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Conformational Analysis and Dipole Moments of Tetra-*O*-methyl-(+)-catechin and Tetra-*O*-methyl-(−)-epicatechin

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Received October 12, 1981*

Abstract: A conformational energy analysis has been performed for tetra-*O*-methyl-(+)-catechin and tetra-*O*-methyl-(−)-epicatechin. Rotation was permitted about five C–O bonds and about the single bond connecting two rings. Eighteen rotational isomers each were assigned for tetra-*O*-methyl-(−)-epicatechin. Relative populations of the rotational isomers are governed by short-range interactions which give rise to five weighting factors, one of which is common to tetra-*O*-methyl-(+)-catechin and tetra-*O*-methyl-(−)-epicatechin. The mean-square dipole moment is most sensitive to the weighting factor common to the two molecules studied. The calculated root-mean-square dipole moment of tetra-*O*-methyl-(−)-epicatechin at 300 K is in excellent agreement with the experimental value of 2.98 D obtained in *p*-dioxane. In the case of tetra-*O*-methyl-(+)-catechin, the calculated root-mean-square dipole moment is larger than the experimental result of 2.45 D if ring conformations in solution are the same as those found in the crystal. Good agreement between theory and experiment for tetra-*O*-methyl-(+)-catechin can be obtained if an alternative ring conformation is assumed. Temperature coefficients were calculated and found experimentally to be positive for both molecules.

Procyanidins are a class of polyphenols commonly found in plants. Among the most widely distributed procyanidins are polymers composed of the flavan-3-ols (+)-catechin and (−)-epicatechin.[1,2] Figure 1 depicts a methylated derivative, tetra-*O*-methyl-(+)-catechin. Tetra-*O*-methyl-(−)-epicatechin is the epimer at C3. Many plant species contain both (+)-catechin and (−)-epicatechin,[3] but other species contain only (+)-catechin or (−)-epicatechin.[3,4] Monomer units are usually found to be linked via C4 to C8, but other linkages (e.g., C4 to C6) are also known.[1,2] All four dimeric procyanidins with a C4–C8 link have been obtained from natural sources.[2–4] Their C4–C6 isomeric pairs are also known natural products.[1,2] Various trimeric procyanidins have also been isolated,[4–7] and the structures of several have been determined.[7] Ther is a pronounced steric hindrance to rotation about the C4–C8 interflavan bond, causing "slow" interconversion of rotational isomers on the NMR time scale at 30°.[1,2] A model building study, conducted with use of CPK space-filling molecular models, suggests two different types of helices can be formed from polymers composed of C4–C8 linked (+)-catechin or (−)-epicatechin.[1,2] A right-handed helix would appear to be favored if the polymer were composed of (+)-catechin, while a left-handed helix would arise if all monomeric units were (−)-epicatechin.

In this paper we initiate a study of conformational properties of procyanidins with use of matrix methods developed by Flory and co-workers[8] to treat linear chain molecules. The matrix approach permits a quantitative assessment of the connection between local covalent structure and conformation-dependent physical properties of a macromolecule. This method may rigorously be applied to both homopolymers and copolymers. Appropriate modifications permit rigorous extension to polymers containing branch points[9,10] or articulated side chains.[11] The ultimate objective is a quantitative description of the manner in which measurable physical properties, such as the mean-square dipole moment, unperturbed dimensions, and rotational state occupancy, are related to degree of polymerization, monomer identity, and dimer linkage pattern. Experimental measurements of these conformation-dependent physical properties would be difficult if free phenolic hydroxyl groups are present because these molecules have a strong tendency for aggregate formation and tend to be hydrated. Consequently this theoretical investigation will focus on methylated derivatives, which are more amenable to experimental study. Theoretical evaluation of conformational

properties of the monomer units, tetra-*O*-methyl-(+)-catechin and tetra-*O*-methyl-(−)-epicatechin, is described here and compared with results obtained from experiment.

Experimental Section

Dipole Moments. Dielectric constants were measured over a temperature range from 15.00 ± 0.04 °C to 30.00 ± 0.02 °C with a Wiss.-Techn. Werkstätten D-812 Weilheim Dipolmeter DM01 operating at 2 MHz and a DFL-2 gold-plated thermostated cell. The basic instrument design was modified to maintain better temperature stability and to obtain dielectric constants by directly measuring the cell oscillator circuit frequency with an Eldorado Model 1608 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 takes place around 35 °C.[12,13] Baker Analyzed *p*-dioxane was purified for use by refluxing at least 24 h over sodium[13] and distilling onto Baker Analyzed type 4Å molecular sieve that had previously been activated at 260 °C. After purification and drying, the refractive index of the dioxane at 25 °C was 1.42012. The literature value is 1.42025.[13] The Dipolmeter was calibrated with thiophene-free Baker Analyzed reagent-grade cyclohexane that had been refluxed and distilled from calcium hydride and dried over a molecular sieve. Solutions used for the dielectric measurements ranged from 0.2% to 1.0% by weight. The cell was washed three times between each run with analytical grade acetone and dried with dry nitrogen.

For a more consistent definition of the small dipole moment temperature coefficient, dielectric constant vs. temperature curves were refined by polynomial least-square analysis for each concentration, as described previously.[14] Dielectric constant vs. concentration data were then obtained from this family of curves at the temperature of interest. The

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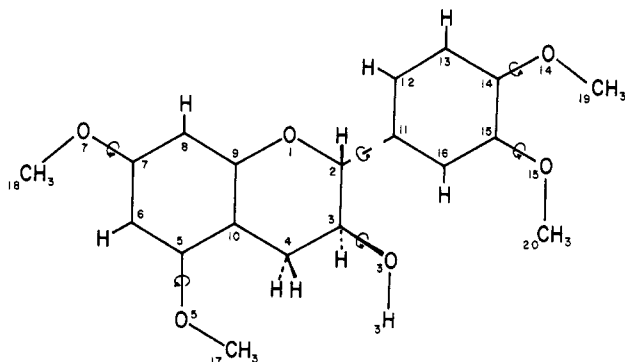(11) Mattice, W. L. *Macromolecules* **1977**, *10*, 1171.
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3360 *J. Am. Chem. Soc., Vol. 104, No. 12, 1982*

Mattice et al.

Figure 1. Structure of tetra-O-methyl-(+)-catechin.

Table I. Bond Lengths and Bond Angle Supplements

bond	length, Å	angle	supplement, deg
O-H	1.00	O-C-C^{ar}	76
C-H	1.10	C-C-C	72
O-C^{ar}	1.38	C-C-O	72
C^{ar}-C^{ar}	1.40	C-O-H	70
O-CH$_3$	1.45	C-C-C^{ar} (ring)	69
O-CH	1.46	C-C-C^{ar}	66
C-C^{ar}	1.52	C-O-C^{ar} (ring)	64
C-C	1.53	C^{ar}-O-CH$_3$	63
		O-C^{ar}-C^{ar}	60
		C-C^{ar}-C^{ar}	60
		C^{ar}-C^{ar}-C^{ar}	60
		C-C^{ar}-C^{ar} (ring)	58
		O-C^{ar}-C^{ar} (ring)	58

dielectric constant and refractive index data were treated by the least-squares method, and the dipole moments were evaluated by the Guggenheim method.[15] 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, and the dipole moment error limits are given within the 95% confidence interval.

Samples. The two samples of approximately 250 mg each of tetra-O-methyl-(+)-catechin and tetra-O-methyl-(−)-epicatechin were prepared by R. W. Hemingway and W. McGraw of the United States Department of Agriculture, Southern Forest Experiment Station, Pineville, Louisiana. The tetra-O-methyl-(+)-catechin was characterized by ^{1}H NMR; mp 143 °C (lit.[16] mp 143 °C; optical rotation in CHCl$_3$ of $[\alpha]_{578}$ −11.1°; and a carbon hydrogen analysis C, 65.7; H, 6.47 compared to that calculated for C$_{19}$H$_{22}$O$_6$ of C, 65.9; H, 6.36. The tetra-O-methyl-(−)-epicatechin showed the expected ^{1}H NMR spectra; mp 143 °C (lit.[17] mp 143 °C; an optical rotation $[\alpha]_{578}$ in CHCl$_3$ of −45.7°; and a carbon hydrogen analysis of C, 65.85; H, 6.61 vs. that calculated for C$_{19}$H$_{22}$O$_6$ of C, 65.9; H, 6.36.

Calculations

Geometry. Bond lengths, bond angles, and ring conformations are based on results obtained from a recent crystallographic study of 8-bromotetra-O-methyl-(+)-catechin.[18] Minor modifications were made in order to eliminate distortions which might arise from crystal packing. For example, lengths found for the twelve C^{ar}-C^{ar} bonds in the crystalline molecule ranged from 135.5 to 145.2 pm, with the average being 140 pm. Since 140 pm is the expected length of a C^{ar}-C^{ar} bond, the crystal structure was adjusted so that all C^{ar}-C^{ar} bonds would have this length. Similar adjustments were made in several other bond lengths and bond angles. The six carbon atoms in each aromatic ring, as well as the atoms to which they are directly bonded, were rendered coplanar in this process. Parameters used are summarized in Table I. Dihedral

Table II. Parameters Used To Formulate 6–12 Potentials[a]

atom or group	α, Å^3	N	r, Å
C	0.93	5	1.7
C^{ar}	1.23	5	1.95
CH$_3$	1.77	7	1.85
H	0.42	0.9	1.2
O	0.64	7	1.5

[a] Polarizability (α), effective number of polarizable electrons (N), and radius (r).

angles in the heteroring were changed by an average of 4.5° in order to maintain ring closure with the modified bond lengths and angles between bonds. Hydroxyl parameters are those used by Scheraga.[19] Bond angles involving nonhydroxyl hydrogen atoms were assigned so that these atoms equally subtend the space available.

Energy Functions. The total conformational energy was taken to be the sum of pairwise 6–12 potentials, intrinsic torsional potentials, and electrostatic interactions evaluated in the monopole approximation. The local dielectric constant was assigned a value of 3.5.[20] Six–twelve potentials were formulated in the manner described by Brant et al.,[20] using atomic polarizabilities, number of polarizable electrons, and radii collected in Table II. Methyl groups were treated as united atoms with methylene parameters. The parameters for C, methyl, and H are from Brant et al.[20] Ethereal oxygen atoms are approximated with use of parameters for an ester oxygen atom, with modification of the atomic polarizability to eliminate the contribution from the partial double bond character of the ester bond.[21] The C^{ar} parameters are those used by Yoon et al.[22]

Partial changes were assigned to oxygen atoms and the carbon atoms to which they were directly bound. These partial changes were assigned so that the reproduce experimentally observed dipole moments for anisole.[23] The values used are +0.2 for C2, C17, C18, C19, and C20, +0.1 for C5, C7, C9, C14, and C15, and −0.3 for O1, O5, O7, O14, and O15. Partial changes for the remaining group (+0.1, −0.44, and +0.34 for C3, O3, and H3, respectively) are those appropriate for a free phenolic group.[19] They serve as an adequate approximation for an aliphatic alcohol.

The intrinsic torsional potential for rotation about a C–C^{ar} bond was sixfold with a barrier height of 0.58 kcal mol^{-1} and maxima when the methyl group was in the plane of the aromatic ring.[24,25] For O–C the intrinsic torsional potential was threefold with maxima at the cis orientation and a barrier height of 2.0 kcal mol^{-1}.[19]

Conformational energies were calculated at 10° intervals for each variable dihedral angle.

Conformational Energy Surfaces

The conformational energy of the methylated monomer units is a function of six dihedral angles specifying the location of the four methyl groups, H3, and rotation about the C2–C11 bond. Casual inspection of CPK space filling molecular models reveals rotational states about bonds C2–C11 and C3–O3 are interdependent, as are rotational states about bonds C14–O14 and C15–O15. In contrast, rotations about bonds C7–O7 and C5–O5 are essentially independent of rotational states adopted at the remaining bonds. These bonds exhibiting independent rotation will be considered first.

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Table III. Dipole Moments, $\langle\mu^2\rangle^{1/2}$, of Tetra-$O$-methyl-(+)-catechin and Tetra-O-methyl-(-)-epicatechin in p-Dioxane

compd	dipole moment, D				10^3 d ln $\langle\mu^2\rangle$/dT
	15 °C	20 °C	25 °C	30 °C	
tetra-O-methyl-(+)-catechin	2.35 ± 0.10	2.40 ± 0.12	2.44 ± 0.17	2.49 ± 0.20	8 ± 20 K^{-1}
tetra-O-methyl-(-)-epicatechin[a]	2.95 ± 0.12	2.97 ± 0.08	2.98 ± 0.05	2.99 ± 0.05	2 ± 8 K^{-1}

[a] When these data are averaged with another run containing higher concentrations, the values are respectively from 15–30°: 2.87 ± 0.12 to 2.88 ± 0.10 D.

Rotational states will be defined through specification of φ_{ijkl}. Here i, j, k, and l are numerical subscripts denoting atoms as numbered in Figure 1. No special notation will be required to differentiate similarly numbered atoms (e.g., C5 and O5) because the intent will be obvious from the context. Subscripts j and k define the atoms at either end of the bond about which rotation occurs. The dihedral angle φ_{ijkl} is zero when atoms i, j, k, and l are planar trans. Positive rotation occurs if atom l moves clockwise with respect to the other three atoms when viewed along the line from atom j to atom k. According to this convention, the structure as drawn in Figure 1 has $\varphi_{8,7,7,18} = 0°$ and $\varphi_{6,7,7,18} = 180°$.

Independent Rotations. The most easily described rotational energy is that associated with the bond from C7 to O7. This bond, as well as three of the five remaining bonds about which rotation is noted in Figure 1, is C^{ar}–O. In the crystalline state,[18] methyl groups affected by rotation about these bonds are found to be approximately in the best plane described by the carbon atoms in the aromatic ring. Hence two equally weighted rotational states, at $\varphi_{8,7,7,18} = 0°$ and 180°, are used for the C7–O7 bond. Severe steric conflict between hydrogen atoms bonded to C4 and to C17 occurs when $\varphi_{6,5,5,17}$ is near 0°. Consequently only one rotational state, at $\varphi_{6,5,5,17} = 180°$, is retained for the bond from C5 to O5.

Interdependent Rotation of o-Methoxyl Groups. Two rotational states, separated by 180°, are assigned to the C14–O14 and C15–O15 bonds. Methyl groups participate in severe steric interactions when $\varphi_{16,15,15,20}$ and $\varphi_{13,14,14,19}$ are both 0°. This combination will be prohibited. Repulsive interactions are eliminated when these two dihedral angles are both 180°. States where one of the dihedral angles is 0° and the other 180° are also tenable, although steric interaction of a methyl group and an oxygen atom probably causes these states to be of higher energy than is the case when both dihedral angles are 180°. This energy will be denoted by E_1, and the corresponding statistical weight is $\omega_1 = \exp(-E_1/RT)$. Thus the four conformations resulting from two rotational isomers for the C14–O14 and C15–O15 bonds have statistical weights of 1, ω_1, ω_1, and 0.

Interdependent Rotation about C2–C11 and C3–O3. Figure 2 depicts the manner in which the conformational energy depends on rotation about bonds between C2 and C11 and between C3 and O3 for tetra-O-methyl-(+)-catechin. Severe steric repulsions yield prohibitively high energies in most regions of the conformational energy map. Interaction of an o-hydrogen atom with O1, O3, or the hydrogen atom bonded to C3 produces high energies for $\varphi_{1,2,11,12}$ unless this dihedral angle is near 130° or 310°. Two equally weighted rotational states, at $\varphi_{1,2,11,12} = 130°$ and 310°, are used for the C2–C11 bond.

Two of the three minima expected for rotation about the C3–O3 bond are perturbed by repulsive interactions with the aromatic ring when $\varphi_{2,3,3,3}$ is near 160°. These interactions elevate and displace the minimum expected at 120°. They also elevate the minimum near 240°, but to a lesser extent than was the case near 120°. The conformational energy surface depicted in Figure 2 suggests three rotational states ($\varphi_{2,3,3,3} = 0°$, 105°, 245°) for the C3–O3 bond. Statistical weights are 1, $\omega_2 = \exp(-E_2/RT)$, and $\omega_3 = \exp(-E_3/RT)$, respectively. Conformational energy calculations yield $0 < E_3 < E_2$, with $E_2 = 1.0$ kcal mol^{-1} and $E_3 = 0.5$ kcal mol^{-1} being reasonable estimates.

Severe repulsive steric interactions also occur over most of the conformation energy surface following epimerization at C3 to produce tetra-O-methyl-(-)-epicatechin (Figure 3). There are still two equally weighted rotational states for the C2–C11 bond, but they have shifted about 10° (to 140° and 320°) from their
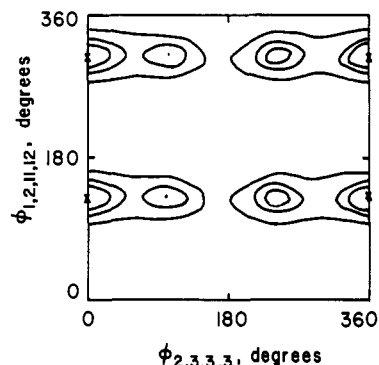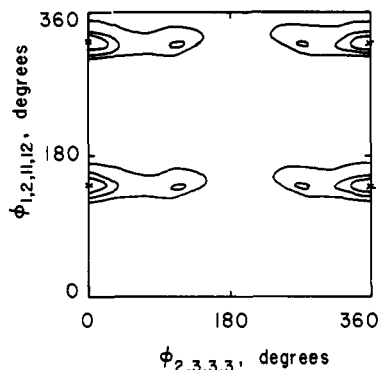

Figure 2. Conformational energy associated with rotation about the C2–C11 and C3–O3 bonds in tetra-O-methyl-(+)-catechin. Energy minima are denoted by "X", and contours are drawn at 1, 2, and 5 kcal mol^{-1} relative to the minimum energy.

Figure 3. Conformational energy associated with rotation about the C2–C11 and C3–O3 bonds in tetra-O-methyl-(-)-epicatechin. Energy minima are denoted by "X", and contours are drawn at 1, 2, and 5 kcal mol^{-1} relative to the minimum energy.

location in tetra-O-methyl-(+)-catechin. Rotation about the C3–O3 bond now produces maximal steric interference with the aromatic ring when $\varphi_{2,3,3,3}$ is near 190°. The three rotational states for the C3–O3 bond are now located at 0°, 115°, and 275°. Their statistical weights are 1, $\omega_4 = \exp(-E_4/RT)$, and $\omega_5 = \exp(-E_5/RT)$, respectively. Conformational energy calculations suggest E_4 and E_5 are both about 1.7 kcal mol^{-1}.

The preceding conformational energy analysis retains 18 rotational isomers for tetra-O-methyl-(+)-catechin and tetra-O-methyl-(-)-epicatechin. For tetra-O-methyl-(+)-cateching there are two rotational isomers each with statistical weights of unity, ω_2, and ω_3 and four rotational isomers each with statistical weights of ω_1, $\omega_1\omega_2$, and $\omega_1\omega_3$. In the case of tetra-O-methyl-(-)-epicatechin, there are two rotational isomers each with statistical weights of unity, ω_4, and ω_5 and four rotational isomers each with statistical weights of ω_1, $\omega_1\omega_4$, and $\omega_1\omega_5$.

Dipole Moments

Experimental. Experimentally observed dipole moments, $\langle\mu^2\rangle^{1/2}$, are collected in Table III. With limited quantities of samples, it was not possible to make consistent multiple runs or study the dielectric behavior over a wide concentration range. In both analyses only three concentration points were determined. Nevertheless, the data clearly demonstrate that tetra-O-methyl-(-)-epicatechin has the larger dipole moment. At 25 °C
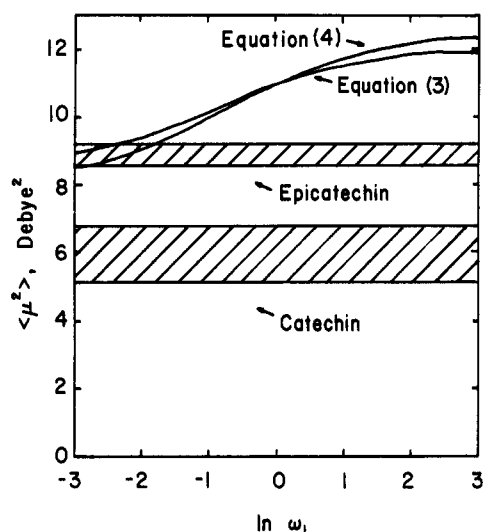
Figure 4. Dependence of $\langle\mu^2\rangle$ from eq 3 and 4 on ω_1. Cross-hatched regions denote the range of $\langle\mu^2\rangle$ defined by experiment.

dipole moments are 2.44 ± 0.17 D for tetra-O-methyl-(+)-catechin and 2.98 ± 0.05 D for tetra-O-methyl-(−)-epicatechin. Temperature coefficients are small and positive.

Theoretical. Averaging the squared dipole moment, μ^2, over all 18 rotational isomers yields

$$\langle\mu^2\rangle = (2/Z_C)(8.59 + 23.66\omega_1 + 3.31\omega_2 + 12.72\omega_1\omega_2 + 8.76\omega_3 + 24.36\omega_1\omega_3) \quad (1)$$

for tetra-O-methyl-(+)-catechin and

$$\langle\mu^2\rangle = (2/Z_E)(8.13 + 24.82\omega_1 + 10.02\omega_4 + 21.86\omega_1\omega_4 + 2.86\omega_5 + 16.04\omega_1\omega_5) \quad (2)$$

for tetra-O-methyl-(−)-epicatechin, where $\langle\mu_2\rangle$ is expressed in debye.[2] The configuration partition functions, Z_C and Z_E, are $2(1 + 2\omega_1)(1 + \omega_2 + \omega_3)$ and $2(1 + 2\omega_1)(1 + \omega_4 + \omega_5)$, respectively. The expressions for the mean-square dipole moments can be simplified by taking advantage of qualitative conclusions derived from the conformational energy analysis. In the case of tetra-O-methyl-(+)-catechin, this analysis suggests $1 + \omega_3 = 1.4$ and $\omega_2 = 0.18$ at 300 K. Clearly $1 + \omega_3 > \omega_2$. If ω_2 is assumed negligible compared to $1 + \omega_3$, a good approximation to eq 1 is

$$\langle\mu^2\rangle = (1 + 2\omega_1)^{-1}(8.6 + 24\omega_1) \quad (3)$$

In the case of tetra-O-methyl-(−)-epicatechin, the conformational energy analysis suggests ω_4 and ω_5 are about 0.06 at 300 K. Since $1 > \omega_4 + \omega_5$; eq 2 can be simplified by neglecting terms in ω_4 and ω_5, yielding

$$\langle\mu^2\rangle = (1 + 2\omega_1)^{-1}(8.13 + 24.82\omega_1) \quad (4)$$

for tetra-O-methyl-(−)-epicatechin.

Equations 3 and 4 demonstrate that $\langle\mu^2\rangle$ for both molecules is determined primarily by ω_1. Figure 4 depicts the manner in which the $\langle\mu^2\rangle$ specified by eq 3 and 4 depend on ω_1. If ω_1 is large, the resulting $\langle\mu^2\rangle$ are larger than those defined by experiment. However, as ω_1 becomes small, the computed $\langle\mu^2\rangle$ for tetra-O-methyl-(−)-epicatechin move into the range defined by experiment. This behavior suggests methyls bonded to O14 and O15 prefer to be oriented so that neither interacts with its neighboring OCH₃. Thus use of E_1, E_4, and E_5 of 1, 1.7, and 1.7 kcal mol⁻¹, respectively, in eq 2 yields $\langle\mu^2\rangle^{1/2} = 3.01$ at 300 K, which is in excellent agreement with the experimental value of 2.98 (±0.05)

D at 300 K for tetra-O-methyl-(−)-epicatechin. Figure 4 predicts positive temperature coefficients if $E_1 > 0$ because ω_1 must go to unity as temperature becomes infinite. The sign of the temperature coefficient is in harmony with that obtained from experiment. The numerical value from eq 2, reported as d ln $\langle\mu^2\rangle/dT$, is 0.3 × 10⁻³ K⁻¹ for tetra-O-methyl-(−)-epicatechin. Experimentally this number is (2 ± 8) × 10⁻³ K⁻¹. The larger experimental value may reflect some solvent interaction, although the large experimental deviation prohibits a definite conclusion.

The foregoing analysis clearly is successful for tetra-O-methyl-(−)-epicatechin, but Figure 4 shows that it is inadequate for tetra-O-methyl-(+)-catechin. We now turn to a consideration of factors which may account for the behavior of tetra-O-methyl-(+)-catechin.

Consequences of Intramolecular Hydrogen Bond Formation or Alternative Heteroring Conformations. The hydroxyl group of tetra-O-methyl-(+)-catechin cannot participate in intramolecular hydrogen bond formation when the heteroring conformation is that found in the crystalline state. In contrast, the hydroxyl group of tetra-O-methyl-(−)-epicatechin is directed toward O1 when the rotational state adopted at the C3—O3 bond is that which merits a statistical weight of ω_4. If a hydrogen bond of significant strength were to form, it would cause ω_4 to become larger than the value used here. If E_4 were to be reduced by 1 or 2 kcal mol⁻¹ by hydrogen bond formation, $\langle\mu^2\rangle^{1/2}$ would rise to 3.05 or 3.13 D, respectively. Thus agreement between experimentally measured and computed $\langle\mu^2\rangle$ does not require, but is compatible with, a weak hydrogen bonding interaction between the hydroxyl group and O1 in tetra-O-methyl-(−)-epicatechin.

Molecular models suggest that tetra-O-methyl-(+)-catechin, but not tetra-O-methyl-(−)-epicatechin, might be able to adopt an alternative conformation of the heteroring in which the C11—C16 ring is axial rather than equitorial. Conformational analysis suggests this structure would have a $\langle\mu^2\rangle^{1/2}$ near 2.7 D. One of the three rotational isomers for the C3—O3 bond causes the hydroxyl group to approach O1 when the heteroring has this alternative conformation. The value of $\langle\mu^2\rangle$ for tetra-O-methyl-(+)-catechin with the alternative heteroring conformation is quite sensitive to the energy assigned to the hydrogen bond. If, for example, the hydrogen bond were to have a strength of only 0.6 kcal mol⁻¹, the calculated $\langle\mu^2\rangle^{1/2}$ falls to 2.47 D, which is well within the range of the experimentally measured value of 2.44 ± 0.17 D for tetra-O-methyl-(+)-catechin.

Relationship to Dimers and Higher Oligomers

Rotations about the bonds considered will exhibit more interdependence in C4—C8 linked dimers than that seen in the monomers. A bulky substituent stereospecifically bonded to C4 will cause the two rotational states for bond C5—O5 to no longer be of the same energy. Rotation about C3—O3 and about C5—O5 may be dependent on rotation about the new bond formed at C4. If the favored conformation about C3—O3 is appreciably altered, the presence of a substituent at C4 may also have an effect on rotation about C2—C11. Similarly, rotation about C7—O7 and C2—C11 should be affected by a bulky substituent bonded to C8. Analysis of these more complicated dimers is in progress.