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THE CAFFEINE–POTASSIUM CHLOROGENATE MOLECULAR COMPLEX

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Key Word Index *Coffea arabica*; Rubiaceae; crystal structure; caffeine potassium chlorogenate molecular complex; polyphenol association.

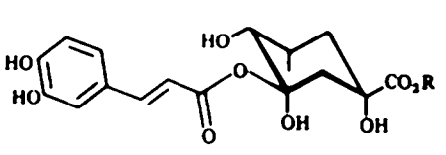
Abstract—The crystal structure of the caffeine–potassium chlorogenate 1:1 molecular complex derived from coffee beans is described. The relationship of this structure to the general question of the mechanisms of polyphenol association and precipitation is commented upon.

INTRODUCTION

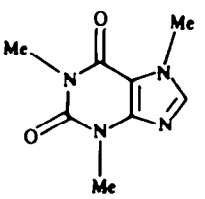
Non-covalent intermolecular forces underlie many biological phenomena enzyme catalysis, hormonal responses, membrane transport, etc. [1]. Understanding the nature of these forces – the problems of molecular recognition and discrimination – has become a major focus of attention in biological chemistry. One facet of this problem concerns plant polyphenols. The profusion and irregular distribution of phenolic compounds in plants has exercised the minds of chemists for many years. Botanists and plant physiologists have likewise pondered their function [2–5]. Plant phenols vary in complexity from the ubiquitous chlorogenic acid (**1**) to, for example, the complex polyphenols frequently referred to as vegetable tannins [6]. They reversibly associate with a wide range of substrates such as proteins and polysaccharides, and studies of these phenomena are not only of intrinsic scientific interest because of their possible involvement in a functional role, but they are also of undoubted practical significance. They determine, for example, the palatability of many foodstuffs [7] such as tea and coffee, wine, beers, cocoa and coca-cola; the nutritional value of crops [8]; and the rate of microbial decomposition of plant tissues in the formation of soils [9]; while extracted plant polyphenols still provide pharmaceutical preparations of medical interest and value [10]. Their ready association with proteins and other macromolecules probably forms the basis of their therapeutic action.

Recent studies [11, 12] have demonstrated some of the macroscopic features of the polyphenol molecular structure necessary for enhanced complexation with proteins and other nitrogenous metabolites. The molecular mechanisms whereby complexation is mediated have remained a subject for circumstantial speculation. Loomis [13] has suggested that hydrogen bonding and hydrophobic effects predominate. In aqueous media natural polyphenols readily associate with some alkaloids. With caffeine (**3**), for example, the complexation is polydentate and aggregates are ultimately formed sufficient to cause precipitation. The stoichiometry of these aggregates is similar in kind to that noted previously for polyphenols and proteins, and is directly related to the initial polyphenol concentration [14]. By extrapolation from crystal structure data it has been proposed [15] that hydrogen bonding and apolar interactions (the exclusion of the solvent water from regions between aroyl and purine rings, for example) dominate the complexation. A model for the precipitation process is suggested in Fig. 1 [15]. A further interesting facet of this work is the observation that in some polyphenolic substrates where there are multiple binding sites complexation often occurs preferentially at just one or two of these sites (C. M. Spencer, R. Martin, T. H. Lilley, E. Haslam and D. Magnolato, unpublished work).

Hydroxycinnamic acids are ubiquitous in the plant kingdom and usually occur as esters or glycosides [16]. The most familiar of these is the 5-*O*-caffeoyl ester of quinic acid, chlorogenic acid (**1**). It may constitute up to 0.1% of the fresh weight of many plant tissues but raw coffee is a rich source and contains 5–8% of this caffeoyl ester. Potassium chlorogenate (**2**) was first isolated from green coffee beans (*Coffea arabica* L.) by Gorter [17] as a crystalline 1:1 complex with caffeine (**3**). Gorter de-



1 R = H
2 R = K



3

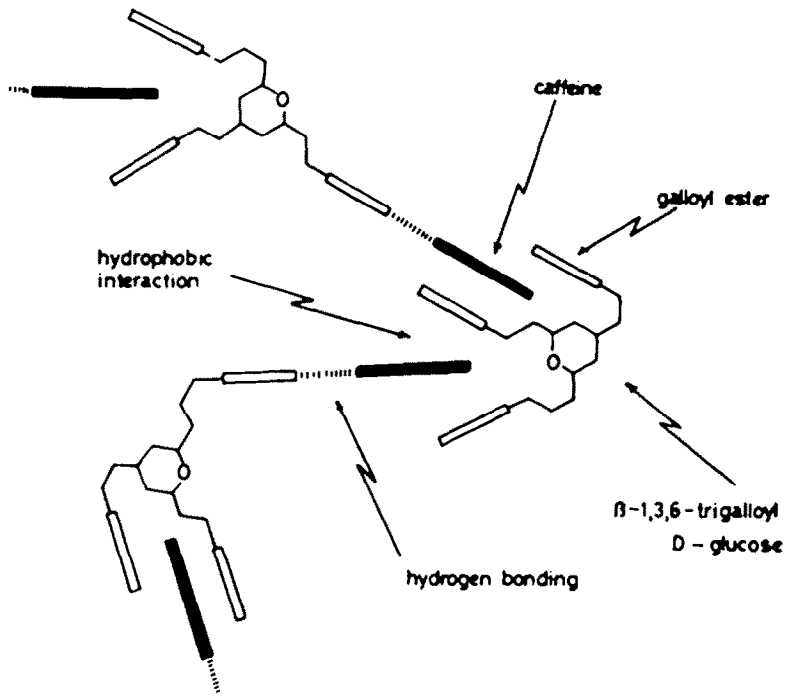


Fig. 1. Caffeine–polyphenol precipitation.

monstrated that the complex was recrystallized unchanged from aqueous ethanol, but its structure and physicochemical properties have, since that date, received scant attention. Sondheimer *et al.* [18] in a partition study considered the influence on complex stability of various stereochemical and structural features but their work failed to identify the nature of the intermolecular forces. In a later investigation, Horman and Viani [19], using NMR spectroscopy, concluded that in aqueous media the caffeine potassium chlorogenate complex was best described as a "hydrophobically bound π molecular complex" and percipiently they suggested that in solution the time-averaged conformation of the complex resembled that shown in Fig. 2. It was proposed that the plane of the caffeine molecule is parallel to the plane of the aromatic ring of the caffeoyl ester group and that the five- *and* six-membered rings of the nitrogen heterocycle are equally involved in complex formation.

RESULTS AND DISCUSSION

The structure of the caffeine potassium chlorogenate complex* was obtained from an X-ray study. Initial attempts using default values with MULTAN-80 [20] were not rewarding. Using a group scattering factor for the caffeine molecule, calculated from its published geometry [22] together with the standard weighted tangent formula [20] a partial solution was derived. Coordinates for the potassium ion and 19 of the heavy atoms comprising the chlorogenate ion were obtained in this way and refined for several cycles using the CRYSTALS [21] package. Fourier methods then allowed the location of the caffeine molecule together with the remaining atoms of the chlorogenate ion and the two oxygen atoms associated with the water of crystallization. The structure was then refined using isotropic and anisotropic temperature factors, and this process was covergent with $R = 6.99\%$. Most of the hydrogen atoms were located from a Fourier map. Where possible, hydrogen atoms were then included in their calculated positions, but hydroxyl hydrogen atoms together with those of the *N*-methyl groups at C (22) and C (23) were located in their found loci. The *N*-methyl group at C (24) was disordered and these hydrogen atoms were eventually included assuming a conformation of this *N*-methyl group similar to that reported for the caffeine barbital complex [23]. Further refinement of the parameters associated with the heavy atoms gave a final R value of 5.51%. Final atomic coordinates are contained in Table 1, and Table 2 lists inter-atomic distances and bond angles.

The structure of the asymmetric unit of the

*Crystal data for potassium chlorogenate·caffeine bishydrate, $C_{16}H_{17}O_9K \cdot C_8H_{10}N_4O_2 \cdot 2H_2O$. $M_r = 622.63$. Space group $P2_12_12_1$, $a = 7.0521$ (3), $b = 11.5848(9)$, $c = 33.8621(27)$ Å, $U = 2766.4$ Å^3, $D_c = 1.49$ g/cm^3, $Z = 4$. Cu K_α radiation ($\lambda = 1.5418$ Å), $\mu = 23.35$ cm^{-1}, $F(000) = 1304$, $R = 0.0551$, $R_W = 0.0621$ for 1682 reflections. $\theta \leq 66°$, $I \geq 2\sigma(I)$. The atomic coordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, U.K.

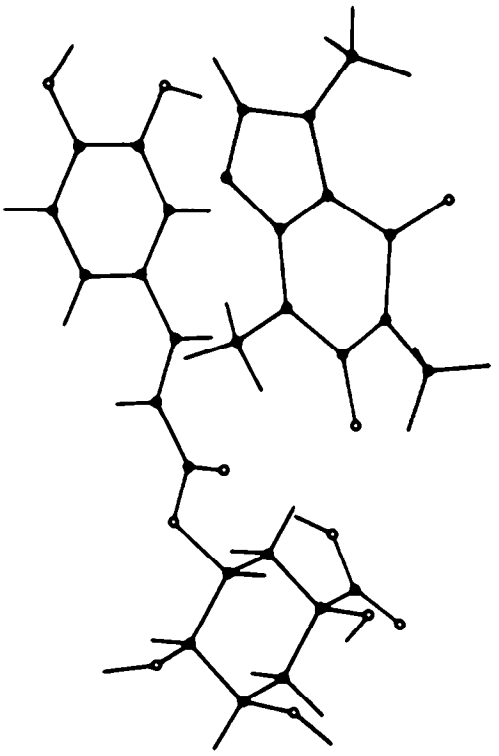


Fig. 2. Time-averaged conformation of the caffeine potassium chlorogenate complex [19].

caffeine–potassium chlorogenate complex is shown in Fig. 3 with the crystallographic numbering. The potassium ion is associated with a number of oxygen atoms (see below) but within the asymmetric unit the oxygen atoms O (6), O (7) and O (10) are coordinated to the alkali metal ion and K$^+$ ··O distances lie between 2.67 and 2.85 Å (Table 3). In addition to this feature, the asymmetric unit is further stabilized by a symmetrical hydrogen bond linking O (1), H (14) and O (12) (Table 4). The aryl ring C (1)–C (6) is planar (maximum deviation from this mean plane is 0.016 Å). Likewise the caffeine molecule is also planar (maximum deviation of 0.004 Å). Within the asymmetric unit these planes lie at an angle of 18.4° to one another.

The complex forms a layer lattice structure with the phenolic nuclei of the chlorogenate ion alternating with the caffeine molecule in stacks; Fig. 4 shows a view down the x-axis of the unit cell. Within each stack the phenolic rings are parallel and alternating caffeine molecules lie inclined at 3.6° to these rings. The centres of the adjacent planes are separated by 3.78 Å. Inspection of Fig. 4 shows that three pairs of atoms most nearly eclipse one another in this stacking array. These atoms are N (2) and C (4)—3.5 Å; N (3) and C(6)—3.62 Å; C (2) and C (10) 3.50 Å.

Two additional factors serve to stabilize this arrangement within the crystal lattice. These are respectively hydrogen bonding and coordination around the potassium ion. The hydrogen bonding network is extensive (Fig. 5; dimensions, Table 4). The potassium cation is associated with a total of seven oxygen atoms in an irregular polyhedral array. In addition to the oxygen atoms involved within the asymmetric unit (see above), also associated with the central potassium ion are both phenolic oxygen atoms of a chlorogenate ion ($-x, \frac{1}{2}+y, \frac{1}{2}-z$), one of the carboxylate oxygen atoms ($\frac{1}{2}+x, \frac{1}{2}-y, -z$) and finally a water molecule ($x-\frac{1}{2}, \frac{1}{2}-y, -z$) (Fig. 6). Table 3 lists these various associated oxygen atoms.

Table 1. Caffeine-potassium chlorogenate complex. Refined atomic coordinates with e.s.d.s in parentheses

K 1	0.1893(3)	0.3071(1)	0.04616(5)
O 12	0.068(1)	0.1612(4)	0.4773(2)
O 13	0.785(1)	0.3324(5)	0.0197(2)
O 1	−0.017(1)	0.0043(4)	0.4261(1)
O 2	−0.079(1)	−0.1596(4)	0.3741(1)
O 3	0.059(1)	0.1834(5)	0.1858(2)
O 4	0.015(1)	−0.0003(5)	0.1684(2)
O 5	0.385(1)	−0.0239(5)	0.1412(2)
O 6	0.3451(9)	0.0886(5)	0.0676(2)
O 7	−0.0485(9)	0.1290(4)	0.0525(2)
O 8	−0.2699(9)	−0.1385(5)	0.0307(2)
O 9	−0.342(1)	0.0453(5)	0.0193(2)
C 1	0.003(1)	0.0860(6)	0.3070(2)
C 2	−0.033(1)	−0.0274(6)	0.3202(2)
C 3	−0.042(1)	−0.0520(6)	0.3591(2)
C 4	−0.008(1)	0.0350(6)	0.3883(2)
C 5	0.023(1)	0.1464(6)	0.3749(2)
C 6	0.028(1)	0.1710(6)	0.3346(2)
C 7	0.011(1)	0.1140(7)	0.2654(2)
C 8	0.003(1)	0.0432(7)	0.2344(2)
C 9	0.029(1)	0.0851(7)	0.1945(2)
C 10	0.056(1)	0.0227(6)	0.1273(2)
C 11	0.230(1)	−0.0479(6)	0.1160(2)
C 12	0.281(1)	−0.0284(6)	0.0730(3)
C 13	0.110(1)	−0.0542(6)	0.0647(2)
C 14	−0.070(1)	0.0084(6)	0.0588(2)
C 15	−0.113(1)	−0.0119(7)	0.1028(2)
C 16	−0.242(1)	−0.0317(7)	0.0339(2)
N 1	0.544(1)	0.3957(5)	0.1433(2)
N 2	0.499(1)	0.5792(6)	0.1162(2)
N 3	0.474(2)	0.7357(7)	0.1645(2)
N 4	0.499(1)	0.6221(7)	0.2186(2)
O 10	0.518(1)	0.4189(5)	0.0770(2)
O 11	0.557(1)	0.3672(7)	0.2113(2)
C 17	0.515(1)	0.4631(8)	0.1109(3)
C 18	0.493(1)	0.6229(8)	0.1539(3)
C 19	0.472(2)	0.7327(9)	0.2066(4)
C 20	0.509(1)	0.5545(8)	0.1859(3)
C 21	0.538(2)	0.4362(8)	0.1827(3)
C 22	0.576(2)	0.2705(8)	0.1373(3)
C 23	0.479(2)	0.6525(9)	0.0807(4)
C 24	0.499(2)	0.589(1)	0.2600(3)

The association of polyphenols with other molecules such as proteins and polysaccharides is a problem of very great practical significance and one with a very long history. This paper brings forward for the first time factual evidence concerning the molecular mechanisms of non-covalent interactions between the heterocycle caffeine (3) and the chlorogenate ion (2). Whilst the tendency has been to emphasize (usually on intuitive grounds) the part played by hydrogen bonding, this work unequivocally demonstrates for the first time *inter alia* the crucial importance not only of hydrogen bonding but also of hydrophobic effects and coordination around a central alkali metal ion in the complexation process. These features are additionally supported by related observations, e.g. the crystal structure of the caffeine–methyl

Table 2. Caffeine–potassium chlorogenate complex. Bond lengths (Å) (e.s.d.s all 0.01 Å) and bond angles (°) (e.s.d.s. 0.6–0.8° for potassium chlorogenate and 0.8–1.0° for caffeine)

	Potassium chlorogenate		
C(1)–C(2)	1.41	O(4)–C(10)	1.45
C(2)–C(3)	1.35	C(10)–C(11)	1.52
C(3)–O(2)	1.37	C(11)–O(5)	1.42
C(3)–C(4)	1.43	C(11)–C(12)	1.52
C(4)–O(1)	1.33	C(12)–O(6)	1.44
C(4)–C(5)	1.39	C(12)–C(13)	1.53
C(5)–C(6)	1.39	C(13)–C(14)	1.52
C(6)–C(1)	1.37	C(14)–O(7)	1.42
C(1)–C(7)	1.45	C(14)–C(16)	1.55
C(7)–C(8)	1.33	C(16)–O(8)	1.26
C(8)–C(9)	1.45	C(16)–O(9)	1.24
C(9)–O(3)	1.20	C(14)–C(15)	1.54
C(9)–O(4)	1.33	C(15)–C(10)	1.51
	Caffeine		
N(1)–C(17)	1.36	N(3)–C(19)	1.43
N(1)–C(22)	1.48	C(19)–N(4)	1.36
C(17)–O(10)	1.26	N(4)–C(24)	1.45
C(17)–N(2)	1.36	N(4)–C(20)	1.36
N(2)–C(23)	1.48	C(20)–C(18)	1.35
N(2)–C(18)	1.37	C(20)–C(21)	1.39
C(18)–N(3)	1.36	C(21)–O(11)	1.26
		C(21)–N(1)	1.42
	Potassium chlorogenate		
C(1)–C(2)–C(3)	121.0	O(4)–C(10)–C(15)	108.7
C(2)–C(3)–C(4)	121.1	C(15)–C(10)–C(11)	110.9
C(2)–C(3)–O(2)	124.1	C(10)–C(11)–C(12)	110.6
O(2)–C(3)–C(4)	114.7	C(10)–C(11)–O(5)	111.5
C(3)–C(4)–O(1)	117.9	O(5)–C(11)–C(12)	111.4
C(3)–C(4)–C(5)	117.1	C(11)–C(12)–C(13)	110.1
O(1)–C(4)–C(5)	124.9	C(11)–C(12)–O(6)	109.7
C(4)–C(5)–C(6)	121.0	O(6)–C(12)–C(13)	111.0
C(5)–C(6)–C(1)	121.1	C(12)–C(13)–C(14)	114.1
C(6)–C(1)–C(2)	118.4	C(13)–C(14)–C(15)	110.7
C(6)–C(1)–C(7)	119.8	C(13)–C(14)–C(16)	111.5
C(2)–C(1)–C(7)	121.8	C(13)–C(14)–O(7)	110.0
C(1)–C(7)–C(8)	128.7	O(7)–C(14)–C(16)	107.2
C(7)–C(8)–C(9)	121.5	O(7)–C(14)–C(15)	108.4
C(8)–C(9)–O(3)	124.9	C(16)–C(14)–C(15)	108.9
C(8)–C(9)–O(4)	111.2	C(14)–C(15)–C(10)	109.5
O(3)–C(9)–O(4)	123.9	C(14)–C(16)–O(8)	117.5
C(9)–O(4)–C(10)	119.1	C(14)–C(16)–O(9)	116.6
O(4)–C(10)–C(11)	107.7	O(8)–C(16)–O(9)	125.9
	Caffeine		
N(1)–C(17)–N(2)	118.2	C(19)–N(4)–C(24)	122.2
N(1)–C(17)–O(10)	119.9	C(24)–N(4)–C(20)	129.6
O(10)–C(17)–N(2)	121.6	N(4)–C(20)–C(18)	108.2
C(17)–N(2)–C(18)	119.3	N(4)–C(20)–C(21)	129.7
C(17)–N(2)–C(23)	118.0	C(18)–C(20)–C(21)	122.0
C(23)–N(2)–C(18)	122.6	C(20)–C(21)–N(1)	113.8
N(2)–C(18)–N(3)	127.0	C(20)–C(21)–O(11)	125.5
N(2)–C(18)–C(20)	121.9	O(11)–C(21)–N(1)	120.8
C(20)–C(18)–N(3)	111.1	C(21)–N(1)–C(17)	124.4
C(18)–N(3)–C(19)	103.9	C(21)–N(1)–C(22)	117.1
N(3)–C(19)–N(4)	108.7	C(22)–N(1)–C(17)	118.4
C(19)–N(4)–C(20)	122.2		

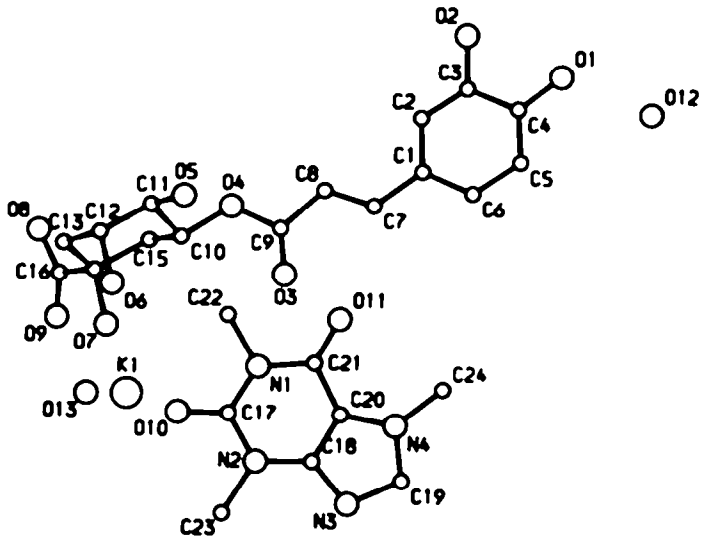


Fig. 3. Asymmetric unit of the caffeine–potassium chlorogenate 1:1 complex –crystallographic numbering.

Table 3. Contacts (Å) to and angles (°) about the potassium atom with relevant symmetry operators

Contacts (Å), symmetry operations					
O(1)	2.75	$-x, \frac{1}{2}+y, \frac{1}{2}-z$	O(9)	2.81	$\frac{1}{2}+x, \frac{1}{2}-y, z$
O(2)	2.83	$-x, \frac{1}{2}+y, \frac{1}{2}-z$	O(10)	2.85	x, y, z
O(6)	2.85	x, y, z	O(13)	2.84	$x-\frac{1}{2}, \frac{1}{2}-y, -z$
O(7)	2.67	x, y, z			

Angles (°) about the potassium atom			
O(1)–K–O(2)	56.0	O(6)–K–O(7)	62.4
O(1)–K–O(6)	144.8	O(6)–K–O(9)	140.6
O(1)–K–O(7)	109.5	O(6)–K–O(10)	90.0
O(1)–K–O(9)	74.4	O(6)–K–O(13)	66.8
O(1)–K–O(10)	81.7	O(7)–K–O(9)	119.1
O(1)–K–O(13)	147.9	O(7)–K–O(10)	146.4
O(2)–K–O(6)	88.9	O(7)–K–O(13)	77.0
O(2)–K–O(7)	81.6	O(9)–K–O(10)	94.3
O(2)–K–O(9)	130.5	O(9)–K–O(13)	75.2
O(2)–K–O(10)	79.1	O(10)–K–O(13)	110.8
O(2)–K–O(13)	153.0		

gallate 1:1 complex [24] which displays a similar stacked layer lattice structure in which in-plane cohesion is achieved by extensive hydrogen bonding, and the effect of alkali metal cations on the self-association of polyphenolic substrates in aqueous media ([15, 23]; C. M. Spencer, R. Martin, T. H. Lilley, E. Haslam and D. Magnolato, unpublished work). Bearing in mind the inherent uncertainties involved in extrapolating from crystal structure data these findings nevertheless substantiate the view that the non-covalent interactions involving phenolic substrates in aqueous media probably utilizes the range of forces outlined above. In their earlier paper, Horman and Viani [19] put forward a model for the structure of the caffeine potassium chlorogenate complex as it exists in aqueous solution (Fig. 2). The model is consistent with the known 'stacking' behaviour of aryl substrates and the magnetic anisotropy associated with such systems. There is, moreover, a striking resemblance (Figs 2 and 4) between this model and the crystal structure of the complex (they differ in the relative orientation of the caffeine and caffeoyl rings), such as to suggest that complexes of the type discussed by Horman and Viani [19] are precursors in crystal formation and growth.

Table 4. Caffeine–potassium chlorogenate complex. Hydrogen bonds (Å) with angles about hydrogen and relevant symmetry operators

	X···Y	X–H	H···Y	X–H···Y
O(1)–H(14)···O(12)	2.58	1.31	1.36	151 (x, y, z)
O(2)–H(13)···O(13)	2.73	1.16	1.78	135 ($-x, y-\frac{1}{2}, \frac{1}{2}-z$)
O(5)–H(15)···N(3)	2.96	0.97	2.09	149 ($x, 1-y, z$)
O(6)–H(16)···O(9)	2.79	0.84	2.03	150 ($1+x, y, z$)
O(12)–H(29)···O(8)	2.78	0.94	1.87	161 ($-x-\frac{1}{2}, -y, \frac{1}{2}+z$)

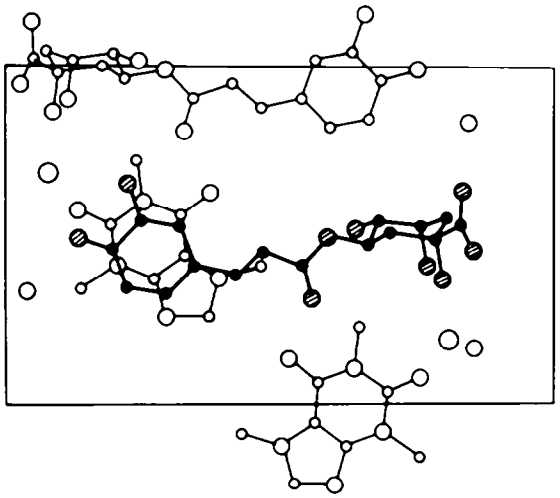


Fig. 4. Caffeine potassium chlorogenate 1:1 complex—layer lattice structure.

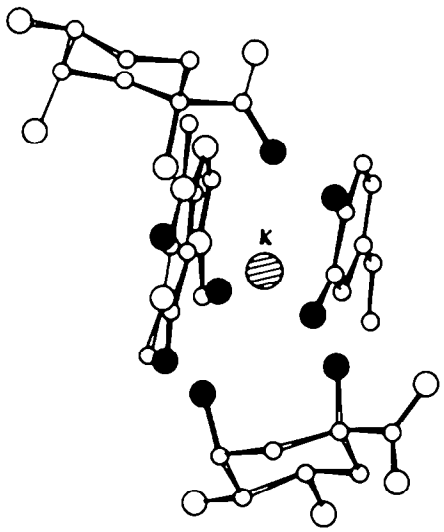


Fig. 6. Caffeine–potassium chlorogenate 1:1 complex coordination around the potassium ion.

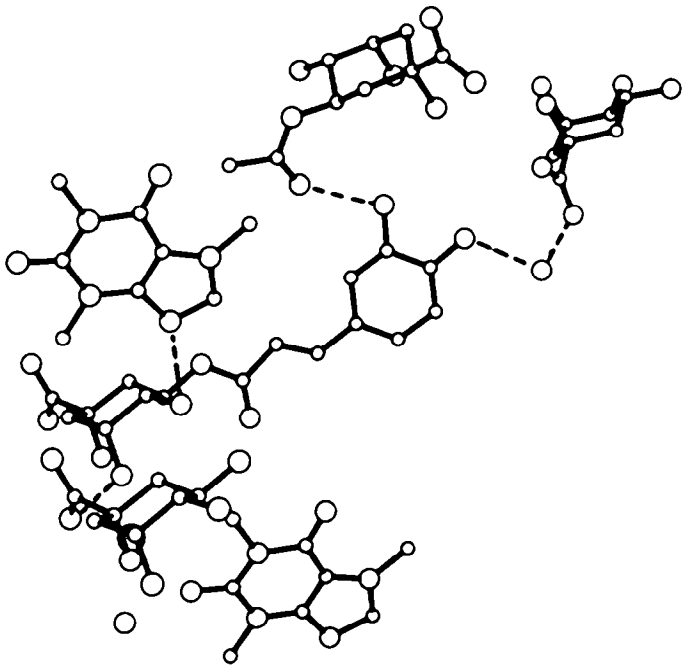
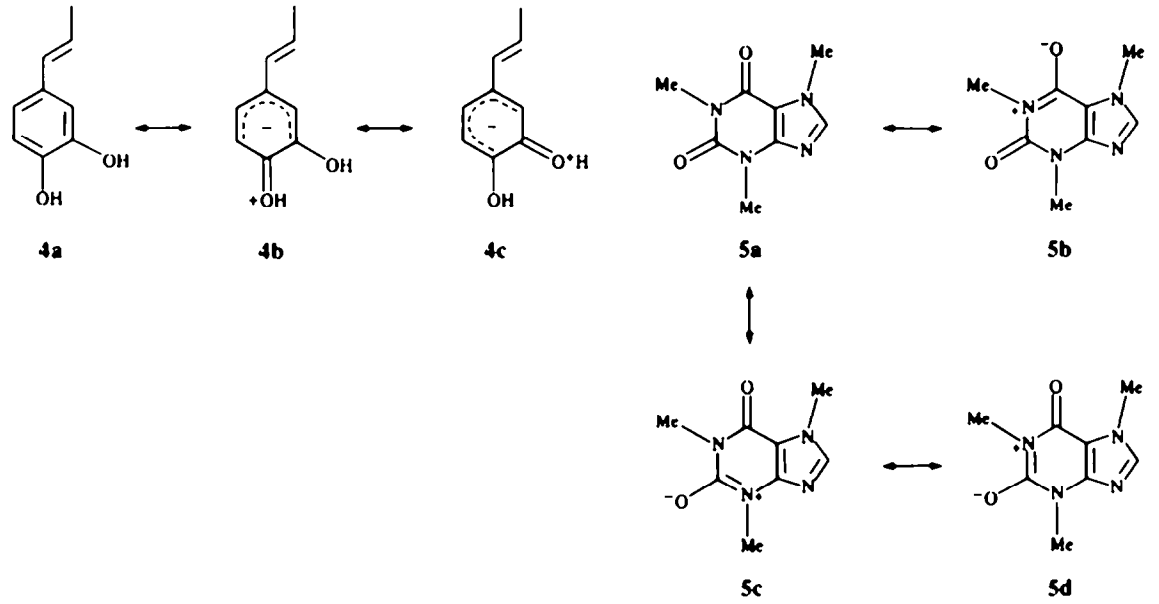


Fig. 5. Caffeine–potassium chlorogenate 1:1 complex hydrogen bonding network.

Some comment should perhaps finally be made of the particular alternating plane to plane stacking arrangement of aromatic nuclei found in the caffeine–potassium chlorogenate and other phenolic–caffeine complexes [24]. π-Molecular complexes formed between aromatic electron donor and acceptor pairs display the same characteristics [25]; however, the UV absorption spectra of the caffeine–phenol complexes examined in these studies show no evidence of UV charge-transfer bonds. The term 'polarization bonding' has been used [25] to describe both charge-transfer bonding [26] and the generally weaker interactions between polar groups of one component and a polarizable second component [27]. For weak non-covalent bonding of this type the principal feature to be expected is the juxtaposition of the polarizable groups of one component and the polarizable regions of the second. It is interesting therefore to note that in the various phenol–caffeine complexes the phenolic groups and associated nuclei are stacked generally above the six-membered ring of the caffeine molecule. This suggests that



4a 4b 4c 5a 5b 5c 5d

in this form of association the two components develop polar characteristics of the type shown (**4a**-**4c**; **5a**-**5d**).

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