Structure–Taste Correlations in Sweet Dihydrochalcone, Sweet Dihydroisocoumarin, and Bitter Flavone Compounds

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The dihydrochalcone derivatives of the bitter flavonoids naringin and neohesperedin are intensely sweet. Phyllodulcin is as sweet as the dihydrochalcones with similar taste properties although its structure apparently resembles that of bitter flavanone or flavone. Multifaceted approaches, including X-ray crystal structure analysis, energy calculation, and structure comparison, have been employed to clarify the structure–taste correlations in these classes of compounds. In the crystal, naringin dihydrochalcone assumes a 'J'-shaped conformation with a fully-extended dihydrochalcone moiety while neohesperidin dihydrochalcone assumes the same overall conformation but with a partially-extended moiety. A 2D conformational energy map of dihydrochalcone obtained using molecular mechanics revealed nine local minima. The pseudoequatorial and pseudoaxial forms of phyllodulcin have the same AM1 energies with a low energy barrier between them. The partially-extended form of dihydrochalcone and the pseudoequatorial form of phyllodulcin which are the maximally superposable conformers are proposed to be the active conformers. The major difference between the structures of flavone and phyllodulcin is not in the overall planarity but in the relative orientation of the pyrone and phenyl ring systems.

Introduction

Most of the known high-potency sweeteners were discovered fortuitously. Despite substantial effort, deliberate searches for new sweeteners have rarely been successful except for compounds that are closely related in structure to an existing sweetener.[1] Rational design is hampered by poor knowledge of the structure–taste relationship, which is difficult to derive due to diversity of chemical structure among sweeteners. The most widely accepted hypothesis concerning the molecular basis of sweetness is that the "AH–B···X" glucophore is required for elicitation of sweet taste.[2] In this model, AH–B stands for the hydrogen bond donor and acceptor and X represents a third hydrophobic binding site. However, this hypothesis sometimes does not account for compounds that possess this glucophore and resemble the sweeteners in structure but are totally tasteless or even bitter. One notable example is the case of the bitter flavone and the sweet dihydroisocoumarin compounds in which apparently subtle structural changes alter the taste property dramatically.

The natural flavonoids naringin (**1**) and neohesperidin (**2**) are bitter, but their dihydrochalcone derivatives **3** and **4** become intensely sweet although they have undesirable taste properties such as slow taste onset and a lingering aftertaste.[3] To improve taste quality, numerous compounds have been synthesized by modifying neohesperidin dihydrochalcone (NEODHC) or aglycone hesperetin dihydrochalcone.[4] Phyllodulcin (**5**), a natural dihydroisocoumarin, is also an intensely sweet compound possessing taste properties similar to those of dihydrochalcone.[5] Since phyllodulcin and NEODHC have a 3-hydroxy-4-methoxyphenyl moiety in common, the isovanillyl group is usually identified as the AH–B glucophore (the A ring portion is usually regarded as X), and the related compounds are sometimes called isovanillyl sweeteners.[6] However, naringin dihydrochalcone (NARDHC) is also very sweet, indicating that this group may not be absolutely required for sweet taste.

Apparently the structure of phyllodulcin resembles that of flavanone or flavone, which is either tasteless or bitter, rather than that of dihydrochalcone. This fact has been utilized in the search of the active conformer of the dihydrochalcone sweetener. Originally DuBois et al. proposed that the active form of dihydrochalcone is the bent or folded form.[4a] They reasoned that the overall structure of phyllodulcin should be different from the essentially planar structure of flavone and concomitantly the active form of phyllodulcin should be the pseudoaxial form. They further claimed, using the mechanical molecular models, that the possible glucophores occupy the common spatial positions in these active forms. However, the X-ray analysis[7] of NEODHC showed that the dihydrochalcone moiety exists in a partially-extended conformation, and the NMR studies[6b,8] of phyllodulcin showed that it exists exclusively in a pseudoequatorial form in solution. These experimental evidences were interpreted as not supporting the active model proposed by DuBois et al.

None of the previous studies, however, provides concrete evidence to deduce the active conformers. Obviously, manipulation of mechanical models involves considerable inaccuracy. The crystal and solution con-

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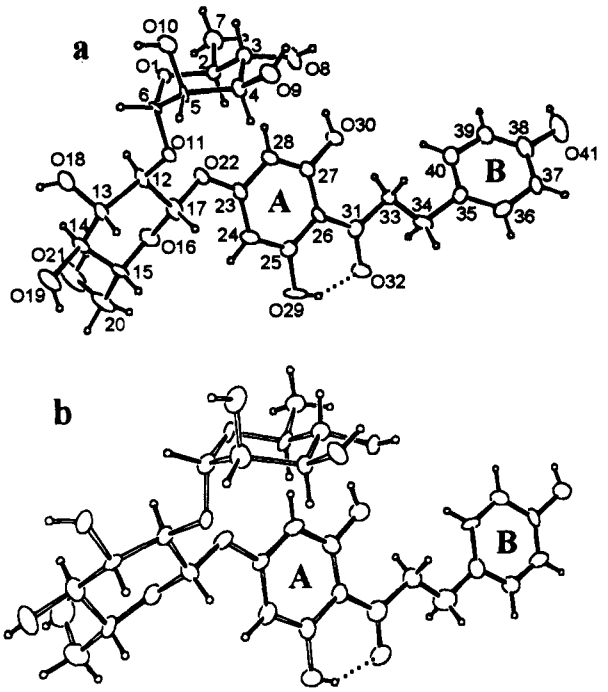


Figure 1. ORTEP drawing of the molecules A (a) and B (b) of naringin dihydrochalcone with atomic numbering scheme.

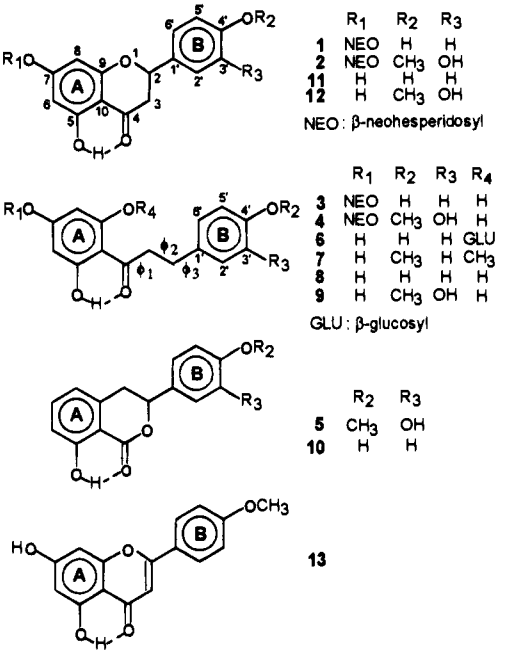
formations may represent the stable forms but not necessarily the active ones in the receptor. Especially, the dihydrochalcone moiety with three rotatable C–C bonds should possess considerable conformational freedom, and in fact, it shows different conformations in several crystal structures including NEODHC, phlorizin[9] (**6**), and 2′,4′-dihydroxy-4,6′-dimethoxy-α,β-dihydrochalcone[10] (DDHC, **7**). Detailed knowledge of the conformational properties of the related compounds is thus necessary for proposition of the active forms. In this study, we determined the crystal structure of NARDHC and analyzed the related crystal structures in detail. We also performed conformational analysis of aglycone naringenin dihydrochalcone (**8**) and phyllodulcin using molecular mechanics (MM) and semiempirical AM1 methods and tried to find the superposable ones from all stable conformers of both compounds. We finally tried to find the reason why flavanones and flavones are not sweet at all.

Results and Discussion

Crystal Structure of Naringin Dihydrochalcone. Both crystals of NARDHC and NEODHC contain two crystallographically independent molecules. The ORTEP[11] drawings of the two NARDHC molecules with atomic numbering scheme are shown in Figure 1. Molecular dimensions agree with those of the related compounds within experimental errors. There is always an intramolecular hydrogen bond between the hydroxyl O(29) and oxo keto O(32) atoms in the related compounds shown in Chart 1. Crystal packing consists of a complicated network of hydrogen bonds involving the β-neohesperidosyl and phenolic oxygen atoms and the water molecules.

A stereoscopic drawing of the superimposed structures of NARDHC and NEODHC is shown in Figure 2. Comparison of the selected torsion angles defining the overall conformations of the related compounds is listed in Table 1. Despite the presence of many rotatable

Chart 1



bonds, both compounds have a very similar overall structure which can be roughly depicted as a 'J' shape with the β-neohesperidosyl (2-*O*-α-L-rhamnosyl-β-D-glucosyl) moiety forming a curved part of the 'J' and the dihydrochalcone aglycone forming a linear segment. However, the structures in detail show subtle but significant and somewhat systematic differences. The conformations of the two independent molecules in each compound are very similar to each other except for the orientation of the B phenyl rings, but the two compounds show significant difference in the extendedness of the dihydrochalcone moieties. The dihydrochalcone moieties in NARDHC as well as in phlorizin and DDHC are fully extended with $\phi_1 \approx 180°$ and $\phi_2 \approx 180°$, while those in NEODHC are partially extended with $\phi_1 \approx 70°$ and $\phi_2 \approx 180°$. The relative orientations of the B phenyl rings in the related compound randomly vary as can be seen in the variable ϕ_3 angles. Dihedral angles between the A and B rings are 43° and 12° in the A and B molecules of NARDHC, respectively. In contrast, the A and B rings are nearly coplanar in phlorizin, while they are nearly perpendicular to each other in DDHC. Orientations of the B rings in the two NEODHC molecules are so different that the 3′-OH groups are situated in the opposite directions.

While the dihydrochalcone moieties are conformationally variable, the β-neohesperidosyl moieties of NARDHC and NEODHC assume very similar conformations as can be seen in the similar torsion angles about the glycosidic linkage (see Table 1). This moiety in naringin[12] also assumes the same conformation although its orientation with respect to the A ring is completely opposite to those in NARDHC and NEODHC with a difference of ~180° in the C(17)–O(22)–C(23)–C(24) torsion angle.

Conformational Analysis. Naringenin dihydrochalcone was used as a model system for conformational analysis of the dihydrochalcone sweetener since aglycone hesperetin dihydrochalcone (**9**), though quite insoluble, is as sweet as NEODHC indicating the β-neohesperidosyl moiety is not absolutely required for sweet

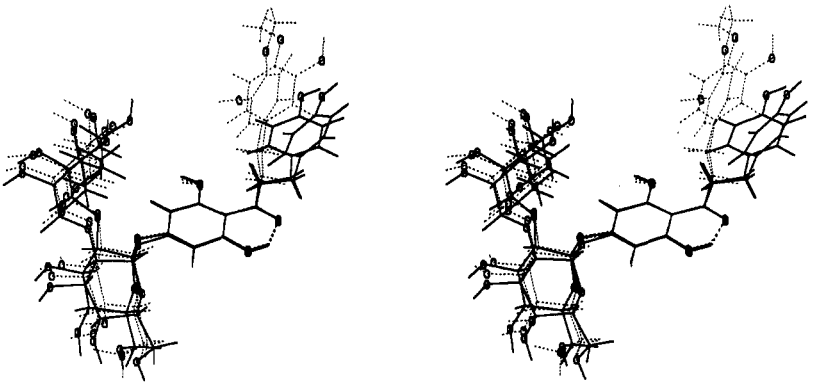


Figure 2. Superimposed crystal structures of naringin dihydrochalcone (solid lines) and neohesperidin dihydrochalcone (dotted lines).

Table 1. Comparison of Selected Tosional Angles (Deg) in the Related Compounds[a]

	NARDHC		NEODHC				
	A	B	A	B	naringin	phlorizin	2′,4′-dihydroxy-4,6′-dimethoxy-α,β-dihydrochalcone
Dihydrochalcone Moiety							
C(25)–C(26)–C(31)–C(33)	−177(2)	−175(2)	−159.6	−168.4	172.6	−175.7	−174.5
C(26)–C(31)–C(33)–C(34)[α]	175(2)	180(2)	76.6	71.4		−179.8	174.7
C(31)–C(33)–C(34)–C(35)[β]	−176(2)	−179(2)	−176.3	179.4		−178.7	−167.4
C(33)–C(34)–C(35)–C(36)[γ]	−46(2)	−14(2)	−112.9	47.1		−175.7	97.1
Carbohydrate Moiety							
C(17)–O(22)–C(23)–C(24)	16(1)	4(1)	17.4	11.3	−176.9		
C(12)–C(17)–O(22)–C(23)	165(1)	159(2)	157.5	164.7	165.3		
O(11)–C(12)–C(17)–O(22)	−73(1)	−71(1)	−64.1	−66.7	−67.1		
C(6)–O(11)–C(12)–C(17)	146(1)	139(1)	138.8	142.8	134.7		
O(1)–C(6)–O(11)–C(12)	−69(1)	−77(1)	−76.3	−73.6	−80.0		

[a] α, β, and γ correspond to ϕ_1, ϕ_2, and ϕ_3, respectively.

taste[4] and the 3′- and 4′-substituents in the B ring do not affect the conformational property of the dihydrochalcone moiety. Previously, an energy profile for dihydrochalcone was obtained as a function of ϕ_1.[6a] This study suffers from local minimum problems in that energy minimization leads to local minima closest to the initial conformer with certain values of ϕ_2 and ϕ_3. Since there are three rotatable C–C bonds in dihydrochalcone, the whole conformational potential energy surface can not be explored in this 1D approach.

The 2D conformational energy map in terms of ϕ_1 and ϕ_2 (Figure 3) was obtained by the newly-developed iterative four-way scanning method incorporated in our MM program.[13] This method can effectively eliminate the local minimum problem by automatically adjusting ϕ_3 to give the lowest energy conformer at each grid point. There are nine distinct local minima at $\phi_1 \approx 180°$, 90°, or −90° and $\phi_2 \approx 180°$, 60°, or −60°. Their torsion angles with ΔE are listed in Table 2, and the superimposed structures are shown in Figure 4. Variation of ϕ_1 for constant ϕ_2 involves relatively low energy barriers (at most 4 kcal/mol) except for the forbidden range of $-50° < \phi_1 < 50°$ so that the **5** ↔ **1** ↔ **6**, **3** ↔ **2** ↔ **7**, and **4** ↔ **9** ↔ **8** conformational transitions may be facile under the normal condition. In contrast, the **1** ↔ **2** ↔ **9**, **3** ↔ **4** ↔ **5**, and **6** ↔ **7** ↔ **8** transitions in which ϕ_2 varies with constant ϕ_1 involve energy barriers higher than 4 kcal/mol. Especially, the **2** ↔ **9** transition involves an energy barrier higher than 6 kcal/mol. Energy variation depends more sensitively on ϕ_2 than on ϕ_1 in the relatively low-energy region, illustrating that the previous 1D approach in terms of ϕ_1 is not appropriate for conformational analysis of dihydrochalcone.

The energy map is approximately centrosymmetric, and there is a pseudomirror symmetry passing through

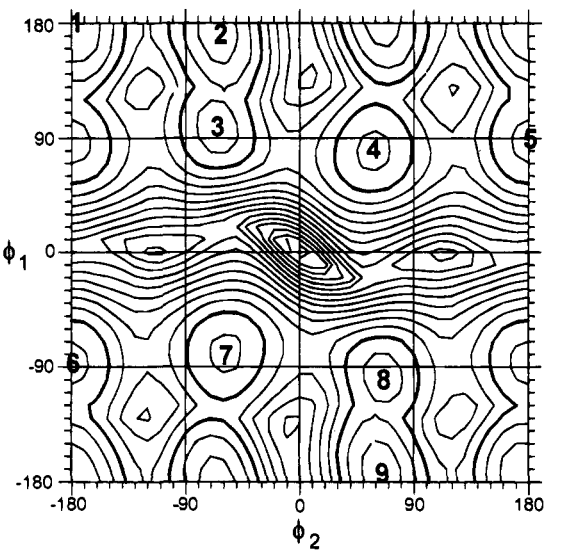


Figure 3. Conformational potential energy map of naringenin dihydrochalcone. The individual conformers are identified with the boldface numbers. The contour level is 1 kcal/mol, and thick lines denote the 3 kcal/mol level from the global minimum.

the A ring plane between the centrosymmetrically-related local minima conformers. The conformers **1**, **5**, and **6** with $\phi_2 = \pm 180°$ can be classifed as the extended form while the rest as the folded or bent form. Chinn et al. previously defined the conformer with $\phi_1 = \pm 90°$ as the folded form,[6a] but it is not correct since the torsion angle that determines whether the overall conformation is extended or folded is not ϕ_1 but ϕ_2. The crystal structures of NARDHC, phlorizin, and DDHC, though their ϕ_3 values are different, correspond to the fully-extended conformer **1** which is the global minimum. The

Table 2. Torsion Angles and Relative Energy of the Local Minima Conformers

no.	ϕ_1 (deg)	ϕ_2 (deg)	ϕ_3 (deg)	ΔE (kcal/mol)
1	180.0	180.0	−90.5	0.0
2	170.0	−60.0	108.0	0.46
3	98.4	−64.9	86.9	1.48
4	80.0	57.9	−96.6	1.72
5	88.6	178.1	−95.3	1.65
6	−87.7	−178.1	96.8	1.67
7	−79.8	−57.4	97.6	1.73
8	−98.1	67.0	94.4	1.58
9	−170.3	61.7	−109.4	0.45

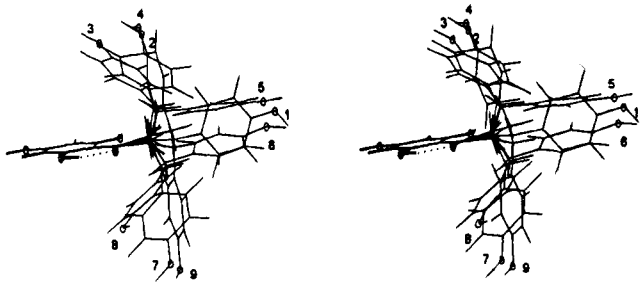


Figure 4. Stereoplot of the superimposed local minima conformers.

crystal structure of DDHC is the same as the global minimum structure in that the B ring is perpendicular to the A ring plane. The crystal structure of NEODHC corresponds to the partially-extended conformer **5** with ΔE of 1.7 kcal/mol. Energy dependency on ϕ_3 was obtained by MM energy minimization and is bimodal with maximum differences of 1.3 and 1.6 kcal/mol for the conformers **1** and **5**, respectively. This as well as the crystal structures indicates that the B ring can rotate freely. It is interesting to note that all four crystal structures reported thus far occur only in the extended forms with $\phi_2 = \pm 180°$, although the bent conformers **2** and **9** with $\phi_2 = \pm 60°$ are the second lowest energy minima conformers with ΔE of 0.5 kcal/mol. Crystal-packing force must be a major factor in this occurrence. Nevertheless it may also be correlated with the tendency shown in the energy map such that variation of ϕ_2 accompanies a rather higher energy barrier than that of ϕ_1 in the low-energy region. The present MM calculation was done in vacuum, but the conformational property would not be drastically different from that in solution since the dihydrochalcone moiety does not involve any special type of the intramolecular interaction such as a hydrogen bond. Therefore, it is very likely that dihydrochalcone in solution exists in the fully- or partially-extended form, as observed in the crystal structures, rather than the bent form.

Relative stability of various conformers of phyllodulcin was assessed by the AM1 calculations of 5,6-dihydro-6-phenyl-α-pyrone used as a model system for phyllodulcin. Enthalpies of formation are −37.10, −37.08, and −35.44 kcal/mol for the *S*-pseudoequatorial, *R*-pseudoaxial, and flat conformers, respectively. These indicate that the stabilities of the equatorial and axial conformers are essentially same and the transition between them does not involve a significant energy barrier. Although the crystal structure of phyllodulcin has not been reported yet, the crystal structure of hydrangenol (**10**), a structural congener, has been determined.[14] It assumes an equatorial conformation as suggested by the NMR studies of phyllodulcin.[6b,8] The flavanone compounds such as naringenin[15] (**11**) and hesperetin[16] (**12**), whose apparent structures are very similar to phyllodulcin, also assume an equatorial conformation in crystal. The planes of the A and B rings are usually not parallel but variably angled to each other,[17] with an exceptional case of naringin[12] which adopts a flat conformation. The MM energy curve upon rotation of the B ring in flavanone and dihydroisocoumarin shows a bimodal shape with energy barriers of 2.0 and 1.5 kcal/mol for the equatorial and axial conformers, respectively, indicating that the B ring can rotate freely as in the case of dihydrochalcone. The result for the equatorial conformer is the same as that reported by Arnoldi et al.[6b] In contrast, most flavones usually assume a flat conformation in crystal partly due to the contribution of the resonance forms with a partial double bond character in the C−C bond joining the two ring systems.[17] Rotation of the B ring in flavone certainly involves a higher energy barrier than those of flavanone and dihydroisocoumarin.

Active Conformation. As stated previously, DuBois et al. proposed that the active conformers are the axial and bent forms for phyllodulcin and dihydrochalcone, respectively.[4a] In contrast, Arnoldi et al. proposed the equatorial form of phyllodulcin as the active one from the NMR evidences showing that it is the most stable form.[6b] Whatever the active forms actually are, an assumption is widely accepted that dihydrochalcone and phyllodulcin with similar taste properties have similar shapes in the taste receptor with the glucophores situated at the same 3D positions, and thus the active forms of both compounds are superposable. In searching the superposable conformers, it should be kept in mind that an active conformer in the receptor does not necessarily have to be the same as or even similar to the global minimum energy conformer. Although the crystallographic and the NMR studies favor the specific, namely, extended and pseudoequatorial, conformers for dihydrochalcone and phyllodulcin, the present energy calculations show that both compounds are flexible to a large extent. Therefore, it seems necessary to consider all stable conformers of both compounds for the search of the active ones, instead of assuming *a priori* an active conformer of one compound and then finding the superposable conformer of the other as previously done.

In this study, all stable conformers of dihydrochalcone with $\Delta E < 3$ kcal/mol generated in 5° intervals of torsion angles ϕ_1 and ϕ_2, were systematically compared with both the equatorial and axial conformers of phyllodulcin by fitting the A phenyl ring atoms and the three atoms (O(29), C(31), and O(32) in Figure 1) in common. Then the degree of overlap of the overall structures as well as the proximity of the 4′-hydroxyl groups was examined. It was found, contrary to the previous notion, that the extended-equatorial pairs generally fit better than the bent-axial pairs. A partially-extended conformer of dihydrochalcone ($\phi_1 = 75°$, $\phi_2 = -170°$, $\phi_3 = 170°$) fits very well with the equatorial conformer of phyllodulcin with the possible glucophores at the common sites as shown in Figure 5a. This conformer is similar to, though not the same as, the crystal structure of NEODHC. The best model ($\phi_1 = 125°$, $\phi_2 = -65°$, $\phi_3 = 95°$) for a bent-axial pair is shown in Figure 5b. On the basis of these results, it becomes possible to propose that

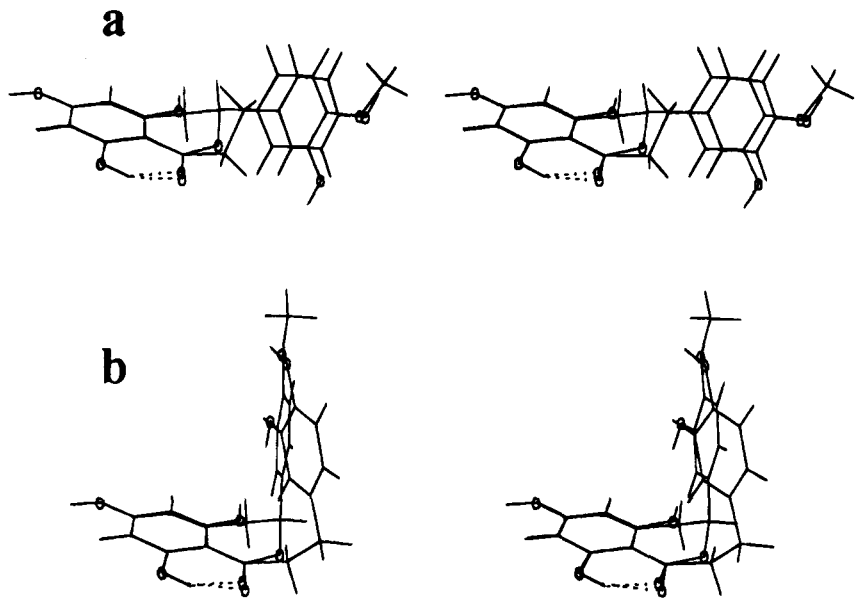


Figure 5. Stereoplots of the superimposed (a) partially-extended (naringenin dihydrochalcone) and pseudoequatorial (phyllodulcin) conformers and (b) bent (naringenin dihydrochalcone) and pseudoaxial (phyllodulcin) conformers.

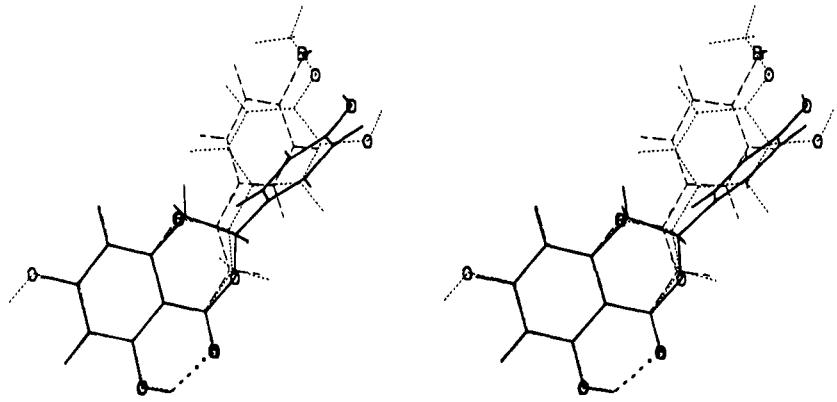


Figure 6. Stereoplot of the superimposed crystal structures of hydrangenol (solid lines), hesperetin (dotted lines), and 4′-bromo-5-hydroxyflavone (dashed lines).

the partially-extended form of dihydrochalcone and the pseudoequatorial form of phyllodulcin are the active or sweet conformers. This model is particularly attractive because both conformers are the most probable conformers in solution as discussed above.

It now remains to find the reason why planar flavone or the equatorial form of flavanone does not elicit sweet taste if the equatorial form of phyllodulcin is the active form. In order to discern any structural differences between the dihydroisocoumarin, flavanone, and flavone compounds, the crystal structures of hydrangenol,[14] hesperetin,[16] and 4′-bromo-5-hydroxyflavone[18] selected as their representative examples were compared. Although acacetin (4′-methoxy-5-hydroxyflavone, **13**) is the most closely-related flavone whose crystal structure has been determined, the crystal structure of 4′-bromo-5-hydroxyflavone was used instead since the atomic coordinates of acacetin have not been published and the two crystal structures are very similar.[19] Superimposition of the three crystal structures (Figure 6) shows two important features somewhat contrary to the general notions. First, the structures of flavanone and flavone are remarkably similar, but that of dihydroisocoumarin is significantly different as far as the directional vector along the C(2)–C(1′) bond joining the two ring systems is concerned (see Chart 1 for the atomic numbering scheme). Concomitantly the 4′-O atoms of flavone and dihydroisocoumarin, at the end of this vector, are separated by ~2 Å despite the relatively small difference in the pyrone rings. Second, there is no significant differences in the overall planarity in the three classes of compounds when the B rings are rotated to be parallel to the A rings. In 4′-bromo-5-hydroxyflavone, the C(2), C(1′), C(4′), and 4′-Br atoms lying on the directional vector are displaced by 0.06, 0.11, 0.27, and 0.42 Å from the A ring plane, showing that the B phenyl ring is slightly bent with respect to the A ring plane. This tendency of bending is also observed in the other flavone compounds showing that flavone is not strictly planar.[20] The corresponding values are 0.62, 0.52, 0.21, and 0.12 Å for hesperetin, showing that there is a bending, and 0.80, 0.76, 0.70, and 0.73 Å for hydrangenol, showing that the two rings are nearly parallel. Relative atomic displacement having a maximum value of ~0.7 Å at the C(2) position decreases along the directional vector and can be reduced further since the bending motion of the B ring is possible due to the more or less flexible pyrone ring.

It has already been pointed out that an apparently small change in the structure of a sweet molecule could lead to total loss of taste, and thus critical geometrical fitting between tastant and receptor is required for

elicitation of sweet taste.[21] Previously Arnoldi et al. proposed that the taste differences between flavone and phyllodulcin originate from a subtle difference in their 3D structures such that phyllodulcin forms a 'step' that conforms to the so-called Schellenberger barrier,[21a] while strictly planar flavone can not.[6b] However, this proposition may not be true since the difference in the overall planarity is not significant enough to distinguish their 3D structures. Instead, we propose that the differences in 3D positions of the possible glucophoric sites including the 4'-O atom may be related to the differences in taste.

Summary

In this study, conformational analysis and structural comparison have been performed in a quantitative way to derive results quite different from those of the previous studies concerning the structure–taste relationships between the dihydrochalcone, dihydroisocoumarin, and flavone compounds. The active conformers of dihydrochaclone and phyllodulcin are the partially-extended and pseudoequatorial conformers, respectively. It may not be the different overall planarity of the whole molecules but the different orientation of the B rings with respect to the A ring that makes the taste properties of phyllodulcin and flavone quite different.

Experimental Section

X-ray Analysis. Transparent crystals were obtained by slow evaporation of an aqueous ethanol solution. Crystal data are $2(C_{27}H_{34}O_{14})\cdot 7H_2O$, $M_r = 1291.2$, monoclinic, space group $P2_1$, $a = 18.470(7)$ Å, $b = 8.360(3)$ Å, $c = 19.877(8)$ Å, $\beta = 96.40(5)°$, $V = 3050.1$ Å^3, $Z = 2$, $D_{calcd} = 1.740$ g cm^{-3}, $F(000) = 1372$, $T = 298$ K, and μ(Cu Kα) = 10.2 cm^{-1} with crystal size of ca. 0.5 × 0.4 × 0.1 mm. Intensity data were collected on a Rigaku AFC4 diffractometer using the $\omega - 2\theta$ method and graphite-monochromated Cu Kα radiation ($\lambda = 1.5418$ Å). Among 3426 independent reflections (h −18–18, k 0–8, l 0–19) measured within $4° < 2\theta < 101°$, 3111 reflections (90.8%) were observed with $I \geq 2\sigma(I)$. No absorption and extinction corrections were made. Numerous efforts to solve the structure using direct methods had failed. The structure was solved by molecular replacement with PATSEE[22] using the 4-glucosyl-2,6-dihydroxyphenyl moiety in the NEODHC crystal structure as a search model. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters using SHELXL-93.[23] H atoms were generated using the HFIX option and included in the structure factor calculation with the isotropic thermal parameters 1.2 times for bonded C or 1.5 times for bonded O atoms. H atoms in the water molecules could neither be located in the difference map nor be generated. The final R and R_w are 0.085 and 0.201 for 3111 observed reflections; 802 variables; goodness of fit on $F = 1.236$; $(\Delta/\sigma)_{max} = 0.014$ [U_{11} of C(23B)] in the final refinement cycle. Largest difference peak and hole were 0.26 and −0.31 eÅ^{-3}, respectively.

Conformational Analysis. A 2D conformational potential energy map of dihydrochalcone was obtained using an in-house MM program based on Allinger's MM2 but working in the internal coordinate system.[13] The MM calculation was performed on 10° grids of ϕ_1 and ϕ_2 with full geometry optimization (except for the fixed torsion angles of ϕ_1 and ϕ_2). Relative stability of the pseudoequatorial and pseudoaxial conformers of phyllodulcin was assessed by AM1 calculations for 5,6-dihydro-6-phenyl-α-pyrone using the AMPAC program.[24] Energy was minimized with respect to all geometrical variables using the PRECISE option. Variation of energy upon rotation of the phenyl ring in dihydrochalcone and phyllodulcin was also obtained using MM. Structure fitting and plotting were done using an in-house molecular graphics program.

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Supporting Information Available: X-ray data of NARDHC including final fractional coordinates, thermal parameters, bond distances, bond angles, relevant geometrical details of intra- and intermolecular hydrogen bonds, and a packing diagram (9 pages). Ordering information is given on any current masthead page.

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