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Interaction between gallocatechin gallate and caffeine in crystal structure of 1:2 and 2:2 complexes

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ABSTRACT

A suspension of (−)-gallocatechin gallate (GCg) and caffeine in water afforded two kinds of complexes, the 1:2 and 2:2 complexes of GCg and caffeine. The crystal structures of the two complexes were determined by X-ray crystallography. The driving force for the formation of the 1:2 and 2:2 complexes was thought to be mainly π–π interactions between the A, B′ rings of GCg and the six-membered rings of caffeines, and those between the B ring of GCg and caffeine, the B′ ring of GCg and caffeine, and the A rings of GCgs, respectively.

It is well known that tea protects against lifestyle-related diseases such as cancer, high blood pressure, diabetes, obesity, and arteriosclerosis.[1,2] Tea is made from leaves of the tea plant (*Camellia sinensis*, Camelliaceae), which includes various catechins and caffeine as major ingredients. Catechins are a group of polyphenols that show various physiologically modulating effects such as anticarcinogenic,[3,4] anti-metastatic,[5,6] and anti-oxidative.[7,8] Special interest has been directed at the gallated catechins, such as (−)-gallocatechin gallate (GCg) (Fig. 1). Recently, Lee et al. indicated that GCg-rich tea catechins in tea beverages may be effective in preventing hyperlipidemia by lowering plasma and hepatic cholesterol concentrations.[9]

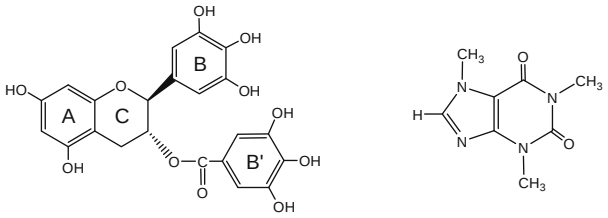
Caffeine belongs to a group of alkaloids (Fig. 1), and has a central nervous system-stimulating effect. Interestingly, it is known that polyphenols form complexes with caffeine, especially in black tea and coffee.[10–13] Various studies on the complexes of catechins and caffeine in solution state have been performed.[14,15] Hayashi et al. reported that an investigation of ^{1}H NMR chemical shift change and NOESY spectra in solutions containing catechins and caffeine showed the participation of A rings of catechins in complexation, as well as of B or B′ rings.[16]

Such complexation is not only an interesting chemical phenomenon, but also may show interesting unique biological activities. It is therefore important to know the detailed structure of the complex of gallated catechin and caffeine in the crystalline state as well as in the solution state. In this study, the crystal structure of the complex of (−)-gallocatechin gallate (GCg) and caffeine was determined by X-ray crystallography, and the interaction between GCg and caffeine moieties in the complex was also investigated.

The suspension of GCg (0.022 mmol) and caffeine (0.022 mmol) in water (130 μL) was heated at 90 °C for 30 min. and was left at room temperature to afford colorless powder (Scheme 1). The powder was recrystallized from water to give colorless needles (crystal A), which contained GCg and caffeine at a molar ratio of 1:2 based on measurement of the integral volume of ^{1}H NMR signals, whereas the same suspension was heated at 90 °C for 30 sec. and was left at room temperature to afford a sticky substance (21.8 mg), which contained GCg, caffeine, and water at a molar ratio of 1:1:22 based on measurement of the integral volume of ^{1}H NMR signals (Scheme 1). The sticky substance crystallized slowly in about 3 months at room temperature to afford colorless needles (crystal B).

The single crystal structure of crystal A was determined by X-ray crystallography (Crystal data 1)[17] and had a space group of $P2_12_12_1$, and the 1:2 complex of GCg and caffeine shown in the ORTEP drawings of Figure 2a. One unit cell of crystal A contained four units of the 1:2 complex, as shown in Figure 2b.

The merohedrally twinned crystal structure of crystal B was also determined by X-ray crystallography[18] and the 2:2 complex of GCg shown in Figure 5b.



(-)-Gallocatechin gallate (GCg) Caffeine

Figure 1.

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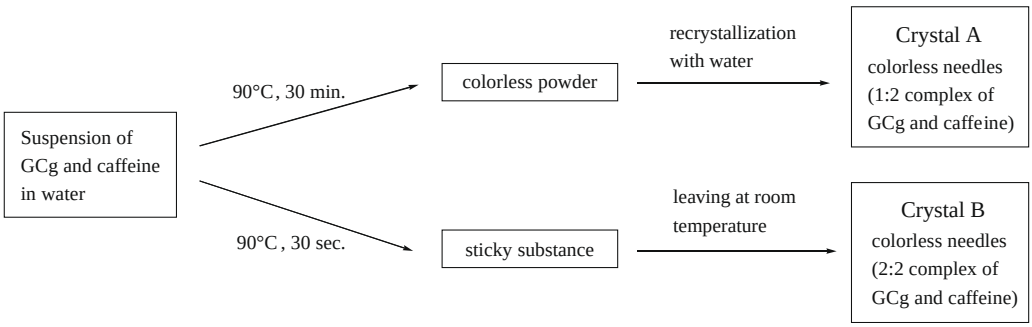

Scheme 1. Preparation of two kinds of crystals of GCg and caffeine complexes.

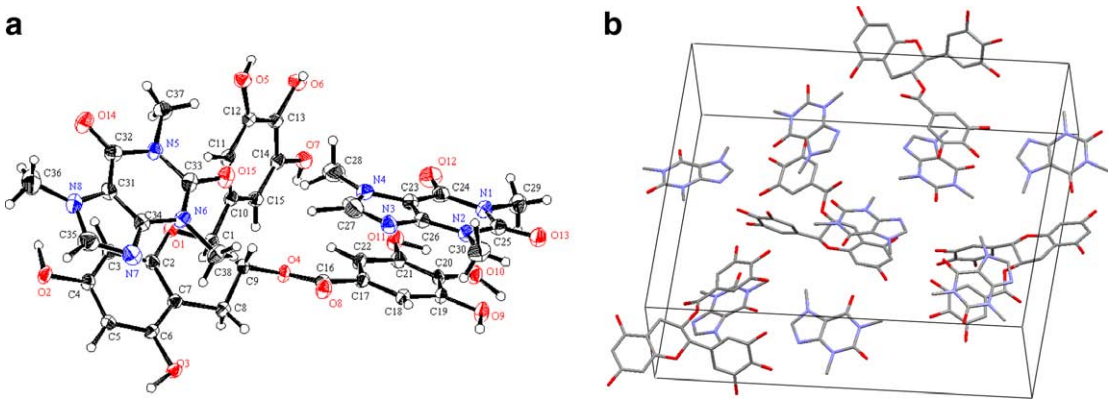

Figure 2. Crystal structure of the 1:2 complex of GCg and caffeine. Crystal solvent is omitted for clarity. (a) ORTEP drawing with thermal ellipsoids at the 30% probability level. (b) One unit cell. Hydrogen atoms are omitted for clarity.

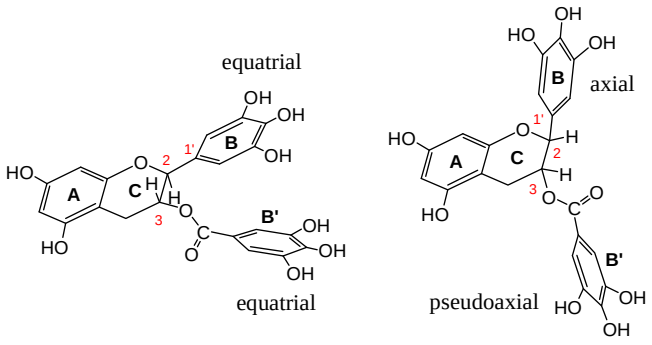

Figure 3. (a) Conformation of GCg moiety of 1:2 and 2:2 complexes and (b) GCg alone.

The dihedral angles of C1′–C2–C3–O and H2–C2–C3–H3 of the GCg moiety of the 1:2 complex are 55.93° and 173.18°, respectively, indicating that both B and B′ rings are in equatorial positions with respect to the C ring (Fig. 3a and Table 1). Both the B and B′ rings of the GCg moiety of the 2:2 complex also take equatorial positions with respect to the C ring (Fig. 3a and Table 1), whereas those of the crystal structure of GCg alone[18] take axial and pseudo-axial positions with respect to the C ring, respectively, as shown in Figure 3b and Table 1. Generally speaking, the equatorial position of a large substitution group is more stable than the axial position. Figure 4 shows the formation of hydrogen bonds in the crystal structures of the 1:2 and 2:2 complexes, and GCg alone. It is thought that the large number of hydrogen bonds in GCg alone (Fig. 4c), compared with the number of those of 1:2 and 2:2 complexes (Fig. 4a and b), makes it possible to take axial and pseudo-axial positions in the B and B′ rings.

Table 1
Dihedral angle in 1:2 and 2:2 GCg complexes and GCg alone

	Dihedral angle (C1′–C2–C3–O)	Dihedral angle (H2–C2–C3–H3)
1:2 Complex of GCg and caffeine	55.93°	173.18°
2:2 Complex of GCg and caffeine	61.05° (average)	176.94° (average)
GCg alone	159.03°	72.80°

A remarkable difference in the layer structure between the crystal structures of the 1:2 and 2:2 complexes and GCg alone was observed (Fig. 5). The units of the 1:2 complex piled up in the same direction almost vertically against the b–c plane, as shown in Figure 5a. The driving force for the formation of the 1:2 complex was thought to be mainly π–π interactions between the A, B′ rings of GCg and the six-membered rings of caffeines.

GCg molecules in the 2:2 complex piled up as shown in Figure 5b, and A and C rings of GCgs faced each other. The π–π interactions between the B ring of GCg and caffeine, the B′ ring of GCg and caffeine, and the A rings of GCgs were formed in the 2:2 complex, whereas GCg molecules in the layer of GCg alone piled up in the same direction as shown in Figure 5c, and no π–π interaction was observed.

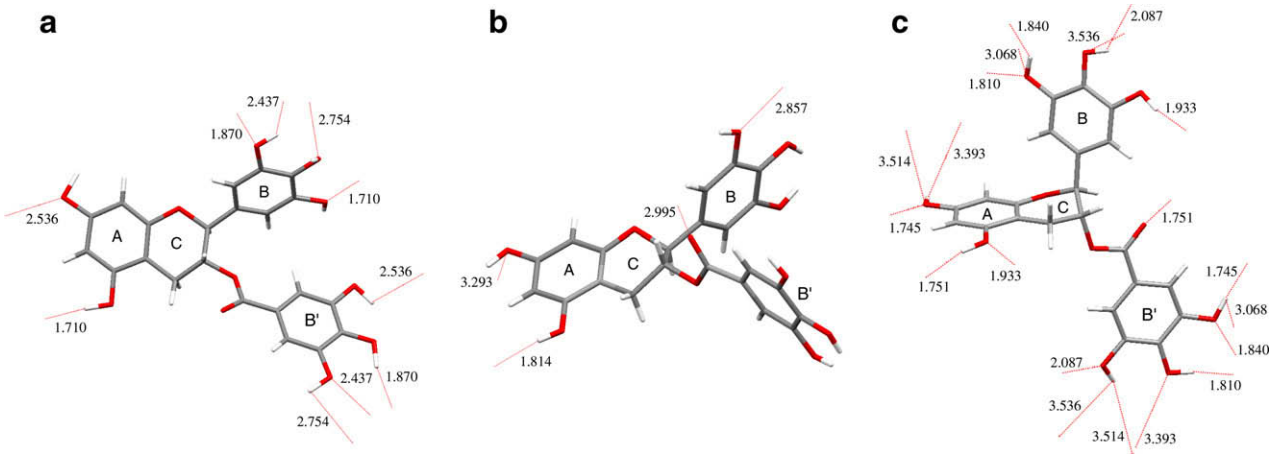

Figure 4. Hydrogen bonds in (a) 1:2 complex of GCg and caffeine, (b) 2:2 complex of GCg and caffeine, and (c) GCg alone. Dotted lines indicate hydrogen bonds.

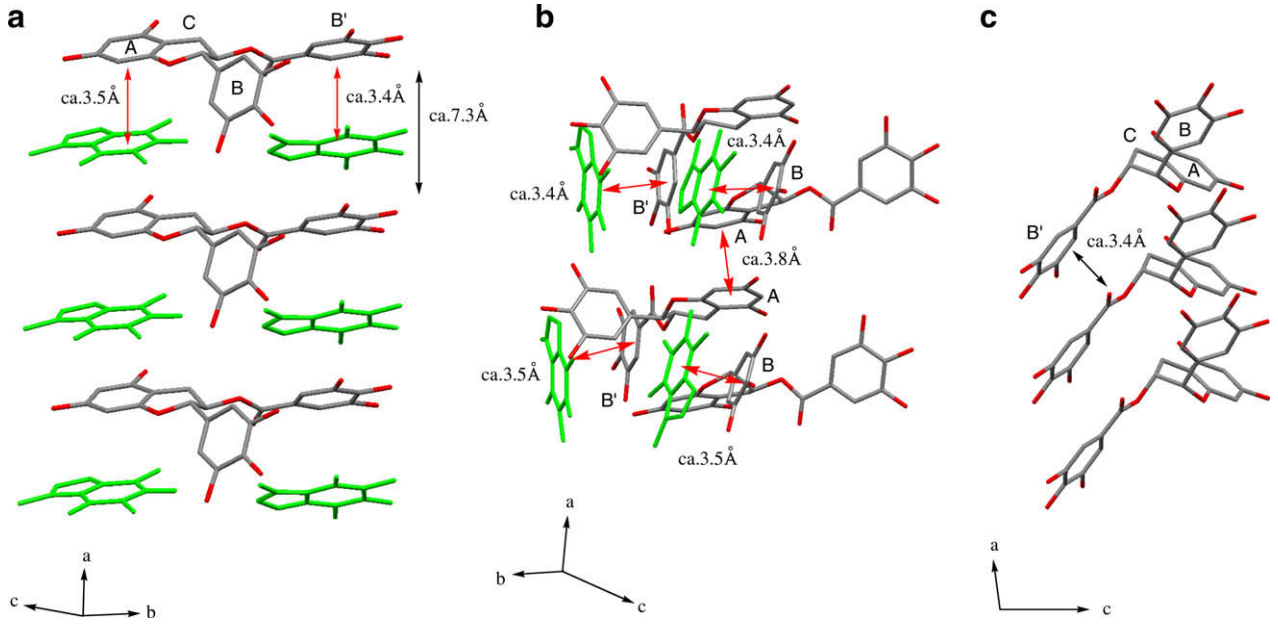

Figure 5. Layer structure of (a) 1:2 complex of GCg and caffeine, (b) 2:2 complex of GCg and caffeine, and (c) GCg alone. Red arrows indicate π–π interaction. Black arrows indicate the distance between planes.

Supplementary data

Supplementary data (crystallographic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.113.

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17. *Crystal data* **1**: A colorless needle crystal having approximate dimensions of 0.41 × 0.06 × 0.04 mm was mounted in a loop. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu-Kα radiation (λ = 1.54187) at 213 K. The structure was solved by SIR2004: Burla, M.C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G.L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R.; 2005 and refined by CRYSTALS Issue 11: Carruthers, J.R.; Rollett, J.S.; Betteridge, P.W.; Kinna, D.; Pearce, L.; Larsen, A.; Gabe, E. Chemical Crystallography Laboratory: Oxford, UK. 1999. Formula: $C_{38}H_{44}N_8O_{18}$. Fw = 900.81. Orthorhombic system, space group: $P2_12_12_1$ with a = 7.2718(16) Å, b = 21.9033(5) Å, c = 24.6028(6) Å. V = 3918.65(15) Å^3, Z = 4, D_{calc} = 1.527 g/cm^3. 7084 unique reflections with R_{int} = 0.051, 4320 reflections with $I > 2\sigma(I)$, R = 0.0524, R_w = 0.1221,

GOF = 0.969. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. 719045 for Crystal data **1**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc,cam.ac.uk).

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