Dipole Moment, Solution, and Solid State Structure of (−)-Epicatechin, a Monomer Unit of Procyanidin Polymers

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The structure of (−)-epicatechin has been determined in the crystalline state. Crystals are orthorhombic, $P2_12_12_1$, a = 670.8(1), b = 1 329.1(3), c = 1 426.2(4) pm, Z = 4, D_c = 1.516 g cm^{-3}, R = 0.041 for 1 624 observations. Intramolecular hydrogen bonds are absent. The aliphatic hydroxy group and three of the four phenolic hydroxy groups participate in intermolecular hydrogen bond formation. The aromatic ring bonded to C(2) is in an equatorial position, but the hydroxy group bonded to C(3) adopts an axial position. Comparison with the published structure for 8-bromotetra-O-methyl-(+)-catechin reveals that epimerization at C(3) alters the fused ring system primarily at C(2) and C(3). The heterocyclic ring is more closely described as a half-chair in (−)-epicatechin than in 8-bromotetra-O-methyl-(+)-catechin. Dipole moments have been measured for (−)-epicatechin in solution. At 300 K the root-mean-square dipole moment is 3.91 ± 0.04 D, and the temperature coefficient is small and negative. The behaviour of the dipole moment is easily rationalized *via* a theoretical rotational isomeric state analysis based on the structure found in the crystalline state.

Plants contain a variety of polyphenols, among which are procyanidin polymers composed of the flavan-3-ols (+)-catechin and (−)-epicatechin.[1–3] The latter molecule is depicted in Figure 1. The epimer at C(3) is (+)-catechin. Linkages giving rise to procyanidins are often between C(4) and C(8), but alternative linkages, e.g., C(4) to C(6), are also known.[1–5] Severe steric hindrances impose stringent restrictions upon rotation about the interflavan bond.[1,2] Assessment of the consequences of these restrictions, using space-filling molecular models, led to the prediction of a helical conformation for C(4)–C(8) linked homopolymers of (+)-catechin or (−)-epicatechin.[1,2] The handedness of these helices depends on the identity of the monomer unit.

The potentially interesting conformational properties of these polymers has stimulated the beginnings[6] of a more rigorous analysis utilizing the powerful matrix methods widely employed with macromolecular systems.[7] Prospects for success in the theoretical analysis are markedly enhanced if detailed structural information is available for the monomers (+)-catechin and (−)-epicatechin. The crystal structure has been published for 8-bromotetra-O-methyl-(+)-catechin,[8] and the structure of 8-bromotetra-O-methyl-(−)-epicatechin[9] has been described. The crystal structure for the parent phenol (−)-epicatechin, described here, was pursued since its structure is of more direct interest relative to the chemistry of proanthocyanidins.

The solution structure of (−)-epicatechin has been probed through measurement of the mean square dipole moment and its temperature dependence. Theoretical evaluation of the conformational properties in solution is carried out *via* a rotational isomeric state scheme based on the structure found in the crystalline state. The theoretical analysis successfully accounts for the behaviour of the dipole moment in solution.

Results and Discussion

Structure in the Crystalline State.—Co-ordinates for the 35 atoms are presented in Table 1, and bond lengths are given in Table 2. Figure 2(A) depicts the ten atoms in the fused ring system of (−)-epicatechin. The six aromatic carbon atoms lie
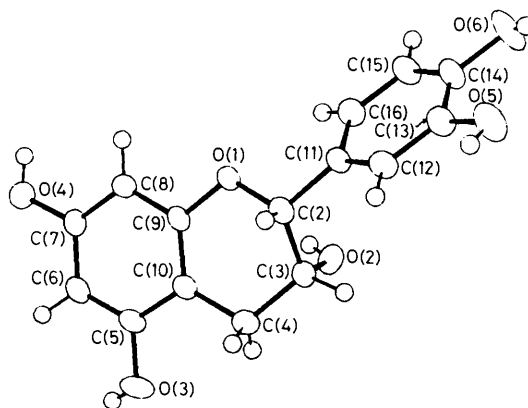

Figure 1. Structure of (−)-epicatechin in the crystalline state

within 1.5 pm of their mean plane. Larger departures from this plane are made by non-hydrogen atoms bonded directly to the aromatic ring. Oxygen O(3) lies 7.3 pm below, and O(4) is 5.0 pm above, the mean plane. The other two bonded non-hydrogen atoms, O(1) and C(4), are part of the heterocyclic ring depicted in Figure 2(A). Puckering of the heterocyclic ring system is most apparent at C(2) and C(3). The aromatic ring bonded to C(2) is placed in an equatorial position, but the hydroxy group bonded to C(3) adopts an axial position.

The structure reported[8] for the fused ring system in 8-bromotetra-O-methyl-(+)-catechin [Figure 2(B)] exhibits similar qualitative features. The six atoms in the aromatic ring lie very close to their mean plane, and the two atoms directly bonded to this ring, O(1) and C(4), lie slightly above this plane. The largest deviations are made by C(2) and C(3), with the former lying above, and the latter below, the mean plane. The most important differences are movements downward by ca. 30 pm for both C(2) and C(3) in (−)-epicatechin. Equatorial positions are adopted by both the aromatic ring bonded to C(2) and the hydroxy group bonded to C(3) in 8-bromotetra-O-methyl-(+)-catechin.

Table 1. Co-ordinates and thermal parameters for (−)-epicatechin

Atom	x	y	z	B_{eq} or B	Atom	x	y	z	B_{eq} or B
O(1)	0.3441(2)	0.4815(1)	0.9028(1)	2.44(3)	C(14)	0.4530(4)	0.1141(2)	0.8657(2)	2.47(4)
O(2)	0.1362(3)	0.4217(1)	0.7318(1)	2.63(3)	C(15)	0.5496(4)	0.1978(2)	0.8307(2)	2.48(4)
O(3)	−0.1451(3)	0.7313(1)	0.8321(1)	3.11(3)	C(16)	0.4695(4)	0.2930(2)	0.8427(2)	2.30(4)
O(4)	0.5084(3)	0.8291(1)	0.9226(1)	2.74(3)	H(2)	0.122(4)	0.406(2)	0.961(2)	1.8(5)
O(5)	0.1906(3)	0.0384(1)	0.9489(2)	3.70(4)	H(3)	0.057(3)	0.369(2)	0.821(1)	1.2(4)
O(6)	0.5370(3)	0.0213(1)	0.8506(1)	3.84(4)	H(41)	−0.160(4)	0.516(2)	0.894(2)	3.7(7)
C(2)	0.1904(3)	0.4054(2)	0.9006(2)	2.16(4)	H(42)	−0.119(4)	0.548(2)	0.791(2)	3.6(6)
C(3)	0.0420(4)	0.4265(2)	0.8216(2)	2.27(4)	H(6)	0.163(4)	0.855(2)	0.882(2)	3.2(6)
C(4)	−0.0603(4)	0.5269(2)	0.8383(2)	2.53(4)	H(8)	0.554(4)	0.633(2)	0.938(2)	2.2(5)
C(5)	0.0464(3)	0.7084(2)	0.8568(2)	2.09(4)	H(12)	0.064(4)	0.226(2)	0.965(2)	3.2(6)
C(6)	0.1852(4)	0.7823(2)	0.8776(2)	2.16(4)	H(15)	0.667(4)	0.191(2)	0.806(2)	3.2(6)
C(7)	0.3747(3)	0.7533(1)	0.9053(1)	2.00(4)	H(16)	0.527(5)	0.354(2)	0.823(2)	3.8(7)
C(8)	0.4250(3)	0.6526(2)	0.9156(2)	2.12(4)	H(20)	0.219(4)	0.463(2)	0.717(2)	3.3(6)
C(9)	0.2824(3)	0.5806(2)	0.8942(2)	1.95(4)	H(30)	−0.147(4)	0.787(2)	0.820(2)	3.1(6)
C(10)	0.0911(3)	0.6053(1)	0.8632(2)	1.97(4)	H(40)	0.616(5)	0.801(2)	0.943(2)	4.5(7)
C(11)	0.2912(3)	0.3047(2)	0.8911(2)	1.98(4)	H(50)	0.078(7)	0.057(3)	0.996(3)	8.4(12)
C(12)	0.1957(3)	0.2200(2)	0.9272(2)	2.34(4)	H(60)	0.486(6)	−0.015(3)	0.890(2)	7.5(10)
C(13)	0.2750(4)	0.1253(2)	0.9147(2)	2.42(4)					

Estimated standard deviations in the last significant digits are shown in parentheses

Table 2. Bond lengths (pm) with standard deviation of the last digit in parentheses

Bond	(−)-Epicatechin	8-Bromotetra-O-methyl-(+)-catechin
C(2)–C(3)	152.9(3)	153.4(17)
C(2)–C(11)	150.6(3)	152.8(17)
C(3)–C(4)	151.9(3)	155.5(18)
C(4)–C(10)	149.8(3)	151.6(17)
C(5)–C(6)	138.6(3)	135.5(20)
C(5)–C(10)	140.5(2)	145.2(19)
C(6)–C(7)	138.6(3)	138.1(19)
C(7)–C(8)	138.9(2)	139.4(19)
C(8)–C(9)	138.7(3)	138.4(17)
C(9)–C(10)	139.6(3)	138.4(17)
C(11)–C(12)	139.4(3)	141.2(16)
C(11)–C(16)	138.9(3)	140.3(18)
C(12)–C(13)	137.8(3)	142.0(19)
C(13)–C(14)	139.1(3)	140.1(20)
C(14)–C(15)	138.1(3)	142.1(18)
C(15)–C(16)	138.5(3)	138.5(19)
O(1)–C(2)	144.5(2)	146.0(13)
O(1)–C(9)	138.6(2)	137.9(15)
O(2)–C(3)	142.9(3)	146.1(13)
O(3)–C(5)	136.6(3)	137.6(17)
O(4)–C(7)	137.1(2)	140.4(15)
O(5)–C(13)	137.6(2)	137.4(15)
O(6)–C(14)	137.3(2)	137.9(16)
C(2)–H(2)	98.3(22)	a
C(3)–H(3)	101.5(20)	
C(4)–H(41)	104.4(26)	
C(4)–H(42)	83.2(29)	
C(6)–H(6)	97.9(26)	
C(8)–H(8)	95.3(23)	
C(12)–H(12)	103.6(26)	
C(15)–H(15)	86.9(27)	
C(16)–H(16)	93.6(28)	
O(2)–H(20)	81.0(27)	
O(3)–H(30)	76.5(26)	
O(4)–H(40)	86.3(31)	
O(5)–H(50)	104.1(43)	
O(6)–H(60)	81.6(38)	

a The structure for 8-bromotetra-O-methyl-(+)-catechin[8] was obtained by including hydrogen atoms at expected positions. These positions were not refined.

Atomic co-ordinates were not included in the account of the structure of 8-bromotetra-O-methyl-(−)-epicatechin.[9] The narrative does, however, describe deviations from planarity of atoms in the heterocyclic ring. Atoms O(1), C(4), C(9), and C(10) 'lie virtually co-planar,' while C(2) and C(3) are found to be below this plane by 4 and 70 pm, respectively. Significant differences are apparent at C(2) and C(3) when the description[9] of the heterocyclic ring system in 8-bromotetra-O-methyl-(−)-epicatechin is compared with the structure for (−)-epicatechin depicted in Figure 2(A). The (−)-epicatechin structure should be of greater interest for the proanthocyanidins. This comparison also suggests that the heterocyclic ring system in (+)-catechin might have a somewhat different structure than that found in 8-bromotetra-O-methyl-(+)-catechin.[8]

An alternative means of expressing the differences in flavan ring structure between 8-bromotetra-O-methyl-(+)-catechin and (−)-epicatechin is *via* torsion angles about bonds in the heterocyclic ring. These torsion angles are presented in parentheses in Figure 2. The largest changes are 12° at O(1)–C(2) and 9° at C(9)–O(1), with the changes being in opposite directions. Torsion angles at the remaining four bonds are altered by 1—6°. Torsion angles at C(9)–O(1) and C(4)–C(10) differ by only 3.5° in (−)-epicatechin, but they differ by 11° in 8-bromotetra-O-methyl-(+)-catechin. The (−)-epicatechin heterocyclic ring is closer to a half-chair than is the heterocyclic ring in 8-bromotetra-O-methyl-(+)-catechin.

The aromatic ring bonded to C(2) is very nearly planar. All six carbon atoms lie within 0.5 pm of the mean plane. The two bonded oxygen atoms are *ca.* 2 pm from this plane, with O(5) and O(6) above. A much larger departure (+10.3 pm) from the mean plane is found for C(2).

The twelve bonds in the two aromatic ring systems of (−)-epicatechin cluster much closer to the expected value of 140 pm than is the case in 8-bromotetra-O-methyl-(+)-catechin. The extreme values found in (−)-epicatechin are 137.8 [for C(12)–C(13)] and 140.5 pm [for C(5)–C(10)]. In 8-bromotetra-O-methyl-(+)-catechin the range is from 135.5 [for C(5)–C(6)] to 145.2 pm [for C(5)–C(10)].[8] The appearance of a greater variability in the (+)-catechin derivative might be attributed in part to the larger uncertainty in atomic positions. The longest bond in the aromatic systems in both molecules is C(5)–C(10).

Intramolecular hydrogen bonds are absent in crystalline (−)-epicatechin. Four of the five hydroxy groups participate in intermolecular hydrogen bond formation. Geometric information for these hydrogen bonds is depicted in Figure 3. No
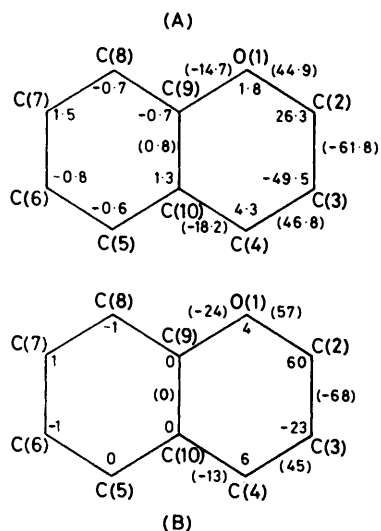
(A)

(B)

Figure 2. Distances (pm) out of the mean plane of the aromatic ring for atoms in the fused ring system of crystalline (A) (−)-epicatechin and (B) 8-bromotetra-O-methyl-(+)-catechin. Torsion angles (°) are denoted by numbers in parentheses. Structural information for 8-bromotetra-O-methyl-(+)-catechin is from ref. 8
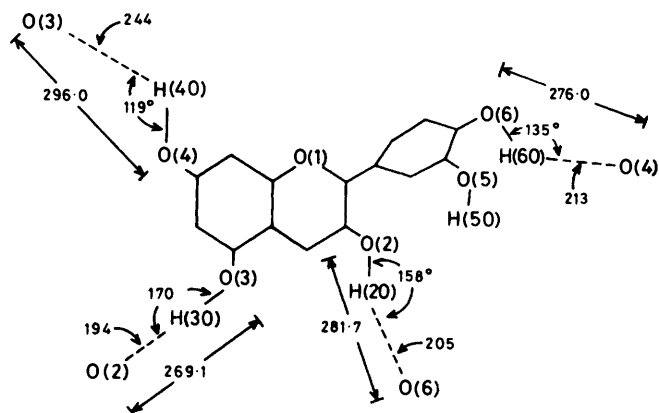

Figure 3. Schematic representation of the intermolecular hydrogen bonding in crystalline (−)-epicatechin. Oxygen–oxygen and hydrogen–oxygen distances are in pm

significant interactions are found for O(1), O(5), or the hydrogen atom bonded to O(5). The hydrogen bond with the shortest H ... O distance, and the one with the smallest departure from linearity, is O(3)–H(30) ... O(2). Application of these two criteria identifies the next best hydrogen bond as O(2)–H(20) ... O(6). The aliphatic hydroxy group, O(2)–H(20), is therefore intimately involved both as a hydrogen bond donor and acceptor.

Dipole Moments.—Root-mean-square dipole moments in p-dioxane are collected in Table 3. At 300 K the dipole moment is 3.91 ± 0.04 D. The temperature coefficient, d ln $<\mu^2>/dT$, is small and negative.

Conformational Energy Analysis.—The conformational energy is a function of six dihedral angles, two of which can be considered to be independent and two pairs of which are interdependent. In all cases the conformational energy surface is dominated by the Lennard-Jones 6—12 and torsional potentials. Minor contributions are made by the electrostatic interactions.

The first conformational energy surface considered is that arising from rotation about the C(7)–O(4) bond. The dihedral angle is denoted φ_A and is considered to be zero for a cis-orientation of C(8)–C(7)–O(4)–H(40). Conformational energy calculations using model bond lengths and bond angles for phenol yield two equivalent minima at φ_A 0 and 180°. However, utilization of the bond lengths and bond angles observed in the (−)-epicatechin crystal produce maxima at these positions due to unfavourable steric interactions between H(40) and the ortho-CH groups. The most severe interaction is with C(6). Minima in the calculation are shifted to φ_A ±90°. The conformation of this O–H group in crystalline (−)-epicatechin corresponds to φ_A −4.1°. This group is involved in intermolecular hydrogen bond formation, a feature which is not taken into account in the theoretical conformational analysis.

In order to accommodate all the above features in the dipole moments analysis, four rotational states are defined for the C(7)–O(4) bond. The two states with φ_A 0 and 180° are assigned statistical weights of one, while the two states at φ_A ±90° have statistical weights of ω_A. As will be seen below, dipole moments provide no information whatsoever on the size of ω_A in solution.

Table 3. Dipole moments of (−)-epicatechin in p-dioxane

Temperature (°C)	$<\mu^2>^{\frac{1}{2}}/D$
15	4.01 ± 0.05
20	3.95 ± 0.04
25	3.91 ± 0.04
30	3.91 ± 0.04
35	3.89 ± 0.05

[a] If the standard deviation is taken from the fit, the temperature coefficient is 10^3 d ln $<\mu^2>/dT = -2.9 \pm 0.7$ K^{-1}. Taking absolute deviations into account makes the temperature coefficient $- 3 \pm 2 \times 10^{-3}$ K^{-1}.

The second rotation considered is about the C(5)–O(3) bond. The dihedral angle is denoted φ_B and is considered to be zero for a cis-orientation of C(6)–C(5)–O(3)–H(30). Conformational analysis yields a region of high energy at φ_B 180 ± 50°. In the crystal, φ_B is 14.6°, which directs it away from the region of high conformational energy. Consequently analysis of the dipole moments will proceed using a single state for φ_B, which is taken to be at 0°.

Rotations C and D are about C(14)–O(6) and C(13)–O(5), respectively. Dihedral angles are taken to be zero for a cis-orientation of C(15)–C(14)–O(6)–H(60) and for C(14)–C(13)–O(5)–H(50). Conformational energy calculations using bond lengths and bond angles found in the crystal yield a single region of low energy near φ_C, φ_D 180,180°. The actual positions of the minima are displaced by ± 40° about φ_C due to steric conflict between H(60) and O(5). The region near φ_C, φ_D 0,0° is found to be of much higher energy due to steric conflicts between H(60) and C(15) and between H(50) and O(6). The regions at 0,0° and 180,180° would, of course, have identical conformational energies if standard geometry was adopted for the aromatic ring and its pendant groups. The conformation adopted in the crystal corresponds to φ_C, φ_D 160.7,167.6°, with H(60) being involved in intermolecular hydrogen bond formation.

For purposes of the dipole moment analysis, two conformations are retained for the φ_C, φ_D pair. A statistical weight of one is assigned when $\varphi_C = \varphi_D = 180°$. The conformation at $\varphi_C = \varphi_D = 0°$ is assigned a weight denoted by ω_{CD}. The conformational energy analysis based on the crystal structure geometry suggests ω_{CD} is extremely small, but use of a standard aromatic ring would produce ω_{CD} 1.

Rotations E and F are about the C(3)–O(2) and C(2)–C(11) bonds, respectively. Reference states for φ_E and φ_F are cis-
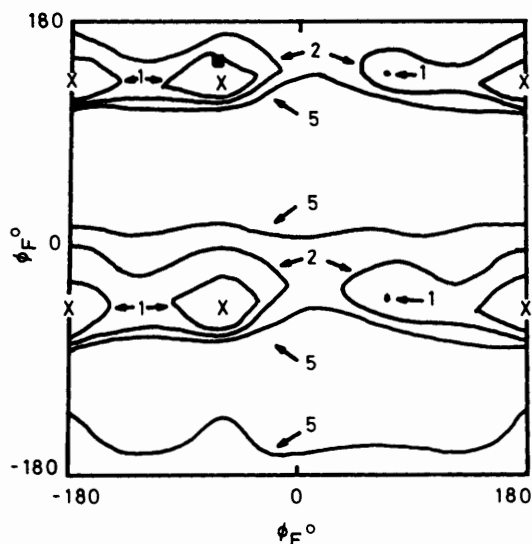
Figure 4. Conformational energy surface for rotations about the C(3)–O(2) (φ_E) and C(2)–C(11) (φ_F) bonds. Essentially identical minima occur at positions denoted by X. Contours are drawn at energies 1, 2, and 5 kcal mol^{-1} above the minima. The square denotes the conformation found in crystalline (–)-epicatechin

orientations for O(1)–C(2)–C(11)–C(16) and for C(2)–C(3)–O(2)–H(20), respectively. The conformational energy surface is depicted in Figure 4. Two equivalent minima, at -50 and $130°$, are found for φ_F. Minima were found at nearly identical positions (-40 and $140°$) in an earlier theoretical analysis of tetra-O-methyl-(–)-epicatechin which employed standard aromatic ring geometry and a slightly different puckering for the heterocyclic ring.[6] There are three energy minima for rotation about φ_E, with the one near $70°$ being 1 kcal mol^{-1} higher in energy than the other two. The weight for this latter state will be denoted by ω_E. The conformation observed in crystalline (–)-epicatechin, denoted by the square in Figure 4, is close to one of the minima in the theoretical conformational energy surface. The earlier theoretical analysis of tetra-O-methyl-(–)-epicatechin also found three low energy states for torsion about C(3)–O(2). Minima for the torsion angle C(2)–C(3)–O(2)–H(20) were predicted near -65, 95, and $180°$, with the latter being the conformation of lowest energy.[6]

In summary, the preceding analysis employs 48 conformations for (–)-epicatechin. There are four states for φ_A, two with statistical weights of 1 and two with statistical weights of ω_A. For φ_E there are three states, two with statistical weights of 1 and one with a statistical weight of ω_E. Both φ_F and the φ_C, φ_D pair have two states each. For φ_F they are equally weighted, but for the φ_C,φ_D pair one has a statistical weight of ω_{CD} relative to the other. Finally, there is a single state for φ_B. The configuration partition function, Z, is given by equation (1).

$$Z = 4(1 + \omega_A)(1 + \omega_{CD})(2 + \omega_E) \qquad (1)$$

Theoretical Mean Square Dipole Moments.—Squared dipole moments were evaluated for each of the 48 conformations. When averaged using the above set of statistical weights, the mean square dipole moment, in D^2, is given by equation (2).

$$<\mu^2> = Z^{-1}(135.3 + 135.1\omega_A + 65.6\omega_{CD} + 65.5\omega_A\omega_{CD} + 36.4\omega_E + 36.4\omega_A\omega_E + 36.3\omega_E\omega_{CD} + 36.2\omega_{CD}\omega_A\omega_E) \quad (2)$$

In excellent approximation, $1 + \omega_A$ can be factored out of the numerator. Since $1 + \omega_A$ is a factor in Z, $<\mu^2>$ provides no
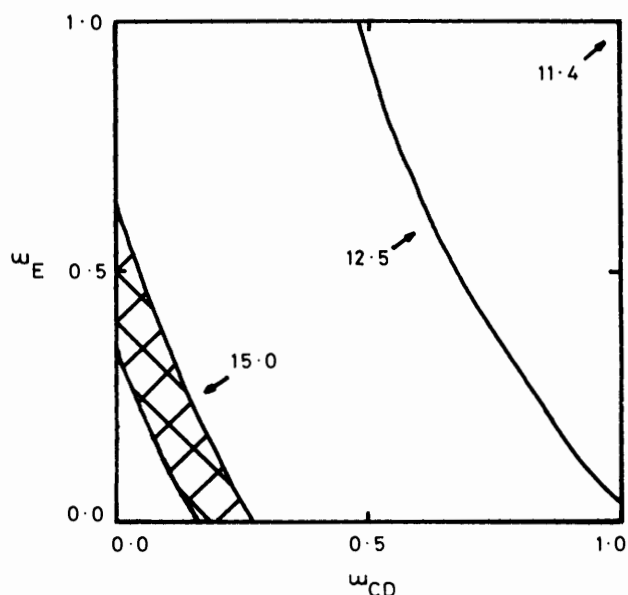

Figure 5. Mean square dipole moment as functions of ω_E and ω_{CD}. A contour line is drawn at 12.5. The maximum squared dipole moment is 16.9 D^2 at $\omega_E = \omega_{CD} = 0$. At the opposite corner, where $\omega_E = \omega_{CD} = 1$, $<\mu^2>$ is 11.4 D^2. The experimental result at 300 K, $<\mu^2>^{\frac{1}{2}}$ 3.91 $\pm$ 0.04 D, is denoted by the cross-hatched region

information about the size of ω_A. Removal of $1 + \omega_A$ from equation (2) leaves (3).

$$<\mu^2> = [(2 + \omega_E)(1 + \omega_{CD})]^{-1} [33.8 + 16.4\omega_{CD} + 9.1\omega_E(1 + \omega_{CD})] \quad (3)$$

Figure 5 depicts $<\mu^2>$ as functions of ω_E and ω_{CD}. The dipole moment is underestimated if $\omega_E = \omega_{CD} = 1$. A dipole moment consistent with experiment can be obtained only if $\omega_{CD} < 0.3$. The other pertinent statistical weight, ω_E, cannot exceed 0.65. If the *ortho* phenolic hydroxy groups had access to two equivalent conformations in solution, ω_{CD} would be equal to one. The experimental dipole moment rules out that assignment. Since the solution experiment demands $\omega_{CD} < 1$, the *ortho* phenolic hydroxy groups in solution continue to retain a preference for the conformation adopted in the solid state. The theoretical conformational energy surfaces lead to ω_E 0.19 and $\omega_{CD} < 0.1$ at 300 K. These assignments yield dipole moments well within the range defined by experiment.

The surface depicted in Figure 5 demands that the temperature coefficient, d ln $<\mu^2>$/dT, be negative. This conclusion follows immediately from the requirement that ω_E and ω_{CD} both approach 1 as the temperature becomes infinite. The sign of the temperature coefficient is in agreement with that deduced from experiment. The temperature coefficient is predicted to be quite small, which is in agreement with experiment.

The theoretical analysis, starting with the crystal structure determined for (–)-epicatechin, provides a satisfying rationalization of the behaviour of the dipole moments in solution.

Experimental

(–)-*Epicatechin.*—Crystalline (–)-epicatechin was prepared from the purchased compound (Fluka) by chromatography on silica gel with chloroform–methanol (85:15 v/v) and slow evaporation of the solvent. Elemental analysis (C, 61.7, H, 5.0. $C_{15}H_{14}O_6$ requires C, 62.1, H, 4.8%) suggested the crystals were essentially free of water of hydration. Crystals began slow

decomposition near 218 °C and began softening at *ca.* 237—239 °C (lit.,[3] 242 °C).

Data Collection (X-*Ray*).—A crystal of dimensions 0.16 × 0.24 × 0.44 mm was used for data collection on an Enraf–Nonius CAD4 diffractometer equipped with Mo-K_α radiation (λ = 71.073 pm) and a graphite monochromator. Cell dimensions and crystal orientation were determined by a least-squares fit of the setting angles of 25 reflections having $14° < \theta < 20°$. Crystal data are $C_{15}H_{14}O_6$, M = 290.3, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 670.8(1), b = 1 329.1(3), c = 1 426.2(4) pm, D_C = 1.516 g cm^{-3}, μ(Mo-K_α) = 1.106 cm^{-1}.

One octant of data having $1° < \theta < 30°$ was collected by the ω–2θ scan method, employing scan rates varying from 0.37 to 3.0° min^{-1} in order to measure all significant data with $I \sim 50\sigma(I)$. A maximum of 180 s was spent on any single scan. Data reduction included corrections for background, Lorentz, and polarization effects, as well as a small absorption correction. The absorption correction was based upon ψ scans of reflections near χ 90°; the minimum relative transmission coefficient was 0.962. of 2 128 unique data measured, 1 626 had $I > 3\sigma(I)$, and were used in the refinement.

Structure Solution and Refinement.—The structure was solved using MULTAN 78[10] which yielded an E map from which positions for all but two of the non-hydrogen atoms were determined. The absolute configuration was chosen to be the same at chiral centre C(2) as that experimentally determined for 8-bromotetra-*O*-methyl-(+)-catechin.[8] Refinement was accomplished by full-matrix least-squares based upon F with weights $\omega = \sigma^{-2}$ (F_o), using the Enraf–Nonius SDP instrument.[11] Non-hydrogen atoms were refined anisotropically; hydrogen atoms were located in difference maps and refined isotropically. Convergence was achieved with R 0.041, R_ω 0.053, and GOF 1.617 for 1 624 observations and 246 variables. No residuals larger than 0.24 e Å^{-3} were present at the conclusion of the refinement. Bond angles, anisotropic thermal parameters, and structure factors are in Supplementary Publication No. SUP 23999 (15 pp.).*

Dipole Moments.—Dielectric constants were measured over the temperature range 15.00—35.00 ± 0.02 °C with a Wiss.-Techn. Werkstatten D-812 Weilheim Dipolmeter DMO1 operating at 2 MHz and a DFL-2 gold-plated thermostatted cell. The temperatures were measured with a Digitec thermometer readable to ±0.01 °C. The basic instrument design was modified to enhance the temperature stability of the oscillators and to obtain dielectric constants by directly measuring the cell oscillator circuit frequency with a Hewlett–Packard 1516A frequency counter. Refractive indices were measured over the same temperature range with a Bausch and Lomb precision refractometer. All solutions were prepared with *p*-dioxane. The limited temperature range examined is due to a significant influence of the *p*-dioxane chair to boat conformational change that appears to take place at *ca.* 35 °C.[12,13] Baker Analyzed or scintillation grade *p*-dioxane was purified for use by refluxing for at least 24 h over sodium[13] and distilling onto molecular sieve that had been previously activated at 350 °C. After purification and drying the refractive index of the dioxane at 25 °C was 1.420 04 as compared with the literature value of 1.420 25.[13] The Dipolmeter was calibrated with Baker Analyzed benzene, refluxed over calcium hydride, and distilled onto activated molecular sieve, and Burdick and

Jackson cyclohexane that was passed through Woelm silica gel. Solutions used for the dielectric measurements ranged from 0.3 to 0.8% by weight. A total of 300 mg of (−)-epicatechin was available for dipole moment measurements.

For consistent definition of the small dipole moment temperature coefficient, dielectric constant *versus* temperature data were first obtained and refined with a second-order polynomial regression analysis. This was done for each concentration as described previously.[6] Dielectric constant *versus* concentration data were then obtained from this family of curves at the temperature of interest. The dielectric constant and refractive index data were treated by the least-squares method and the dipole moments were evaluated by the Guggenheim method.[14] Standard deviations were derived from the least-squares data and were used to obtain an estimate of error for the dipole moment through the statistical propagation of error equation. The error analysis takes into account the fundamental reproducibility of the calibration curve. The dipole moments reported in Table 3 are at the 95% confidence level.

Conformational Energy Calculations.—Unless specifically stated to the contrary, the molecular geometry was that found in the crystalline state. The conformational energy was evaluated at 10° intervals for the variable dihedral angles. It was taken to be the sum of 6—12 potentials, intrinsic torsional potentials, and electrostatic interactions, the latter being evaluated in the monopole approximation using a local dielectric constant of 3.5. Most of the parameters are identical with those used in the conformational analysis of tetra-*O*-methyl-(−)-epicatechin.[6] The intrinsic torsional potential for the C^{ar}–O bond was two-fold with a barrier height of 3.1 kcal mol^{-1} and a minimum at the *cis*-orientation.[15] For the C–O bond the torsional potential was three-fold with a barrier height of 1.07 kcal mol^{-1} and a maximum at the *cis*-orientation.[16]

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