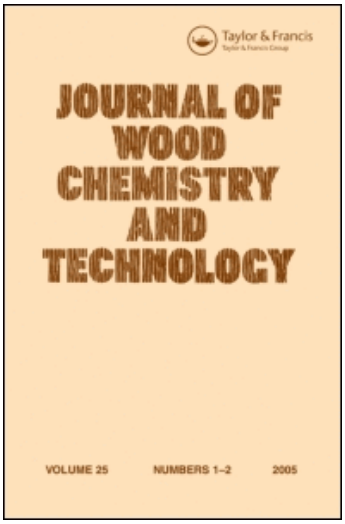

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Base-Catalyzed Reactions of (–)-Epicatechin: Formation of Enantiomers of Base-Catalyzed Reaction Products from (+)-Catechin

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ABSTRACT

Three compounds were isolated from the base-catalyzed reaction products of (−)-epicatechin at pH 12 and 40°C. From the results of the NMR and CD measurements, these were revealed to be the enantiomers of catechinic acid, catechinic acid stereoisomer and diarylpropanol-catechinic acid dimer formed from the base-catalyzed reactions of (+)-catechin. Thus, it has been demonstrated that both rearrangement and dimerization reactions as well as epimerization take place in the base-catalyzed reaction of (−)-epicatechin, similar

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to that of (+)-catechin. These results support that the quinone methide intermediate is formed during the base-catalyzed reactions, and the configuration of the hydroxyl group at C-3 should influence significantly the stereoselectivity of the subsequent reactions.

Key Words: Base-catalyzed reaction; (−)-Epicatechin; Catechinic acid; Catechinic acid stereoisomer; Diarylpropanol-catechinic acid dimer; Enantiomer.

INTRODUCTION

It is well known that condensed tannins are able to adsorb diverse proteins. However, the protein-adsorbing capacity of condensed tannins is generally not as high as hydrolyzable tannins because their rotational degree of freedom is smaller due to the presence of pyran-rings in the molecules.[1] Therefore, we have assumed that the development of the method for opening the pyran-rings leads to an improvement of the protein-adsorbing capacity and the related various biological activities of condensed tannins.

We have been studying base-catalyzed reactions of (+)-catechin, an abundant monomer unit of condensed tannins, in order to obtain the pyran-ring opened products. On the base-catalyzed reactions of (+)-catechin, several investigations have been reported. They have shown that *ent*-epicatechin,[2] catechinic acid (CA),[2,3] catechinic acid stereoisomer (CAS),[4] and diarylpropanol-catechinic acid dimer (DCAD)[5] are formed, and that these reactions are supposed to proceed through opening of the pyran-ring to give the quinone methide intermediate, followed by intramolecular or intermolecular nucleophilic attack on the intermediate.

(−)-Epicatechin, which is an epimer at the C-3 position of (+)-catechin, is also an abundant flavanol monomer constituting condensed tannins. On the base-catalyzed reactions of (−)-epicatechin, there has been little investigation undertaken so far. Kiatgrajai et al.[2] has shown that *ent*-catechin is formed by epimerization at the C-2 position of pyran-ring in the reactions of (−)-epicatechin. However, the formation of CA, especially its absolute stereochemistry has not been confirmed. In addition, reaction products other than CA obtained from the base-catalyzed reactions of (−)-epicatechin have not yet been characterized. In this study, the reactions of (−)-epicatechin at pH 12 and 40°C were investigated to clarify the reaction mechanisms and to compare the reaction products with those of (+)-catechin.

RESULTS AND DISCUSSION

Base-catalyzed reaction of (−)-epicatechin was carried out at pH 12 and 40°C in a sealed reaction vial for 24 h because under these conditions, CA, CAS, and DCAD were formed in the reaction of (+)-catechin.[4] The reaction of (−)-epicatechin gave two main and one minor compounds, similar to that of (+)-catechin. One of the main products (**1**) was detected at the same R_f values as CA on two-dimensional cellulose TLC (2D-TLC). This compound showed the same coloration as CA after spraying of vanillin-HCl reagent.[6] The FAB-MS spectrum showed $[M+H]^+ = 291$, indicating that **1** has the same molecular weight as CA. In addition, the ^1H and ^{13}C NMR spectra of **1** were in agreement with those of CA. These results indicate that **1** is identical with CA or its enantiomer. The minor compound (**2**) was identified with CAS or its enantiomer due to the coincidence of Rf values and coloration on 2D-TLC, FAB-MS spectrum ($[M+H]^+ = 291$) and ^1H and ^{13}C NMR spectra with CAS.[4] Another main compound (**3**) was expected to be DCAD or its enantiomer due to the coincidence of Rf values and coloration on 2D-TLC and FAB-MS spectrum ($[M+H]^+ = 581$) with DCAD. This was confirmed by the fact that ^1H and ^{13}C NMR spectra of the methyl ether derivative of **3** were in agreement with those of the methyl ether derivative of DCAD.[5]

Circular dichroism (CD) of **1–3** was examined to clarify their absolute stereochemistry. The CD spectra of them are shown in Fig. 1 together with those of CA, CAS, and DCAD. The spectra of **1–3** were revealed to be symmetrical to those of CA, CAS, and DCAD, respectively in the region of 200–350 nm. These results clearly indicate that the base-catalyzed reactions of (−)-epicatechin give the enantiomers of CA, CAS, and DCAD.

Proposed reaction mechanisms for the base-catalyzed reactions of (−)-epicatechin are shown in Fig. 2. In alkaline medium, quinone methide intermediate is formed through opening of the pyran-ring of (−)-epicatechin. As the configuration of C-3 is retained in this reaction, the intermediate is an enantiomer of the quinone methide intermediate formed from (+)-catechin.[2–5] Then, the subsequent intramolecular or intermolecular nucleophilic reaction should proceed in a similar manner to the base-catalyzed reactions of (+)-catechin. The *si*-face attack of A-ring carbanion on the C-2 carbon takes place to form the enantiomer of CA (**1**) as a major product because the cyclohexanone ring can take a stable chair conformation in which the catechol B-ring and the hydroxyl group are equatorial.[2,3] On the other hand, the *re*-face attack of A-ring carbanion on the C-2 carbon takes place to form the

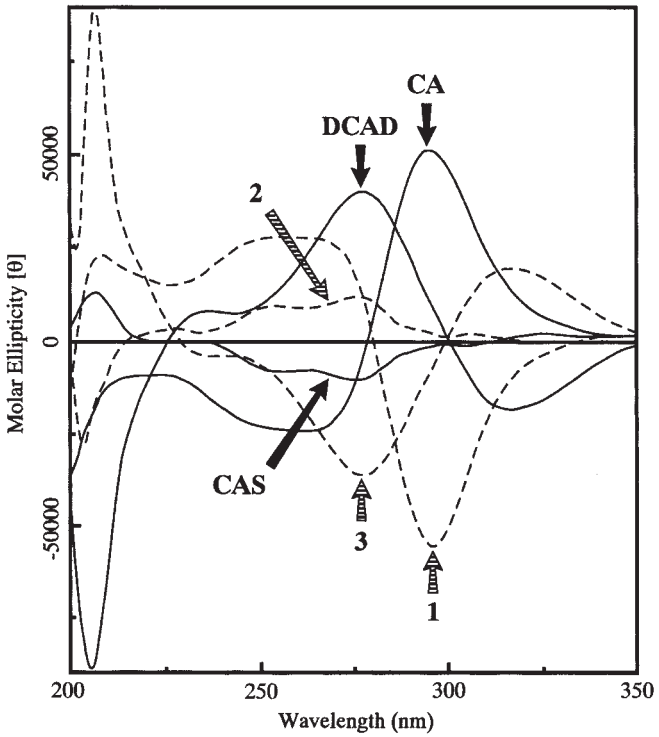

Figure 1. CD spectra of **1**, **2**, **3**, catechinic acid (CA), catechinic acid stereoisomer (CAS) and diarylpropanol-catechinic acid dimer (DCAD) in methanol.

enantiomer of CAS (**2**) as a minor product that adopts a boat conformation in which the catechol B-ring is equatorial but the hydroxyl group is axial.[4] The intermolecular attack of other (−)-epicatechin molecule on the C-2 carbon takes place to form the enantiomer of DCAD (**3**).[5] Thus, it has been demonstrated that both rearrangement and dimerization reactions, as well as an epimerization reaction to give *ent*-catechin,[2] take place in the base-catalyzed reactions of (−)-epicatechin, similar to those of (+)-catechin. The formation of the enantiomeric products from (+)-catechin and (−)-epicatechin supports the proposed reaction mechanism, that is, the quinone methide intermediate is formed during the base-catalyzed reactions. In addition, it is considered that the configuration of the hydroxyl group at C-3 of the quinone methide intermediate should influence significantly the stereoselectivity of the subsequent epimerization, rearrangement and dimerization reactions.

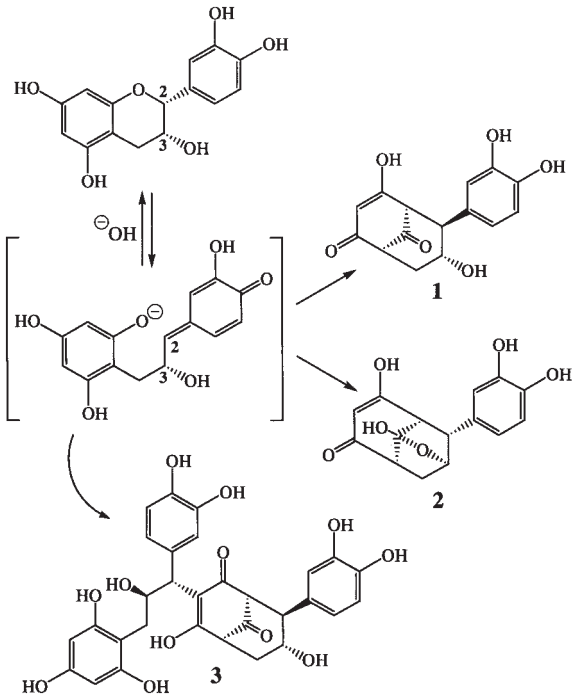

Figure 2. Proposed reaction mechanisms for the base-catalyzed reactions of (−)-epicatechin.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a JEOL ALPHA-500 spectrometer. FAB-MS spectra were obtained using a JEOL HX-110A spectrometer. CD spectra (in methanol) were measured with a JASCO J-720W spectrometer at room temperature (ca 25°C).

Base-Catalyzed Reaction of (–)-Epicatechin at pH 12 and 40°C

Base-catalyzed reaction of (−)-epicatechin (1000.0 mg) at pH 12 and 40°C was done according to the same procedure as the reaction of (+)-catechin.[4] The reaction product (779.0 mg) was applied to a Sephadex LH-20 column eluted with EtOH to obtain three fractions

(fractions I, II, and III). Fraction I was evaporated to give 482.6 mg of **1**. FAB-MS *m/z*: 291 $[M+H]^+$. ^1H and ^{13}C NMR spectral data (in pyridine-d_5 at 25°C) were in agreement with those of CA.[4] Fraction II was further purified by Sephadex LH-20 column chromatography eluted with MeOH-H_2O (1:1, v/v) to give 11.9 mg of **2**. FAB-MS *m/z*: 291 $[M+H]^+$. ^1H and ^{13}C NMR spectral data (in pyridine-d_5 at 25°C) were in agreement with those of CAS.[4] Fraction III was further purified by Sephadex LH-20 column chromatography eluted with MeOH–H_2O (1:1, v/v) to give 69.9 mg of **3**. FAB-MS *m/z*: 581 $[M+H]^+$. Methylation of **3** with dimethyl sulfate gave several products. The main product was isolated by preparative silica gel TLC developed with benzene–EtOH–H_2O–AcOH (200:47:15:1, v/v/v/v, upper phase). FAB-MS *m/z*: 679 $[M+H]^+$. ^1H and ^{13}C NMR spectral data (in $CDCl_3$ at 25°C) were in agreement with those of the methyl ether derivative of DCAD.[5]

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