JOC Article

Experimental and DFT ^{1}H NMR Study of Conformational Equilibria in *trans*-4′,7-Dihydroxyisoflavan-4-ol and *trans*-Isoflavan-4-ol

Kalevi Pihlaja,*,† Petri Tähtinen,† Karel D. Klika,† Tuija Jokela,‡ Auli Salakka,‡ and Kristiina Wähälä‡

Structural Chemistry Group, Department of Chemistry, University of Turku, Vatselankatu 2, FIN-20014 Turku, Finland, and Laboratory of Organic Chemistry, Department of Chemistry, University of Helsinki, P.O. Box 55, FIN-00014 Helsinki, Finland

kalevi.pihlaja@utu.fi

Received April 8, 2003

The solution-state conformational equilibria of *trans*-4′,7-dihydroxyisoflavan-4-ol (**1**) and *trans*-isoflavan-4-ol (**2**) were assessed based on the temperature dependence of their vicinal coupling constants $J_{H-2\alpha,H-3}$ and $J_{H-3,H-4}$ in comparison to values calculated with density functional theory (DFT) methods at the B3LYP/cc-pVTZ//B3LYP/6-31G(d,p) level of theory. For each half-chair conformer, several rotamers with respect to the C-4 hydroxyl and C-3 phenyl were calculated and the overall diequatorial-to-diaxial ratio at 298 K was assessed as 66:34 for **1** and 73:27 for **2**. The syntheses of **1** and **2** are described.

Introduction

Isoflavan-4-ols, suggested human metabolites of dietary-based isoflavones,[1,2] are being actively studied for drug development. For example, *cis*- and *trans*-4′,7-dihydroxyisoflavan-4-ol possess antitumor activity against human prostate cancer cells[3] and are known potent antioxidants.[4] Furthermore, they may represent a novel series of cardioprotective therapeutics.[5] The conformational analysis is also of interest as biological activities are determined to various degrees by the adopted conformations of the substrates.[6] The chemical transformations of the readily available isoflavones,[7] e.g. isoflavone → isoflavanone → isoflavan-4-ol (see Scheme 1), are not necessarily straightforward for polyhydroxylated species, but can be accomplished under certain conditions.[3] Thus, we have developed an expedient route to *trans*-4′,7-dihydroxyisoflavan-4-ol (**1**).[3] This compound was assessed as an equilibrium of diequatorial (**1eq**) and diaxial (**1ax**) conformers which were interconverting rapidly on the NMR time scale (Scheme 2). This equilibrium was approximately evaluated[3] based on the ^{13}C chemical shift of C-2 as a 77:23 mixture (**1eq**:**1ax**) at ambient temperature, and then by application of the Karplus equation[8] to $J_{H-2\alpha,H-3}$ and $J_{H-3,H-4}$ resulting in a similar ratio of 68:32. The cis isomer of **1**, by contrast, was considered to be anancomeric in a half-chair conformation with the C-3 aryl group equatorially orientated and the hydroxyl at C-4 axially orientated based on the limiting values of $J_{H-2ax,H-3}$ (ca. 12.1 Hz) and $J_{H-2eq,H-3}$ (ca 3.7 Hz) which suggest the adoption of a sole structure.[3] Thus, interestingly, the behavior of this pair of stereoisomers is in discord with expectations where the opposite scenario might have been anticipated.

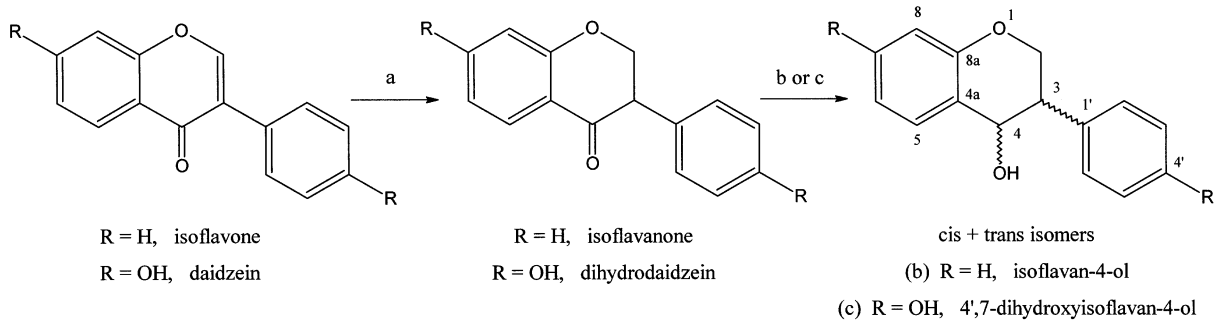
To describe the conformational status of **1** more thoroughly we have now examined the temperature dependence of the conformational equilibria in **1** and in *trans*-isoflavan-4-ol (**2**) using variable-temperature NMR combined with high-level molecular modeling calculations. It has been recently demonstrated[9] that coupling constant calculations for the limiting conformations can be of great help in estimating conformational equilibria and evaluating which of the minimum energy conformations fits best with the experimental results. This approach serves particularly well for obtaining limiting values when good model values for the coupling constants are lacking and, as experienced in this study, decoalescence of the spectra is unattainable.

* Address correspondence to this author. Phone: 358-(2)-3336750. Fax: 358-(2)-3336750.
† University of Turku.
‡ University of Helsinki.

(1) (a) Kelly, G.; Nelson, C.; Waring, M.; Joannou, G.; Reeder, A. *Clin. Chim. Acta* **1993**, *223*, 9. (b) Heinonen, S.; Wähälä, K.; Adlercreutz, H. *Anal. Biochem.* **1999**, *274*, 211.
(2) Wähälä, K.; Salakka, A.; Adlercreutz, H. *Proc. Soc. Exp. Biol., Med.* **1998**, *217*, 293.
(3) Wähälä, K.; Koskimies, J. K.; Mesilaakso, M.; Salakka, A.; Leino, T. K.; Adlercreutz, H. *J. Org. Chem.* **1997**, *62*, 7690.
(4) Arora, A.; Nair, M. G.; Strasburg, G. M. *Arch. Biochem. Biophys.* **1998**, *356*, 133.
(5) Chin-Dusting, J. P. F.; Fisher, L. J.; Lewis, T. V.; Piekarska, A.; Nestel, P. J.; Husband, A. *Br. J. Pharm.* **2001**, *133*, 595.
(6) James, L. C.; Roversi, P.; Tawfik, D. S. *Science* **2003**, *299*, 1362.
(7) (a) Wähälä, K.; Hase T.; Adlercreutz, H. *Proc. Soc. Exp. Biol., Med.* **1995**, *208*, 27. (b) *Phytochemical Dictionary. A Handbook of Bioactive Compounds from Plants*, 2nd ed.; Harborne, J. B., Baxter, H., Moss, G. P., Eds.; Taylor & Francis: London, UK, 1999; Chapter 38, p 458.
(8) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona C. *Tetrahedron* **1980**, *36*, 2783.
(9) Tähtinen, P.; Bagno, A.; Klika, K. D.; Pihlaja, K. *J. Am. Chem. Soc.* **2003**, *125*, 4609 and references therein.

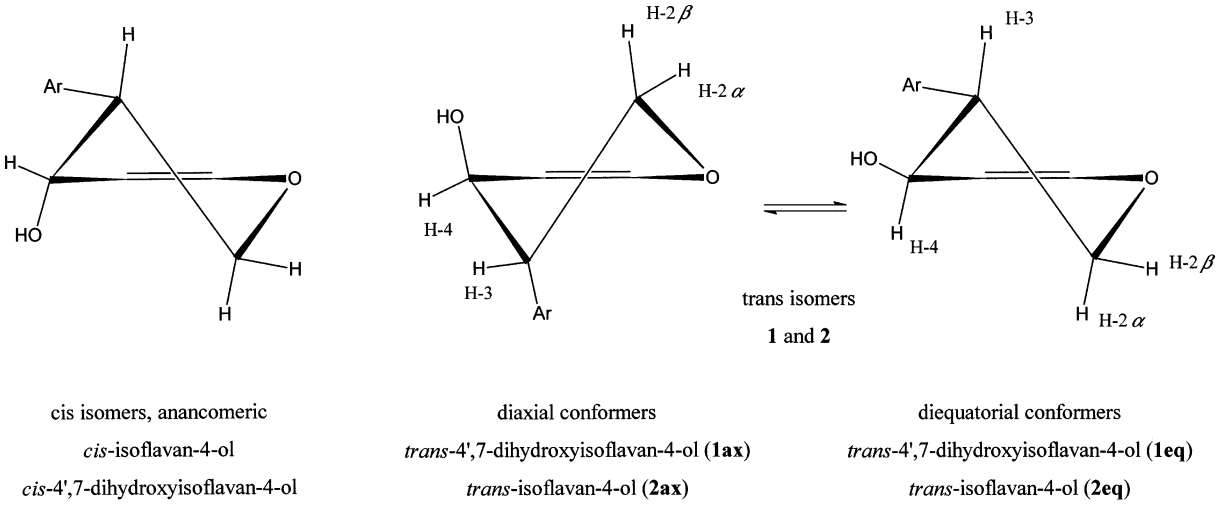
10.1021/jo0301200 CCC: $25.00 © 2003 American Chemical Society
Published on Web 08/12/2003

SCHEME 1. The Structures of the Isoflavones, Isoflavanones, and the Isoflavanols Together with the Numbering System in Use[a]



[a] Reaction conditions: (a) Pd/C, NH_4OCHO, MeOH, reflux; (b) $Li(t\text{-}Buo)_3AlH$, THF, 25−30 °C; (c) LiBH4, THF, 0 °C.

SCHEME 2. The Generalized Half-Chair Conformations Adopted by the Isoflavan-4-ols Looking Across the Heterocyclic Ring toward the Fused Aromatic Ring. Cis Isoflavan-4-ols Can Be Anancomeric with Only One Conformer Predominating[3] while the Trans Isoflavan-4-ols Are an Equilibrium Mixture of Diequatorial and Diaxial Half-Chair Conformations[a]



[a] The α and β H-2 protons are so indicated.

Results and Discussion

After full assignment of the ^1H and ^{13}C NMR spectra of **1** and **2**, accomplished routinely by using a standard set of homonuclear and heteronuclear shift correlation experiments (COSY, CHDEC/HMQC, and HMBC) supplemented by long-range COSY and homonuclear decoupling experiments to assess the presence of long-range $J_{H,H}$ couplings, ^1H and ^{13}C NMR spectra were also acquired at various temperatures in the range 178−323 K. However, the spectra essentially remained in the fast exchange region and for neither nucleus could coalescence be traversed as the inversion barrier between the two interconverting forms is just not sufficiently high enough to enable freezing of the conformational equilibria above 173 K in either of the compounds at the field strength used (B_o = 11.75 T).

^1H chemical shifts and $J_{H,H}$ coupling constants were obtained from the ^1H NMR spectra of **1** and **2** by spin analysis employing the PERCH iteration software[10] using the full-spin system at 298 K and these are reported in the Experimental Section. For ^1H spectra acquired at other temperatures, the $J_{H,H}$ coupling constants of H-2, H-3, and H-4 were similarly extracted with use of PERCH but as an isolated spin system, i.e., the long-range couplings of H-3 into the phenyl substituent and H-4 into the fused aromatic moiety were neglected without the introduction of any significant error. The spin analysis at very low temperatures was hampered by the deteriorating quality of the field homogeneity, particularly when the spin system was very high order and/or the lines became increasingly exchange-broadened as the rate of conformational exchange slowed. Nonetheless, the change in the observed time-averaged couplings could be obtained reliably for the pertinent spins. Both the geminal coupling $J_{H-2\alpha,H-2\beta}$ and the vicinal coupling $J_{H-2\beta,H-3}$ (the latter alternating between axial/equatorial and equatorial/axial dispositions in the exchanging conformations) in this respect served as controls for assessing the reliability of the extracted spins as they remained essentially invariant with respect to temperature. That is to say, their variation with temperature is well below that required for extracting useful conformational information but was helpful in the aforementioned regard.

(10) See for example: Laatikainen, R.; Niemitz, M.; Weber, U.; Sundelin, J.; Hassinen, T.; Vepsäläinen, J. *J. Magn. Reson., Ser. A* **1996**, *120*, 1 (or the program website at http://www.uku.fi/perch.html).

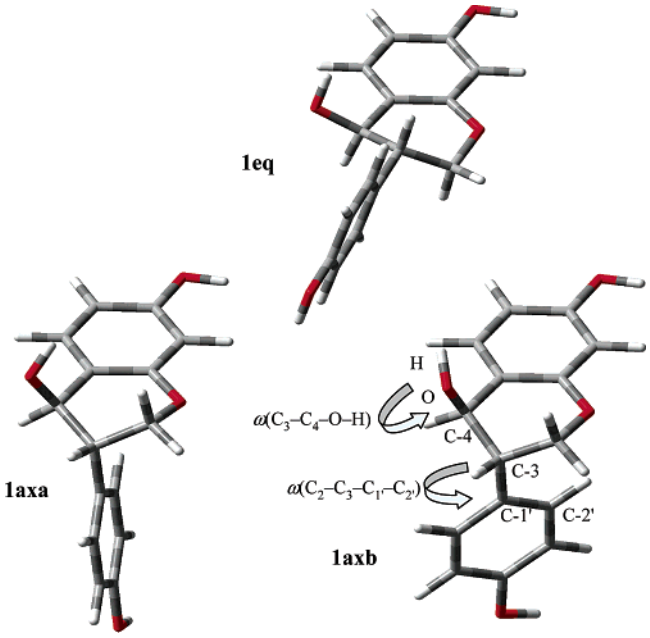


FIGURE 1. Optimized half-chair conformations for **1**:**1eq** (top) with 3,4-diequatorial substituents, $\omega(C_{2-C3-C1'-C2'}) = -63.09°$ and $\omega(C_{3-C4-O-H}) = 72.23°$; **1axa** (bottom left) with 3,4-diaxial substituents, $\omega(C_{2-C3-C1'-C2'}) = -78.48°$ and $\omega(C_{3-C4-O-H}) = 100.91°$; and **1axb** (bottom right) with 3,4-diaxial substituents, $\omega(C_{2-C3-C1'-C2'}) = -26.11°$ and $\omega(C_{3-C4-O-H}) = 154.43°$.

A thorough conformational search was then conducted, particularly with respect to rotation of the C-3 phenyl and C-4 hydroxyl. The conformational search tool implemented in HyperChem yielded no conformations for the heteroring other than the diequatorially and the diaxially substituted half-chairs. The orientation of the phenyl ring with respect to the heterocyclic moiety is defined by the torsion angle ω(C2−C3−C1′−C2′) while the ω(C2−C3−O−H) torsion angle defines the various *staggered* orientations of the C-4 hydroxy group. It was found that for the diequatorial conformers of both **1** and **2**, only one orientation of the C-3 phenyl ring (ca. −60°) represented local energy minima. For the diaxial conformers of both **1** and **2**, two orientations of the C-3 phenyl were found to represent local energy minima at ca. −80° and −25° (denoted by **axa** and **axb**, respectively, appended to the structure number, see Figure 1). Since the hydroxyl at C-4 can attain one of three *staggered* conformations, each of these orientations was tested to make a total of 9 input structures (3 × 3) for each of **1** and **2**, i.e., all possible combinations of the C-3 phenyl and C-4 hydroxyl alignments were optimized. In three cases (one for **1** and two for **2**), the optimization led to the C-4 hydroxyl adopting a different *staggered* orientation to the starting position and degenerate structures resulted. Of these resulting 15 structures, in one case for **1**, the optimization yielded a transition state structure (one imaginary frequency was found, vide infra) providing a final set of 14 minimum energy structures. Two rotamers with respect to the C-4′ hydroxyl were also optimized for **1**, but the resulting vicinal coupling constants of H-3 were found to be independent of the C-4′ hydroxyl orientation. These rotamers were therefore not considered for further evaluation and the particular orientation of the C-4′ hydroxyl in the structures under consideration is considered irrelevant. It is assumed that a similar result would also be obtained regarding the orientation of the C-7 hydroxyl in **1**. Following optimization, vibrational analysis was performed and only in one case was an imaginary frequency found—leading to that structure being discarded—and which proved that all optimized structures were true minima on the potential energy surface. All spin−spin couplings involving H-3 were then obtained for the optimized geometries by applying a perturbation to this proton. These computational results are summarized in Table 1.

We then searched for the pair of conformers (one diequatorial and one diaxial), the respective coupling constants of which provided the best fit to the observed values of $J_{H-2\alpha,H-3}$ and $J_{H-3,H-4}$ at the different temperatures. By best fit it is meant that the two pairs of couplings $J_{H-2\alpha,H-3}$ and $J_{H-3,H-4}$ in the two selected conformers give consistent agreement with respect to the evaluated mole fractions over a range of temperatures. The mole fractions for the conformers at each temperature were evaluated by means of the equation

$$J_{obsd} = X_{eq} \times J_{ax,ax} + X_{ax} \times J_{eq,eq}$$

where X_{eq} is the mole fraction of the equatorial conformers, $X_{ax} = 1 - X_{eq}$, and $J_{ax,ax}$ represents the coupling between two axially orientated protons (as is the case in the diequatorial conformers), etc.

The equation

$$\Delta G° = -RT \ln K_T = \Delta H° - T\Delta S°$$

where $K_T = X_{eq}/X_{ax}$, was then applied to derive the enthalpy ($\Delta H°$) and entropy ($\Delta S°$) terms. The mole fractions were then recalculated at each particular temperature as determined by these $\Delta H°$ and $\Delta S°$ parameters of the conformational equilibrium and applied to the pairs of best-fit couplings (i.e., the couplings were weighted according to their mole fractions and summed) to obtain couplings which can then be directly compared to the observed values. To distinguish these values from others, they are referred to as the derived coupling constants.

Table 2 lists the observed coupling constants for the protons of the heterocyclic moiety at all temperatures measured together with the derived coupling constants for $J_{H-2\alpha,H-3}$ and $J_{H-3,H-4}$. For each compound, a pair of conformers was found that provided two sets of calculated coupling constants yielding, in each case, excellent agreement such that deviations of the resulting derived *J*s from the corresponding observed values were well under 1% in all but one case. The best fit between the calculated and observed coupling constants was obtained in both cases for the diequatorial conformer with a torsion angle of ω(C3−C4−O−H) ca. 72° and for the diaxial conformer with torsion angles of ω(C3−C4−O−H) ca. 155° and ω(C2−C3−C1′−C2′) ca. −81°, i.e., the very same pair of conformers for each compound **1** and **2** was found to provide very effective values. It is not claimed, however, that the selected pair of conformers used to obtain the derived coupling constants are the sole conformers, or representative of overwhelmingly dominating conformers, in a solution of the diequatorial or diaxial forms. Rather,

TABLE 1. Relative Stabilities, Torsion Angles, and Calculated (and calibrated) H-3 Vicinal Coupling Constants of the Optimized Geometries for the Various Local Minimum Energy Conformers Found for Isoflavanols 1 and 2[a]

structure	ΔE^b (kJ mol^{-1})	$\Delta G°$ [c] (kJ mol^{-1})	$\omega(C_{2-C3-C1'-C2'})$[d] (deg)	$\omega(C_{3-C4-O-H})$[e] (deg)	calcd (and calibrated) vicinal couplings of H-3 (Hz) $J_{H-2\alpha,H-3}$	$J_{H-2\beta,H-3}$	$J_{H-3,H-4}$
1eq	0.00	0.00	−63.09	72.23	**11.56**	3.95	**9.79**
	0.14	0.16	−58.67	−61.22	11.98	3.86	9.19
J_{pwa}[f]					11.77	3.91	9.50
Karplus[g]					11.2		10.5
1axa	4.68	0.06	−78.48	100.91	1.66	3.27	1.41
	3.16	2.12	−80.76	154.00	**1.66**	3.44	**1.75**
	7.95	7.65	−81.16	−69.38	1.92	3.10	1.41
1axb	0.92	1.78	−26.11	154.43	1.33	3.95	2.59
	7.29	8.91	−27.10	−68.85	1.49	3.61	2.17
J_{pwa}[f]					1.58	3.48	1.79
Karplus[g]					1.9	-	1.8
2eq	0.00	0.00	−58.49	−61.82	11.90	3.86	9.36
	−0.06	0.10	−61.91	71.71	**11.56**	3.95	**9.95**
J_{pwa}[f]					11.73	3.91	9.65
2axa	4.50	3.16	−81.57	155.45	**1.66**	3.53	**1.66**
	6.04	3.89	−77.51	93.35	1.66	3.36	1.24
	9.25	9.23	−81.66	−69.43	1.83	3.19	1.24
2axb	1.79	3.61	−23.33	156.04	1.33	3.86	2.51
	8.25	10.12	−23.60	−68.50	1.49	3.61	2.17
J_{pwa}[f]					1.56	3.57	1.81

[a] Numbers in bold are the values found to be the best-fit values for evaluation of the conformational equilibrium (vide infra). The estimated error for the calibrated coupling constants is 0.5 Hz, which is twice the standard error. [b] Relative energies calculated at the B3LYP/6-31G(d,p) level of theory. [c] $\Delta G°$ values were obtained from vibrational analysis calculations by subtraction of the sums of the electronic and thermal free energies. [d] The $\omega(C_{2-C3-C1'-C2'})$ torsion angle defines the orientation of the phenyl group to the heterocyclic moiety. [e] The $\omega(C_{3-C4-O-H})$ torsion angle defines the various *staggered* orientations of the hydroxyl group. [f] The population-weighted average (pwa) of J based on $\Delta G°$ and evaluated separately for the diaxial and diequatorial conformers. [g] The values calculated[3] by application of the Karplus equation[8] on structures optimized using Macromodel[11] or SYBYL[12] programs are shown for comparison.

TABLE 2. Observed, Derived,[a] and Population-Weighted Averaged[b] (pwa) Vicinal and Geminal Couplings of the Heterocyclic Ring for Isoflavanols 1 and 2 over the Temperature Range 173−323 K in CD_3OD

	couplings for isoflavanol **1**[c] (Hz)								couplings for isoflavanol **2** (Hz)							
	$J_{H-2\beta,H-3}$	$J_{H-2\alpha,H-3}$			$J_{H-3,H-4}$			$J_{H-2\alpha,H-2\beta}$	$J_{H-2\beta,H-3}$	$J_{H-2\alpha,H-3}$			$J_{H-3,H-4}$			$J_{H-2\alpha,H-2\beta}$
T (K)	obs	obs	deriv	pwa	obs	deriv	pwa	obs	obs	obs	deriv	pwa	obs	deriv	pwa	obs
323									3.58	8.61	8.61	8.7	7.45	7.48	7.3	−11.18
298	3.54	8.17	8.16	8.3	7.03	7.03	6.9	−11.09	3.60	8.84	8.88	9.0	7.70	7.70	7.6	−11.18
273	3.52	8.42	8.41	8.6	7.22	7.23	7.1	−11.10	3.55	9.17	9.18	9.35	7.93	7.96	7.8	−11.21
248	3.49	8.73	8.71	8.9	7.46	7.47	7.3	−11.11	3.49	9.54	9.50	9.7	8.22	8.22	8.1	−11.27
223	3.41	9.09	9.06	9.2	7.74	7.76	7.6	−11.12	3.57	9.81	9.87	10.1	8.55	8.53	8.4	−11.25
198	3.46	9.50	9.46	9.6	8.05	8.08	7.9	−11.02	3.78	10.22	10.24	10.45	8.73	8.85	8.7	−11.17
173									3.52	10.59	10.61	10.8	9.16	9.15	9.0	−11.01
RT[d]	3.56	8.27			7.05			−11.03								

[a] The derived values are based on the half-chair conformations providing the best-fit values. The values giving the best fit for $J_{H-2\alpha,H-3}$ are 11.56 and 1.66 Hz for both **1** and **2**; for $J_{H-3,H-4}$, they are 9.79 and 1.75 Hz for **1** and 9.95 and 1.66 Hz for **2**. [b] Derived values that are based on the population-weighted average coupling constants. For $J_{H-2\alpha,H-3}$, they are 11.77 and 1.58 Hz for **1** and 11.73 and 1.56 Hz for **2**; for $J_{H-3,H-4}$, they are 9.50 and 1.79 Hz for **1** and 9.65 and 1.81 Hz for **2**. [c] The ^1H NMR spectrum for isoflavanol **1** was not measured at 323 K and was too exchange broadened at 173 K to be amenable to spin analysis. [d] Values measured[3] in acetone-d_6 at ambient temperature.

it is considered that their calculated coupling constants approach the correct limiting values.

Since we believe, however, that a large number of diequatorial and diaxial rotamers are present, and interconversion between them is rapid, we also evaluated the population-weighted averages of the calculated coupling constants (J_{pwa}) for all diequatorial and diaxial subsets of **1** and **2** (see Table 1) to derive the conformational equilibria as described in the above equations. Applying the derived thermodynamic data to the J_{pwa} values provided analogous derived values in the same manner that was performed for the best-fit values to obtain the derived values. These results are also listed in Table 2. The reasonably good agreement provided by the J_{pwa} values lends credence to the evaluation.

The ensuing thermodynamic parameters evaluated for the conformational equilibria in both cases are presented in Table 3. The values of the mole fractions reported[3] previously for isoflavanol **1** are very close to the values obtained here. Of note is the distinct positions of the two equilibria for isoflavanols **1** and **2**, the source of which is not immediately apparent. Although solvent effects, due to practical limitations, were not included in the calculations, nevertheless the fit between the experimental and derived coupling constants for both **1** and **2** is excellent

TABLE 3. Thermodynamic Data for the Conformational Equilibria of 1 and 2

structure, basis	$\Delta H°$ (kJ mol^{-1})	$-\Delta S°$ (J K^{-1} mol^{-1})	$-\Delta G°$(298 K) (kJ mol^{-1})	X eq:ax at 298 K
1, best-fit Js	3.25	5.5	1.60	66:34
1, J_{pwa}	3.2	5.1	1.68	66:34
2, best-fit Js	4.3	6.2	2.45	73:27
2, J_{pwa}	4.6	6.9	2.50	73:27

and even exceeds the accuracy of the experimental coupling constants. Furthermore, there were only negligible differences between the coupling constants extracted from the spectra of **1** obtained with methanol-d_3 as the solvent in comparison to acetone-d_6 (see Table 2). The difference therefore in the conformational equilibria between **1** and **2** might be solely due to inherent structural factors which the calculations have managed to successfully model and not accountable only by solvation. On the other hand, given that the direction of the equilibrium shift is opposite to what is generally observed for various anomeric-type effects whereby electron-withdrawing groups stabilize axial orientations, stereoelectronic effects are not so easily invoked to explain the shift in the equilibrium position.

These coupling constant calculations thus show that improving theoretical methods, together with ever-increasing computational power, further enhances the potential to model conformational equilibria and structures by calculating the crucial coupling constants of suitable minimum energy forms.[9] The results here bear strong testament to the efficacy of the method.

Experimental Section

Computational Method. For the molecular modeling calculations, initial structures were first constructed with the program HyperChem and then pre-optimized utilizing the MM^+ method implemented within that program.[13] The ensuing variety of conformational structures obtained were untangled by using the search tool of HyperChem. The resulting structures were then optimized with the *Gaussian 98W* program package,[14] using density functional theory at the B3LYP/6-31G(d,p) level.[15−19] This level of theory for geometry optimization was previously found to be adequate for the reliable calculation of ^{1}H NMR parameters.[9,20] Vibrational analysis calculations were performed by using 1 bar, 298.25 K, and a scaling factor of 0.9804[21] to verify that all optimized structures are true minima on the potential energy surface and to provide $\Delta G°$ values by subtraction of the sums of the electronic and thermal free energies. For the evaluation of the spin−spin coupling constants, the Fermi contact contribution was calculated by using Gaussian 98W by finite perturbation theory ("Field" keyword) at the spin-unrestricted B3LYP/cc-pVTZ[22] level. Tight SCF convergence criteria were always used.[20,23] A perturbation of 10^{-2} au was applied to H-3 to obtain all couplings to this proton. As previously discussed,[9,20] the calculations of the paramagnetic and diamagnetic spin−orbit terms (PSO and DSO, respectively) were omitted since their addition in the general case leads to a negligible effect because they are of similar magnitude and opposite in sign, at least for the case of homonuclear proton couplings.[9,20,24−27] The spin-dipole (SD) term was not calculated as it is generally known to be negligible and is computationally expensive.[28] Calibration of the calculated coupling constants was then made as described previously[9] by adjusting their value with use of the following equation: $J_{calib} = 1.1169 \times J_{uncalib} - 0.0277$. The equation was obtained as the result of a linear regression analysis ($R^2 = 0.996$) of the plot of the experimental against calculated coupling constants of selected structurally well-defined compounds, including a perhydrocyclopenta[*d*][1,3]-oxazine derivative, two perhydro[1,3]benzoxazine derivatives, furan, *o*-dichlorobenzene, *o*-bromochlorobenzene, 2,4- and 2,5-dichlorophenol, 3a,7a-methano-1*H*-indene, and naphthalene.[9,20] The structures of the calibration compounds were optimized and their coupling constants calculated with the same methodology as described above for **1** and **2**.

***trans*-2,3-Dihydro-7-hydroxy-3-(4-hydroxyphenyl)-4*H*-benzopyran-4-ol** (*trans*-4′,7-dihydroxyisoflavan-4-ol, **1**) was obtained by the reduction of dihydrodaidzein (4′,7-dihydroxyisoflavanone), using an excess of lithium borohydride in THF as previously described.[3] The resulting mixture of *cis*- and *trans*-4′,7-dihydroxyisoflavan-4-ol was separated by preparative HPLC with use of an RP-18 column (C-18, 7 μm, 19 × 150 mm) and isocratic elution (MeOH−H_2O, 48:52). Dihydrodaidzein was obtained by catalytic transfer hydrogenation[29] of daidzein[30] with ammonium formate. ^{1}H NMR δ/ppm: 7.213 (ddd, $J_{H-6} = 8.41$, $J_{H-4} = 0.79$, $J_{H-8} = 0.31$ Hz, H-5); 7.064 (AA′BB′X m, $J_{H-3'(B)} = 8.41$, $J_{H-2'(A')} = 2.75$, $J_{H-3'(B')} = 0.34$, $J_{H-3} = 0.48$ Hz, H-2′); 6.718 (AA′BB′X m, $J_{H-2'(A)} = 8.41$, $J_{H-3'(B')} = 2.34$, $J_{H-2'(A')} = 0.34$, $J_{H-3} = 0.22$ (unresolved, unr) Hz, H-3′); 6.395 (dd, $J_{H-5} = 8.41$, $J_{H-8} = 2.43$, $J_{H-4} = 0.11$ (unr) Hz, H-6); 6.217 (dt, $J_{H-6} = 2.43$, $J_{H-4} = 0.33$, $J_{H-5} = 0.31$ Hz, H-8); 4.734 (br d, $J_{H-3} = 7.03$, $J_{H-5} = 0.79$ (unr), $J_{H-2\alpha} = 0.40$ (unr), $J_{H-8} = 0.33$ (unr), $J_{H-2\beta} = 0.27$ (unr), $J_{H-6} = 0.11$ (unr) Hz, H-4); 4.250 (d(AB)d, $J_{H-2\alpha} = -11.09$, $J_{H-3} = 3.54$, $J_{H-4} = 0.27$ (unr) Hz, H-2β); 4.160 (d(AB)dd, $J_{H-2\beta} = -11.09$, $J_{H-3} = 8.17$, $J_{H-4} = 0.40$ Hz, H-2α); 2.984 (~td, $J_{H-2\alpha} = 8.17$, $J_{H-4} = 7.03$, $J_{H-2\beta} = 3.54$, $J_{H-2'} = 0.48$ (unr), $J_{H-3'} = 0.22$ (unr) Hz, H-3). ^{13}C NMR δ/ppm: 159.20 (s, C-7); 157.46 (s, C-4′); 156.89 (s, C-8a); 131.94 (s, C-1′); 131.04 (d, C-5); 130.09 (d, C-2′); 117.99 (s, C-4a); 116.36 (d, C-3′); 109.64 (d, C-6); 103.39 (d, C-8); 69.90 (d, C-4); 69.33 (t, C-2); 47.73 (d, C-3).

***trans*-2,3-Dihydro-3-phenyl-4*H*-benzopyran-4-ol** (*trans*-isoflavan-4-ol, **2**) was obtained from the reduction of isoflavanone in THF by the dropwise addition of a THF solution of Li(*t*-BuO)$_3$AlH (10 equiv) at 25−30 °C. The reaction was

(11) Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. *MacroModel*, Version 3.1; Department of Chemistry, Columbia University: New York.
(12) *SYBYL*, Molecular Modeling Software, Version 6.1; Tripos Associates, Inc.: St. Louis, MO, 1994.
(13) *HyperChem*, Release 7.0 for Windows; Hypercube Inc.: Gainesville, FL, 2002.
(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 2001.
(15) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098.
(16) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(17) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(18) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.
(19) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. In *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
(20) Bagno, A. *Chem. Eur. J.* **2001**, *7*, 1652.
(21) Foresman, J. B.; Frisch, Æ. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian Inc.: Pittsburgh, PA, 1996; p 64.
(22) Kendall, R. A.; Dunning, T. H., Jr.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
(23) Bagno, A. *Chem. Eur. J.* **2000**, *6*, 2925.
(24) Lazzeretti, P.; Malagoli, M.; Zanasi, R.; Della, E. W.; Lochert, I. J.; Giribet, C. G.; Ruiz de Azúa, M. C.; Contreras, R. H. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 4031.
(25) Onak, T.; Jaballas, J.; Barfield, M. *J. Am. Chem. Soc.* **1999**, *121*, 2850.
(26) Czernek, J.; Lang, J.; Sklenár, V. *J. Phys. Chem. A* **2000**, *104*, 2788.
(27) Sychrovský, V.; Gräfenstein, J.; Cremer, D. *J. Chem. Phys.* **2000**, *113*, 3530.
(28) Helgaker, T.; Jaszunski, M.; Ruud, K. *Chem. Rev.* **1999**, *99*, 293.
(29) Wähälä, K.; Hase, T. A. *Heterocycles* **1989**, *28*, 183.
(30) Wähälä, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005.

quenched by satd aqueous NH_4Cl and the resulting solution extracted with EtOAc. The resulting 66:34 mixture (combined yield 99%) of *trans*- and *cis*-isoflavan-4-ol was separated by flash chromatography over silica gel, yielding **2** as white crystals, mp 97 °C (from *n*-hexanes−Et_2O), lit.[31] mp 98 °C. ^1H NMR δ/ppm: 7.443 (dddd, $J_{H-6} = 7.70$, $J_{H-7} = 1.70$, $J_{H-4} = 0.87$, $J_{H-8} = 0.40$ Hz, H-5); 7.307 (AA′BB′CX m, $J_{H-2'(A)} = 7.78$, $J_{H-4'} = 7.46$, $J_{H-3'(B')} = 1.49$, $J_{H-2'(A')} = 0.58$, $J_{H-3} = 0.15$ (unr) Hz, H-3′); 7.278 (AA′BB′CX m, $J_{H-3'(B)} = 7.78$, $J_{H-2'(A')} = 1.96$, $J_{H-4'} = 1.23$, $J_{H-3'(B')} = 0.58$, $J_{H-3} = 0.46$ Hz, H-2′); 7.235 (AA′BB′C m, $J_{H-3'} = 7.46$, $J_{H-2'} = 1.23$ Hz, H-4′); 7.159 (dddd, $J_{H-8} = 8.24$, $J_{H-6} = 7.26$, $J_{H-5} = 1.70$, $J_{H-4} = 0.62$ Hz, H-7); 6.923 (ddd, $J_{H-5} = 7.70$, $J_{H-7} = 7.26$, $J_{H-8} = 1.19$, $J_{H-4} = 0.21$ (unr) Hz, H-6); 6.789 (ddt (dist), $J_{H-7} = 8.24$, $J_{H-6} = 1.19$, $J_{H-5} = 0.40$, $J_{H-4} = 0.34$ Hz, H-8); 4.907 (br d, $J_{H-3} = 7.69$, $J_{H-5} = 0.87$ (unr), $J_{H-7} = 0.62$ (unr), $J_{H-8} = 0.34$ (unr), $J_{H-2\alpha} = 0.31$ (unr), $J_{H-2\beta} = 0.28$ (unr), $J_{H-6} = 0.21$ (unr) Hz, H-4); 4.309 (d(AB)dd, $J_{H-2\alpha} = -11.18$, $J_{H-3} = 3.61$, $J_{H-4} = 0.28$ Hz, H-2β); 4.263 (d(AB)dd, $J_{H-2\beta} = -11.18$, $J_{H-3} = 8.84$, $J_{H-4} = 0.31$ Hz, H-2α); 3.132 (∼td, $J_{H-2\alpha} = 8.84$, $J_{H-4} = 7.69$, $J_{H-2\beta} = 3.61$, $J_{H-2'} = 0.46$ (unr), $J_{H-3'} = 0.15$ Hz, H-3). ^{13}C NMR δ/ppm: 155.90 (s, C-8a); 141.04 (s, C-1′); 129.97 (d, C-5); 129.91 (d, C-7); 129.67 (d, C-3′); 129.19 (d, C-2′); 128.12 (d, C-4′); 126.88 (s, C-4a); 121.66 (d, C-6); 117.30 (d, C-8); 69.97 (d, C-4); 69.34 (t, C-2); 48.35 (d, C-3).

(31) Chidiak, H.; Kirkiacharian, S. *Arm. Khim. Zh.* **1996**, *49*, 94.

Acknowledgment. Financial support from the Academy of Finland {grant nos. 4284 (K.P.) and 78253 (K.W.)} and from the Emil Aaltonen Foundation (T.J.) is gratefully acknowledged. The assistance of Prof. Alessandro Bagno (Università di Padova), whose advice and guidance with the computational work has been most influential, is also gratefully acknowledged. The authors also thank the Center for Scientific Computing (CSC, Finland) for a generous allocation of computational time.

Supporting Information Available: General experimental information (including description of the NMR) and computational data for all structures (Cartesian coordinates, energies, and the number of imaginary frequencies). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0301200