Crystal Structure of Complex of Gallocatechin Gallate and Caffeine

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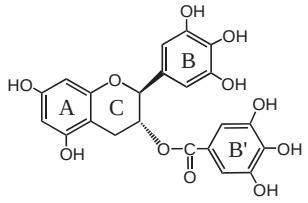
A merohedrally twinned crystal of the complex of (−)-gallocatechin gallate and caffeine was prepared in aqueous solution, and X-ray crystallographic analysis was performed. The driving force for the formation of the complex was thought to be mainly the π–π interaction between the B′ ring of GCg and caffeine, the B ring of GCg and caffeine.

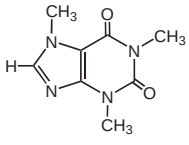
Catechins are a group of polyphenols included in the leaves and buds of the tea plant (*Camellia sinensis*, Camelliaceae). The role of such molecules in the prevention of cancer and cardiovascular disease, antiaging activity, and dietetics has received a great deal of attention.[1–3] Special interest has been directed at the gallated catechins, such as gallocatechin gallate (GCg), because it may be a bioactive constituent of green tea catechins (Scheme 1). A recent study indicates that GCg rich tea catechins in tea beverages may be effective in preventing hyperlipidemia by lowering plasma and hepatic cholesterol concentrations.[4]

Caffeine is also a representative compound in the leaves and buds of the tea plant, and has a central nervous system-stimulating effect (Scheme 1). Interestingly, it is known that polyphenols form complexes with caffeine, especially in black tea and coffee.[5–8] Maruyama et al. have noted that some gallated catechins have a strong affinity for caffeine, and assumed that these catechins bound a caffeine molecule in the space formed from B and B′ rings on the basis of ^{1}H NMR chemical shift changes in gallated catechins.[9] Cai et al. reported that in catechins such as (+)-catechin and (−)-epicatechin, A and C rings provided a general site for caffeine association, but in gallated catechins such as (+)-catechin gallate and (−)-epigallocatechin gallate (EGCg), the galloyl ester becomes the preferred site for complexation.[10] Furthermore, Hayashi et al. reported that an investigation of the ^{1}H NMR chemical shift change and NOESY spectra in a catechins and caffeine solution showed the participation of the A rings of catechins in complexation, as well as that of the B or B′ rings.[11]

Such complexation is an interesting chemical phenomenon, and may have some 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 liquid state. The crystal structure of the complex of (−)-gallocatechin gallate (GCg) and caffeine has been investigated and determined by X-ray crystallography. Also, the crystal structure of GCg alone has been determined to compare the crystal structure.



(-)-Gallocatechin gallate (GCg)



Caffeine

Scheme 1.

GCg (0.022 mmol) and caffeine (0.022 mmol) were added to water (130 μL) at 90 °C and left at room temperature to afford a sticky substance (21.85 mg), which contained GCg, caffreine, and water at a mole ratio of 1:1:22 based on measurment of the integral volume of ^{1}H NMR signals. The sticky substance crystallized slowly to give needles. The resulting merohedrally twinned crystal structure of the complex of GCg and caffeine was determined by X-ray crystallography (crystal data 1)[12] and revealed that one cell contains eight units consisting of 2 molecules of GCg and 2 molecules of caffeine, as shown in Figure 1a. The molecular arrangements of the crystal structure is quite interesting (Figure 1b). The driving force for complex formation was thought to be mainly the π–π interaction between the B′ ring of GCg and caffeine, the B ring of GCg and caffeine. The

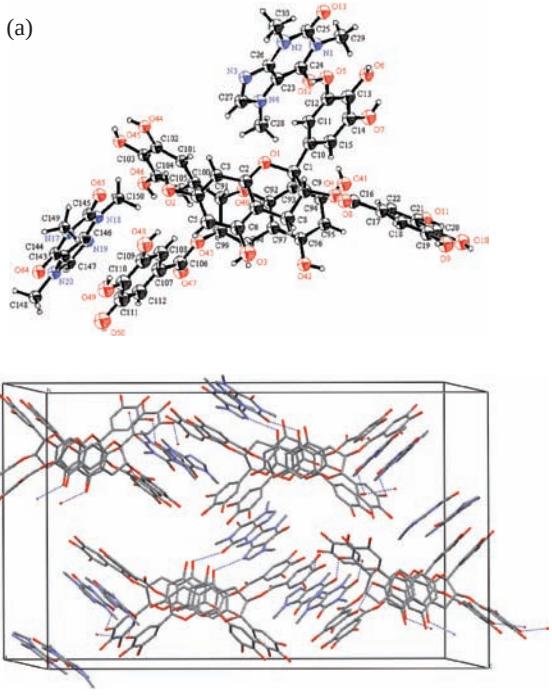


Figure 1. Crystal structure of GCg and caffeine complex Crystal solvent is omitted for clarity. (a) ORTEP drawing of GCg and caffeine complex with thermal epllisoids at the 20% probability level. (b) Layer structure and intermolecular hydrogen bonding of GCg and caffeine complex. Hydrogen atoms are omitted.

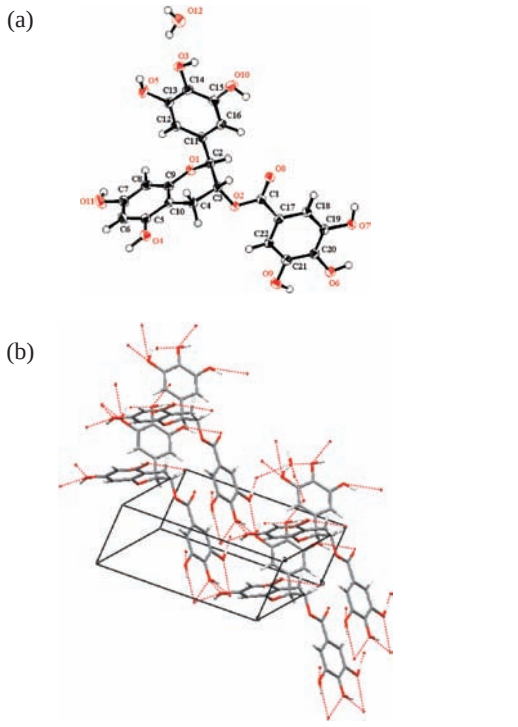


Figure 2. Crystal structure of GCg: (a) ORTEP drawing of GCg with thermal epllisoids at the 50% probability level. (b) Layer structure and intermolecular hydrogen bonding of GCg.

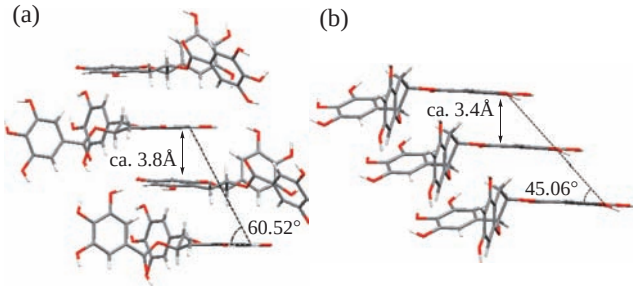


Figure 3. Layer of GCg: (a) the complex of GCg and caffeine. Caffeine is omitted for clarity. (b) GCg alone.

average dihedral angles of C10–C1–C9–O4 and H1–C1–C9–H9 are 61.05° and 176.94°, respectively, indicating that B and B′ rings are both in equatorial positions with respect to the C ring.

Next, a mixture of GCg and EGCg in water afforded a single crystal of GCg due to difference in solubility between GCg and EGCg. Its crystal structure was determined by X-ray crystallography (crystal data 2)[13] and showed the presence of an intermolecular hydrogen bond network between GCg molecules (Figure 2). The significant hydrogen bonds are O3–H11···O9 2.087 Å, O4–H5···O8 1.750 Å, O5–H10···O7 1.840 Å, O6–H16···O5 1.810 Å, O10–H12···O4 1.933 Å. The average dihedral angles of C11–C2–C3–O2 and H2–C2–C3–H3 are 159.03° and 72.80°, indicating that B and B′ rings are in axial and pseudoaxial positions with respect to the C ring, respectively.

A remarkable difference in the layer structure of GCg between the crystal structures of the complex and GCg alone was observed. In the GCg layer in the complex, GCg molecules piled up, as shown in Figure 3a, and A and C rings of GCgs faced each other, and the A rings formed a π–π interaction. Whereas in the layer of GCg alone, GCg molecules piled up in the same direction, as shown in Figure 3b.

References and Notes

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12 Crystal data **1**: A colorless needle crystal having approximate dimensions of $0.25 \times 0.10 \times 0.10\,\mathrm{mm}^3$ was mounted in a loop. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with filtered Cu Kα radiation ($\lambda = 1.54187\,\mathrm{nm}$) at 93 K. The structure was elucidated by SIR2002: M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, **2003** and refined by *SHELX97*, G. M. Sheldrick, **1997**. Formula: $C_{30}H_{40}N_4O_{19}$. Fw: 760.66. Monoclinic system, space group: $P2_1$ with $a = 17.8888(3)$ Å, $b = 23.1862(4)$ Å, $c = 37.0552(7)$ Å. $V = 14909.8(5)$ Å^3, $Z = 16$, $D_{calc} = 1.355\,\mathrm{g/cm}^3$. 12018 unique reflections with $R_{int} = 0.000$, 5985 reflections with $I > 2\sigma(I)$, $R = 0.1589$, $R_w = 0.3962$, GOF = 1.132.
13 Crystal data **2**: A colorless block crystal having approximate dimensions of $0.40 \times 0.21 \times 0.15\,\mathrm{mm}^3$ was mounted in a loop. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu Kα radiation ($\lambda = 1.54187\,\mathrm{nm}$) at 223 K. The structure was elucidated by SIR2004: M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, **2005** and refined by *CRYSTALS Issue 11*, J. R. Carruthers, J. S. Rollett, P. W. Betteridge, D. Kinna, L. Pearce, A. Larsen and E. Gabe, Chemical Crystallography Laboratory, Oxford, UK, **1999**. Formula: $C_{22}H_{20}O_{12}$. Fw: 476.39. Monoclinic system, space group: $P2_1$ with $a = 4.8135(11)$ Å, $b = 16.8259(4)$ Å, $c = 12.4737(3)$ Å. $V = 1002.60(4)$ Å^3, $Z = 2$, $D_{calc} = 1.578\,\mathrm{g/cm}^3$. 3378 unique reflections with $R_{int} = 0.029$, 3335 reflections with $I > 2\sigma(I)$, $R = 0.0343$, $R_w = 0.0979$, GOF = 1.002. Crystallographic data reported in this manuscript have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. 715903 for Crystal data **1** and No. 715904 for Crystal data **2**. 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 e-mail: deposit@ccdc, cam.ac.uk).

Published on the web (Advance View) January 31, 2009; doi:10.1246/cl.2009.230