



Dedicated to Professor Alexandru T. BALABAN
on the occasion of his 90th anniversary

PROGRAM FOR PREDICTION DIHEDRAL ANGLE FROM VICINAL COUPLING CONSTANT WITH 3-SPHERE APPROACH

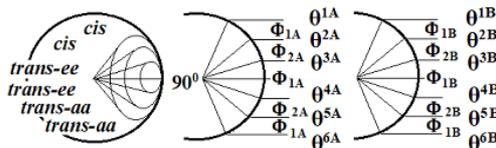
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3-Sphere approach is applied on prediction dihedral angle $\theta_{\text{HnHn+1}}[\text{deg}]$ only from vicinal coupling constant ${}^3J_{\text{HnHn+1}}[\text{Hz}]$ with Java script, in comparison with angles calculated from the differences between two atoms of carbon chemical shift ($\Delta\delta_{\text{CnCn+1}}[\text{ppm}]$) and Karplus equations. The trigonometric equations 1, 2 ensuring the right sign along the D-, L series rule.



$$\begin{aligned}\sin^{-1}\cos(\theta^{\text{nB}}) &= \theta^{\text{nA}} \\ \theta^{\text{nB}} &= f({}^3J_{\text{HH}}[\text{Hz}]) \\ \theta^{\text{nA}} &= \theta_{\text{HnHn+1}}[\text{deg}] \\ n &= 1-6\end{aligned}$$

INTRODUCTION

Karplus is a general method¹ for the calculation of the dihedral angle ($\theta_{\text{HnHn+1}}[\text{deg}]$) from vicinal coupling constant (${}^3J_{\text{HnHn+1}}[\text{Hz}]$) using the valence bond theory,^{2,3} equation optimized and/or particularized by other.^{4,5} The degree of non-planarity can be determined accurately from knowledge of the torsional angles⁶ using models for pseudorotation.⁷ In this paper we proposed 3-sphere approach for prediction of the dihedral angles only from vicinal coupling constant with the hypersphere trigonometric eq. 1, equation which gives information about the sign of the predicted dihedral angle, ensuring a good correlation between dihedral angle and vicinal coupling constant.

3-Sphere approach, a method in three steps:
1. Two characteristic angles are calculated from

NMR data; 2. Construction of the units with seven sets angles; 3. Calculation of the dihedral angles having right stereochemistry and sign with hypersphere equation.⁸ The higher number of angles under seven set unit rule is drastically reduced with the prediction program.

RESULTS

Geometric spatial distribution of two protons with *cis*- or *trans*-stereochemistry on HCC'H' fragment is represented on three concentric cones, where six possible angles (θ^{nA} , $n = 1 - 6$) have two characteristic angles ϕ_1 and ϕ_2 , relative to three arbitrary points P_1 - P_3 (Fig. 1). 3-Sphere is a higher dimensional space, analogue to a sphere with four charts, where each chart is part of the circle to an open interval, and together cover the whole circle. Six dihedral angles can be place in west and east,

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up and down, relative to ± 90 [deg], on three concentric circles, 2D projective plane of 2-manifold, occurring twelve positive and negative angles. As going from north to south, values of the torsional angles are placed up on three concentric cones, with angles $2x\theta^{\text{cis}}$, $2x\theta^{\text{cis}}$, $2x\theta^{\text{trans-ee}}$, and down three concentric cones, with angles $2x\theta^{\text{trans-aa}}$, $2x\theta^{\text{trans-aa}}$, $2x\theta^{\text{trans-ee}}$. Three concentric cones having the angle of the first cone ϕ_1 , second angle $\phi_1 + 2\phi_2$, and third angle $3\phi_1 + 2\phi_2$, in east side as well as on west side (Fig. 1), six plus two meridian and longitudinal circles, mimic of the Root system-Lie group.⁹

In other representation, in set A are placed angles θ^{nA} and in set B angles half ϕ_{1A} and ϕ_{2A} of set A, namely θ^{nB} of set B, with $n = 1-6$. Sets A and B are in close relationships with set C through ϕ_2 of set A ($\phi_{2A} = \theta^{1C}$, $\phi_{2B} = \theta^{1C \text{ or } 2C}$). Tessellation of the spherical coordinates $\sin\theta^{\text{nA}} = R_m = \cos\theta^{\text{nB}}$ leading to the hypersphere trigonometric equation I. Translation from 4D to 3D point out through

three sets of angles, and hypersphere trigonometric equation. R^4 is a complex C^2 with Hopf coordinate or quaternion (H),⁹ Euler's analog.

$$\text{Eq. 1: } \sin^{-1}(\cos\theta^{\text{nB}}) = \theta^{\text{nA}},$$

where ${}^3J_{\text{HH}} = f(\theta^{\text{nA}}, \phi)$: with $n = 1-6$, and $\phi = f(\phi_1/2, \phi_2)$, or ${}^3J_{\text{HH}} = f(\theta^{\text{nA}}, \theta^{\text{nB}})$: with $n = 1-6$, and $\phi = \theta^{\text{nB}}$; *cis* stereochemistry: $\theta^{\text{nB}} = (2x{}^3J_{\text{HH}}^{\text{cis}})^2$, *trans* stereochemistry: $\theta^{\text{nB}} = ({}^3J_{\text{HH}}^{\text{trans}})^2$, and θ^{nA} the predicted dihedral angle with right stereochemistry and sign.

In Table 1 are compared dihedral angles of iminocyclitols¹⁰ **1**, **2** and α -, β 5-iodo-methyl-D-ribofuranoses¹¹ **3a,b** (Figure 2), predicted only from ${}^3J_{\text{HnHn+1}}$ with 3-sphere Java script program, with dihedral angles calculated from the differences between two atoms of carbon chemical shift with hypersphere trigonometric^{12, 13} eq. 2. and Karplus equations^{2,3,5} (K1-K3).

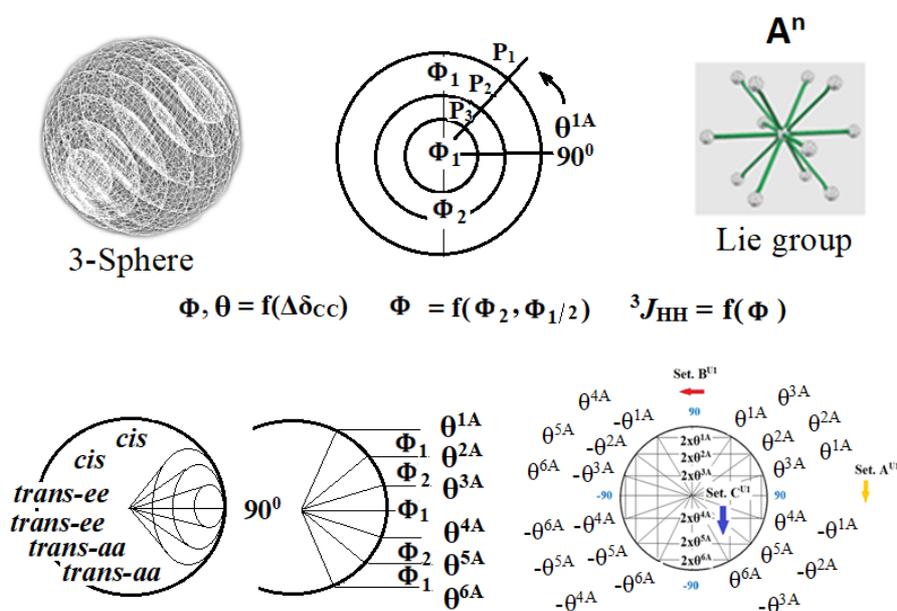


Fig. 1 – Dihedral angles with *cis*-, *trans* stereochemistry on 3-sphere and Lie group theories.

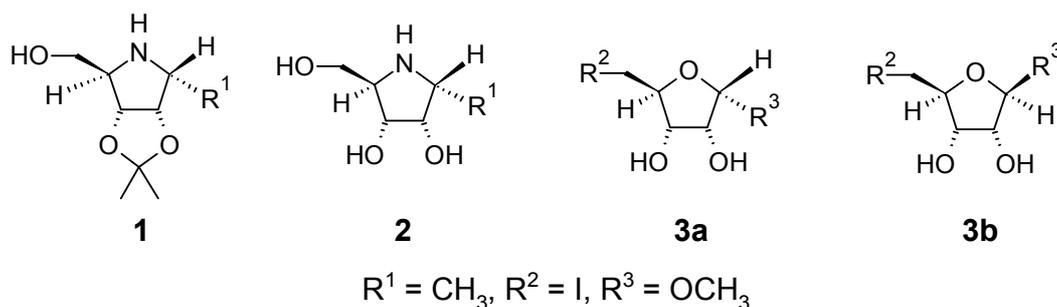


Fig. 2 – Iminocyclitols **1**, **2** and α -, β 5-iodo-methyl-D-ribofuranoses **3a,b**.

Table 1

Dihedral angles θ^{nA} [deg] predicted with Java script program in comparison with angles calculated from the differences between two atoms of carbon chemical shifts $\Delta\delta_{CnCn+1}$ [gauss] and Karplus eq. K1-K3.

Entry	H _n H _{n+1}	$^3J_{HH}^{exp}$ [Hz] ^c	θ^{nB} [deg] ^a	θ^{nA} [deg] ^a	$\Delta\delta_{CnCn+1}$ [gauss] ^{b,c}	$\theta_{HH}^{eq,2}$ [deg]	θ_{HH}^{K1} [deg]	θ_{HH}^{K2} [deg]	θ_{HH}^{K3} [deg]
1.	<i>Cis</i> : H ₁ H ₂ 1	4.1	67.24	22.76	0.7759	ea ^{6,1} : 20.88	44.12	54.83 ^g	48.31
2.	<i>Cis</i> : H ₂ H ₃ 1	5.4	116.64	-26.63	0.0224	ae ^{6,1} : -28.71	35.16	59.80	37.59
3.	<i>Trans</i> : H ₃ H ₄ 1	0	0	90.00	0.5154	ee ^{4,1} : 91.02	80.11	75.26	69.63
		0.5 (bs)	0.25	90.25			90 ^{*eq.K1}		
4.	<i>Cis</i> : H ₁ H ₂ 2	3.1	38.44	51.55	0.3249	ae ^{5,2} : 51.73	50.90	50.05 ^g	57.02
5.	<i>Cis</i> : H ₂ H ₃ 2	3.9	60.83	29.15	0.0560	ea ^{6,1} : 26.78	45.47	54.97	49.99
6.	<i>Trans</i> : H ₃ H ₄ 2	8.8	77.44	-167.4 ^g	0.1375	aa ^{6,1} : -168.9 ^g	132.13	167.70	137.7
7.	<i>Cis</i> : H ₁ H ₂ 3a^e	3.0 ^d	36	53.99	0.8102	ea ^{5,2} : 54.24	51.59	49.53 ^h	57.96
8.	<i>Cis</i> : H ₁ H ₂ 3a^f	6.0 ^d	144	-53.99	0.8057	ae ^{5,2} : -53.68	30.73	57.52	32.43
9.	<i>Trans</i> : H ₃ H ₄ 3b^e	6.0 ^d	36	-126 ^{g,1}	0.19047	aa ^{5,2} : -125.5 ^g	155.6 ^j	177.52 ^j	152.42 ^j

a. Bcisd or Btransd, Acisd or Atransd, b. $\Delta\delta_{CnCn+1}$ [gauss] = 0.0280118x $\Delta\delta_{CnCn+1}$ [ppm], c. **1**-CDCl₃, **2**-D₂O, $^3J_{HH}$ 400MHz, δ_{Cn} 75MHz,¹⁰ d. **3**-CDCl₃, $^3J_{HH}$ 300MHz,¹¹ e. PPh₃:I₂:imidazole = 2:1:2, HF, reflux, 2h, 48%, α : β 1:5.33, 3:0 [Hz], f. PPh₃:I₂:imidazole = 2:1:2, THF, MW, 20min, 17%, α : β 1.6.39, 6:0 [Hz], g. sign under D-serie rule, h. *trans-ee*^{3,2} 70.46, i. eq. 1: $\sin^{-1}\cos(36) = 54$, *cis*→*trans*: $180 - 54^{2A} = 126^{5A}$, eq. 2: $\cos^{-1}\sin(126) = 36$, $(36)^2 = 6$ [Hz], j. *trans-aa*^{6,1} (120 + *cis*) or *trans-ee*^{3,2} (120 - *cis*), instead of *trans-aa*^{5,2} (probably 180 - *cis*).

Eq. 2:^{12, 13} $\cos^{-1}(\sin\theta^{nA}) = (\theta^{nB})^{1/2}/m = ^3J_{HH}$,
where $m = 2$ *cis*, $m = 1$ *trans*,

Eq. K1:² $^3J_{ab} = J^0 \cos^2\theta_{HH} - 0.28$ ($0^\circ < \theta_{HH} < 90^\circ$),
 $^3J_{ab} = J^{180} \cos^2\theta_{HH} - 0.28$ ($90^\circ < \theta_{HH} < 180^\circ$);
 $^3J_{ab} = J^0 \cos^2\theta_{HH}^*$,

Eq. K2:³ $^3J_{ab} = 1.1 + 17 \cos^2\theta_{HH}$,

Eq. K3:⁵ $^3J_{ab} = 7.76 \cos^2\theta_{HH} - 1.10 \cos\theta_{HH} + 1.40$.

DISCUSSION

Using 3-sphere, a hypersphere in 4-dimensional space, and Lie group theories three

sets of angles (A, B, C) are comprise on one circle (Fig. 1). The angles of set A are in close relationships with angles of sets B and C, since half ϕ_{1A} is equal with θ_{1B} and ϕ_{2B} with θ_{1C} . Three sets of angles mimic of translation from 4D to 3D, extended to other two pair of angles giving the unit with seven set angles, with θ^{1A} and θ^{1B} equals with ϕ_{2CA1} and ϕ_{2CA2} . The *cis*-, *trans-ee*^{4,1} and *trans-aa*^{5,2}, *-aa*^{6,1} stereochemistry results from seven sets unit and *trans-ee*^{3,2} stereochemistry from shadow of seven sets unit, totally 14 sets ensuring the right stereochemistry and sign along trigonometrics equation 1 and 2 (Fig. 3).⁸

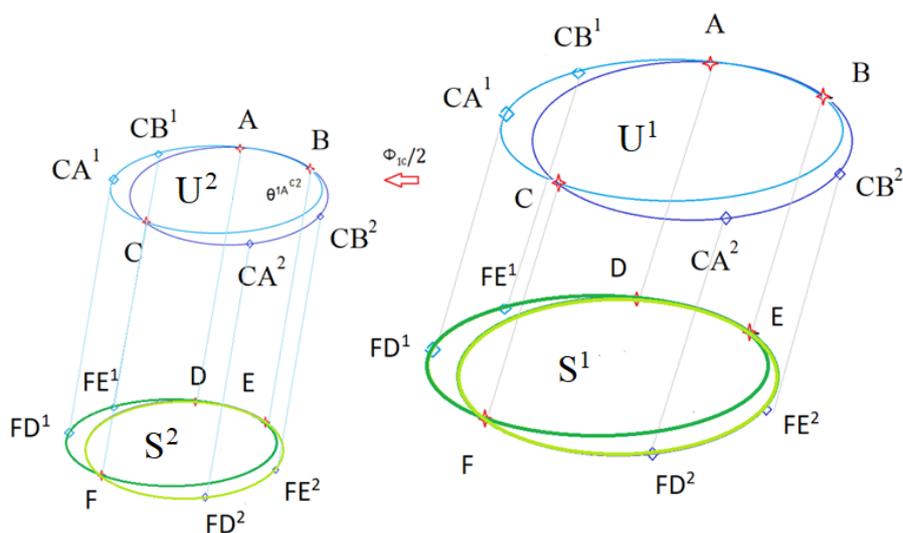


Fig. 3 – Seven sets unit (U^N : A, B, C, CA1, CB1, CA2, CB2) with corresponding shadow sets (S^N : D, E, F, FD1, FE2, EF1, EF2).

The number of units can be increased through half ϕ_1 of set C, until the last unit (U^N) is almost equal with first unit (U^1). The shadow sets unit (S^N) follow same rule as seven sets unit (U^N) or the *trans-ee*^{3,2} rule, where the differences between ϕ_{2N} and half ϕ_{1N} (with N: A, B, C, CA1, CB1, CA2, CB2) is equal with first angle of corresponding shadow set ($\theta^{1DS} = \phi_{1AU}/2 - \phi_{2AU}$).⁸

Iminocyclitols¹⁰ **1**, **2** and α -, β -5-iodo-methyl-D-ribofuranoses¹¹ **3a,b** (Fig. 2) are selected for demonstrating the performances of the method, since $^3J_{HnHn+1}$ of sugars **1-3** cover few representative problems: the sign of dihedral angles, the case of vicinal constant couplings of 0 and 8.8[Hz], and the *cis/trans* stereochemistry results from $^3J_{HnHn+1}$ of 6[Hz]. Predicted angles only from $^3J_{HnHn+1}$ [Hz] have differences of ~ 2 [deg] relative to angles calculated from $\Delta\delta_{CnCn+1}$ [gauss] (Table 1). The calculated angles are found in unit 1, excepting θ_{H1H2} (**2**) with 53.78[deg], 3.03[Hz] in unit 1 and 51.73[deg], 3.09[Hz] in unit 2.⁸

The sign of the dihedral angle predicted with Java script program (Table 1, Entry 1 and 2) is positive for 4.1[Hz] (22.76[deg]) and negative for 5.4[Hz] (-26.63[deg]). Under the D, -L series rule the sign of θ_{H3H4} is negative, since for positive or negative *trans-aa*^{6,1} dihedral angle (Table 1, Entry 6) with eq. 1 the sign⁸ is under cylindrical algebraic decomposition algorithm (CAD): $(-X)^{1/2} = +/-Y$, and with eq. 2 for negative angle (-167.43[deg] *trans-aa*^{6,1}) the value of the calculated $^3J_{HH}$ increased at 10.25[Hz], relative to 8.8[Hz] for positive *trans-aa*^{6,1} angle.

Two representative values are observed for a vicinal constant coupling of 0[Hz], 90 and 69[deg] (Table 1, Entry 3), the last one calculated with eq. K3 claim that the +/-120 rule between dihedral and torsional angle (*trans/cis*) must be replaced with "A, B, C sets rule". In this light, eq. K1-K3 for a vicinal constant coupling of 6[Hz] under 180 rule have the stereochemistry in agreement with trigonometric eq. 2 (Table 1, Entry 9. *i.e.* 180 - 57.52 = 122.48[deg] *trans-aa*^{5,2} relative to 120 + 57.52 = 177.52[deg] *trans-aa*^{6,1}). Under shadow unit rule an angle around 69[deg] in U^1 becomes 87[deg] in S^1 ($\cos^{-1}\sin(\theta^{1D}) = \theta^{3S1}$, $\theta^{1D} = \phi_{1A}/2 - \phi_{2A}$).⁸ Inadvertence between *trans-ee*^{6,1} and *trans-ee*^{5,3} stereochemistry (Table 1, Entry 6) result also with Karplus equations K1-K3 in case of $^3J_{HH}$ 8.8[Hz]. The values of J_{vic} for $\phi = 90^\circ$ are very small, and is probably reasonably to ignore the constant of 0.28 in organic chemistry application.¹⁴

Selective iodination of α - and β -methyl D-ribofuranoses¹¹ (**3a,b**), having ratio of anomers 0.50:0.45, and coupling constants $\alpha:\beta$ 3:0[Hz], with iodotriphenylphosphonium iodide complex [Ph_3P+I-I^-] generated in situ, gives different vicinal coupling constants: 3:0[Hz] under reflux and 6:0[Hz] under microwave. Predicted and calculated dihedral angles of -53.99, -53.68[deg] (Table 1, Entry 8) and 126.0, 125.50[deg] (Table 1, Entry 9) with *cis* or *trans* stereochemistry results for a vicinal coupling constant of 6[Hz], relative to positive angles with *cis* stereochemistry 53.99, 54.24[Hz] for a vicinal coupling constant of 3[Hz] (Table 1, entry 7). *Cis* stereochemistry¹¹ was established for $^3J_{HH}$ of 6[Hz] based on recorded carbon chemical shift (δ 102^a and 109^b[ppm]), confirmed by molecular models, in agreement with a good correlation between eq. 1 and eq. 2, out of +/-120 rule.

EXPERIMENTAL

The program for prediction dihedral angle only from recorded $^3J_{HnHn+1}$ with 3-sphere approach can be obtained from the authors (cmitan@yahoo.com, petrufilip@hotmail.com). Java script code^{15,16} and Notepad++ are used for realization of the program. In the explorer prompt windows (Script Prompt) are introduced the vicinal coupling constants in Hz for *cis* or/and *trans* stereochemistry, one of them can be omitted, and instead of $^3J_{HH}$ value is write "undefined". Angles Bcisd, Acid or/and Btransd, Atransd are displayed on webpage, and the alert message Hello World! must be closed. Dihedral angles are Acid and Atransd[deg], and corresponding vicinal coupling constants ($^3J_{HH}^{cis}$, $^3J_{HH}^{trans}$ [Hz]) results from angles Bcisd and Btransd[deg]. The vicinal coupling constant for *trans-ee* stereochemistry will be introduced in *cis* explorer prompt windows.

CONCLUSIONS

The hypersphere trigonometric equation 1 ensures prediction of the dihedral angles only from vicinal coupling constant with right stereochemistry and sign, two factors with great importance in calculation of the conformation and configuration. Models for calculation the conformation, the phase angle of the pseudorotation (P[deg]) and the angle of deviation from planarity (θ_m [deg]), used three torsional angles or two torsional angles.⁷ The higher number of angles under seven set unit of 3-sphere approach can be reduced with eq. 1 to an approximated value with differences around 2[deg], following by the identification all the angles with calculated vicinal

coupling constant almost equal with recorded one in U^N ($N = 1, 2, 3, \dots, n; n \sim 1$). A program for calculation of the dihedral angles from NMR data with 3-sphere approach is under work. The vicinal coupling constant can be predicted with eq. 2 from dihedral angle obtained from X-ray or other method.

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