Stereochemical Structure and Intermolecular Interaction of Complexes of (−)-Gallocatechin-3-*O*-gallate and Caffeine

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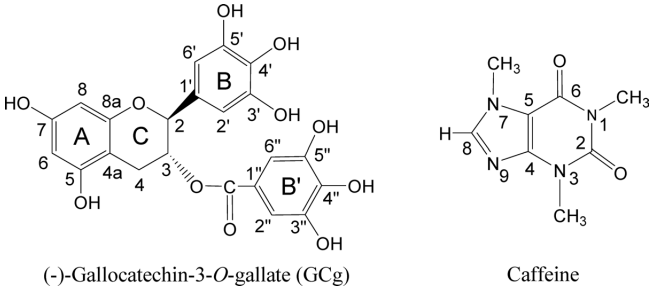
A suspension containing an equimolecular amount of (−)-gallocatechin-3-*O*-gallate (GCg) and caffeine in water was heated at 90 °C for 30 min to give a 1 : 2 complex of GCg and caffeine. X-Ray crystallographic analysis of crystal of the 1 : 2 complex showed that π–π interactions formed between the A, B′ rings of GCg and the two six-membered rings of caffeine. Whereas, the same suspension was heated at 90 °C for 30 s to give a sticky substance, 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. The sticky substance crystallized slowly to give a 2 : 2 complex of GCg and caffeine. X-Ray crystallographic analysis of crystal of the 2 : 2 complex showed that the A and C rings of GCg moieties faced each other, and face-to-face π–π interactions formed between the B ring of GCg and caffeine, the B′ ring of GCg and caffeine.

Key words (−)-gallocatechin-3-*O*-gallate; caffeine; X-ray crystallographic analysis; intermolecular interaction

Tea (*Camellia sinensis*, Camelliaceae) has been consumed worldwide since ancient times to maintain and improve health. Many researchers have investigated the components of tea and their physiological activities. Catechins are one of the major ingredients of tea and they belong to the flavan-3-ol family of flavonoids. It is well known that these have various beneficial effects such as anti-hypercholesterolemic,[1,2] anti-bacterial,[3,4] anti-oxidative,[5,6] and anti-cancereffects.[7,8] In particular, the majority of tea catechin studies have focused on (−)-epigallocatechin-3-*O*-gallate (EGCg), which is a gallate-type catechins, because it was thought to be the most abundant and have high biological activity. Recently, (−)-gallocatechin-3-*O*-gallate (GCg), which is a diastereomer of EGCg at the C2 position, has also attracted attention for its more effective biological activity than EGCg for certain diseases, such as hyperlipidemia.[9,10]

Caffeine is an alkaloid that has a central nervous system stimulating effect and is also the other major ingredient of tea. Interestingly, it is known that polyphenols form complexes with caffeine, especially in black tea and coffee.[11—14] Such complexes were thought to be unique stereostructures and to form interesting molecular interactions between catechins and caffeine.

Thus, many researchers have been investigating the structure of the complexes of catechins and caffeine. Maruyama *et al.* noted that some gallate-type catechins have a strong affinity for caffeine, and assumed that these catechins bound caffeine molecules in the space formed from B and B′ rings on the basis of ^{1}H-NMR chemical shift changes in gallate-type catechins.[15] Haslam *et al.* reported that in nongallate-type catechins such as (+)-catechin and (−)-epicatechin, the A and C rings provided a general site for caffeine association, but in gallate-type catechins such as (+)-catechin gallate and EGCg, the galloyl ester becomes the preferred site for complexation.[16] Furthermore, Hayashi *et al.* reported that an investigation of the ^{1}H-NMR chemical shift change and nuclear Overhauser effect spectroscopy (NOESY) spectra in catechins and caffeine solution showed the participation of Catechin A rings in complexation, as well as B or B′ rings.[17] These structural studies of the complexes of catechins and caffeine were performed in solution using NMR techniques, but their complete structures were still unclear and the detailed interactions between catechins and caffeine have not been elucidated sufficiently.



(-)-Gallocatechin-3-*O*-gallate (GCg) Caffeine

Fig. 1. (−)-Gallocatechin 3-*O*-gallate (GCg) and Caffeine

In this study, we focused on gallate-type catechin GCg (Fig. 1), and two crystals of the 1 : 2 and 2 : 2 complexes of GCg and caffeine could be prepared by two different crystallization methods. And X-ray crystallographic analyses of the complexes were performed to determine the crystal structures and to elucidate the detailed interaction between GCg and caffeine moieties.[18] Furthermore the conformation of GCg moieties of the 1 : 2 and 2 : 2 complexes was compared with that of GCg alone in crystal state.[19]

Results

Preparation of a Crystal of 1 : 2 and 2 : 2 Complexes of GCg and Caffeine A suspension containing an equimolecular amount of GCg and caffeine in water was heated at 90 °C for 30 min to give a colorless powder (Chart 1), which was recrystallized from water to give colorless needles (crystal A).

Whereas the same suspension was heated at 90 °C for 30 s to give a sticky substance (Chart 1), 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. The sticky substance crystallized slowly at room temperature to give colorless needles (crystal B).

Stereochemical Structure of the 1 : 2 Complex of GCg

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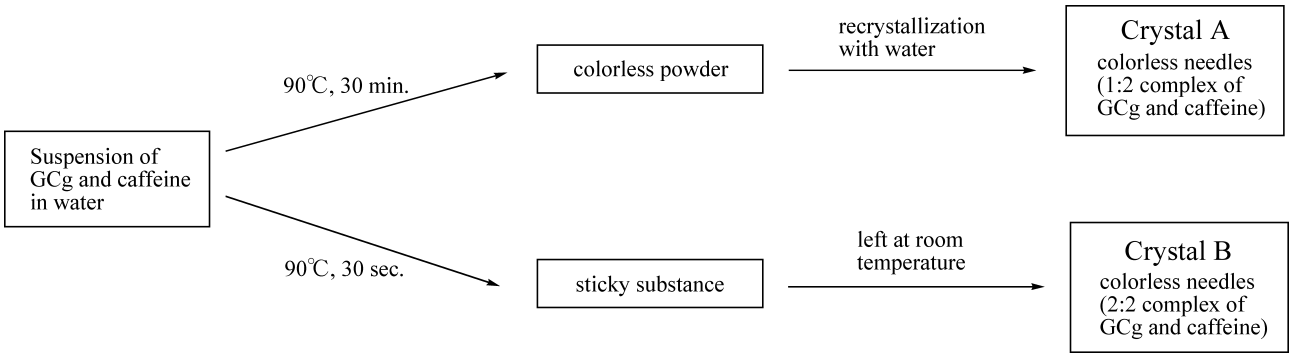

Chart 1. Preparation of Two Crystals of the Complexes of GCg and Caffeine

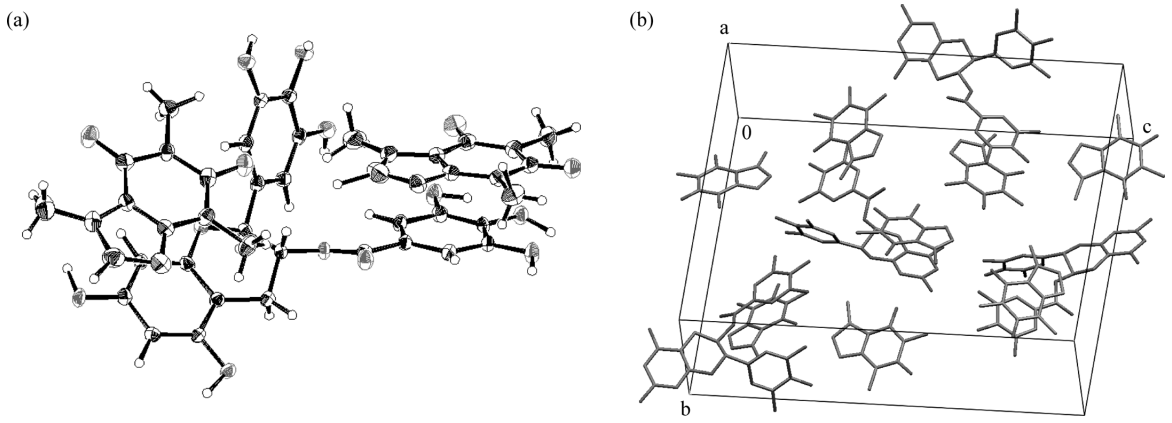

Fig. 2. Crystal Structure of the 1 : 2 Complex of GCg and Caffeine

(a) ORTEP drawing with thermal ellipsoids at a 30% probability level. (b) One unit cell. Hydrogen atoms and crystal solvent are omitted for clarity.

and Caffeine The single crystal structure of crystal A (0.41×0.06×0.04 mm) was determined to be a 1 : 2 complex of GCg and caffeine by X-ray crystallographic analysis and was orthorhombic with the space group $P2_12_12_1$. One unit cell dimensions were a=7.2718(2) Å, b=21.9033(5) Å and c=24.6028(6) Å, respectively. An ORTEP drawing and a one unit cell of the 1 : 2 complex of GCg and caffeine are shown in Fig. 2. In a unit of the 1 : 2 complex, the two caffeine molecules were located above the A and B′ rings of a GCg molecule. One unit cell contained four units of the 1 : 2 complex of GCg and caffeine and twelve water molecules as crystal solvent (Fig. 2b).

In the layer structure shown in Fig. 3a, units of the 1 : 2 complex of GCg and caffeine piled up parallel in the same direction to the *a*-axis. The distances between A and A, and B′ and B′ of GCg molecules were 6.87, 6.77 Å, respectively, and two caffeine molecules were located in almost the middle of the A rings and B′ rings of GCgs, as shown in Fig. 3b. The A and B′ rings of one GCg (the upper GCg) were face to face with six-membered rings of the two caffeines, but those of the other (the lower GCg) slightly shifted to the six-membered rings of caffeine. The distance between the A and B′ rings of the upper GCg and the two caffeine molecules were 3.29 Å and 3.34 Å, respectively.

The angles between the plane of B′ ring of the GCg (the upper GCg) and the plane of caffeine, the plane of the GCg A ring (the lower GCg) and the plane of caffeine were 2.3° and 4.4°, respectively, indicating that the two caffeine molecules slightly tilted to the plane of B′ and A rings of GCg (Fig. 3c).

Stereochemical Structure of the 2 : 2 Complex of GCg and Caffeine The crystal structure of crystal B (0.25×0.10×0.10 mm) was also determined to be a 2 : 2 complex of GCg and caffeine by X-ray crystallographic analysis and was monoclinic with the space group $P2_1$. One unit cell dimensions were a=17.8888(3) Å, b=23.1862(4) Å and c=37.0552(7) Å, respectively. An ORTEP drawing and one unit cell of the 2 : 2 complex of GCg and caffeine are shown in Fig. 4.

In a unit of the 2 : 2 complex of GCg and caffeine, the A and C rings of the two GCg molecules faced each other, and the B and B′ rings of GCgs were face to face with the two caffeine molecules. One unit cell contained eight units consisting of the 2 : 2 complex, and ninety-six water molecules as crystal solvent (Fig. 4b).

In the layer structure, units of the 2 : 2 complex of GCg and caffeine piled up parallel to the *a*-axis, and the A and A rings of GCgs faced each other (Fig. 5). The averaged distance between the A and A rings of GCgs was *ca.* 3.8 Å and the averaged angle between the plane of the A and A rings of GCgs was *ca.* 10.0°.

Packing of the 2 : 2 complex of GCg and caffeine in the cell down the *a*-axis is shown in Fig. 6. All caffeine molecules were sandwiched between B and B′ rings of GCgs or B′ and B′ rings of GCgs. Each caffeine molecule and the B and B′ rings of the GCg molecule were arrayed regularly in the order of B′ ring, caffeine, B′ ring, caffeine, and B ring. The averaged distances between each ring were *ca.* 3.2 Å, *ca.* 3.3 Å, *ca.* 3.3 Å, and *ca.* 3.4 Å, respectively. Furthermore, caffeine molecules, which were between B′ and B′ rings of

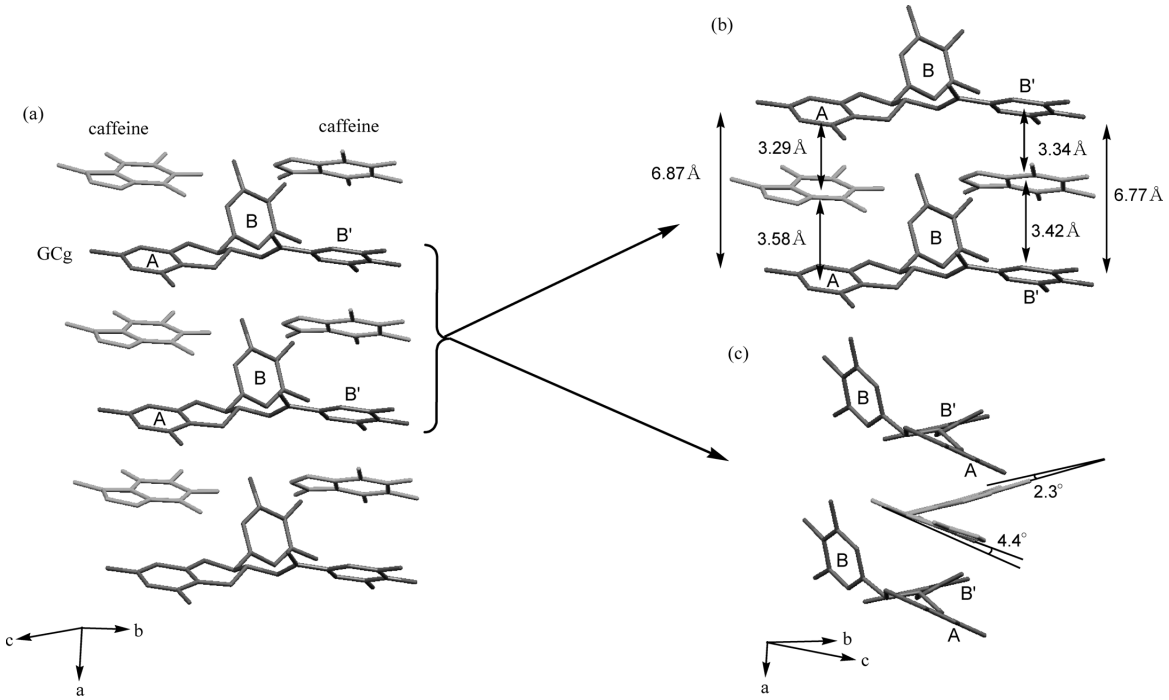

Fig. 3. Layer Structure of the 1 : 2 Complex of GCg and Caffeine

Light grey molecules are caffeine. Hydrogen atoms and crystal solvent are omitted for clarity. (a) Layer structure of the 1 : 2 complex of GCg and caffeine. (b) A portion of Fig. a. (c) Fig. c rotates Fig. b 90 degrees on the *a*-axis.

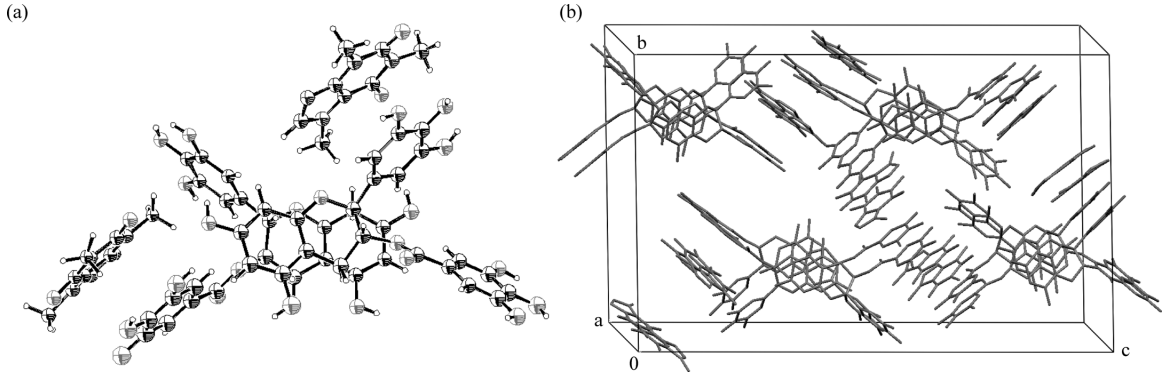

Fig. 4. Crystal Structure of the 2 : 2 Complex of GCg and Caffeine

(a) ORTEP drawing with thermal epllisoids at a 20% probability level. Crystal solvent is omitted for clarity. This OPTEP drawing structure is one of 4 units of the 2 : 2 complex of GCg and caffeine, and asymmetric unit was formed by 4 units, which are delicately different structure each other, but are the almost same. (b) One unit cell. Crystal solvent and hydrogen atoms are omitted for clarity.

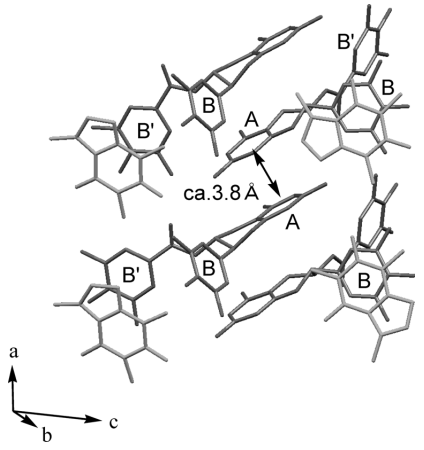

Fig. 5. Layer Structure of the 2 : 2 Complex of GCg and Caffeine

Hydrogen atoms and crystal solvent are omitted for clarity. Light grey molecules are caffeine.

GCgs, were also sandwiched between B and B rings of GCg molecules. These caffeine molecules were surrounded on four sides by the two B rings of GCgs and the two B′ rings of GCgs.

Conformation of GCg GCg molecule has conformational flexibility, including orientation of the linkage between B and B′ and C rings owing to puckering of the pyran C ring. On the other hand, the caffeine molecule has a plain and rigid xanthine skeleton. In the GCg molecule moiety of the 1 : 2 complex, the torsion angles of C1′-C2-C3-O and H2-C2-C3-H3 are 55.9° and 173.2°, respectively. It was found that the B and B′ rings of GCg were in both equatrial positions with respect to the C ring of the GCg molecule (Fig. 7a, Table 1). The B and B′ rings of the GCg moiety of the 2 : 2 complex also take both equatorial positions with respect to the C ring, as well as those of the 1 : 2 complex of GCg and caffeine (Fig. 7a, Table 1).

Whereas, in the GCg alone, the torsion angles of C1′-C2-

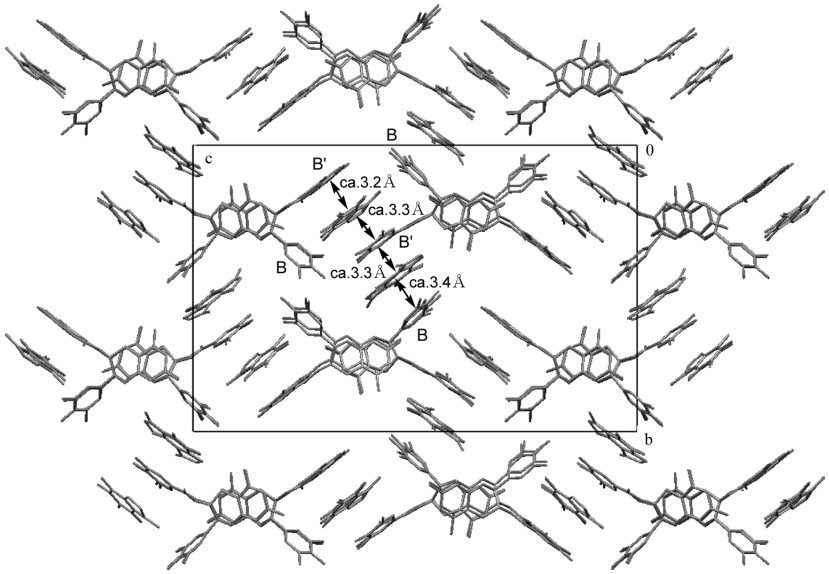

Fig. 6. Packing of the 2 : 2 Complex of GCg and Caffeine in the Cell Down the *a*-Axis

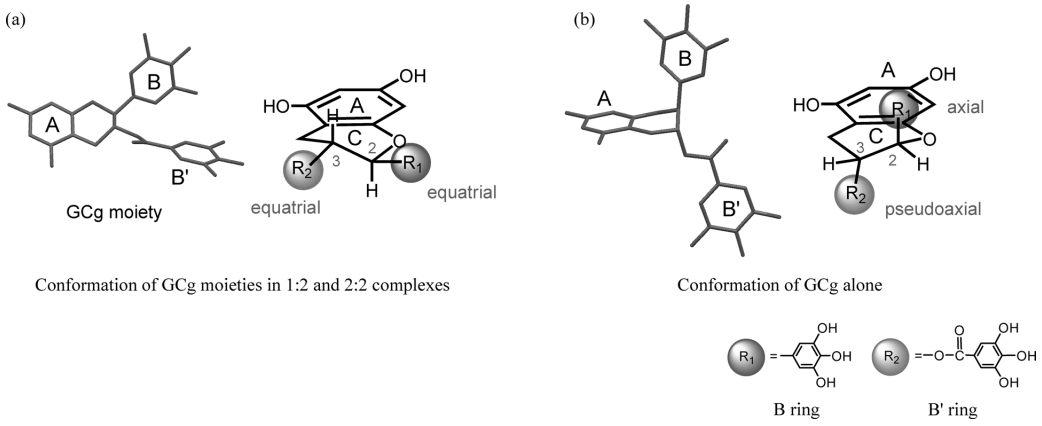

Fig. 7. Conformation of GCg Alone and the GCg Moiety of the 1 : 2 and 2 : 2 Complexes of GCg and Caffeine in the Crystalline State
(a) GCg moiety of the 1 : 2 and 2 : 2 complexes of GCg and caffeine. (b) GCg alone.

Table 1. Torsion Angle in the 1 : 2 Complex of GCg and Caffeine and GCg Alone

	Torsion angle (C1′-C2-C3-O)	Torsion angle (H2-C2-C3-H3)
1 : 2 complex of GCg and caffeine	55.9°	173.2°
2 : 2 complex of GCg and caffeine	61.1° (average)	176.9° (average)
GCg alone	159.0°	72.8°

C3-O and H2-C2-C3-H3 are 159.0° and 72.8°, respectively, indicating that those of the crystal structure of GCg alone take axial and pseudoaxial positions with respect to the C ring, respectively (Fig. 7b, Table 1).

Discussion

Molecular interactions such as Van der Waals' forces of non-covalent bond are weaker forces than covalent bond, but play a very important role to form such a complex of GCg and caffeine. Therefore, intermolecular interactions between GCg and caffeine moieties for forming the 1 : 2 and 2 : 2 complexes were investigated.

In the 1 : 2 complex, the two caffeine molecules were sandwiched between the A and B′ rings of GCgs, then face-to-face π–π interactions (light grey arrows in Fig. 8) formed between the A and B′ rings of the upper GCg and the six-membered rings of caffeine, and offset π–π interactions (dotted-line arrows in Fig. 8) formed between the A and B′ rings of the lower GCg and the six-membered rings of caffeine. Also, a CH–π interaction (black arrow in Fig. 8) formed between the B ring of the lower GCg and methyl group bound to N7 of caffeine (distance 2.85 Å). As shown in Fig. 8 and Table 2, three intermolecular hydrogen bonds between GCgs, GCg and caffeine (grey dotted-lines in Fig. 8) were observed in the 1 : 2 complex.

The intermolecular interactions between GCg and caffeine moieties to form the 2 : 2 complex of GCg and caffeine were investigated in addition to the 1 : 2 complex. All caffeine molecules were sandwiched between the B and B′ rings or B′ and B′ rings of GCgs by face-to-face π–π interactions (grey arrows in Fig. 9). Also, CH–π interactions (black arrow in Fig. 9) formed between the B ring of GCg and the methyl group bound to N3 of caffeine (averaged distance *ca.* 3.0 Å), the B ring of GCg and the methyl group bound to N7 of caffeine (averaged distance *ca.* 2.8 Å). As shown in Fig. 9 and Table 3, eight intermolecular hydrogen bonds between

GCgs, GCg and caffeine (grey dotted-lines in Fig. 9) were observed in the 2 : 2 complex.

Conclusion

The crystals of the 1 : 2 and 2 : 2 complexes of GCg and caffeine prepared by the two different crystallization methods were determined by X-ray crystallographic analysis, and revealed different and common points concerning their molecular interactions and crystal structures.

The four kinds of intermolecular interaction observed in the 1 : 2 complex were face-to-face π–π interaction, offset π–π interaction, CH–π interaction, and an intermolecular hydrogen bond, while the three kinds of intermolecular interaction observed in the 2 : 2 complex were face-to-face π–π interaction, CH–π interaction and an intermolecular hydrogen bond. Therefore, the 1 : 2 and 2 : 2 complexes were thought to be formed with the cooperative effect of four and three intermolecular interactions, respectively. Upon forming the 1 : 2 and 2 : 2 complexes, the face-to-face and offset π–π interactions and the CH–π interaction are thought to play an important role to bind GCg with caffeine, and the intermolecular hydrogen bond is thought to play an important role to bind GCg with GCg.

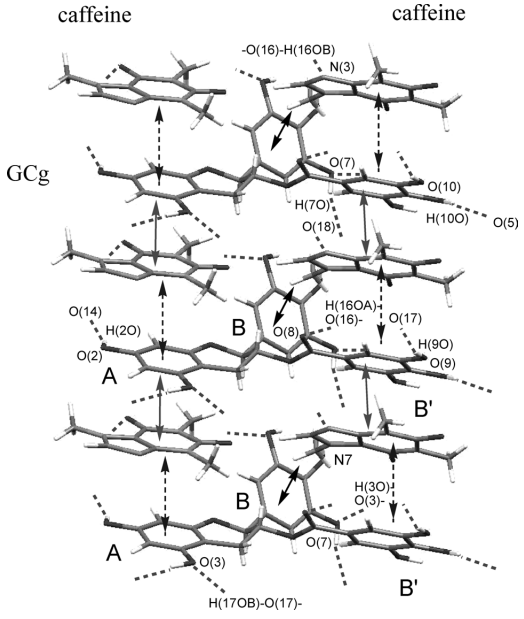

Fig. 8. Intermolecular Interactions between GCg and Caffeine for Forming the Crystal Structure of the 1 : 2 Complex

Light grey, dotted-line and black arrows and grey dotted-line indicate face-to-face π–π interactions, offset π–π interactions, CH–π interaction and intermolecular hydrogen bonds, respectively.

Experimental

Materials GCg was purchased from Nagara Science Co., Ltd., Japan. Caffeine was purchased from Sigma-Aldrich Co., U.S.A. GCg and caffeine were used without further purification.

Preparation of a Crystal of the 1 : 2 Complex of GCg and Caffeine A suspension of GCg (0.022 mmol) and caffeine (0.022 mmol) in water (130 μl) was heated at 90 °C for 30 min and left at room temperature to give a colorless powder. The powder was recrystallized from water to give colorless needles, which contained GCg and caffeine at a molar ratio of 1 : 2 based on measurement of the integral volume of ^{1}H-NMR signals. The melting points of the crystal was 160—162 °C.

Preparation of a Crystal of the 2 : 2 Complex of GCg and Caffeine

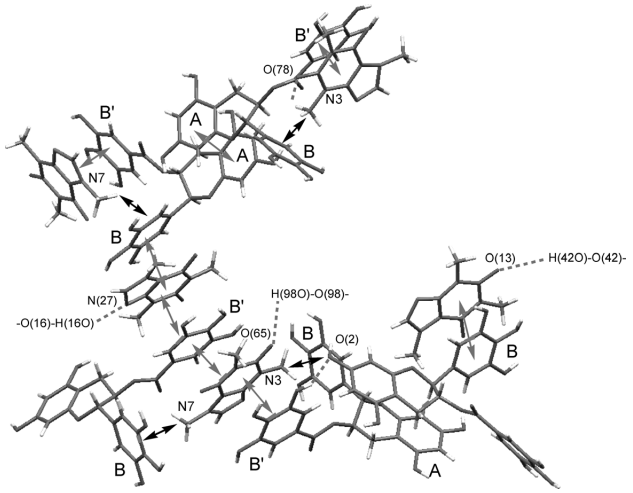

Fig. 9. Intermolecular Interactions between GCg and Caffeine for Forming the Crystal Structure of the 2 : 2 Complex

Grey and black arrows and grey dotted-lines indicate face-to-face π–π interactions, CH–π interactions and interaction hydrogen bonds, respectively.

Table 2. Selected Hydrogen Bonds in the 1 : 2 Complex of GCg and Caffeine

D–H	A	D…A	D–H	H…A	∠D–H…A
OH(2O)[a] C7 of GCg	O(14) C6 of caffeine	2.727	1.11	1.66	160.8
OH(3O) C5 of GCg	O(7) C3′ of GCg	2.752	1.05	1.71	174.1
OH(10O) C4″ of GCg	O(5) C5′ of GCg	2.894	1.06	1.87	161.5

a) Atom label in ORTEP drawing.

Table 3. Selected Hydrogen Bonds in the 2 : 2 Complex of GCg and Caffeine

D–H	A	D…A	D–H	H…A	∠D—H…A
OH(16O)[a] C5 of GCg	N(27) N9 of caffeine	2.729	0.84	1.89	174.8
OH(18O) C5′ of GCg	O(78) C2 of caffeine	2.660	0.84	1.83	167.0
OH(42O) C5 of GCg	O(13) C2 of caffeine	2.657	0.84	1.82	177.6
OH(46O) C5′ of GCg	O(39) C2 of caffeine	2.513	0.84	1.71	160.4
OH(48O) C5″ of GCg	O(2) C7 of GCg	2.816	0.84	2.06	149.9
OH(81O) C5 of GCg	O(52) C2 of caffeine	2.621	0.84	1.78	177.9
OH(85O) C5′ of GCg	O(26) C2 of caffeine	2.657	0.84	1.82	173.6
OH(98O) C5′ of GCg	O(65) C2 of caffeine	2.570	0.84	1.74	168.5

a) Atom label in ORTEP drawing.

Table 4. Crystal and Experimental Data of the 1 : 2 and 2 : 2 Complexes of GCg and Caffeine

	1 : 2 complex	2 : 2 complex
Chemical formula	$C_{38}H_{44}N_8O_{18}$	$C_{30}H_{40}N_4O_{19}$
Chemical formula moiety	$C_{22}H_{18}O_{11}$, $2(C_8H_{10}N_4O_2)$,$3(H_2O)$	$C_{22}H_{18}O_{11}$, $C_8H_{10}N_4O_2$, $6(H_2O)$
Formula weight	900.81	760.66
Crystal size	0.41×0.06×0.04 mm	0.25×0.10×0.10 mm
Crystal system	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (No. 19)	$P2_1$ (No. 4)
Unit cell parameters	a=7.2718(2) Å	a=17.8888(3) Å
	b=21.9033(5) Å	b=23.1862(4) Å
		β=104.0480(10)°
	c=24.6028(6) Å	c=37.0552(7) Å
Volume	3918.7(2) Å^3	14909.8(5) Å^3
Calculated density	1.527 g/cm^3	1.355 g/cm^3
Z	4	16
F(000)	1888.0	6400.0
Index ranges	h=−8→7	h=0→16
	k=−26→27	k=0→21
	l=−29→29	l=−33→32
Collected reflections	36270	12028
Unique reflections	7084	12018
Goodness of fit	0.969	1.132
R_1 for F_0>2 sigma (F_0)	0.0524	0.1589
wR for all data	0.1221	0.3962
Maximum difference peaks e/Å^3	0.92	0.76
Minimum difference peaks e/Å^3	−0.87	−0.38

Next, the same suspension was heated at 90 °C for 30 s and left at room temperature to give a sticky substance (21.8 mg). This sticky substance 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. The sticky substance crystallized slowly over about 3 months at room temperature to give colorless needles, which contained GCg and caffeine at a molar ratio of 2 : 2 based on measurement of the integral volume of ^{1}H-NMR signals. The melting points of the crystal was 155—157 °C.

X-Ray Crystal Structure Analysis of the 1 : 2 Complex of GCg and Caffeine A single crystal of the 1 : 2 complex of GCg and caffeine was determined by X-ray crystallographic analysis at 213 K. X-Ray intensity data of 36270 reflections (of which 7084 were unique) were collected on a Rigaku RAXIS RAPID II imaging plate area detector with graphite monochromated Cu$K\alpha$ radiation (λ=1.54187 Å). The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SIR2004[20] and expanded using Fourier techniques.[21] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F^2 was based on 7084 observed reflections and 622 variable parameters and converged with unweighted and weighted agreement factors of: $R=\sum||Fo|-|Fc||/\sum|Fo|=0.0524$, $Rw=[\sum(w(Fo^2-Fc^2)^2)/\sum w(Fo^2)^2]^{1/2}=0.1221$. The standard deviation of a unit weight observation was 0.97. A Sheldrick weighting scheme was used. Plots of $\sum w(|Fo|-|Fc|)^2$ *versus* $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.92 and −0.87 e/Å^3, respectively. All calculations were performed using the CrystalStructure[22,23] crystallographic software package. The crystal and experimental data of the 1 : 2 complexes of GCg and caffeine was shown in Table 4.

X-Ray Crystal Structure Analysis of the 2 : 2 Complex of GCg and Caffeine A crystal of the 2 : 2 complex of GCg and caffeine was determined by X-ray crystallographic analysis at 93 K. X-Ray intensity data of 12028 reflections (of which 12118 were unique) were collected on a Rigaku RAXIS RAPID II imaging plate area detector with graphite monochromated Cu$K\alpha$ radiation (λ=1.54187 Å). The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SIR2002[24] and expanded using Fourier techniques.[21] The final cycle of full-matrix least-squares refinement on F^2 was based on 12018 observed reflections and 1116 variable parameters and converged with unweighted and weighted agreement factors of: $R=\sum||Fo|-|Fc||/\sum|Fo|=0.1589$ ($I>2.00\sigma(I)$), $Rw=[\sum(w(Fo^2-Fc^2)^2)/\sum w(Fo^2)^2]^{1/2}=0.3962$. The standard deviation of a unit weight observation was 1.13. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.76 and −0.38 e/Å^3, respectively. All calculations were performed using the CrystalStructure[22,23] crystallographic software package except for refinement, which was performed using SHELXL-97.[25] Refinement was performed using the reflection data of 1.1 Å resolution because sufficient intensity data of reflections could not obtain. In order to improve the ratio of reflections/parameters, all the non-hydrogen atoms were refined isotropically and the flat six-membered rings were treated as rigid groups. None of the water hydrogen atoms could be located on the difference electron density maps. The crystal and experimental data of the 2 : 2 complexes of GCg and caffeine was shown in Table 4.

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