712; fax: +81492861712; E–mail: [fujisawa@dent.meikai.ac.jp](mailto:fujisawa@dent.meikai.ac.jp).

to form conjugates and reactive haptens.

Eugenol transforms into eugenol–quinone methide (**1**) as an intermediates *via* a phenoxyl radical due to the one–electron oxidation. A previous study of commercial geraniol prepared from *Java citronella* oil for use in Japanese beetle baits reported that eugenol underwent dimerization [6]. We recently reported that dimers of eugenol dehydrodieugenol A (**2**) showed the less cytotoxicity [7] and greater antiinflammatory activity than parent eugenols [8]. Thus, it is of interest to study the synthesis of eugenol dimer. In the present study, we investigated the dimerization reaction pathway based on a PM3 calculation.

## 2 MATERIALS AND METHODS

Eugenol was obtained from Tokyo Kasei (Tokyo, Japan). Dehydrodieugenol A (3,3'–dimethoxy–5,5'–di–2–propenyl–1–1'–biphenyl–2,2'–diol) (**2**) was prepared according to the following procedure [9]: Briefly, eugenol (3.28 g, 20 mmol) was added to a mixture of CuCl(OH) and TMEDA (4.6 mg, 0.2 mmol) in dichloromethane of 100 ml and was stirred at 20° C for 5 h in open air. Concentration followed by colum chromatography (silica gel, hexane:ether = 9:1) afforded **2** (2.6 g). Its yield was 79% and its melting point was 105° C (ethanol). <sup>13</sup>C– and <sup>1</sup>H–NMR of **2** in DMSOd6 yielded the following.  $\delta$ C: 39.09 (–CH<sub>2</sub>CH=CH<sub>2</sub>), 55.79 (OMe), 110.83 (C3), 115.24 (CH=CH<sub>2</sub>), 122.76 (C5), 125.84 (C6), 129.57 (C4), 138.01 (CH=CH<sub>2</sub>), 141.71 (C1), and 141.75 (C2).  $\delta$ H: 3.24 (–CH<sub>2</sub>CH=CH<sub>2</sub>), 3.78 (OMe), 5.01–5.08 (CH=CH<sub>2</sub>), 5.59 (CH=CH<sub>2</sub>), 5.95 (CH–CH<sub>2</sub>), 6.53 (H3), 6.73 (H5) and 8.08 (OH).

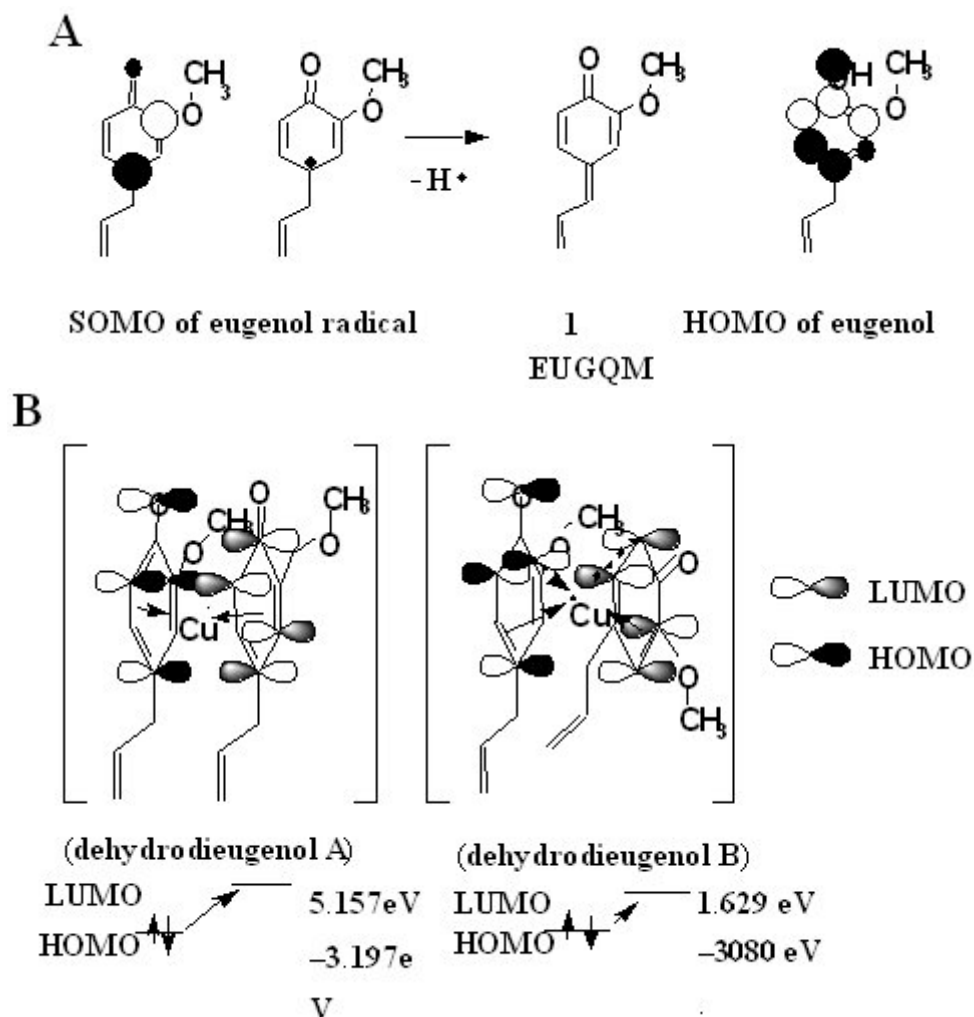
### 2.1 Molecular Orbital Calculations

Molecular geometries of eugenol were optimized by semiempirical molecular orbital method, MOPAC PM3 method (CACHe). The following indices were investigated: heat of formation, energy of HOMO, SOMO or LUMO. The computer programs of the INDO/1 were provided by the CACHe system.

## 3 RESULTS AND DISCUSSION

Following the method of Noji *et al.* [10], we examined the dimerization of eugenol under conditions of oxidation of eugenol with hydrogen peroxide plus Fe (II). The poor yield (approximately 20 %) of this procedure was found to be the worthless method of choice for preparing of this compound (**2**). Next, we examined the dimerization of eugenol under conditions of oxidation of eugenol with Cu(I) plus amines in air [11]. The yielding (%) of compound **2** for NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, (CH<sub>3</sub>)<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>NH<sub>2</sub>, (CH<sub>3</sub>)<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)H, and N(–CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>N was 26, 26, 35, and 24, respectively. This procedure also led to a low yield of approximately 24–35%, even

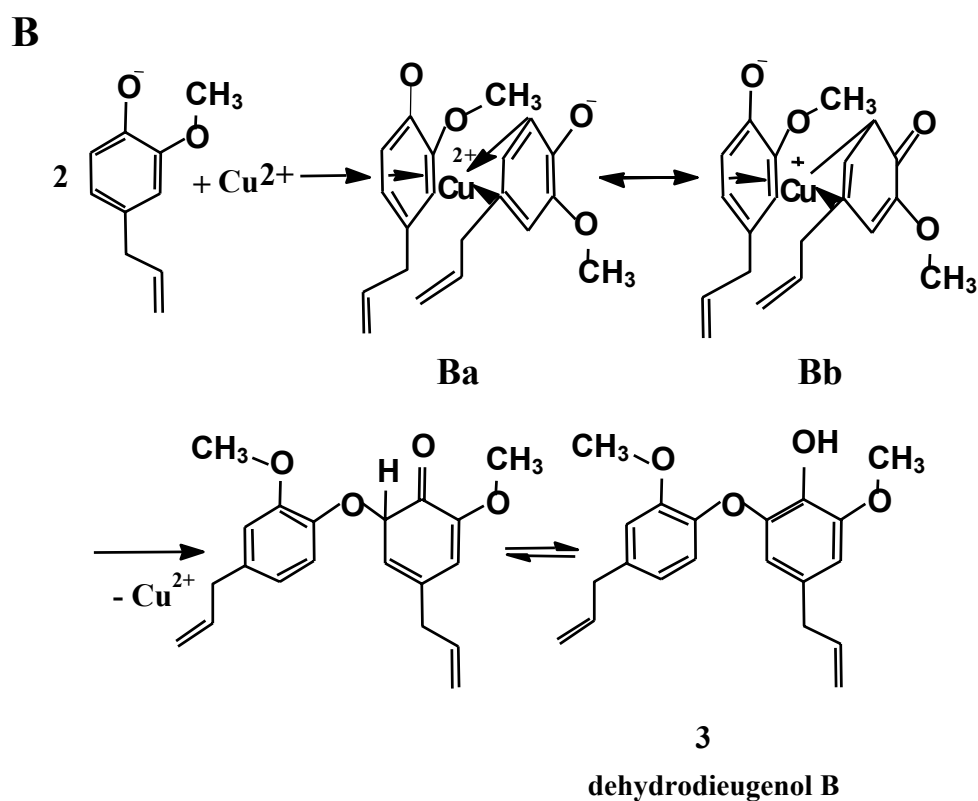
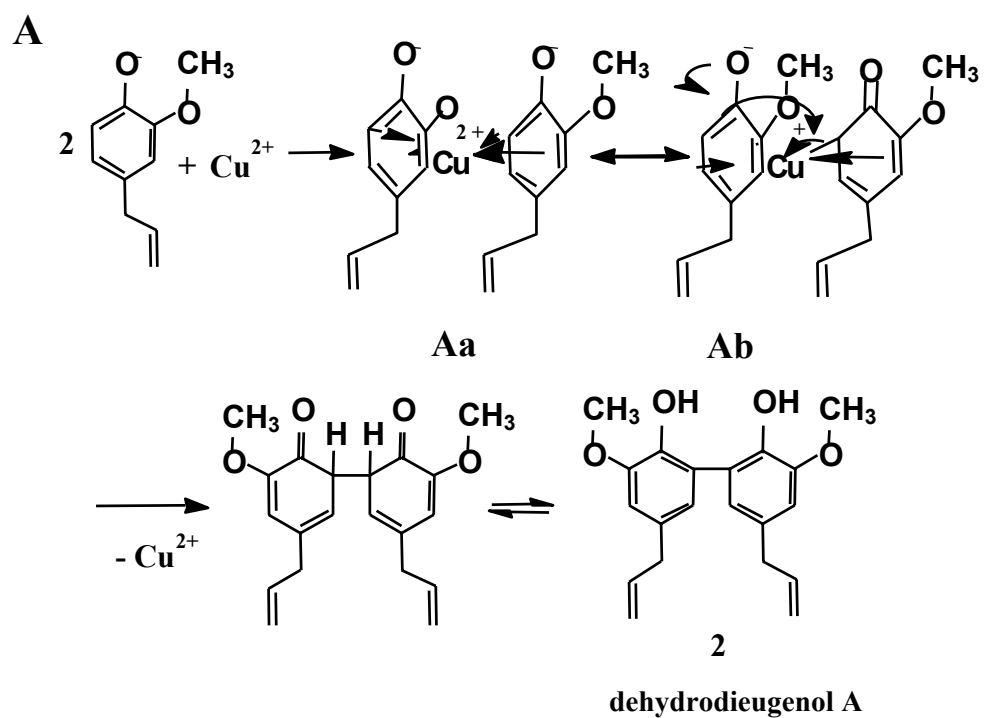
though effective diamines were selected.



Scheme 1

Next, we examined the dimerization of eugenol in  $\text{CuCl}(\text{OH})/\text{TMEDA}$  in dichloromethane in air at 20 °C. The simplicity and excellent yield (approximately 79%) of **2** made it the method of choice for preparing this compound. Other lignin-like compounds were also produced. A PM3 study (Scheme 1) showed that eugenol would be likely to form a dimer in the presence of copper ions, but not of oxygen alone due to the high density of carbon atom found in the benzene ring of eugenol (see, HOMO of eugenol). Through one-electron oxidation, eugenol quinone methide, EUGQM (**1**) could be formed from eugenol (see, SOMO of eugenol).

Previous studies have reported the synthesis of stable form of EUGQM from eugenol in acetonitrile, but its half-life is approximately 5 min in water [12]. Our hypothesis was that in the course of dimerization reaction pathway derived from the formation of a complex between eugenol and copper, dehydrodieugenol A (**2**) and dehydrodieugenol B (**3**) could be synthesized.



Scheme 2

Thus, using an INDO/1 method we calculated which compound would be suitable as a possible dimerization reaction pathway. The calculation suggested that a sandwich-type  $\pi$ -complex would be most preferably complex between eugenol and copper. The most active site of the nucleophilic reaction to eugenols is located in oxygen of phenoxides; however, the most active site of the electrophilic reaction is located in positions, C6 of eugenols, suggesting that eugenols would undergo dimerization due to cross-linking by  $\text{Cu}^{+2}$  complex between ortho positions (C6) of the hydroxyl groups of eugenols as shown in the reaction pathway (Scheme 2).

The eigenvalue (eV) of HOMO and LUMO orbitals of compound **2** (Cu-complex, systematic) was  $-3.197$  and  $5.157$ , whereas that of compound **3** (Cu-complex,  $60^\circ$  staggered) was  $-3.080$  and  $1.629$ , respectively. The distance between C6 position ( $\text{\AA}$ ) of compound **2** and **3** was  $2.953$  and  $3.039$ , respectively. The very short distance between positions 6, and the great perturbation energy that is estimated by the difference in eigenvalue between HOMO and LUMO for the complex-A and B suggest the possibility of synthesis of both dimer of **2** and **3** could be synthesized.

However, our study found that compound **2** was synthesized, but compound **3** was not. The reason why compound **3** was not synthesized may be due to the fact that a complex-B with T-4 coordination is more unstable than the complex-A with ST-4 coordination. PM3-aided dimerization reaction pathway supported the experimental results. In a further study, we synthesized dimeric compounds from BHA (2-*t*-butyl-4-methoxyphenol), MMP (2-methoxy-4-methylphenol, DBP (2, 4-di-*t*-butylphenol) in  $\text{CuCl}(\text{OH})/\text{TMEDA}$  in dichloromethane in air, obtaining excellent yield (above 80%); bis-BHA (3,3'-di-*t*-butyl-5,5'-dimethoxy-1,1'-biphenyl-2,2'-diol) [1,13], bis-MMP (3,3'-di-dimethoxy-, 5,5'-dimethyl-1,1'-biphenyl-2,2'-diol) [1], bis-DBP (3,3',5,5'-tetra-*t*-butyl-1,1'-biphenyl-2,2'-diol) [14]. The PM3 study suggests the synthesis of compound **3** may be possible when eugenols are capable of forming a complex with six-coordinating metals. Computer-aided synthesis is a useful tool in the design of new compounds.

## 4 CONCLUSIONS

Dimerization reaction of eugenol carried out in  $\text{CuCl}(\text{OH})/\text{TMEDA}$  in dichloromethane in air at  $20^\circ\text{C}$ . Eugenols gave dehydrodieugenol A in approximately 79% yield. The dimerization of reaction pathway was discussed based on the PM3 calculation.

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## Biographies

**Seiichiro Fujisawa** is Professor of Dentistry, Chairman of Department of Oral Diagnosis at Meikai University School of Dentistry. Major research projects are free radical mechanism of toxicity, catalysis and protection.

**Mariko Ishihara** is chemist, lecturer at Meikai University School of Dentistry.

**Ichiro Yokoe** is Professor of Pharmaceutical Chemistry at Josai University School of Pharmaceutical Science.