Dedicated to the memory of Professor Sorin Roşca (1938–2021)

RECTANGLE AS MANIFOLD ON RELATIONSHIPS BETWEEN VICINAL CONSTANT COUPLINGS $^3J_{HH}$, ^{1}H, ^{13}C-CHEMICAL SHIFTS AND DIHEDRAL ANGLES

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Dihedral angles with right sign and stereochemistry are calculated with 3-sphere method in four steps having as main manifold equations the rectangle geometries, skew or middle lines transformed in circles. Non-coplanar Villarceau circles (eq. 4) gives better result for all stereochemistry of iminocyclitols **1**-**5**, since middle (eq. 6) and antirectangle circles (eq. 7) are the best solution for vicinal coupling constants $^3J_{HH}$[Hz] of 3.1 (**2**-*cis*-D-H_1H_2), 4.8 (**3**-*cis*-L-H_1H_2) and 5.4 (**1**-*cis*-D-H_2H_3), 5.2 (**4**-*cis*-L-H_2H_3). Results pointing out the influence of carbon and proton chemical shift δ[ppm] on calculation of the dihedral angle θ_{HnHn+1}[deg] in close relationships with vicinal coupling constant $^3J_{HH}$[Hz], through the vicinal angle ϕ [deg].

$$\theta^{An} = 2x[(\Delta\delta_{HnHn+1} \text{ x } \Delta\delta_{CnCn+1})/2)x90]^{1/2}: \text{n=2, } cis\text{-}ea, ae, trans\text{-}ee$$

$$\theta^{An} = [(\Delta\delta_{HnHn+1} \text{ x } \Delta\delta_{CnCn+1})/2)x90]^{1/2}: \text{n=1, } trans\text{-}aa^{6,1}$$

$$\theta^{An} = 2x[90x(\Delta\delta_{HnHn+1} + \Delta\delta_{CnCn+1})/2]^{1/2}, \text{n=2, } cis\text{-}ea, \text{-}ae, trans\text{-}ee$$

$$\theta^{An} = [90x(\Delta\delta_{HnHn+1} - \Delta\delta_{CnCn+1})/2]^{1/2}, \text{n = 1, } trans\text{-}aa^{6,1}$$

INTRODUCTION

The shape of the universe, 3-manifold locally reassembles Euclidean 3-dimensional space.[1] A point increasing to a circle is transformed to a torus,[2] able to undergo homotopy,[3] continuum transformation from torus to rectangle (Fig. 1). The intersection of a torus with a plane gives polar curvatures, class of the spiric section, the inverse of the conic section.[4] I. Conic section with centre of inversion at one focus: ellipse, hyperbola, parabola having as invers of the conic limaçons with no loop, cardioid, limaçons with inner loop. II. Ellipse or hyperbola with centre of inversion at vertex: Conchoid of the Sluze and Cissoid of Diocles. III. Ellipse and hyperbola with

centre of inversion at the centre: hippopede, lemniscate of Bernulli.[5]

Topologically a ring torus is homeomorphic to the cartesian product of two circles: $T^2 = S^1xS^1$, a compact 2-manifold of genus 1. Each distinct point of the two-sphere comes from a distinct circle of the three-sphere. Every point on the two-sphere produces a fiber that is a circle. Torus in 2D is a product of two circles – a modified version of the spherical coordinates system – having toroidal and poloidal coordinates, with cylindrical coordinates (and helices as geodesics), a limit case of the conic. Other pair of two torus circles result by cutting a torus oblique trough the center, namely Villarceau circles.[1,2]
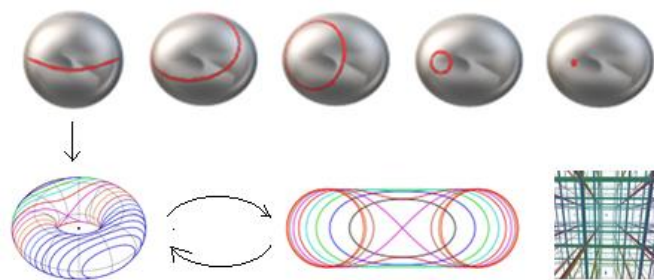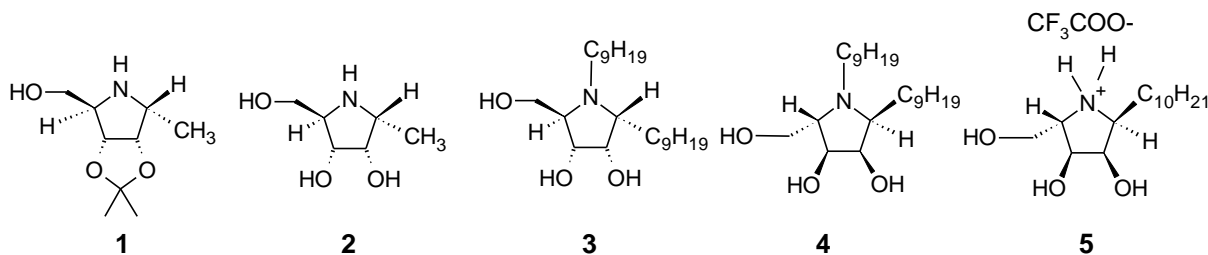
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Fig. 1 – 3-Sphere model: 4D-projiection to 3D-dimension.

Fig. 2 – Iminocyclitols with α-D-ribitol (**1-3**) and β-L-ribitol (**4**, **5**) stereochemistry.

The dihedral angle of the five membered rings can be calculated empiric from the difference(s) in chemical shifts between two atoms of carbon and/or two protons in close relationships with vicinal constant coupling ($^3J_{HH}$) using a 3-sphere model and cyclide cycles:[6-8] torus-conic section, rectangle, quaternion coordinate and Villarceau circles.

RESULTS AND DISCUSSION

The rectangle geometries disclosed in this paper, respectively the trapezoid and anti-trapezoid with two or all unequal (irregular) sides relative to Bennett linkage,[9] a parallelogram with vertices on a tetrahedron. The shape of the folding of a single stranded DNA viral genome in 3D nanostructures, designed to be motion controlled.[10]

$^3J_{HH}$ scalar coupling constant calculated from 2D ^{1}H-^{1}H COSY[11] or 3D HCH-COSY.[12] The protein Capsid(1-48)*, *N*-terminal region of the nucleocapsid of the hepatitis C virus, 57th amino acid fragment, was analyzed with pulse sequence involving the PARADISE acquisition, a selective 2D-NMR correlation (COSY) spectra.[13] Constraints of the deoxyribose dihedral angles in DNA are determined with 3D ^{13}C-resolved in-phase [^{1}H-^{1}H]-COSY (3D HCH-COSY), yielding $^3J_{HH}$ from intensity ratio of ^{13}C-resolved ^{1}H-^{1}H diagonal peaks and cross peaks.[12]

Iminocyclitols[14] (Fig. 3) with α-D-ribitol **1-3** and β-L-ribitol **4**, **5** stereochemistry are members of a series of pyrrolidine bearing side chain at *N*- and/or at C_1, synthesized *via exo*-amino-*L*-lyxose to *endo*-imino-*D*-ribitol rearrangement with inversion of stereochemistry at C_4, and tested on the BVDV, surrogate for hepatitis C virus (HCV). 2D NMR correlation spectroscopy COSY and HMQC were used for accurate attribution of the proton and carbon chemical shifts of the iminocyclitols **1-5**. The constant couplings of **1-5**, chosen for demonstrating the accuracy of the methods, cover representative values for *cis* and *trans* stereochemistry.[15]

The vicinal coupling constant $^3J_{HH}$[Hz] is the most useful NMR data for calculating dihedral angles,[16] integer in conformational[17, 18] and configurational analysis.[19] The main advantages of Karplus equations, only from the vicinal coupling constant can be calculated dihedral angles from two equations or one equation,[16] then must be applied the sign rule, Hlyne-Prelog-Bucourt-Eyring: "The torsional angle is positive if the bond in front has to be turned clockwise in order to eclipse the rear bond",[20] Hendricksons,[21] or Toromanoff,[22] then transformed into exocyclic torsional angles.[23] The sign of the endocyclic torsional angles calculated with Karplus polynomial has been established by Altona and Sunderalingam, in case of ribose stereochemistry on mononucleosides and nucleotides.[24]

3-Sphere method enable: 1. the calculation of the dihedral angles with right sign and stereo-chemistry, 2. offer a higher number of manifold equations for every interval of vicinal coupling constant, 3. in the absences of one of NMR data (proton $\delta_{H_nH_{n+1}}$ or carbon $\delta_{C_nC_{n+1}}$ chemical shift [ppm]) exist alternatives.[8, 25]

From the vicinal coupling constant $^3J_{HH}$[Hz] point of view, two protons with *cis-* or *trans*-stereochemistry on HCC'H' fragment can be drowning on two intersecting disks (Fig. 3), were the dihedral angle and the vicinal angle, an angle result from the vicinal coupling constant $^3J_{HH}$[Hz], are in close relationship. Hopf fibration describe 3-sphere as circles on 4D and 2-spheres as points on 3D, such as each distinct point of 2-sphere is mapped from a distinct circle of 3-sphere. A theory highlighting in our case the direct relationships between dihedral angle ($\theta_{H_nH_{n+1}} = \theta^{An}$) and vicinal angle ($\phi = \theta^{Bn}$), considering the angle θ^{An} a point of set A equal with a sum or differences between two angles (two points) of set B ($\phi_B = f(\phi_{2B}, \phi_{1B/2})$). With trigonometric equation (Eq. 1) can be calculated both angles each from other, and with algebraic equation[6] the vicinal angle ϕ[deg] followed by the corresponding vicinal coupling constant. The trigonometric equation fit well with algebraic equation[6] if dihedral angle with *cis, trans* stereochemistry and corresponding vicinal angle are drown on six sets angles on two units (**U1**: A, B, C; D, E, A; F, G, B and **S1**: A, B, C; D, E, A; F, G, B)[8], two pair of Venn diagrams with three sets of angles. Six dihedral angles with *cis, trans* stereochemistry on three concentric cons reassembles one set angles. The first angle of set A is equal with half ϕ_1 of set B and first angle of set B equal with half ϕ_1 of set A, ϕ_2 of sets A and B equal with first and second angles of set C, totally three sets angle on one unit, a hypersphere in 4D. Angles around 69-70[deg] indicated unit U1 and around 60-64[deg] unit S1. Characteristics for unit U1 are dihedral angles with *trans-ee*[4,1] stereo-chemistry and for unit S1 angles with *trans-ee*[3,2] stereochemistry. Extinction at three pair of Venn diagrams on seven sets unit can be made through the first angles of sets A and B equals with ϕ_2 of sets D and F (Fig. 3).[8]
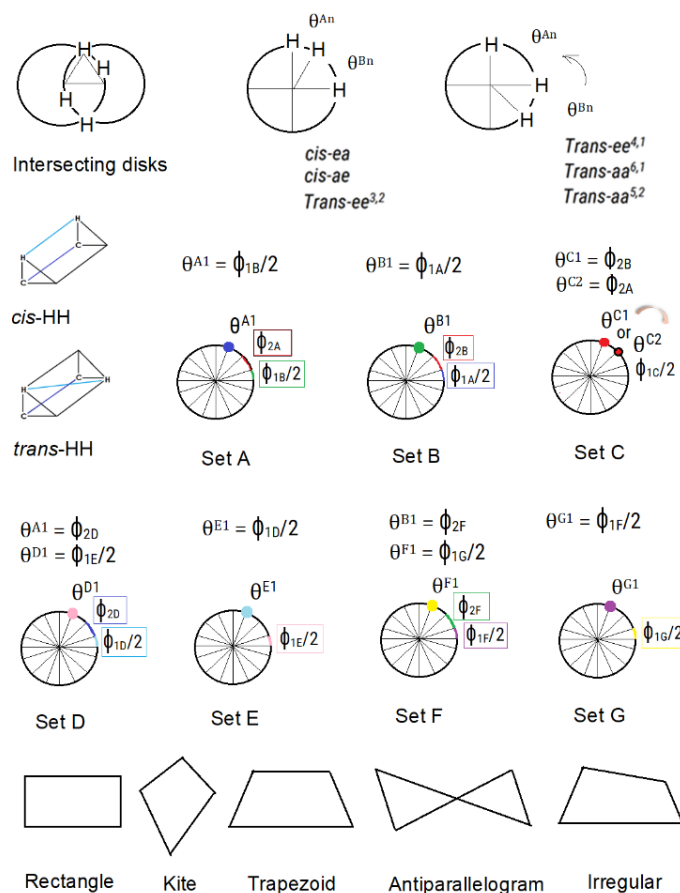

Fig. 3 – Dihedral and vicinal angles ($\theta_{H_nH_{n+1}} = \theta^{An}$, $\phi = \theta^{Bn}$[deg], n = 1-6) under seven sets angles rule. Rectangle representation and its corresponding geometric forms.

Table 1

Dihedral angles calculated with 3-sphere-rectangle method

Entry	H_nH_{n+1}	$^3J_{HH}{}^{exp}$ [Hz][a]	θ^{pred} [deg]	$\Delta\delta_{CnCn+1}$ $\Delta\delta_{HnHn+1}$ [ppm][a]	θ^{An} [deg]	$\theta_{HnHn+1}{}^{b}$ [deg]	$^3J_{HH}{}^{calc}$ [Hz]	Manifold equations[c]
1.	**1**-*Cis*: H_1H_2	4.1	22.76	27.7 1.41	83.84 2.14 59.46	ea[6,1]: 23.84[U1A1] ea[6,1]: 21.43[U1C1] ea[6,1]: 20.35[U1C1]	4.06 4.14 4.17	$\Delta\delta_{CnCn+1}*\Delta\delta_{HnHn+1}$ $1/\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$ $\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$
2.	**1**-*Cis*: H_2H_3	5.4	-26.63	0.8 0.11	12.79 11.14	ae: -26.02[S1B1] ae: -26.56[S1B1]	5.38 5.39	$1/\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$ $1/\Delta\delta_{CnCn+1}-1/\Delta\delta_{HnHn+1}$
3.	**1**-*Trans*: H_3H_4	0.1 (d H_3)	89.95	18.4 1.16	61.96 59.33	ee[3,2]: -88.01[S1B3] ee[3,2]: -88.88[S1B3]	0.70 0.52	$\Delta\delta_{CnCn+1}*\Delta\delta_{HnHn+1}$ $\Delta\delta_{CnCn+1}+1/\Delta\delta_{HnHn+1}$
4.	**2**-*Cis*: H_1H_2	3.1	51.55	14.1 0.45	33.79 2.39 51.17 9.68	ae[5,2]: 52.41[S1C2] ae[5,2]: 49.20[U1A2] ae[5,2]: 51.17[U1A2] ae[5,2]: 50.31[U1A2]	3.06 3.19 3.11 3.15	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$ $1/\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$ $\Delta\delta_{CnCn+1}+1/\Delta\delta_{HnHn+1}$ $1/\Delta\delta_{CnCn+1}+1/\Delta\delta_{HnHn+1}$
5.	**2**-*Cis*: H_2H_3	3.9	29.15	0.2 0.1	1.89	ea[6,1]: 28.10[S1B1]	3.93	$1/\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$
6.	**2**-*Trans*: H_3H_4	8.8	167.43	4.9 0.68	12.24	aa[6,1]: -167.75[U1A6]	8.81	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$ c
7.	**3**-*Cis*: H_1H_2	4.8	-2.159	8.8 0.91	13.57 4.31	ea[6,1]: -2.62[U2B1] ea[6,1]: -2.15[S1D1]	4.81 4.79	$\Delta\delta_{CnCn+1}+1/\Delta\delta_{HnHn+1}$ $1/\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$
8.	**3**-*Cis*: H_2H_3	5.2	-18.15	1.5 0.1	5.19	ae[6,1]: -18.26[U1A1]	5.2	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$
9.	**3**-*Trans*: H_3H_4	0.1 (t H_3)	89.95	4.7 1.23	87.74	ee[3,2]: -87.74[S1A3]	0.751	$\Delta\delta_{CnCn+1}*\Delta\delta_{HnHn+1}$
10.	**4**-*Cis*: H_1H_2	4.8	-2.159	2.7 0.92	21.14 25.52	ea[6,1]: -3.43[S1A1] ea[6,1]: -4.47[S1B1] ea[6,1]: -2.23[S1F1]	4.83 4.85 4.80	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$ $\Delta\delta_{CnCn+1}+1/\Delta\delta_{HnHn+1}$
11.	**4**-*Cis*: H_2H_3	5.2	-18.15	1.6 0.08	17.38 9.90	ae[6,1]: -17.38[U1A1] ae[6,1]: -19.80[U1C1]	5.18 5.23	$\Delta\delta_{CnCn+1}+1/\Delta\delta_{HnHn+1}$ $1/\Delta\delta_{CnCn+1}-1/\Delta\delta_{HnHn+1}$
12.	**4**-*Trans*: H_3H_4	0.1 (bs)	89.85	1.8 1.21	19.79	ee[3,2]: 89.39[S1A3]	0.60	$\Delta\delta_{CnCn+1}*\Delta\delta_{HnHn+1}$
13.	**5**-*Cis*: H_1H_2	2.8	58.63	8.2 0.62	30.25	ae[5,2]: 59.74[S1B2]	2.75	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$
14.	**5**-*Cis*: H_2H_3	3.6	38.15	1.3 0.09	4.587	ea[6,1]: 36.940[U1C2]	3.64	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$
15.	**5**-*Trans*: H_3H_4	8.8	167.43	10.1 0.71	17.96	aa[6,1]: 167.96[U1B6]	8.82	$\Delta\delta_{CnCn+1}*1/\Delta\delta_{HnHn+1}$

a. δc, δ_H[ppm], ^1H 400MHz, ^{13}C 75MHz: **1**-CDCl$_3$, **2**-D$_2$O, **3**-CDCl$_3$, **4**-CDCl$_3$, δ_H **5**-CDCl$_3$, δc **5**-CD$_3$OD[15]; b. sign in D-ribitol series result from molecular models; c. non-coplanar Villarceau circles: $\Delta\delta_{HnHn+1}$ x $\Delta\delta_{CnCn+1} = \Delta\delta_{HnHn+1}/(1/\Delta\delta_{CnCn+1})$.

Eq. 1: $^3J_{HH} = [\cos^{-1}(\sin\theta_{HnHn+1})]^{1/2}/m = \phi^{1/2}/m$, with m = 2 *cis, trans-ee*; m = 1 *trans-aa*, $\phi = f(\phi_2, \phi_{1/2})$, $\theta_{HnHn+1} = \theta^{U1A}$ dihedral angle, angle of set A [deg], $\phi = \theta^{U1B}$ vicinal angle, angle of set B [deg]. The transformation from U1 to S1 can be made with algebraic eq. 2 and from S1 to U1 with eq. 3.[8]

Eq. 2: $\sin^{-1}\cos(\phi_{U1B}) = \theta_{HnHn+1}{}^{S1A3}$, *trans-ee*[3,2]: $\phi_{U1B} = \phi_{U1B2} - \phi_{U1B1}/2$,

where $\phi_{U1B} = \theta^{S1B1}$ the first angle of set A on unit S, $\theta_{HnHn+1}{}^{S1A3}$ – the third angle of set B, the dihedral angle with *trans-ee*[3,2] stereochemistry.

Eq. 3: $\phi_{1U1B} = [60 - \theta^{S1B1}]/1.5$ and $\theta^{U1A1} = \phi_{1U1B}/2$,

where ϕ_{1U1B} = half ϕ_1 of set B of unit U1 results from S1 having in set B an angle around 60[deg], θ^{U1A1} – the first angle of set A of unit U1.

Skew circles:

Eq. 4: $\theta^{An} = nx[(\Delta\delta_{HnHn+1} \times \Delta\delta_{CnCn+1})/2)x90]^{1/2}$: n = 2, *cis-ea, ae, trans-ee*,

Eq. 5: $\theta^{An} = nx[(\Delta\delta_{HnHn+1} \times \Delta\delta_{CnCn+1})/2)x90]^{1/2}$: n = 1, *trans-aa*[6,1],

Middle circles:

Eq. 6: $\theta^{An} = nx[90x(\Delta\delta_{HnHn+1} + \Delta\delta_{CnCn+1})/2]^{1/2}$: n = 2, *cis-ea, ae, trans-ee*,

Eq. 7: $\theta^{An} = nx[90x(\Delta\delta_{HnHn+1} - \Delta\delta_{CnCn+1})/2]^{1/2}$: n = 1, *trans-aa*[6,1].

where θ^{An} – an angle of set A from unit U or S, $\Delta\delta_{HnHn+1}$, $\Delta\delta_{CnCn+1}$ – the differences between two consecutive protons and two atoms of carbon [ppm].

3-Sphere is a method in three steps:[8] 1. Prediction of the dihedral angles only from the vicinal coupling constant,[26] 2. Calculation of the angle of set A with manifold equations – skew and middle line of rectangle – from the differences between two atoms of carbon and protons chemical shifts δ_{XnXn+1}[ppm], with X = C, H. 3. Building of seven sets angles for the calculated angle of set A, choosing one pair of three sets angles, transformed it in six sets angles on two units, and choose the dihedral angle with value almost equal with predicted angle. The vicinal coupling constant can be calculated from the calculated dihedral angle as test verification. The sign doesn't result from the manifold equations, result from the first step or from the calculation of the vicinal coupling constant.

Under rectangle geometries (trapezoid or irregular), non-coplanar lines, middle line and anti-rectangle middle line, the differences between two atoms and proton chemical shifts are transformed from radians in degrees with eq. 4-7, and calculated dihedral angles with *cis* and *trans* stereochemistry (Table 1) for imonocyclitols **1-5**. Most of the angles calculates with rectangle geometries are found on first pair of three set angles, excepting the L-ribitol **4**-*cis*-H₁H₂ where the best angle was found in third pair of three set angles (Table 1, entry 10). For a vicinal coupling constant of 4.8[Hz], in case of D-ribitol **3-***cis*-H₁H₂ (Table 1, entry 7) result angles -2.85^{U2B1} and -2.15^{S1D1}[deg] from eq. 6 and 4, and in L-ribitol **4**-*cis*-H₁H₂ (Table 1, entry 10) angles of -3.43^{S1A1} and -4.85^{S1B1}[deg] from the eq. 4 and 6. The last angle under seven sets rule become -2.23^{S1F1}[deg]. Combination of the inverse function relative to recorded differences in chemical shift gives better results for 3.1[Hz], alternatively to eq. 6 (Table 1, entry 4). Other differences between the D- and L-series occurs for a vicinal coupling constant of 5.2[Hz], where eq. 4 (Table 1, entry 8) and eq. 7 (Table 1, entry 11) gives angles almost equals with predicted angles only from vicinal coupling constant. The influence of chemical shift on the curvature, and no at list on the dihedral angles, has been demonstrated for vicinal coupling constants of 5.2 and 4.8[Hz] in D and L-series. A strange symmetry between the vicinal coupling constant of 4.1 and 3.1[Hz], the angles of set A calculates from carbon chemical shift in gauss[6] are dihedral

angles if in first case the differences between two atoms of carbon is divided by two, and in second case is multiplied by two. Resulting that the manifold equation[6-8] must be established for every C_n-C_{n+1} shape, or can be used only one manifold equation under the six sets rule. The eq. 4 with n = 1/2 follow the vicinal angle rule (eq. 1) and give sometimes better result as eq. 4 with n = 2 (Table 1) for *cis* stereochemistry under unit rule. The manifold eq. 4 (n= ½ *cis*, *trans-ee*, 1 *trans-aa*) under the vicinal angle rule probably is most preferred for calculation of the dihedral angles with Java Script. Available programs for calculation of the dihedral angles are GeometryangleRevRom.html based on *skew circles*, middle circles eq. 4-7 and JvicinalGeometry.html based on relationships between the vicinal angle and vicinal coupling constant for all stereochemistry in agreement with algebraic equation.[27]

CONCLUSIONS

3-Sphere method[27] enable the calculation of the dihedral angles with right sign and stereochemistry through trigonometric equation 1, relationship between dihedral angle and corresponding vicinal coupling constant and vice versa, and manifold equations 4-7 which transformed NMR data in one angle of set A$_i$ (i = 1-6). Angle used for building of six sets angles on two units, from which is choose the calculated dihedral angle with value almost equal with the predicted one.

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