Assessment by Molecular Mechanics of the Preferred Conformations of the Sixteen C(4)–C(6) and C(4)–C(8) Linked Dimers of (+)-Catechin and (−)-Epicatechin with Axial or Equatorial Dihydroxyphenyl Substituents at C(2)

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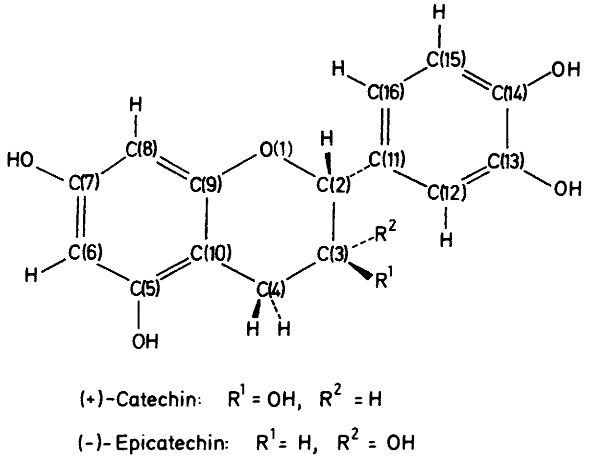
The molecular mechanics program MM2 has been employed for a conformational analysis of 16 dimers of (+)-catechin and/or (−)-epicatechin that have axial dihydroxyphenyl substituents at C(2). Monomer units are linked by 4α–6, 4α–8, 4β–6, and 4β–8 interflavan bonds. There is a two-fold rotation about the bond between monomer units, as has previously been shown to be the case for dimers with equatorial dihydroxyphenyl substituents at C(2). The exact value of the dihedral angle at the local minima is influenced by the stereochemistry at both C(3) and C(4) of the unit that is bonded through C(4). Heterocyclic rings occupy a range of conformations that parallel those seen when the substituents at C(2) occupy equatorial positions. Variations in the heterocyclic ring conformations are obtained by co-ordinated motion of C(2) and C(3) with respect to the mean plane of the fused atomic ring system.

Plants contain a variety of polyphenols that include polymers formed from two flavan-3-ols, (+)-catechin and (−)-epicatechin.[1–4] Figure 1 depicts the two monomers, which differ in configuration at C(3). Two recent reports[5,6] describe the conformation of (−)-epicatechin in the crystalline state. These studies report the same conformation for (−)-epicatechin, but higher resolution is provided by Fronczek *et al.*[5] Comparable information is not available for un-derivatized (+)-catechin due to the absence of suitable crystals. Crystals suitable for structure determination by *X*-ray diffraction have been obtained with three derivatives, 8-bromotetra-*O*-methyl-(+)-catechin,[7] penta-*O*-acetyl-(+)-catechin,[8] and (+)-catechin-(4α-2)-phloroglucinol heptamethyl ether.[9]

Taken together, the available crystal structures suggest the heterocyclic ring can adopt several different conformations. The dihydroxyphenyl ring at C(2) is placed in a pseudo-equatorial position in (−)-epicatechin, 8-bromotetra-*O*-methyl-(+)-catechin, and (+)-catechin-(4α–2)-phloroglucinal heptamethyl ether, but it occupies a pseudo-axial position in crystalline penta-*O*-acetyl-(+)-catechin. There are also important differences in the heterocyclic rings in the three compounds that have the substituent at C(2) in a pseudo-equatorial position. In (−)-epicatechin the heterocyclic ring is best described as a half-chair that has been distorted toward a C(3)-sofa, but in 8-bromotetra-*O*-methyl-(+)-catechin and (+)-catechin-(4α–2)-phloroglucinol heptamethyl ether the heterocyclic ring is a half-chair that is distorted toward a C(2)-sofa.

The crystal structures for the three derivatives of (+)-catechin show that the conformation of the heterocyclic ring is influenced by the nature of the substituents. Therefore the conformation of the heterocyclic ring in oligomers and polymers might be different from that seen in the monomers. The interflavan bond in naturally occurring polymers is often from C(4) to C(8),[10,11] but there are other types of bonds, such as C(4) to C(6).[12–14] Figure 2 depicts examples of dimers with both types of bonds. Recently[15] we performed a conformational analysis, using MM2,[16] of all 16 C(4)–C(8) and C(4)–C(6) linked dimers in which the dihydroxyphenyl substituents at C(2) occupy equatorial positions. The dimers are listed in Table 1. All 16 dimers exhibit two minima upon rotation about the interflavan bond. The 64 optimized heterocyclic rings, obtained for both rings in each of the two rotational isomers for the 16 dimers, exhibit a continuous range of variation in conformation. The heterocyclic rings in crystalline (−)-epicatechin, 8-bromotetra-*O*-methyl-(+)-catechin, and (+)-catechin(-4α–2)-phloroglucinol heptamethyl ether fall well within the range revealed by the MM2 calculations.



(+)-Catechin: $R^1 = OH$, $R^2 = H$

(−)-Epicatechin: $R^1 = H$, $R^2 = OH$

Figure 1. Structures and numbering system for the carbon and oxygen atoms in (+)-catechin and (−)-epicatechin

Here attention is directed to the same 16 dimers, but with the conformations of the heterocyclic rings adjusted so that the dihydroxyphenyl substituents at C(2) are in axial positions. Heterocyclic rings with axial dihydroxyphenyl groups at C(2) are less common than those with equatorial substituents, both in solution[9] and in the crystalline state.[5–9] Nevertheless, the structure of crystalline penta-*O*-acetyl-(+)-catechin clearly demonstrates the occurrence of the axial orientation. One objective here is the definition of the range of heterocyclic ring conformations to be expected when the substituent at C(2) occupies an axial position. A second objective is to ascertain whether the heterocyclic ring conformation responds to the type of interflavan linkage, rotational isomerism, and the identity of the monomers as it does when the dihydroxyphenyl group at C(2) is in the equatorial position.

Results and Discussion

Axial versus *Equatorial Substituents at* C(2).—The fact that the equatorial dimers are generally more stable than the axial

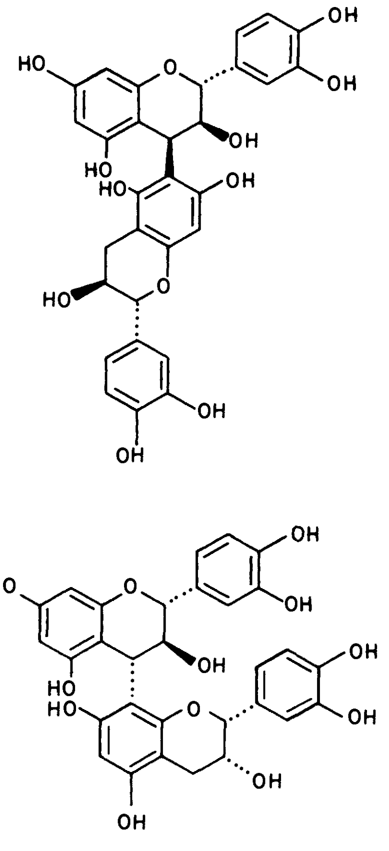


Figure 2. Two of the sixteen dimers considered in this study. The dimers shown are (+)-catechin-(4β-6)-(+)-catechin (top) and (+)-catechin-(4α-8)-(−)-epicatechin (bottom)

Table 1. Dimers studied

Abbreviation	Dimer
(I)	(+)-Catechin-(4α–6)-(+)-catechin
(II)	(+)-Catechin-(4α–6)-(−)-epicatechin
(III)	(−)-Epicatechin-(4α–6)-(+)-catechin
(IV)	(−)-Epicatechin-(4α–6)-(−)-epicatechin
(V)	(+)-Catechin-(4α–8)-(+)-catechin
(VI)	(+)-Catechin-(4α–8)-(−)-epicatechin
(VII)	(−)-Epicatechin-(4α–8)-(+)-catechin
(VIII)	(−)-Epicatechin-(4α–8)-(−)-epicatechin
(IX)	(+)-Catechin-(4β–6)-(+)-catechin
(X)	(+)-Catechin-(4β–6)-(−)-epicatechin
(XI)	(−)-Epicatechin-(4β–6)-(+)-catechin
(XII)	(−)-Epicatechin-(4β–6)-(−)-epicatechin
(XIII)	(+)-Catechin-(4β–8)-(+)-catechin
(XIV)	(+)-Catechin-(4β–8)-(−)-epicatechin
(XV)	(−)-Epicatechin-(4β–8)-(+)-catechin
(XVI)	(−)-Epicatechin-(4β–8)-(−)-epicatechin

Table 2. Locations, widths, and relative energies of the local minima[a]

		k/kcal mol^{-1} rad^{-1}		Energy difference
Dimer	φ (°)	$\varphi > 0$	$\varphi < 0$	(kcal mol^{-1})
(I)	74 (102), −102 (−80)	29 (14)	33 (8)	−0.4 (−1.2)
(II)	78 (100), −102 (−80)	11 (18)	23 (8)	0.4 (−1.3)
(III)	82 (86), −100 (−86)	32 (21)	35 (11)	−2.6 (0.2)
(IV)	84 (94), −96 (−84)	32 (15)	25 (12)	−2.5 (−3.4)
(V)	74 (100), −102 (−78)	29 (12)	10 (36)	−1.3 (2.5)
(VI)	74 (98), −104 (−80)	29 (21)	14 (21)	1.4 (1.7)
(VII)	84 (82), −104 (−90)	42 (13)	13 (18)	0.5 (3.2)
(VIII)	86 (86), −104 (−92)	49 (11)	19 (13)	2.6 (2.3)
(IX)	84 (90), −92 (−90)	14 (15)	15 (14)	0.3 (1.5)
(X)	86 (92), −94 (−90)	17 (22)	11 (14)	0.6 (1.6)
(XI)	78 (94), −100 (−80)	16 (9)	20 (10)	1.1 (3.3)
(XII)	78 (96), −100 (−80)	16 (10)	21 (10)	0.6 (3.3)
(XIII)	96 (92), −88 (−88)	20 (6)	20 (30)	−1.3 (−3.9)
(XIV)	94 (94), −90 (−88)	11 (21)	11 (24)	−1.3 (−0.7)
(XV)	84 (104), −98 (−82)	20 (28)	20 (20)	−0.1 (−3.6)
(XVI)	84 (98), −100 (−80)	11 (14)	11 (13)	0.3 (−3.6)

[a] The results for dimers with equatorial dihydroxyphenyl rings, as reported in ref. 15, are presented in parentheses. The energy difference is the energy at the minimum near 90° minus the energy at the minimum near −90°.

dimers is readily apparent during several of the optimizations. Starting structures for (IX)—(XII) with axial substituents at C(2) and $\varphi < 0$ converge to optimized structures that place these substituents in *equatorial* positions. (During the optimization, the heterocyclic rings flip to the more stable conformation.) The bottom ring in (I) also flips so that its substituent at C(2) is in the equatorial position. The strategies employed for optimization in these cases are described in the last paragraph in the Calculations section. The conformations reported here for the axial dimers should be understood to be those found at local minima in the energy surface.

The reverse flips of the heterocyclic ring were not encountered in our earlier study of the dimers with equatorial dihydroxyphenyl groups at C(2). If the initial structure has equatorial substituents at C(2), so does the optimized structure.

Torsion about the Interflavan Bond.—As in the earlier study of dimers with equatorial dihydroxyphenyl groups at C(2), the atoms that define φ, the dihedral angle at the interflavan bond, are C(3)–C(4)–C(8)–C(9) in C(4)–C(8) linked dimers and C(3)–C(4)–C(6)–C(5) in C(4)–C(6) linked dimers. All dimers exhibit two-fold minima for this rotation and the mean planes of the two fused ring systems are approximately perpendicular to one another at the minima, as was the case also in the dimers with equatorial substituents at C(2). The values of φ at the local minima are listed in Table 2. The numbers in parentheses are the φ values at the local minima when the dihydroxyphenyl groups at C(2) occupy equatorial positions, as reported earlier.[15] The minima cluster very close to ±90°.

The configuration of the hydroxy group at C(3) of the upper unit and the attachment of the interflavan bond at C(4) of this unit have an influence on the values of φ at the local minima. All φ values from Table 2 are plotted in Figure 3, but they are segregated into two groups. The left-hand portion of Figure 3 shows φ in dimers (I), (II), (V), (VI), (XI), (XII), (XV), and (XVI) do not occur exactly at ±90°, but instead tend to be displaced *ca.* 10° from this value. These dimers have a pseudo-*cis* orientation of the hydroxy group at C(3) of the upper unit and C(5), C(7), or C(9) of the bottom unit when φ is exactly ±90°. This repulsive interaction is relieved by a small rotation away from ±90°. There is no pseudo-*cis* interaction in dimers (III), (IV), (VII)—(X), (XIII), and (XIV) when φ is exactly ±90°. The right-hand portion of Figure 3 shows that φ for these dimers tend to cluster much closer to ±90°.

Severe repulsive interactions cause the local minima to be quite narrow. The minima are not truly parabolic, but it is nevertheless useful to fit the energies within 1 kcal mol^{-1} of the minimum energy, E(min), to equation (1). Broader local

$$E - E(\text{min}) = k[\varphi - \varphi(\text{min})]^2 \qquad (1)$$

minima have smaller values of k. The best values of k are collected in Table 2. There is a tendency for somewhat narrower

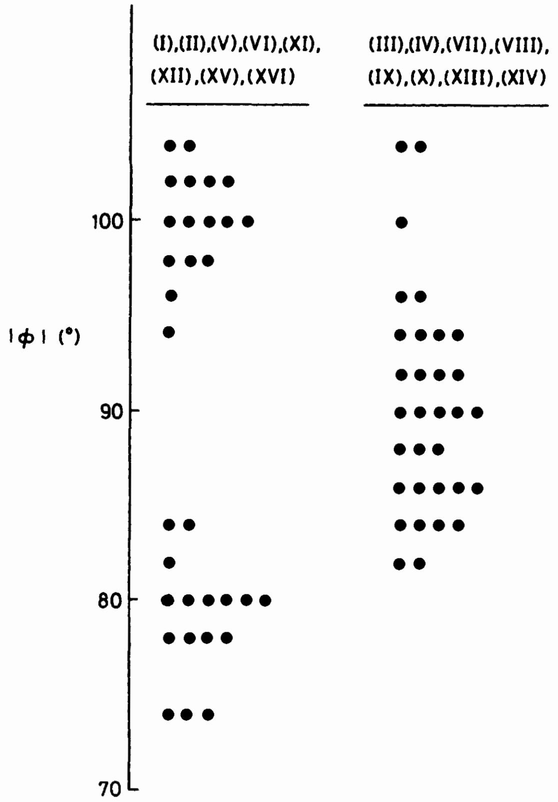


Figure 3. Distributions for the absolute value of the dihedral angle at the interflavan link in dimers with axial or equatorial substituents at C(2)

Table 3. Heterocyclic ring conformations in dimers with axial substituents at C(2)[a]

Dimer	φ	Distances (pm)	Dihedral angles (°)
(I)	−102	0, −55, 17, −2	24, −53, 61, −37, 6, 2
		−8, −52, 28, −2	16, −49, 64, −44, 12, 4
	74	−2, −53, 21, −2	22, −52, 61, −39, 8, 2
		−1, −46, 30, −2	18, −49, 63, −44, 13, 2
(II)	−102	0, −60, 11, −1	26, −56, 60, −34, 3, 2
		−10, −57, 24, −4	16, −50, 65, −45, 13, 4
	78	−1, −58, 15, −1	24, −54, 60, −35, 5, 3
		0, −36, 40, −5	14, −46, 64, −49, 18, 1
(III)	−100	0, −59, 17, −2	25, −55, 63, −38, 6, 2
		−7, −53, 24, 5	17, −49, 63, −44, 12, 3
	82	−2, −57, 20, 2	22, −53, 63, −40, 8, 3
		0, −34, 40, −3	13, −44, 62, −47, 17, 1
(IV)	−96	−1, −59, 14, −1	25, −55, 62, −36, 5, 3
		−10, −57, 25, −4	16, −50, 65, −46, 13, 4
	84	−2, −57, 19, −2	22, −53, 62, −39, 7, 3
		0, −32, 44, −3	13, −44, 63, −49, 18, 1
(V)	−102	5, −48, 15, −5	24, −50, 56, −34, 7, 0
		3, −36, 24, −4	18, −44, 51, −36, 12, −1
	74	−1, −27, 44, −2	11, −40, 60, −48, 19, 1
		0, −54, 13, 1	24, −52, 55, −32, 4, 1
(VI)	−104	2, −51, 18, −6	23, −52, 60, −37, 9, 0
		2, −31, 34, −3	15, −42, 56, −42, 15, 0
	74	−1, −30, 43, −3	12, −41, 60, −48, 18, 1
		−1, −54, 15, 1	24, −52, 57, −34, 5, 2
(VII)	−104	3, −44, 23, −4	20, −49, 58, −38, 9, 1
		−1, −45, 18, −5	19, −45, 54, −36, 10, 0
	84	−1, −39, 32, −2	16, −44, 60, −44, 13, 1
		1, −42, 26, 1	19, −48, 57, −39, 10, 1
(VIII)	−104	3, −49, 18, −5	22, −52, 63, −43, 12, 0
		−1, −36, 31, −4	15, −43, 56, −41, 15, 0
	86	−1, −39, 32, −3	16, −44, 60, −44, 14, 1
		1, −43, 25, 0	20, −48, 58, −38, 10, 1
(IX)	−92	−10, −50, 27, −1	14, −46, 60, −43, 13, 3
		−6, −28, 54, 6	10, −41, 60, −48, 18, 3
	84	−1, −60, 16, 0	19, −50, 59, −38, 8, 4
		−2, −16, 58, 3	6, −36, 59, −50, 22, 2
(X)	−94	−10, −48, 29, −1	14, −45, 60, −44, 14, 3
		−5, −28, 54, 5	9, −42, 63, −51, 19, 3
	86	−10, −61, 16, 0	19, −50, 59, −38, 8, 4
		−1, −17, 60, 3	7, −38, 62, −52, 22, 2
(XI)	−100	−8, −44, 34, −1	13, −44, 61, −46, 15, 3
		−4, −31, 46, 4	11, −42, 60, −47, 17, 3
	78	−8, −52, 26, −1	17, −48, 62, −43, 12, 3
		1, −22, 49, −1	9, −39, 59, −49, 20, 1
(XII)	−100	−8, −42, 36, −1	12, −43, 61, −46, 16, 2
		−6, −32, 51, 5	10, −43, 63, −50, 18, 3
	78	−8, −52, 26, −1	17, −48, 62, −43, 12, 3
		2, −20, 54, −1	7, −40, 62, −51, 21, 1
(XIII)	−88	−13, −62, 20, 0	18, −51, 63, −42, 10, 5
		2, −15, 58, 3	8, −38, 59, −50, 22, 1
	96	−6, −81, −12, 1	32, −61, 57, −25, −5, 4
		−8, −42, 32, −3	12, −43, 59, −44, 15, 3
(XIV)	−90	−12, −61, 21, 0	17, −51, 63, −42, 10, 4
		1, −18, 58, 2	9, −40, 62, −52, 22, 1
	94	−7, −82, −13, 0	32, −61, 57, −25, −5, 4
		−8, −44, 34, −3	13, −45, 62, −46, 16, 3
(XV)	−98	−11, −54, 28, 0	15, −40, 64, −45, 12, 4
		3, −10, 61, 4	7, −37, 58, −50, 22, 0
	84	−4, −77, −13, 0	31, −59, 54, −23, −6, 3
		−7, −44, 34, −4	13, −45, 60, −45, 15, 3
(XVI)	−100	−11, −54, 29, 0	15, −49, 65, −45, 13, 4
		2, −7, 67, 4	6, −36, 61, −53, 25, 0
	84	−3, −77, −18, 1	32, −58, 50, −18, −9, 3
		−7, −44, 32, −4	14, −46, 62, −46, 16, 2

[a] φ Denotes the C(3)–C(4)–C(8)–C(9) and C(3)–C(4)–C(6)–C(5) dihedral angle, respectively, in C(4)–C(8) and C(4)–C(6) linked dimers. The order of distances out of the mean plane of the fused aromatic ring system is O(1), C(2), C(3), C(4). The order of dihedral angles is C(10)–C(9)–O(1)–C(2), C(9)–O(1)–C(2)–C(3), O(1)–C(2)–C(3)–C(4), C(2)–C(3)–C(4)–C(10), C(3)–C(4)–C(10)–C(9), C(4)–C(10)–C(9)–O(1). For each φ, the first set of parameters is for the monomer linked through C(4) and the second set is for the monomer linked through C(6) or C(8).

minima in the dimers that have axial substituents at C(2). Average values of k are 21 and 16 kcal mol^{-1} rad^{-1} for axial and equatorial dimers, respectively. Since the k values have a rough inverse correlation with vibrational entropy, the C(2) equatorial substituents are favoured for both energetic and entropic reasons.

The last column in Table 2 gives the difference in energy at the two local minima. Many of these differences are sufficiently small so that significant populations of both minima can be expected at ordinary temperatures. Reorientation of a subset of the 10 hydroxy groups can produce a rather large change in energy. Therefore there can be appreciable alterations in energy without any change in φ or the conformation of the heterocyclic rings. For this reason it is easier to define φ and the conformation of the heterocyclic rings at an energy minimum than the value of the energy at the minimum.

Puckering of the Heterocyclic Ring at C(2) *and* C(3).—Heterocyclic ring conformations for the dimers with axial substituents are summarized in Table 3. The heterocyclic rings are characterized by the distances out of the mean plane of the fused aromatic ring system[17] for atoms O(1), C(2), C(3), and C(4), and also by the dihedral angles for the six bonds in the heterocyclic ring.

The distances of C(2) and C(3) out of the mean plane of the

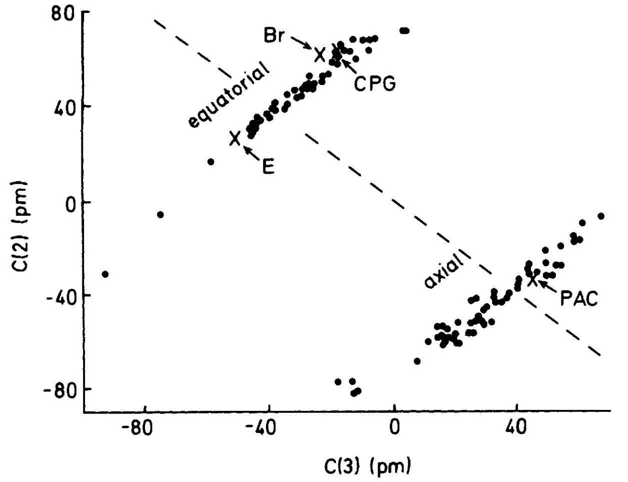


Figure 4. Distances of C(2) and C(3) from the mean plane of the fused aromatic ring system in the (+)-catechin and (−)-epicatechin units in dimers in which the substituents at C(2) are either axial or equatorial. The data for the axial dimers are from Table 3, and data for the equatorial dimers are from ref. 15. X At the heads of the four arrows denote the conformations found in the crystal structures of (−)-epicatechin (E), 8-bromotetra-*O*-methyl-(+)-catechin (Br), (+)-catechin-(4α-2)-phloroglucinol heptamethyl ether (CPG), and penta-*O*-acetyl-(+)-catechin (PAC). The dashed line is C(2) = −C(3)

fused ring system are depicted in Figure 4, along with equivalent data for the dimers with equatorial substituents at C(2), as reported in ref. 15. The conformations of the heterocyclic rings observed in crystalline (−)-epicatechin,[5] 8-bromotetra-*O*-methyl-(+)-catechin,[7] (+)-catechin-(4α–2)-phloroglucinol heptamethyl ether,[9] and penta-*O*-acetyl-(+)-catechin[8] are denoted by a × in Figure 4. The points for the two types of dimers cluster around two nearly parallel straight lines. As noted earlier,[15] most of the heterocyclic rings in dimers with equatorial substituents at C(2) cluster around a line that extends from the point for crystalline (−)-epicatechin to the point for (+)-catechin-(4α–2)-phloroglucinol heptamethyl ether. No such line can be defined by available crystal structures for heterocyclic rings in which the C(2) substituent occupies an axial position because there is only one such structure, and therefore only one point! It is the MM2 data that provide the evidence that heterocyclic rings with axial substituents at C(2) also can occupy a range of conformations. Both sets of data in Figure 4 show that C(2) and C(3) can easily make co-ordinated movements of 40 pm or more with respect to the mean plane of the fused aromatic ring system. Most of the heterocyclic rings can be described as half-chairs. There is a slight tendency for distortion toward a C(2) sofa if the substituent at C(2) is equatorial, and the trend favours at C(3) sofa when the substituent at C(2) is axial.

Dihedral Angles in the Heterocyclic Ring.—The first line in Table 4 shows the averages of the dihedral angles, along with the standard deviations, for the structures in Table 3. The averages and standard deviations are nearly identical in absolute value (but the averages are opposite in sign) with those obtained when the substituents at C(2) occupy equatorial positions. The averages agree reasonably well with the dihedral angles in crystalline penta-*O*-acetyl-(+)-catechin, which are presented at the bottom of Table 4. The second and third lines in Table 4 show that separate averages over each type of monomer unit are virtually indistinguishable, as was also the case when the substituents at C(2) were in equatorial positions. There is a greater difference between top and bottom units, as shown by the entries in the fourth and fifth lines. More detailed analysis demonstrates that the greatest variability in heterocyclic ring conformations is seen in the dimers that have a 4β–8 link. When the substituents at C(2) occupy equatorial positions, it is the dimers with a 4α–8 link that exhibit the greatest variation in heterocyclic ring conformations.

Table 4. Summary of dihedral angles in the heterocyclic rings[a]

Structure	Mean (standard deviation) (°)					
All	17(7),	−47(5),	60(3),	−42(7),	12(7),	2(1)
(+)-Catechin	17(7),	−47(6),	59(3),	−41(7),	12(7),	2(2)
(−)-Epicatechin	16(6),	−47(6),	61(3),	−43(8),	13(7),	2(1)
Top units	20(6),	−50(5),	60(3),	−39(7),	8(7),	3(1)
Bottom units	13(5),	−44(4),	60(3),	−46(5),	16(5),	2(1)
Crystalline penta-*O*-acetyl-(+)-catechin	18	−47	61	−44	16	−1

[a] The order of mean is C(10)–C(9)–O(1)–C(2), C(9)–O(1)–C(2)–C(3), O(1)–C(2)–C(3)–C(4), C(2)–C(3)–C(4)–C(10), C(3)–C(4)–C(10)–C(9), C(4)–C(10)–C(9)–O(1), which is the same order as dihedral angles in Table 3. Top units are those linked through C(4), and bottom units are those linked through C(6) or C(8). The last line describes the structure observed for penta-*O*-acetyl-(+)-catechin in the crystalline state.[8]

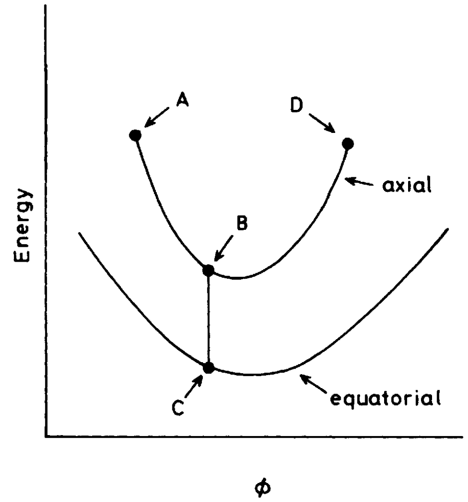


Figure 5. Schematic picture of an optimatization of a dimer, starting at A. The substituents at C(2) are in axial positions on the curve A–B–D, but they flip to equatorial positions at C

Calculations

Use of the MM2 algorithm for analysis of this class of compounds is appropriate because it produces optimized structures that are in good agreement with the conformations adopted by (−)-epicatechin and (+)-catechin-(4α–2)-phloroglucinol heptamethyl ether in the crystalline state.[9] Starting structures used in the present work are based on earlier MM2 calculations of (+)-catechin and (−)-epicatechin with the dihydroxyphenyl groups in the axial position. Penta-*O*-acetyl-(+)-catechin crystallizes with this structure. Two monomer units with the desired starting structures are linked to produce one of the 16 dimers described in Table 1. Refinement was achieved by a method similar to that used in the study of the dimers with equatorial substituents at C(2).[15] First, the starting structure of the dimer was optimized by MM2, seeking a local minimum of the total steric energy. Then the dihedral angle about the interflavan bond was varied using the standard dihedral driver method to examine the minima. The step size was chosen to be 2° to minimize the uncertainty in calculated energies. In cases where a kink (or depression) appeared in the profile, the rotation was reversed to smoothen the kink. The energy calculation was performed with several added parameters that describe motion associated with the aromatic rings.[18,*] The added parameters are the same as those used in the study of the monomers.[9]

The preference for equatorial positions of the dihydroxyphenyl substituents at C(2) is apparent in several of the optimizations. The behaviour of several dimers is presented in schematic fasion in Figure 5. Optimization might start from A, where both heterocyclic rings have axial substituents at C(2). Upon driving the linkage torsion by the dihedral driver method, the energies of the optimized structures decrease, and the substituents at C(2) remain axial. This path is from A to B in Figure 5. However, at some point, such as B, there is an unexpected sharp decrease in energy to C, but no change in φ. Upon examination of the structure at C, it is found that the heterocyclic rings have flipped so that there are now equatorial substituents at C(2). In circumstances where this flip occurs, the curve for axial dimers was completed by either of two strategies. One strategy is to start a new optimization with an axial dimer at position D in Figure 5. The alternative strategy is to return to the vicinity of A, but to use different conformations of the heterocyclic rings for the starting structure. Use of an alternative starting conformation for the heterocyclic rings would sometimes make it easier for the minimizer in MM2 to retain the C(2) substituents in the axial positions.

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[*] C(Ar)–C(Ar) stretching parameters $K(S) = 8.067$ and $L(O) = 1.391$, C(Ar)–O–lone pair bending parameters $K(B) = 0.350$ and $\theta(O) = 108.00$, and the following torsional parameters (in the order $V1$, $V2$, $V3$ for each torsion): C(Ar)–C(Ar)–C(Ar)–C(Ar), −0.93, 9.0, 0.0; H–C(Ar)–C(Ar)–H, −0.93, 9.0, 0,0; C(Ar)–C(Ar)–C(Ar)–H, −0.93, 9.0, −1.06; H–C(Ar)–C(Ar)–O, −0.93, 9.0, 0.0; C(Ar)–C(Ar)–C(Ar)–O, −0.93, 9.0, 0.0; C(Ar)–O–C(sp^3)–C(Ar), 0.0, 0.0, 0.403.