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PREDICTING HETEROCYCLIC RING COUPLING CONSTANTS THROUGH A CONFORMATIONAL SEARCH OF TETRA-O-METHYL-(+)-CATECHIN

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Abstract–A GMMX[c] conformational search routine gives a family of conformations that reflects the Boltzmann-averaged heterocyclic ring conformation as evidenced by accurate prediction of all three coupling constants observed for tetra-O-methyl-(+)-catechin.

Interest in the conformations of proanthocyanidins (condensed tannins) has grown with the increasing realization that definition of the conformational flexibility of polyphenols is essential to understanding their biological significance as well as their traditional uses such as leather manufacture.[1,2] Early work on the conformational properties of poly(flavans) focused on rotation about the interflavanoid bond[3,4,5] where energy barriers[6,7] are often so high that distinct rotamers are observed in ^{1}H and ^{13}C NMR spectra. Where distinct rotamers were not observed on an NMR time-scale, their rotational dynamics were studied by Bergmann[8] and Cho[9] through analysis of time-resolved fluorescence spectra.

Heterocyclic ring flexing between the A- (axial B-ring) and E- (equatorial B-ring) conformations was first observed by an A-conformation in the crystal structure of penta-O-acetyl-(+)-catechin[10] whereas $^{3}J_{HH}$ coupling in the heterocyclic ring suggested neither an E- nor an A-conformation on an NMR time-scale. Porter[11] further examined flexing of the pyran ring through comparisons of the coupling constants observed for heterocyclic ring protons of a broad spectrum of flavan derivatives. The proportions of A- and E- conformations of these compounds have been estimated by a numeric averaging of the $^{3}J_{HH}$ predicted from various proportions of the optimized A- and E-conformers.[12]

A recent study[13] centered on an evaluation of A-/E- flip of tetra-O-methyl-(+)-catechin starting with the crystal structure and using Tripos (Sybyl 4.1) molecular dynamics calculations. The $J_{2,3}$ coupling constant was estimated by averaging values predicted for the optimized A- and E- conformers weighted in the relative populations of the two conformers. The discrepancy between the molecular dynamics predicted $J_{2,3}$ = 7.3 Hz vs the observed values of 8.1 Hz prompted us to explore a conformational search approach to calculate a family of conformers that, when averaged using the Boltzmann distributions, might more closely predict the time-averaged conformation observed in solution by NMR.

The GMMX 1.0 program[14] was used to search conformational space. This global searching program makes use of the MMX force field of PC-Model[15] and a number of ideas put forth by Saunders et al.[16] The method selected was a combination of the grid and Monte Carlo coordinate searches. The MMX file was set up using PC-Model 486 treating the aromatic carbons as type-40 atoms. No pi calculations were done on the aromatic oxygen atoms. The hydrogen bond

[c]Mention of trade names does not imply endorsement by the U.S. Department of Agriculture.

function and dielectric constant dependence were also investigated. The electrostatic part of the force field was examined using dipole/dipole interactions. Searches were allowed to run until the normal cut-off criteria were reached at a rate of better than one structure per minute.

Search bond variables were established according to the numbering of the tetra-O-methyl-(+)-catechin molecule shown in Figure 1 in both the Equatorial and Axial conformers. The bonds selected as part of the grid search were: the pyran ring bonds C(4)-C(3), C(3)-C(2) and C(2)-O(1), each with 12 degrees of freedom; the C(3)-O(2) with 3 degrees of freedom; C(2)-C(11) with 6 degrees of freedom; and 4 methoxy bonds, C(5)-O(3), C(7)-O(4), C(13)-O(5) and C(14)-O(6) bonds that were restrained to 2 degrees of freedom representing the 0° and 180° orientations. Pyran ring closure angles were left at the default values. Searches were started using both axial and equatorial conformations and allowed to run to the programmed completion. The theoretical number of conformers for compounds with this many degrees of freedom is approximately 1.8×10^5.

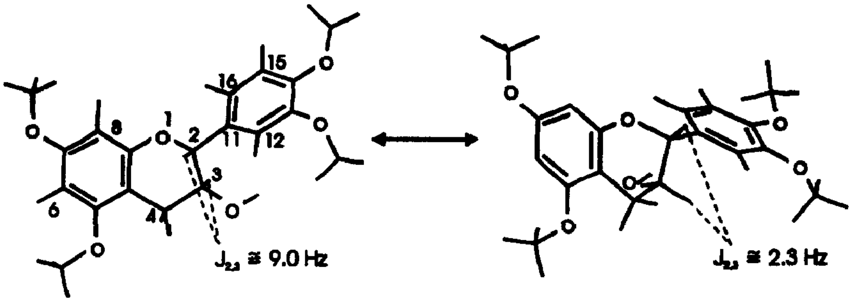

Figure 1. Equatorial-axial conformers with limiting J_{23} coupling constants and atom numbering for tetra-O-methyl-(+)-catechin.

GMMX first searches the conformational space without carbon hydrogens attached. For this phase of the search typically 5000 to 9000 conformers were found. After the energies were ordered and the 3.5 kcal/mol cut-off criteria applied, 900-1400 structures were selected to be re-minimized two times with their carbon hydrogen atoms first deleted and then added, shaking out the conformers that were identical in energy and structure as well as some that were in non-minimum energy states. After this was completed, the file was further re-minimized without shaking the hydrogens until either no more conformers were deleted or the coupling constants did not change. In these last analyses, the Boltzmann populations were determined for the ensemble covering an energy span of 3.0 kcal/mol, and selected torsion angles, coupling constants, and interatomic distances were examined. The vicinal proton coupling constants were Boltzmann-averaged over all of the conformations remaining in ensemble according to Equation 1.

$$< J > = \sum_{i=1} P_i \, J_i \qquad [1]$$

Here J_i is computed within the program by the Haasnoot/Altona equation[17] which has been used previously on this compound.[13] The probability, P_i, of a conformer existing is evaluated from Equation 2 where $\exp(-E_i/RT)$ is the Boltzmann factor with the sum evaluated at 300 °K referenced to $E_1 = 0$.

$$P_i = Exp\left(-E_1 \,/ RT\right) / \sum_{i=1} Exp\left(-E_1 / RT\right) \qquad [2]$$

Table 1 shows the variation of the searches with different starting conditions. What is striking is how well the proton coupling constants are reproduced. Although starting with different initial structures gives slightly different ensembles, the overall average properties agree very well with the experimental results. Note that the sets with the OH hydrogen bonding appear to give the best results. The $J_{2,3}$ values agree much better with the experimental value than that calculated ($J_{2,3}$= 7.3 Hz) with molecular dynamics. It should be pointed out here that earlier[13] coupling constant calculations have assumed a molecular distribution in just two average states. One state represents an average A- and the other represents an average E-conformer.

Table 1. GMMX search results on tetra-*O*-methyl-(+)-catechin.

	Conformational Search						
Parameters	EQ., ϵ=1.5 HBOND ON	EQ., ϵ=4.0 HBOND ON	EQ., ϵ=1.5 HBOND OFF	EQ., ϵ=4.0 HBOND OFF	AX, ϵ=1.5 HBOND ON	AX, ϵ=1.5 HBOND OFF	Observed
Total number[a]	8540	4957	9058	7935	3569	5188	
Unique	924	943	1424	1371	846	872	
Final ensemble[c]	376	347	425	428	369	395	
E_{MIN}, kcal/mol	32.10	32.45	31.91	32.34	31.95	32.39	
$J_{2,3}$	8.15	8.16	7.68	7.68	8.16	7.87	8.1
$J_{3,4,\ equatorial}$	5.25	5.20	5.06	5.05	5.24	5.12	5.5
$J_{3,4,\ axial}$	9.84	9.88	9.33	9.33	9.86	9.53	9.0

[a]The total number of conformers found during the search.

[b]The number of unique conformers kept without carbon hydrogens attached within a 3.5 kcal/mol window.

[c]The final ensemble of conformers with carbon hydrogen attached within a 3.0 kcal/mol window.

Figure 2 shows the conformational distribution of the C(2)-C(3) torsional angles collected within a 3.0 kcal/mol window of energy and Figure 3 shows the conformational torsion angle distribution for the C(2)-C(11) bond for the B-ring. It is interesting to compare Figure 2 with molecular dynamics results using the Sybyl force field recently published by Mattice.[13] The data reported here represent more narrow distributions of angles for C(2)-C(3) centered around 178° and 293° than was observed using molecular dynamics. The narrow representation of the plot arises partly from the "tight" torsional constants and the energy cut-off use; however, the average center of 293° found in this study is substantially different from the 300° found in the earlier study[13]. Figure 3 shows the C(2)-C(11) bond torsion distributed over a wide range.

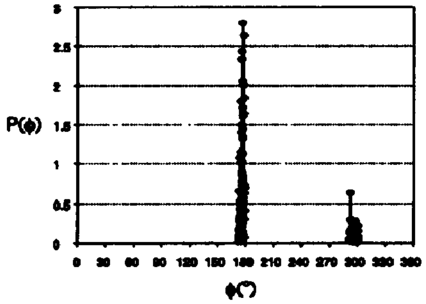

Figure 2. GMMX predicted populations (%) of C(2)-C(3) torsional angles.

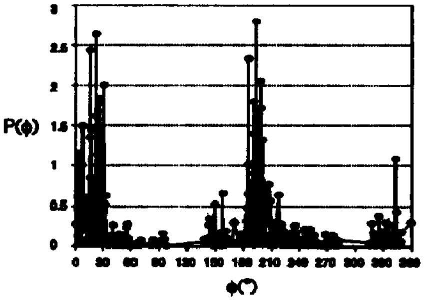

Figure 3. GMMX predicted populations (%) of C(2)-C(11) torsional angles.

In conclusion, this study describes a method for generating a reasonable representation of the NMR solution proton coupling constants for flavans, and suggests that it is better to determine the axial/equatorial physical properties by making use of a Boltzmann sum over the total conformational ensemble rather than assuming a distribution of time spent between axial and equatorial conformer idealized states.

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