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Effect of Cyclodextrins on the Thermal Epimerization of Tea Catechins

Hisako Okumura¹, Masaki Ichitani², Takanobu Takihara² and Ko-Ki
Kunimoto*¹

¹ *Graduate School of Natural Science & Technology, Kanazawa University,
Kakuma-machi, Kanazawa 920-1192, Japan*

² *Central Research Institute, Ito En, Ltd., 21 Mekami, Makinohara,
Shizuoka 421-0516, Japan*

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E-mail: kunimoto@sgkit.ge.kanazawa-u.ac.jp

Abstract

The epimerization of tea catechins was investigated at pH 5.5 and 120 °C, in the absence/presence of cyclodextrins (CDs). In the absence of CDs, a considerable amount (ca. 20%) of side reaction products originated from other than the epimerization (designated as “others”) was formed during the reaction of gallated catechins. Addition of β -CD to the reaction solution reduced an amount of the “others” to a few %, while other CDs with different cavity sizes showed little effect. Generally, addition of β -CD had an effect of improving the epimerization ratio of tea catechins, $[\text{nonepi-catechin}]/([\text{epi-catechin}] + [\text{nonepi-catechin}])$, by suppressing the formation of “others”. MO calculations using the PM3 method suggested that nonepi-type catechins are thermodynamically more stable than the epi-type counterparts, rationalizing the epimerization ratio in favor of nonepi-type catechins.

Keywords: tea catechins, thermal epimerization, cyclodextrin, epi-catechins, nonepi-catechins

introduction

Polyphenols are active components responsible for beneficial effects of green tea drinking. Green tea leaves (*Camellia sinensis L.*) contain catechins, low-molecular-mass polyphenols, which make up as much as 30 % of the dry weight of green tea leaves. Tea catechins belong to the flavan-3-ol class of flavonoids, consisting of two aromatic rings (A-, B-rings) connected by a pyran ring (C-ring). As shown in Fig. 1, they are classified, according to their stereochemical configuration, into epi-type catechins with a 2,3-*cis* configuration and nonepi-type catechins with a 2,3-*trans* configuration on the C-ring. In tea leaves, most catechins exist as epi-type, whereas the nonepi-type catechins form less than 10 % of the total tea catechin (Lin *et al.*, 1998). The major four catechins in green tea leaves are (-)-epigallocatechin 3-gallate ((-)-EGCg), (-)-epicatechin 3-gallate ((-)-ECg), (-)-epigallocatechin ((-)-EGC), (-)-epicatechin ((-)-EC). Of the tea catechins, (-)-EGCg is the most abundant one, accounting for 54% to 59% of total green tea catechins. (Hara, 2001). It has been known that epi-type catechins undergo epimerization in hot aqueous solution and yield corresponding nonepi-type isomers (Yamamoto *et al.*, 1997; Seto *et al.*, 1997). In manufacturing canned and

bottled tea drinks, the products are usually autoclaved for pasteurization at 120 °C for several minutes. The relatively high amount of (-)-GCg found in tea drinks was attributed to the epimerization product of (-)-EGCg during the autoclave treatment (Chen *et al.*, 2001; Xu *et al.*, 2003; Huang *et al.*, 2004). Since tea catechins and their epimers are reported to have different physiological effects, it is important to determine the factors that affect the epimerization equilibrium of tea catechins (Ikeda *et al.*, 2003).

Cyclodextrins (CDs) are cyclic oligosaccharides made of six, seven, and eight D-glucopyranosyl residues (α -, β -, and γ -cyclodextrin, respectively) linked by (α -1,4) glycosidic bonds. CDs are able to form inclusion compounds by capturing a number of compounds into their hydrophobic cavities (Wenz, 1994; Szejtli, 1998). Such inclusion complexes induce modification of the physicochemical properties of the 'guest' molecules, particularly in terms of water solubility and solution stability. For this reason, CDs are used to increase the water solubility of hydrophobic compounds or minimize undesirable properties such as odor or taste in certain food additives (Szejtli and Osa, 1996). Kurihara and Hamabe (Kurihara & Hamabe, 1999) reported on the effect of β -CD on the stability of catechins. Guest-host

interactions between tea catechins and cyclodextrins (CDs) have been extensively studied using NMR spectroscopy and the molecular modeling approach. However, there are no reports about the effect of cyclodextrin on the epimerization reaction of tea catechins. In this work, we have investigated the effect of CDs on the heat-epimerization of tea catechins. Dependence of concentration and cavity size of CDs were also discussed. In order to assess the relative stability between the epi-type catechins and nonepi-type catechins, semi-empirical quantum mechanics calculations were undertaken using the PM3 method as implemented in MOPAC 2002.

Materials and Methods

Materials Authentic catechins, (-)-EC, (-)-EGC, (-)-ECg, (-)-EGCg, (+)-C, (-)-GC, (-)-Cg and (-)-GCg were obtained from Funakoshi (Tokyo, Japan). Purities of all of these catechins were >98%. α -Cyclodextrin (α -CD), β -cyclodextrin (β -CD), γ -cyclodextrin (γ -CD), Hydroxypropyl- β -cyclodextrin (HP- β -CD), Methyl- β -cyclodextrin (Me- β -CD) were purchased from Tokyo Kasei Kogyo co. (Japan) and used without further purification. Doubly distilled, undeoxygenated water was used for preparation of buffer solution.

Other solvents and reagents were of special grade.

Sample preparation and epimerization condition Each catechin sample was dissolved in a McIlvaine (pH 5.5, 0.1 M citrate-0.2 M phosphate) buffer solution to make 2 mM solution. In order to estimate the effect of various CDs, catechin solution was also prepared in the presence of designated amount of CDs. The catechin solution was placed in a screw-cap tube, which were heated at 120 °C for a designated reaction time using the dry thermo bath MG-2200 (Eyela, Japan). After cooling down the sample tube, an aliquot of the incubation solution (10 μ L) was taken up and analyzed by HPLC.

HPLC analysis The HPLC system consisted of a Shimadzu (Kyoto, Japan) LC-10ATvp pump, a Shimadzu SPD-M10Avp uv detector and a Shimadzu CTO-10Avp column oven. Chromatographic separation of catechins and their epimers were carried out on a CAPCELLPAK C18 (4.6 \times 100 mm, 3 μ m, Shiseido Co., Ltd, Tokyo, Japan). The HPLC conditions were as follows: column temperature, 40 °C; sample size, 10 μ L; mobile phase,

methanol/water including 0.5% phosphoric acid 18:82 (v/v); flow rate, 0.8 mL/min; and measurement wavelength, 280 nm. The standard solution (45, 65, and 85 $\mu\text{g/mL}$) was prepared by diluting a stock solution of catechin (0.1 mg/mL) in 0.06 M ascorbic acid solution. The calibration curves were prepared from the peak area of 10 μL of each standard solution.

MO Calculation MO Calculations were carried out on a personal computer, using semiempirical quantum mechanics package, MOPAC 2002 which implemented with CAChe 5.0 software (Fujitsu Co. Ltd, Japan). The initial structure of (-)-EC was taken from the reported X-ray data (Fronczek *et al.*,1984) and those of other catechins were generated by adding the appropriate substituents to the (-)-EC structure. The geometry optimization of catechins in gas phase was performed by the semiempirical PM3 method (Stewart, 1989). The molecular geometry in simulated water was also calculated by taking account of the solvent effect using the semiempirical conductor-like screening model (COSMO) algorithm incorporated in MOPAC 2002 (Klamt, 1993). In all cases, the PRECISE option was used to provide higher accuracy within the calculation.

Results and Discussion

Thermal epimerization between (-)-EGCg and (-)-GCg

In the thermal epimerization of non-gallated catechins, the equilibrium is established between nonepi- and epi-catechins, where the equilibrium position is shifted toward the former. Thus, the concentration ratio of (+)-C and (+)-EC was reported to fall into 3:1 in favor of (+)-C (Kiatgrajai *et al.*, 1982). In order to examine the equilibrium position for gallated catechins, we have carried out the epimerization between (-)-EGCg and (-)-GCg using the reported optimum temperature and pH (120 °C, pH 5.5) (Seto *et al.*, 1997). When the (-)-EGCg solution was heated, concentrations of unconverted (-)-EGCg and a converted product, (-)-GCg, appeared to decrease and increase, respectively, exponentially with reaction time, as shown in Fig.2. These findings are consistent with the report that the degradation of (-)-EGCg during heat processing follows a pseudo first-order kinetics (Komatsu *et al.*, 1993; Zimeri *et al.*, 1999). The concentration of (-)-EGCg decreased to a minimum (42.2 %), while that of (-)-GCg increased to

a maximum value (38.2 %) in the 10 min reaction. At any reaction time, however, the sum of the (-)-EGCg and (-)-GCg concentrations does not amount to 100 %. It has been pointed out that the thermal degradation other than epimerization could occur during thermal processing of tea catechins. Those degradation reactions include dimerization (Roginsky *et al.*, 2005), hydrolysis (Ito *et al.*, 2003), oxidative and polymerization reactions (Hatano *et al.*, 2004). Here, we designate the unidentified degradation products other than the epimerization product as “others”. The concentration of “others” was also plotted in the figure. Prolonged reaction time of 15 min resulted in a further decrease of (-)-ECCg and the amount of “others” increases concomitantly, while the amount of (-)-GCg was unchanged. These results show that the degradation and epimerization of catechins occurred concurrently and nonepi-type (-)-GCg is more stable than epi-type (-)-EGCg during thermal processing.

Fig. 3 shows the result of the epimerization reaction using (-)-GCg as a starting material. Concentrations of unconverted (-)-GCg and a converted product, (-)-EGCg, appeared to decrease and increase, respectively, exponentially with reaction time, similar to those shown in Fig.2. This

similarity in overall trends clearly indicates that the inter-conversion between (-)-EGCg and (-)-GCg occurs in these reactions. The concentration of (-)-GCg decreased to a minimum (46.7 %), while that of (-)-EGCg increase to a maximum value (38.9%) in the 10 min reaction. It is noting that the decreasing rate of an unconverted (-)-GCg and the increasing rate of “others” are slower compared to the results in Fig. 2. These observations suggest that non-epi-catechins with a 2,3-*trans* configuration are more resistant to thermal processing than epi-catechins with a 2,3-*cis* configuration. These phenomena could explain why the concentrations of catechins in green tea extract were increased upon thermal processing (Kim *et al.*, 2000).

Effect of cyclodextrins on the epimerization of (-)-EGCg and (-)-GCg

Epimerization reaction of (-)-EGCg was carried out in the presence of various CDs. Table 1 summarizes concentrations of (-)-GCg (converted) and (-)-EGCg (unconverted) in the 10 min reaction. When β -CD was added to the reaction solution at half the concentration of (-)-EGCg (1 mM), concentration of the converted increased from 38.2 to 55.8 % and that of the unconverted decreased from 42.2 to 37.2 %. Concentration of the “others”

drastically decreased from 19.6 to 7.0 %. These trends become more prominent as the concentrations of β -CD increased. Addition of ten times the concentration of (-)-EGCg (20 mM) appeared to have the similar effect as the equimolar β -CD. On the contrary, additions of α -CD and γ -CD have little effects on the reaction. It is clear, from these results, that the β -CD addition effectively suppresses the formation of the “others” during thermal epimerization and, eventually, promotes the epimerization. Since Me- β -CD and HP- β -CD also have the same effect, the cavity size of β -CD is a critical factor for suppressing the formation of the “others”.

Epimerization behavior of tea catechins and effect of β -CD

Table 2 summarizes the results of the epimerization reactions of tea catechins in the absence and presence of β -CD. Regardless of the absence of β -CD, non gallated catechins such as (+)-C and (-)-EGC have lower levels of the “others” compared to gallated catechins, (-)-EGCg, (-)-GCg and (-)-ECg. The epimerization ratios for (+)-C and (-)-EGC (ca. 0.70) are close to the reported values (Seto *et al.*, 1993). On the contrary, gallated catechins show rather low values (0.38-0.48) of the epimerization ratios and a large amount

of the “others” in the absence of β -CD. These findings indicate that the galloyl moieties of gallated catechins are labile to thermal degradation that leads to lowering the epimerization reaction. The epimerization ratios of (-)-EGCg, (-)-GCg and (-)-ECg increase to 0.72, 0.75 and 0.67, respectively, in the presence of β -CD. From these results, it is suggested that addition of β -CD stabilizes the epimer pairs by suppressing the others reactions such as dimerization (Roginsky *et al.*, 2005), hydrolysis (Ito *et al.*, 2003), oxidation and polymerization (Hatano *et al.*, 2004).

Mechanistic consideration of epimerization

Mehta and Whalley first proposed the mechanism for the epimerization of (+)-C to (+)-EC (Mehta & Whalley, 1963). The principal step is the opening of the pyran ring to form the quinone methide, which then reclosures to give either (+)-C (*Re*-face) or (+)-EC (*Si*-face). Epimerizations of other tea catechins are expected to follow the same reaction mechanism. The results in Table 2 suggest the intrinsic epimerization ratio is about 0.70 which is observed for (+)-C and (-)-EGC where the formation of the “others” is minimized. This value suggests that non-epi-catechins with a 2,3-*trans*

configuration are more stable than epi-catechins with a 2,3-*cis* configuration. In order to estimate the relative stability, the molecular geometries of the epi-catechins and their isomers were optimized and heats of formation were calculated both in the gas phase and in simulated water using the semi-empirical PM3 method. Similar molecular geometries were obtained for both cases. Heats of formations of catechins calculated in simulated water are lower than those in gas phase by 13-22 kcal/mol, indicating all the catechins are stabilized in water. In Table 3, the calculated results using simulated water approximation are summarized. Inspection of Table 3 indicates the heat of formation of epi-catechin is 1-2 kcal/mol higher than that of the corresponding non-epi-catechin. Although very small, this systematic difference in heat of energy shows thermodynamic stability of non-epi-catechin compared to epi-catechin. It is noting that the the calculated $r(\text{C}_2\text{-O})$ bond length of epi-catechin is longer than that of corresponding non-epi-catechin. This bond is scissile during the formation of the quinone methide intermediate. The $r(\text{C}_2\text{-O})$ bond of the epi-catechin is more easily cleaved than that of the corresponding non-epi-catechin, which results in the epimerization equilibrium toward non-epi-catechin.

The quinone methide intermediate is rather labile and side reactions other than epimerization are also suggested to occur from this intermediate (Sears et al., 1974; Kennedy et al., 1984). Both epi-catechins and nonepi-catechins are also labile to dimerization (Roginsky *et al.*, 2005), hydrolysis (Ito *et al.*, 2003), oxidation and polymerization (Hatano *et al.*, 2004). Although the detailed mechanism is still to be studied, the host guest interaction of β -CD with catechins may protect these chemical species from thermal degradation.

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Figure Captions

Fig. 1 Structures of major green tea catechins and their epimers

Fig. 2 Degree of conversion for EGCg (2.0 mM) at pH5.5, 120 °C.

(○ : (-)-EGCg, △ : (-)- GCg, □ : Others)

Each plotted point is the mean of triplicate sample analyses.

Fig. 3 Degree of conversion for GCg (2.0 mM) at pH5.5, 120°C.

(○ : (-)- EGCg, △ : (-)- GCg, □ : Others)

Each plotted point is the mean of triplicate sample analyses.

Fig. 4 Reaction mechanism for the epimerization of (-)-EGCg to (-)-GCg

Table 1. Effect of β -CD derivatives on the epimerization of (-)-EGCg (2.0 mM) at 120 °C, pH5.5 (McIlvain buffer).

CDs	Conc.(mM)	Converted* (%)	Unconverted* (%)	Others (%)
none		38.2	42.2	19.6
β -CD	1.0	55.8	37.2	7.0
	2.0	67.4	30.6	2.0
	20.0	68.9	26.7	4.4
α -CD	2.0	38.2	38.4	23.4
γ -CD	2.0	40.4	39.1	20.5
Me- β -CD	2.0	73.3	26.7	< 0.1
HP- β -CD	2.0	67.9	32.1	< 0.1

* The unconverted and the converted stand for (-)-EGCg and its epimer, (-)-GCg, respectively.

Table 2. Effect of β -CD on the epimerization of tea catechins (2.0 mM) at 120 °C, pH 5.5 (McIlvain buffer).

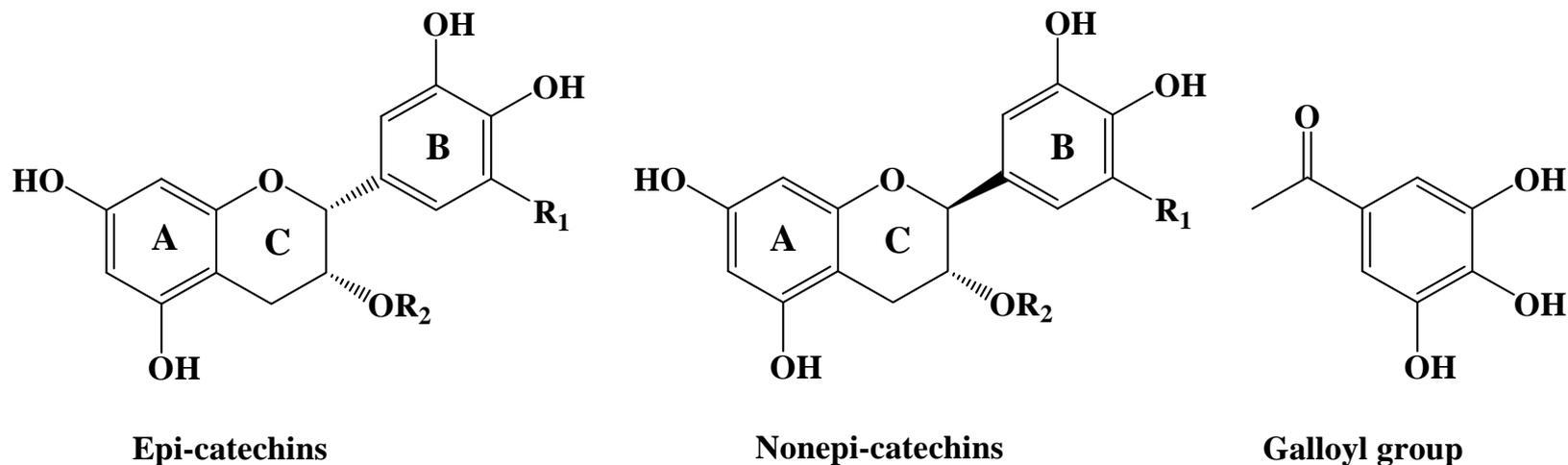
System		Converted (%)	Unconverted (%)	Epimerization Ratio*	Others (%)
(-)-EGCg	none	38.2	42.2	0.47	19.6
	β -CD	67.4	30.6	0.72	2.0
(-)-GCg	none	38.9	46.7	0.55	14.4
	β -CD	34.7	45.8	0.75	19.5
(-)-ECg	none	31.0	51.0	0.38	17.9
	β -CD	39.3	31.9	0.67	28.8
(+) -C	none	28.5	64.1	0.69	7.4
	β -CD	26.3	62.6	0.70	11.0
(-)-EGC	none	67.4	29.0	0.70	3.6
	β -CD	70.2	29.7	0.70	0.1

* The epimerization ratio is obtained by the formula, [nonepi-catechin]/([epi-catechin] + [nonepi-catechin])

Table 3. Heats of formation, ΔH_f (kcal mol⁻¹) of tea catechins and their epimers calculated using the PM3 method.

Catechins	Heats of formation (ΔH_f) (kcal mol ⁻¹)	$\Delta(\Delta H_f)$ (kcal mol ⁻¹)	$r(C_2-O)$ /Å
(-)-EGCg	-409.02		1.4327
(-)-GCg	-411.16	2.14	1.4257
(-)-ECg	-365.21		1.4340
(-)-Cg	-366.16	0.95	1.4265
(-)-EGC	-268.99		1.4340
(-)-GC	-270.54	1.55	1.4265
(-)-EC	-223.95		1.4354
(-)-C	-225.52	1.57	1.4276

* $\Delta(\Delta H_f) = \Delta H_f(\text{epi-catechin}) - \Delta H_f(\text{nonepi-catechin})$



	Substituent			Substituent	
Epi-catechins	R1	R2	Nonepi-catechins	R1	R2
(-)-EC	H	H	(-)-C*	H	H
(-)-ECg	H	Galloyl	(-)-Cg	H	Galloyl
(-)-EGC	OH	H	(-)-GC	OH	H
(-)-EGCg	OH	Galloyl	(-)-GCg	OH	Galloyl

* Green tea leaves contain (+)-C, an enantiomer of (-)-C, instead of (-)-C as a major component.

Fig. 1

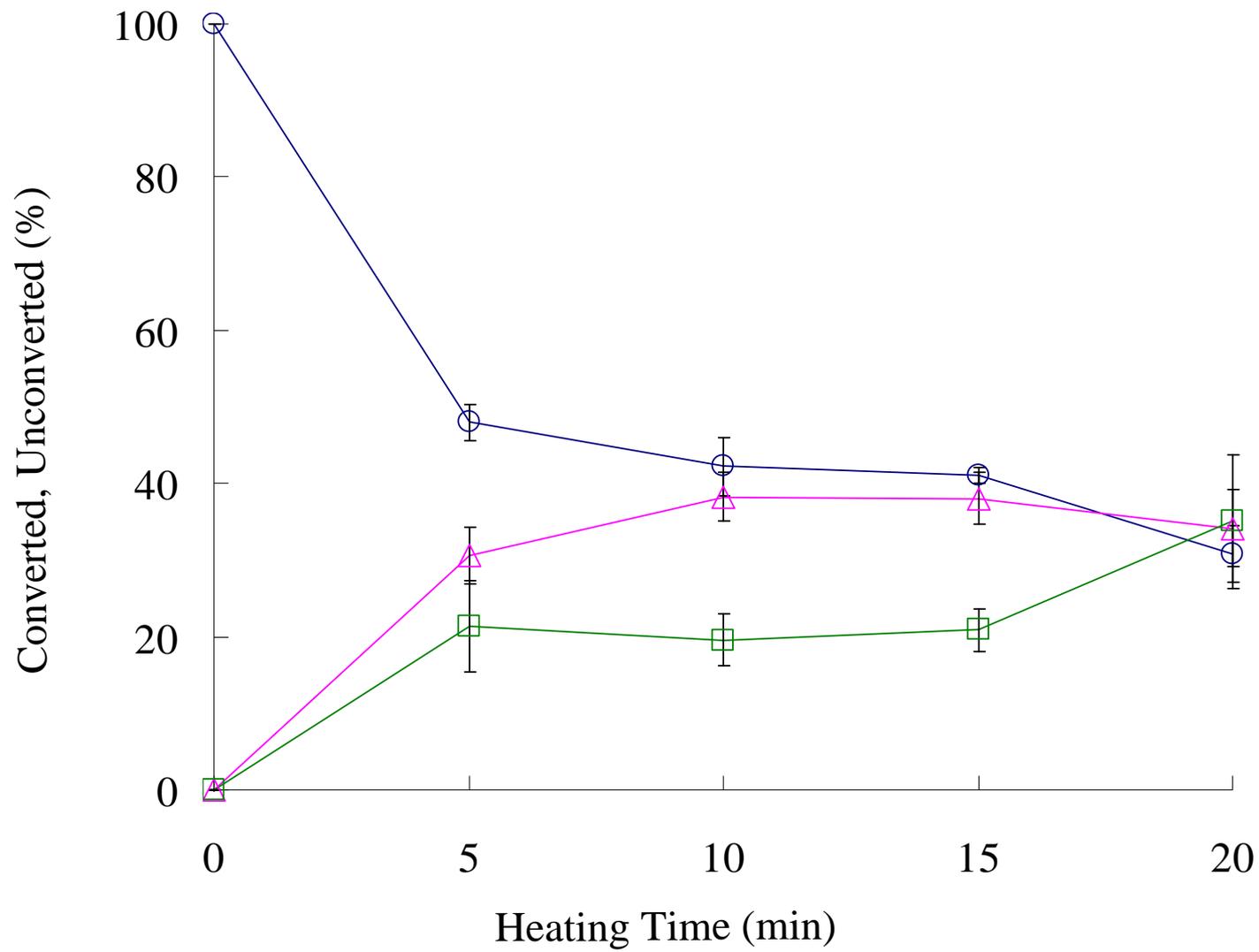


Fig.2

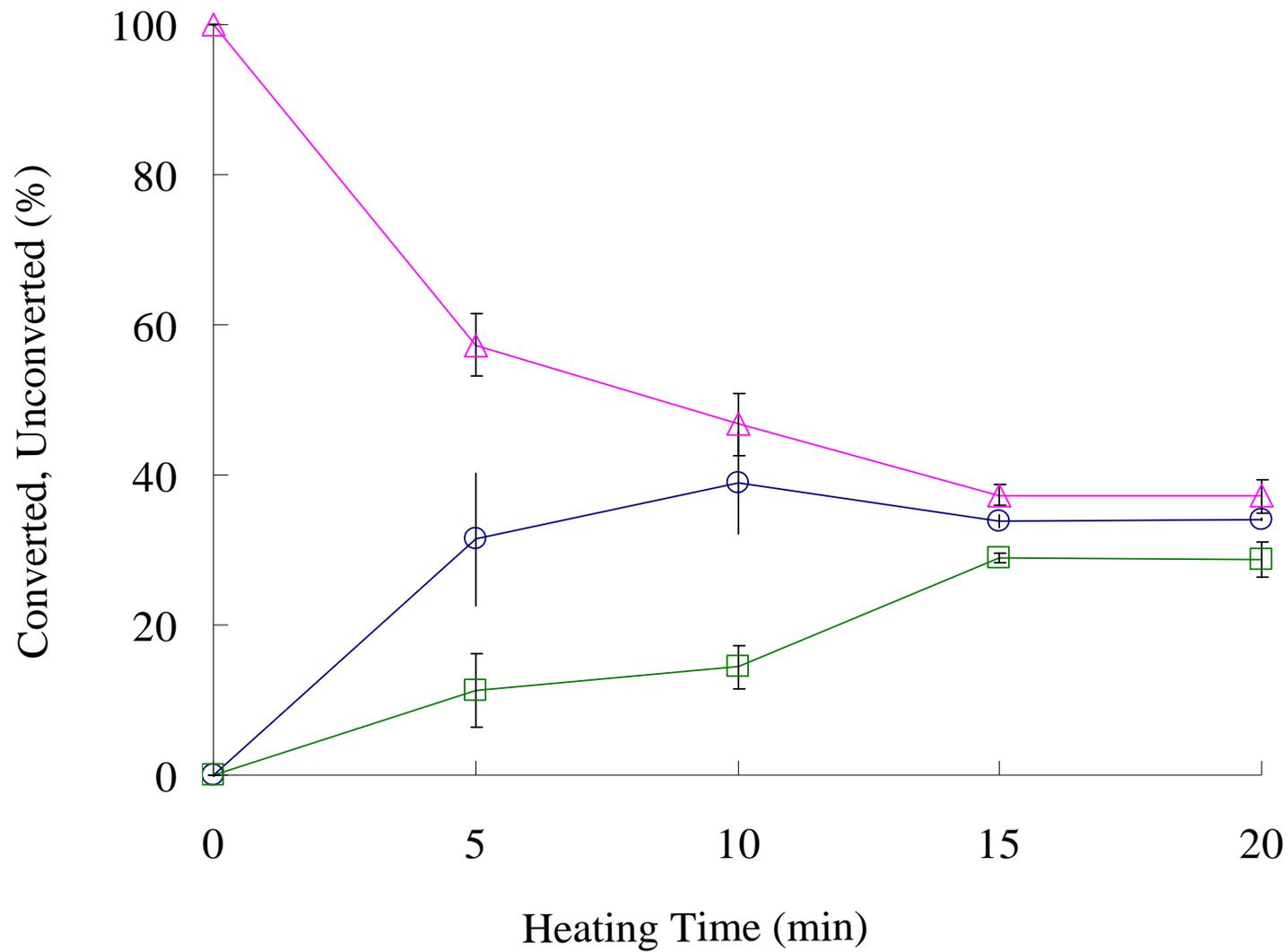


Fig. 3

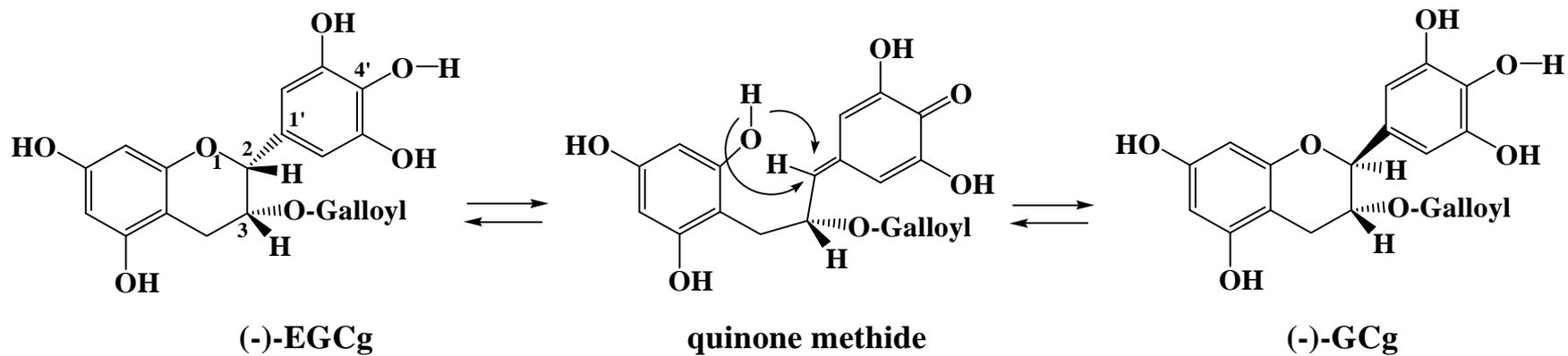


Fig. 4