Aromatic Ring Current Shifts:

Implications for Conformations in Presence of Local and Global Torsional Motions With Respect to a Site in Macromolecules

S.Aravamudhan
Department of Chemistry
North Eastern Hill University
PO NEHU Campus Mawkynroh Umshing
SHILLONG 793022 Meghalaya
saravamudhan@nehu.ac.in

The aromatic ring current shifts are useful in certain contexts to infer the proton locations with respect to the aromatic ring present at a specified site within a biological macromolecule. But, there have been ambiguities in applying this method when it was found that the procedure and equations can be applied for using the calculated ring current shift values on the basis of the geometrical specifications. Since in solid crystals only fixed orientations are encountered, the sensitivity of the isotropic ring current shifts (presuming a localized free-fast rotation of aromatic ring in the solid matrix) can be good enough by taking into consideration the possible range of variations in torsional angles. But, if it has to be applied in solution state the considerations are different due to the fact that there should be an explicit averaging of shift values corresponding to the displacements during torsional motions.

Considering the uncertainties reportedly encountered in such contexts, an effort is being made to find out the possibility of improving the efficacy of the ring current shift applications by calculating the full tensor form of the aromatic ring current shifts instead of using only the equations given for the isotropic values of the ring current shifts.

1. One of the striking instance of possible improvement would be due to the fact that, the isotropic shifts are non zero only if the susceptibility tensor is anisotropic (-49×10^{-6}**)** as in the case of Aromatic Ring. There could be similar contributions also from other groups but with *“much less anisotropy”* whose contributions to isotropic shift values would be negligible. This is the reason always aromatic ring current is considered predominantly to contribute by the “through space” magnetic dipole model.

It may be possible to find that the trace value range is much less than the range of variation of ‘xx’ (a generalized reference to the component along the magnetic field direction) component by the full tensor calculation. Thus the sensitivity can be better for fixing the coordinates. When the motions are not fast enough, then the isotropic “averaging” over all orientations may not be applicable. The isotropic shift equation requires that during the motion the proton position remains unchanged in the Aromatic Molecule Fixed coordinate axes system. If the proton is not in any way fixed by chemical bonding relative to the aromatic system but there is a relative motion of the aromatic frame work and the radial vector of the proton with respect to the six-fold symmetry axis of the aromatic ring, then the equations for isotropic average shifts are no longer relevant but by the full tensor equation can be subjected to appropriate coordinate transformations and the full shielding tensor can be calculated for the displacements under a torsional motion and after from the set of the full tensors calculated appropriate averaging can be effected..

A simplified “model” calculation would be presented for the case (i) when the radial proton vector is fixed with respect to the six fold symmetry axis (local motion) and for the case (ii) when the radial vector oscillates (global motion) with respect to the six fold symmetry axes to examin for the advantages of the calculation of Full Tensor over the only isotropic ring current shift values.
http://www.geocities.com/sankarampadi/ForIbs2006.html

Sheet_1: Abstract

Sheet_2: Index

Sheet_3: Molecular and Laboratory axes systems which are relevant for calculation methods when the motions in macromolecules are recognized as interdependent or independent motions locally and globally

Sheet_4: Diagrammatic illustration of the possible motions of the aromatic ring and the protons in the neighborhood of the aromatic ring

Sheet_5: Further details and explanations for the motions referred to earlier and depicted [in Sheet_4].

Sheet_6: The equations and the methods used for the chemical shift calculations which are essentially a calculation of induced fields due to aromatic ring currents.

Sheet_7: Aromatic ring Susceptibility as the Benzene ring Susceptibility Tensor; Some shift values calculated using this tensor for certain specific contexts to familiarize the methods and tabulations in this context; Further indications and comments on the motions and the consequences on the induced fields at protons due to the ring current effect.

Sheet_8: A typical graphical display of the calculations using the Tensor Form equations; isotropic shift values to be compared with already reported values in literature; these values are for the proton-ring centre distance of 20 A°. Values for a distance of 5 A° can be obtained by multiplying the induced field values by 64 since the distance is reduced by a factor of 4; the shift values are dependent on [**(distance)** $^{-3}$].

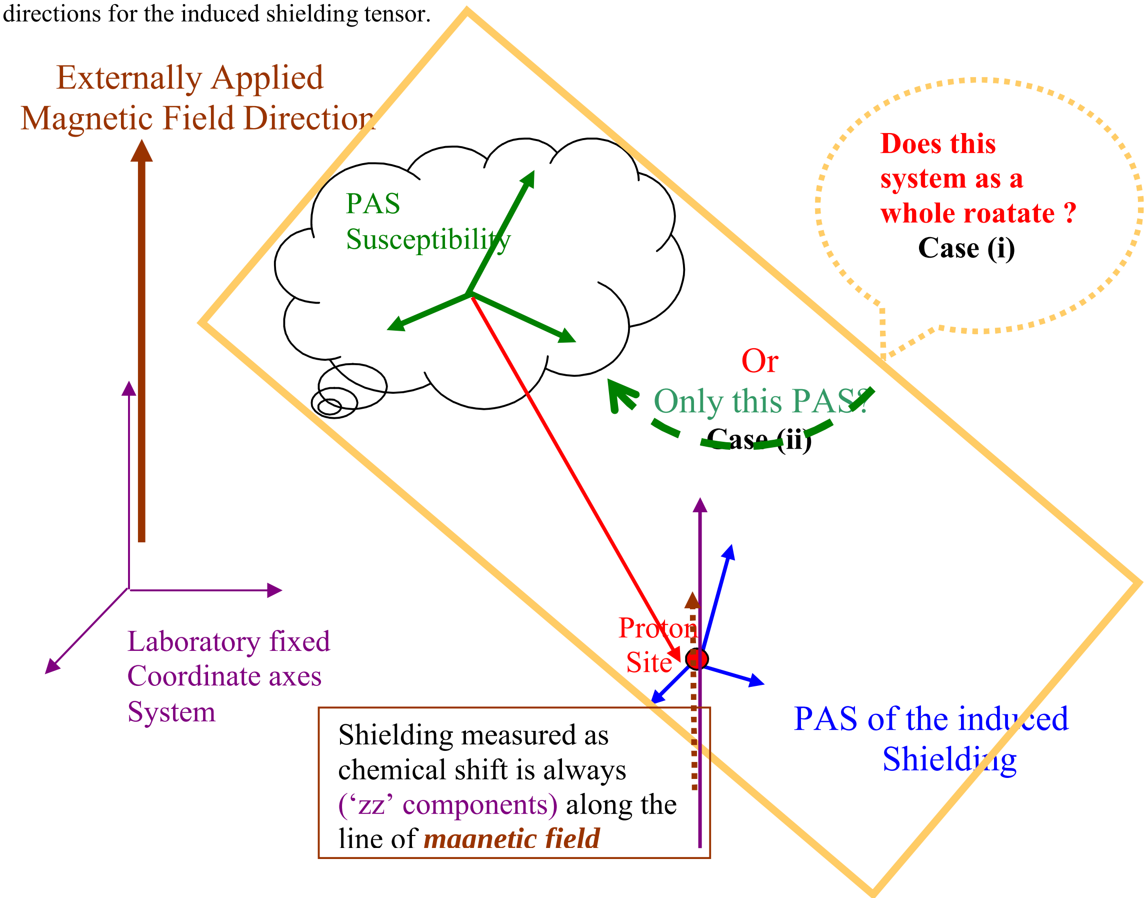
Sheet_9: More elaborate tabulation of calculated results to become familiar with the reading of reported data for purposes of applying for the cases of vibrations and torsional motions.

Sheet_10: A graphical display of the results in the form of a rotation pattern for appropriately interpolating and reading out values for specific motional situations.

Sheet_11: A specific hypothetical case of how the Tensor Form can be useful when the isotropic values cannot be indicative of the motional state of the system. And further results as captions for graphical plots in the subsequent sheets.

Sheet_12 to Sheet-16: Different variations of considering the motions in the system and their corresponding displays as rotation patterns to become conversant with the required visualizations for applications

Characteristics of Susceptibility and the Resulting Shielding when the Molecular System Rotates : Consequences of the Variety of Time Scales for the Rotational motion: When the Diamagnetic Magnetic Susceptibility (Tensor) **induces** magnetic fields the resulting induced field would also be a tensor property. The Principal (Axes System PAS) Directions of the Susceptibility Tensor would not inherently be the Principal directions for the induced shielding tensor.

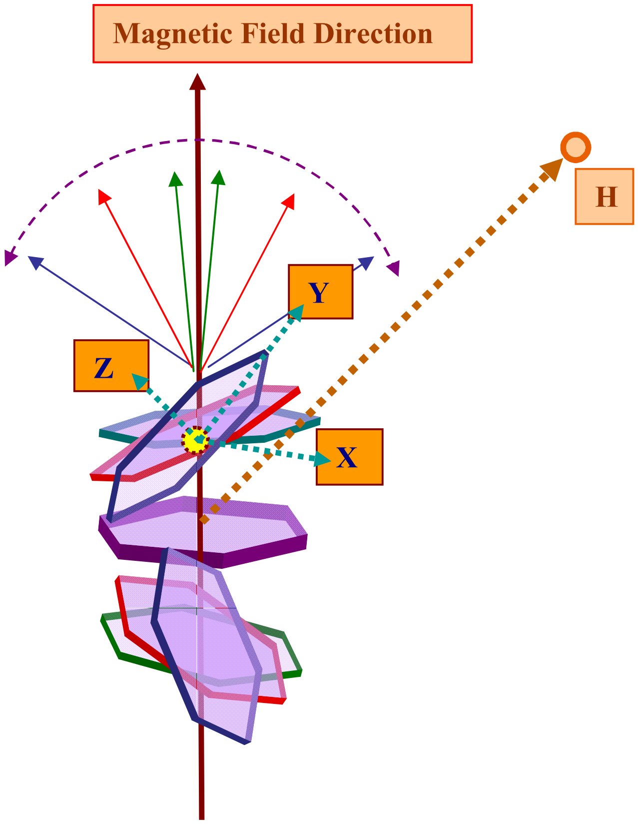


Shielding measured as chemical shift is always ('zz' components) along the line of ***maanetic field***

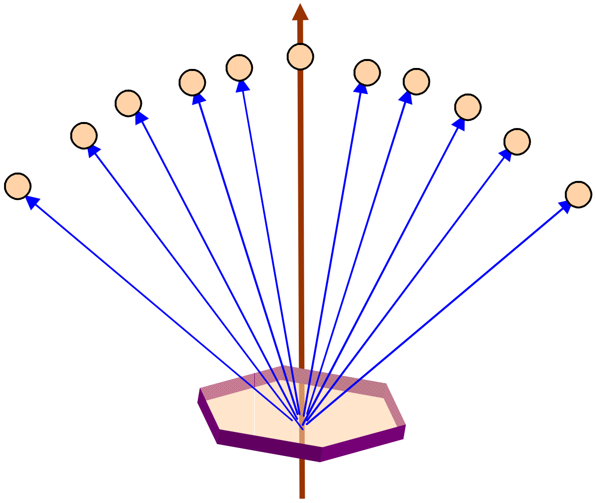
Case (i): The Proton Site is within the molecule, the PAS of Susceptibility and shielding are have fixed relative dispositions with respect to the Molecular Axes System. In this case, when the molecule is subjected to fast istropic rotations, only the ANISOTROPIC (In the case of aromatic ring this is the quoted value of -49 x 10^{-6}) part of the Susceptibility Tensor results in a non-vanishing contribution to the isotropic shielding. Isotropic susceptibility tensor results in zero value for the isotropic shielding at the proton site**.** **Case (ii):** *The proton is located outside the molecule and the proton, hence, is not bonded to any atoms within the molecule. This is the type of situation which occurs frequently in large Biomolecules. When the molecule has time dependent motions, the molecular symmetry axes do not hold time-independent orientations with the Vector connecting the proton to the origin of magnetic moment within the molecule.This has been further classified into two cases subsequently as case(1) and case(2)*

Case (i) above is the familiar case where at appropriately fast rotational motions the ring current effects can be estimated by the Conventional Equations for the isotropic Chemical shift contributions. In this context it is suggested here that the relevant materials in this context may be looked for in the references included for the Abstract of IBS2004 as can be found at the Web Page http://geocities.com/inboxnehu_sa/NSCMB2004.html These references are reproduced below:[1] "NMR in Medicine and Biology", K.H.Hausser and H.R.Kalbitzer, p102, Springer Verlag (1991).[2] "Application of Ring Current effects…",Stephen J.Perkins in 'Biological magnetic resonance Vol.4' p193, Edited by Lawrence J.Berliner and Jaques Reuben, Plenum Press(1982)[3] "Investigating the Feasibility …" by S.Aravamudhan page 501, Proceedings of the Joint 29th Ampere-13th ISMAR International Conference,TU Berlin 1998.[4] Poster presentations by S.Aravamudhan at the Annual Meetings of IBS at UOM Chennai in 2002 and at IIT Roorkee in 2003. See the Webpage link http://geocities.com/amudhan20012000/Confview_link.html at the reference for Abstract for IBS2005 http://geocities.com/inboxnehu_sa/NSCMB2004.html

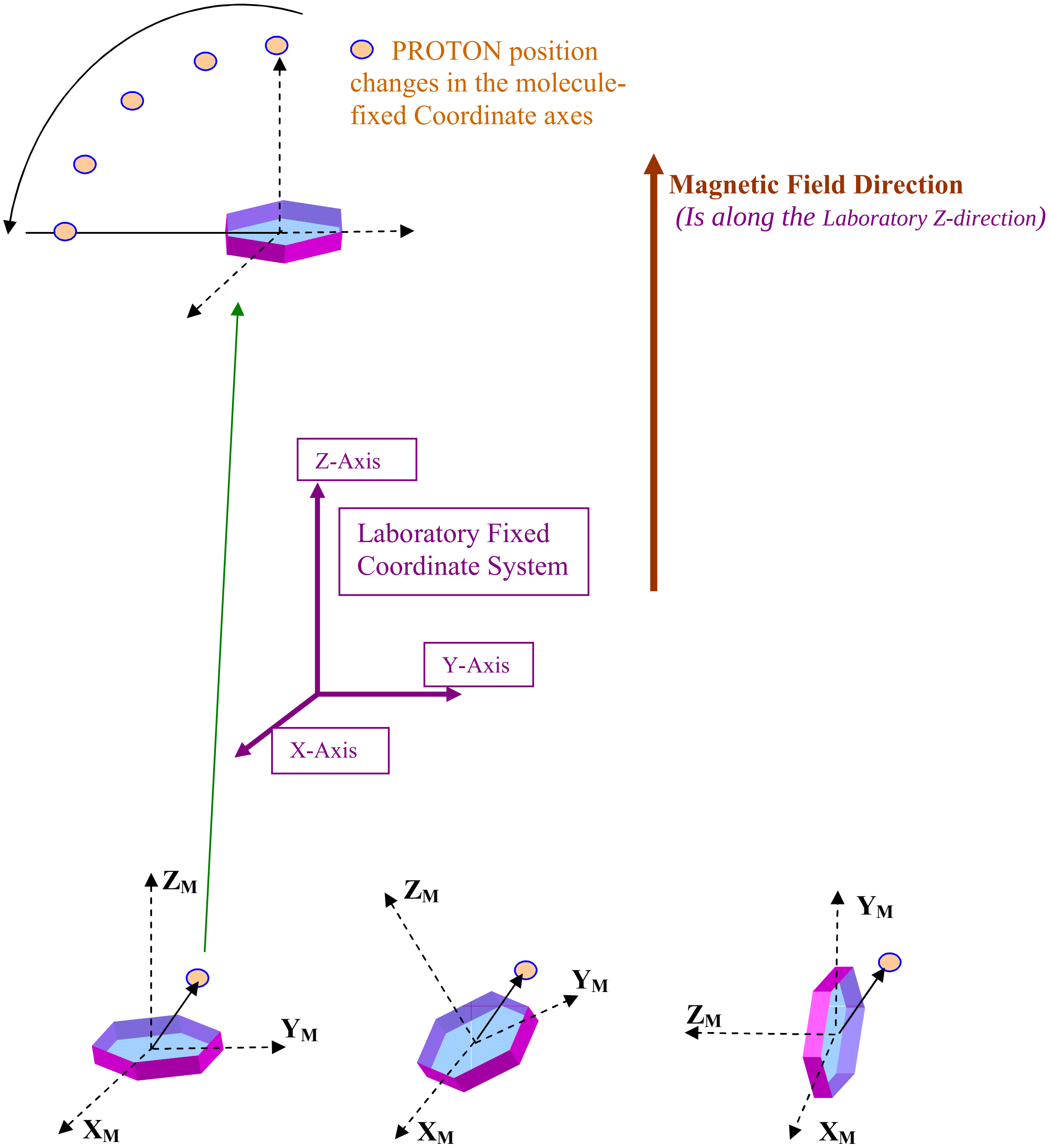
CASE-(i) *Aromatic PAS changes orientation* w.r.to Magnetic Field, *Proton position vector remains fixed* w.r.to Magnetic field



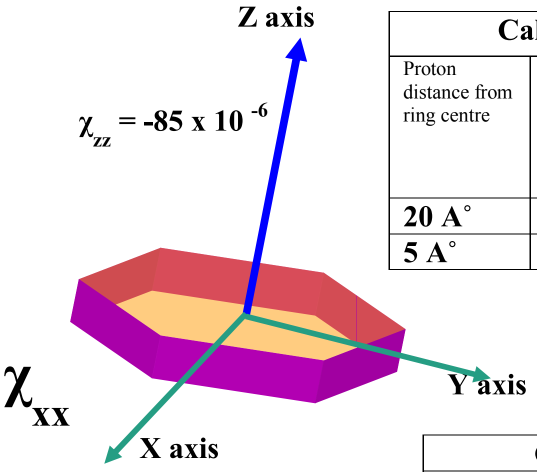
CASE-(ii) Only *Proton Position Vector Changes orientation* with Magnetic Filed; The *Molecular PAS remains fixed* in orientation w.r.to Magnetic Field direction.



Case: 2 Aromatic Ring remains at fixed orientation with respect to the Lab. Fixed Axes system



Case:1 Proton position in the Lab. Fixed System is unaltered; the aromatic ring changes orientation in Lab frame of reference. Obviously, the angle of the proton position vector with respect to the molecular symmetry axis ($\mathbf{Z_M}$) varies. This makes the conventional equations (used for isotropic ring current shifts) not applicable.



Calculated ring current shifts ppm

Proton distance from ring centre	Trace Angle with mol-Z=0	Field parallel to Z	
		ZZ component	
		Proton on Z-axis	Proton in Ring plane
20 A°	0.000668806839	0.003411	-0.001705
5 A°	0.042803637696	0.218304	-0.10912

Calculated ring current shifts ppm

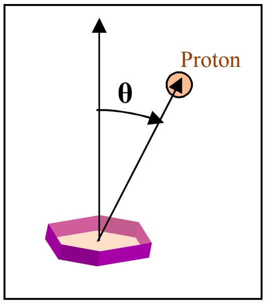
Proton distance from ring centre	Trace Angle with mol-Z=90	**Field parallel to Y**	
		YY-component	
		Proton || Y	Proton Perpendicular to Y
20 A°	-0.000334402779	0.001404	-0.000702
5 A°	-0.021401777856	0.089856	-0.044928

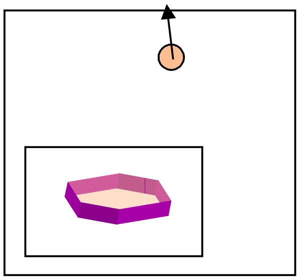
$\chi_{yy} = \chi_{yy} = -35 \times 10^{-6}$

$-85 - (-35) = -50 \times 10^{-6}$ =Anisotropy

The above experimentally measured Susceptibility Tensor can be decomposed and fragmented into 24 group-/bond-/atom-/ring-current-/tensors which, when added up, result in the experimental molecular values for the benzene ring.

http://saravamudhan.tripod.com/shield_demag_susceptibility/id2.html

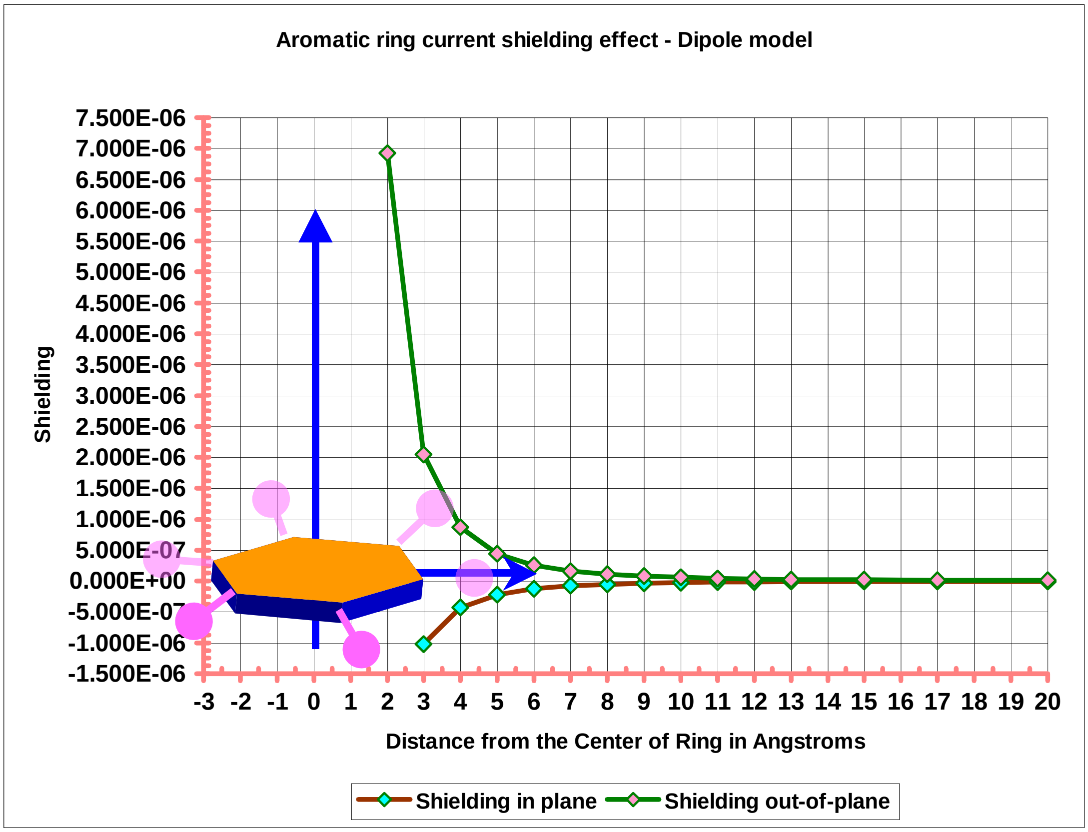


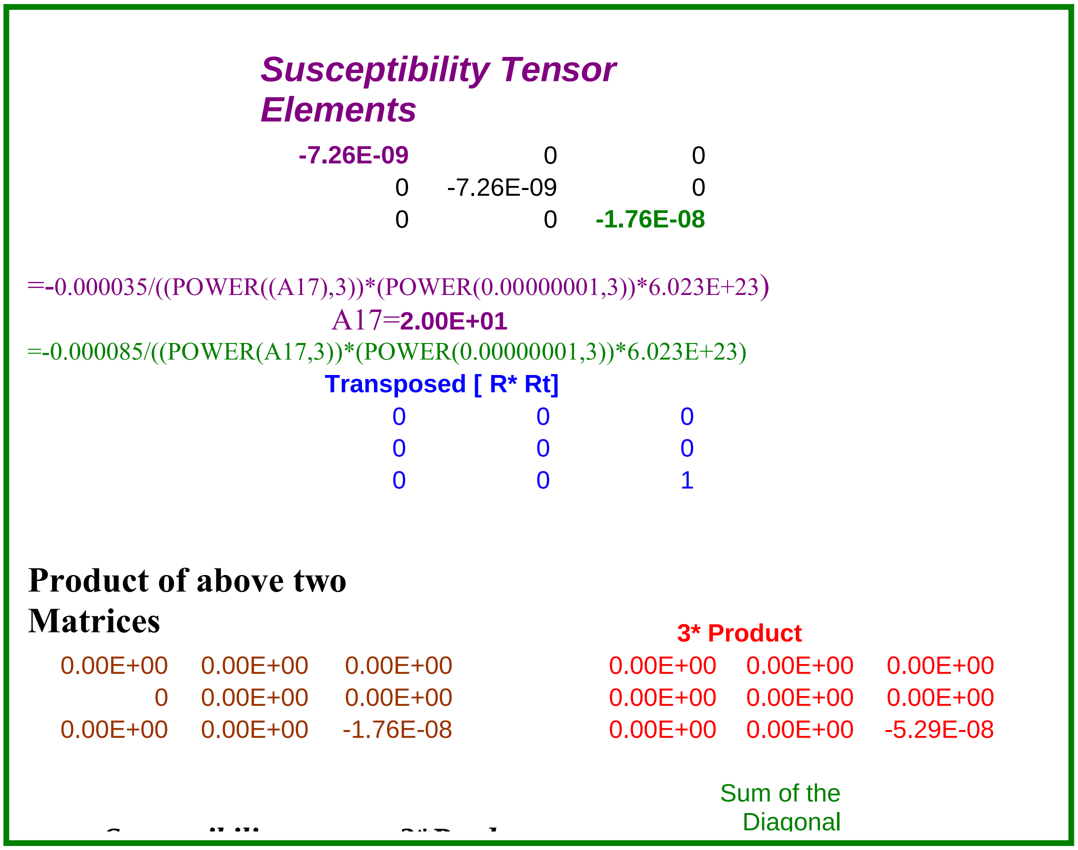


When the ring undergoes anisotropic motion when proton is held fixed, or when proton undergoes partial rotations when the ring is held fixed, it is not always valid to consider only the isotropic chemical shift values at the proton.

When the molecule as a whole with a bonded proton undergoes fast Rotation randomly (isotropic motion), then at the proton only the the isotropic average shift can be measured the value of which depends on the fixed angle θ

When the aromatic ring alone undergoes the fast rotation when the proton (not bonded to ring) in the neighborhood of the ring is attached to the same macromolecule: The susceptibility tensor can be equivalent to an isotropic value so that there is no anisotropy of the susceptibility. Then the shift induced at the proton would be averaged to zero value.





Susceptibility Tensor Elements

-7.26E-09	0	0
0	-7.26E-09	0
0	0	-1.76E-08

=-0.000035/((POWER((A17),3))*(POWER(0.00000001,3))*6.023E+23)

A17=**2.00E+01**

=-0.000085/((POWER(A17,3))*(POWER(0.00000001,3))*6.023E+23)

Transposed [R* Rt]

0	0	0
0	0	0
0	0	1

Product of above two Matrices

0.00E+00	0.00E+00	0.00E+00
0	0.00E+00	0.00E+00
0.00E+00	0.00E+00	-1.76E-08

3* Product

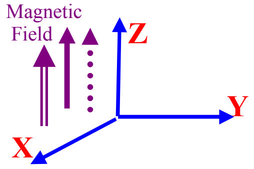
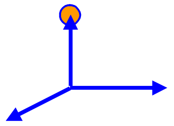
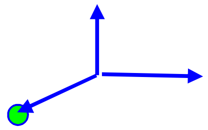
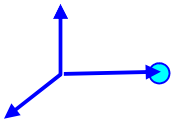
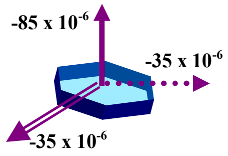
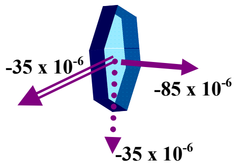
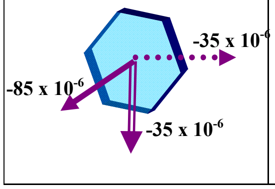
0.00E+00	0.00E+00	0.00E+00
0.00E+00	0.00E+00	0.00E+00
0.00E+00	0.00E+00	-5.29E-08

Sum of the Diagonal

Calculated Shielding Tensors relevant for the discussions on ring current effects

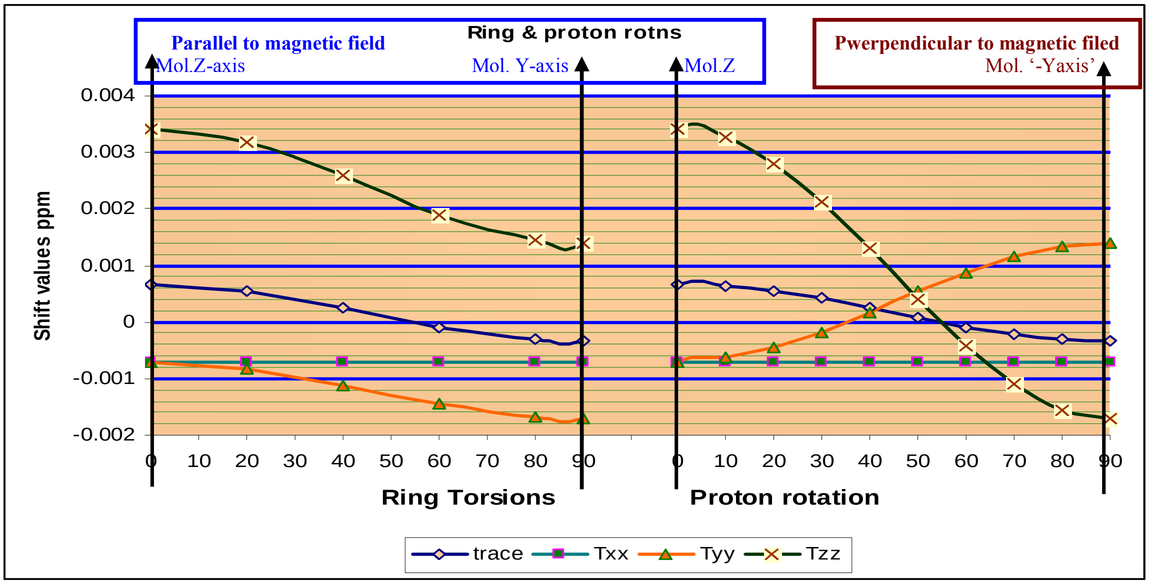
Six-fold symmetry axis has the largest susceptibility Principal component value of $-85 \text{ x } 10^{-6} = \chi_{\parallel}$

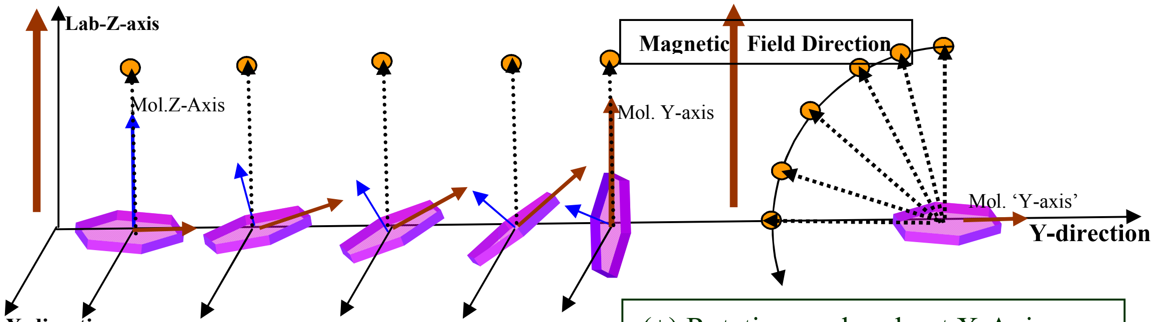
The tensor being axially symmetric, the component in the perpendicular plane = $-35 \text{ x } 10^{-6} = \chi_{\perp}$

 **Direction** of Field	PROTON **Location** at 20 A˚ from ring centre		
			
	INDUCED FIELD TENSOR x y z x -0.000702 0.000000 0.000000 y 0.000000 -0.000702 0.000000 z 0.000000 0.000000 **0.003411** TRACE = 0.000668806839	INDUCED FIELD TENSOR x y z x 0.001404 0.000000 0.000002 y 0.000000 -0.000702 0.000000 z 0.000004 0.000000 **-0.001705** TRACE = -0.000334402779	INDUCED FIELD TENSOR x y z x -0.000702 0.000002 0.000000 y 0.000002 0.001404 0.000002 z 0.000000 0.000004 **-0.001705** TRACE = -0.000334402692
	INDUCED FIELD TENSOR x y z x -0.000702 0.000000 0.000000 y 0.000000 **-0.001705** 0.000000 z 0.000000 0.000000 0.001404 TRACE = -0.000334403419	INDUCED FIELD TENSOR x y z x 0.001404 0.000000 0.00000 y 0.000000 **-0.001705** 0.000000 z 0.000002 0.000000 -0.000702 TRACE = -0.000334403419	INDUCED FIELD TENSOR x y z x -0.000702 0.000002 0.000000 y 0.000004 **0.003411** 0.000004 z 0.000000 0.000002 -0.000702 TRACE = 0.000668805733
	INDUCED FIELD TENSOR **-0.001705** 0.000000 0.000000 0.000000 -0.000702 0.000000 0.000000 0.000000 0.001404 TRACE = -0.000334403419	INDUCED FIELD TENSOR **0.003411** 0.000000 0.000004 0.000000 -0.000702 0.000000 0.000002 0.000000 -0.000702 TRACE = 0.000668806257	INDUCED FIELD TENSOR **-0.001705** 0.000004 0.000000 0.000002 0.001404 0.000002 0.000000 0.000002 -0.000702 TRACE = -0.000334402692

········▶ Symbol for magnetic Field being along Y-axis in the molecular plane
⇒ along the X-axis and ➞ along the molecular Z-axis (6fold axis)
Protons on the three axis at the same 20 A˚ distance from ring centre are distinguished by the respective filling colors. These colors are used to shade the highlighted values of the tensor components in the table

0.003411 This number indicates this is for the orange colored proton on the Z-axis of the Lab Frame for magnetic field parallel to Molecular Z-axis [$\chi_{\parallel}$] lab Z-axis and when the six-fold molecular axis is parallel to Lab-Z axis For the variety of orientations of the molecule and magnetic fields, the highlighted values correspond to the observable ring current chemical shift values, which are the components of the tensor parallel to the magnetic field directions. With the visualizations gained by the familiarity with the above table, it should be further simpler enough to follow the rotation patterns depicted in the plots in the remaining sheets.



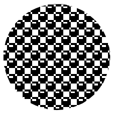


(+) Rotation angles about X-Axis

Angle of Torsion/ Rotation	Shift Tensors_Ring Torsion X Y Z	Trace of tensor To the left Trace values are same; But the corresponding Tensors are not idebntical	Trace of Tensor to the right	Shift Tensors_Proton Rotation X Y Z
0 degrees	x -0.000702 0.000000 0.000000 y 0.000000 -0.000702 0.000000 z 0.000000 0.000000 **0.003411**	0.000668806839	0.000668806839	x -0.000702 0.000000 0.000000 y 0.000000 -0.000702 0.000000 z 0.000000 0.000000 **0.003411** Z
20 degrees	-0.000702 0.000000 0.000000 0.000000 -0.000820 0.001548 0.000000 -0.000774 **0.003176**	0.000551452511	0.000551567471	-0.000702 0.000000 0.000001 0.000000 -0.000456 0.000677 0.000001 0.001644 **0.002813**
40 degrees	-0.000702 0.000000 0.000000 0.000000 -0.001117 0.002371 0.000000 -0.001186 **0.002582**	0.000254303886	0.000254654238	-0.000702 0.000001 0.000001 0.000001 0.000167 0.001037 0.000002 0.002519 **0.001299**
60 degrees	-0.000702 0.000000 0.000000 0.000000 -0.001455 0.002085 0.000000 -0.001043 **0.001906**	-8.3600673E-005	-8.31395082E-005	-0.000702 0.000001 0.000001 0.000001 0.000877 0.000913 0.000002 0.002217 **-0.000424**
80 degrees	-0.000702 0.000000 0.000000 0.000000 -0.001675 0.000823 0.000000 -0.000412 **0.001465**	-.000304152811	-0.000303909677	-0.000702 0.000002 0.000000 0.000002 0.001340 0.000362 0.000001 0.000878 **-0.001550**
90 dehrees	-0.000702 0.000000 0.000000 0.000000 -0.001705 0.000000 0.000000 0.000000 **0.001404**	-0.000334403419	-0.000334402692	-0.000702 0.000002 0.000000 0.000002 0.001404 0.000002 0.000000 0.000004 **-0.001705**
Finally Proton is along Molecule 'y' Axis Magnetic Field along Lab Z-axis 'same as 'Molecule Y-axis'(-35.0 for susceptiblilty)			Finally proton is along Molecule '-Y-axis' Magnetic Field along Lab 'Z-axis" same as 'Molecule Z-axis' (-85.0 susceptibility)	
When the system is static as in solids, the Shift values observed are the Values corresponding to the Lab-ZZ component of the tensors..				

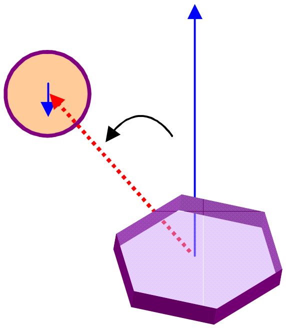
Calculation of induced field with the Magnetic Dipole Model using point dipole approximations.

$$\sigma_{\mathbf{i}}=\Sigma_i \chi_{\mathbf{i}} / R^3_i \, [1-(3.\mathbf{RR}_{\mathbf{i}} / R^5_i)]$$



Induced field Calculations using these equations and the magnetic dipole model have been simple enough when the summation procedures were applied as described in the previous presentations and expositions.

Isotropic Susceptibility Tensor



$$\tilde{\chi} = \begin{bmatrix} \chi & 0 & 0 \\ 0 & \chi & 0 \\ 0 & 0 & \chi \end{bmatrix} \qquad |\vec{R}| = r$$

$$\sigma_{zz} = \frac{\chi}{r^3} - \frac{3 \bullet r^2 \bullet \cos^2(\theta) \bullet \chi}{r^5} \qquad = \sigma$$

Induced field Calculations using these equations and the magnetic dipole model have been simple enough when the summation procedures were applied as would be described in this presentation.

$$\tilde{\sigma} = \frac{\tilde{\chi}}{r^{3}} - \frac{3 \bullet \left[\vec{R} \; \vec{R} \right] \bullet \tilde{\chi}}{r^{5}}$$

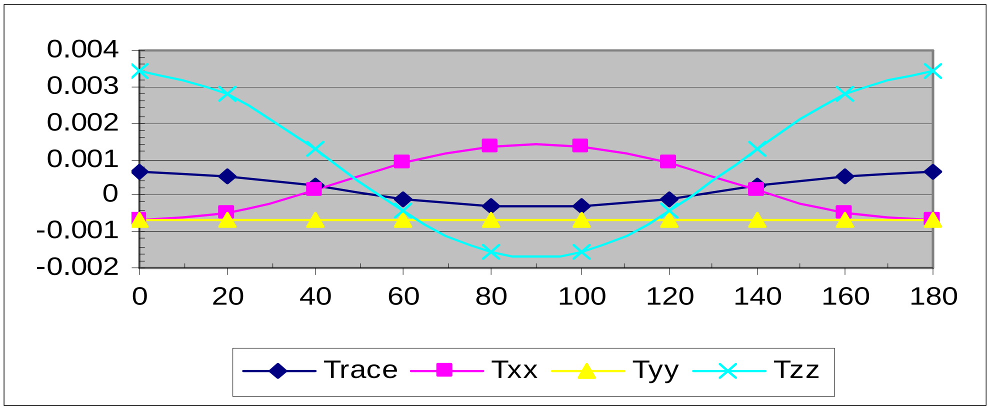
$$\begin{bmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{bmatrix} = \frac{\begin{bmatrix} \chi_{xx} & \chi_{xy} & \chi_{xz} \\ \chi_{yx} & \chi_{yy} & \chi_{yz} \\ \chi_{zx} & \chi_{zy} & \chi_{zz} \end{bmatrix}}{r^3} - \frac{3 \bullet \begin{bmatrix} xx & xy & xz \\ yx & yy & yz \\ zx & zy & zz \end{bmatrix} \bullet \begin{bmatrix} \chi_{xx} & \chi_{xy} & \chi_{xz} \\ \chi_{yx} & \chi_{yy} & \chi_{yz} \\ \chi_{zx} & \chi_{zy} & \chi_{zz} \end{bmatrix}}{r^5}$$

In a fixed molecular system which is not undergoing tumbling isotropic rotational motions what is measurable is the shielding & hence the shift corresponding to the **element** $\boldsymbol{\sigma}_{\mathbf{zz}}$ in the tensor and **not the trace** $\frac{1}{3}\,(\boldsymbol{\sigma}_{\mathbf{xx}} + \boldsymbol{\sigma}_{\mathbf{yy}} + \boldsymbol{\sigma}_{\mathbf{zz}})$

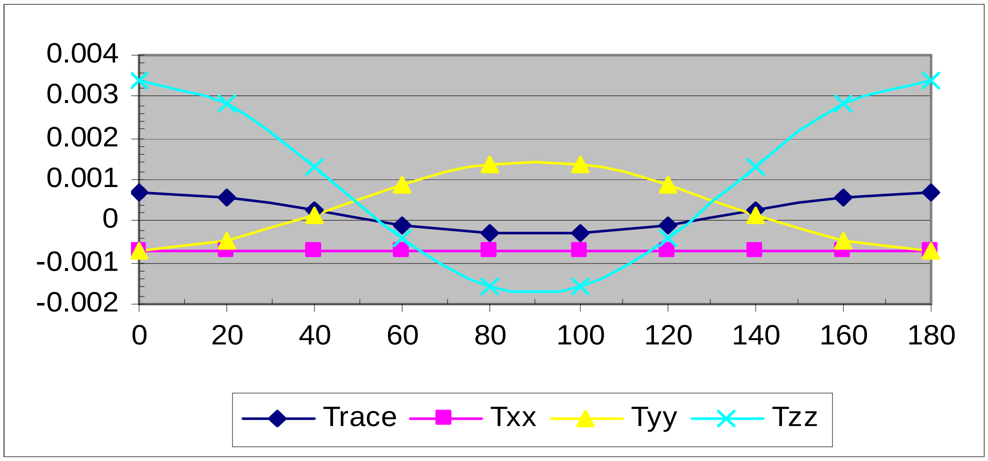
Consider a rapid torsional motion of the ring locatable on the graph around the 40 degrees orientation. Let the amplitudes of oscillation be from 20 through 40 to 60. Then the averaged Tzz value would be **0.002555**
A rotational vibration of the protons corresponding to the Right hand side graph around 40 degrees with extrema at 20 and 60 would result in averaged Tzz = **0.001229**
Where as when trace is considered for both cases would result in the same average value: 0.0002407 which is different from either of the above two.
Thus calculating the full shielding tensor provides the possibility to distinguish the necessary structural aspects; but using the isotropic values could be ambiguous and thus can be erroneous.
The following sheets_12_&_13 contain graphical outputs of calculations for which the figure captions are provided in the following TextBox

Graphs are for the following combinations of independent rotations of ring (0-180 in steps of 20) and proton (0-180 in steps 0f 20) about the respective axes indicted in sequential list below

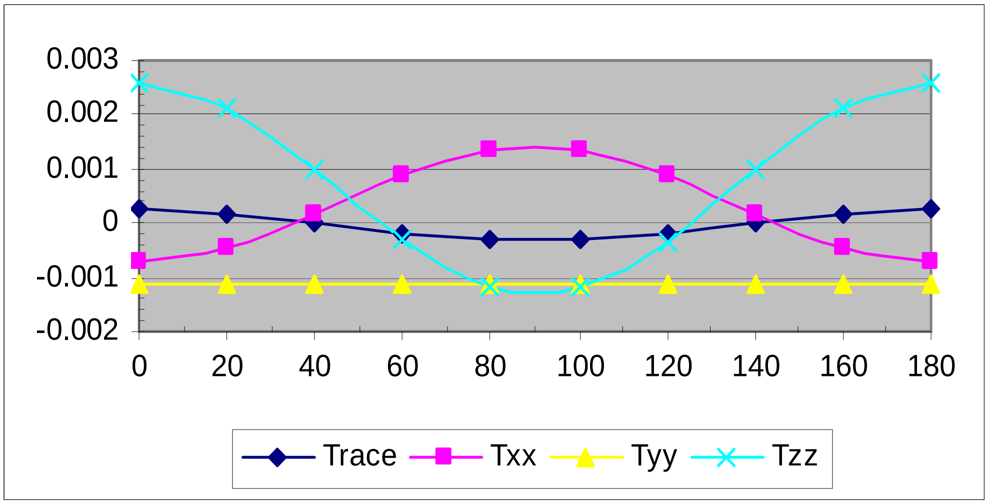
<table>
<tr><th>Graph No</th><th colspan="2">Ring (aromatic)</th><th colspan="2">Proton (not bonded)</th></tr>
<tr><th></th><th>Rotation about</th><th>Angle</th><th>Rotation about</th><th>Angle</th></tr>
<tr><td>1.</td><td>NONE</td><td>0 deg</td><td>Lab-Y axis</td><td>0-180 degrees</td></tr>
<tr><td></td><td colspan="4">Tyy is invariant, 'trace' same trend as Tzz, range of Tzz is more than trace</td></tr>
<tr><td>2.</td><td>NONE</td><td>0 deg</td><td>Lab-X axis</td><td>0-180 degrees</td></tr>
<tr><td></td><td colspan="4">'trace' same as for 1. and Txx is invariant. Other features similar to 1.</td></tr>
<tr><td>3.</td><td>Lab-X axis</td><td>Held fixed at 40 deg</td><td>Lab-Y axis</td><td>0-180 degrees</td></tr>
<tr><td></td><td colspan="4">Tyy invariant, trace and Tzz trend similar, variation ranges are less; all features similar to 1.</td></tr>
<tr><td>4.</td><td>Lab-X axis</td><td>Held fixed at 40 deg</td><td>Lab-X axis</td><td>0-180 degrees</td></tr>
<tr><td></td><td colspan="4">Trends are describable in similar ways as for 1., 2., &3.</td></tr>
<tr><td>5.</td><td>Lab-X axis</td><td>Held fixed at 80 deg</td><td>Lab-Yaxis</td><td>0-180 degrees</td></tr>
<tr><td></td><td colspan="4">Variations in trace much less and other trends are similar to the previous cases</td></tr>
<tr><td>6.</td><td>Lab-X axis</td><td>Held fixed at 80 deg</td><td>Lab-X axis</td><td>0-180 degrees</td></tr>
<tr><td></td><td colspan="4">the trends being as per the earlier graphs, the ranges of variations in Tyy are more</td></tr>
</table>



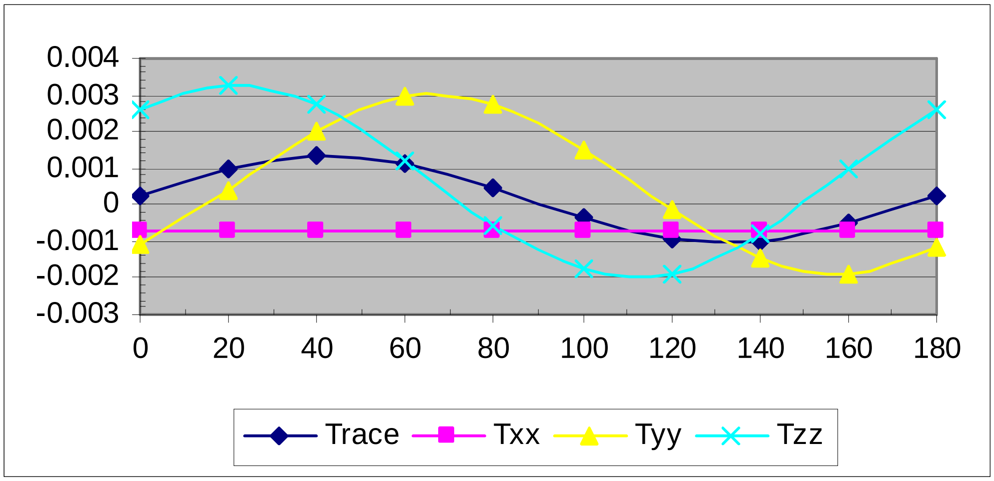
Graph_1



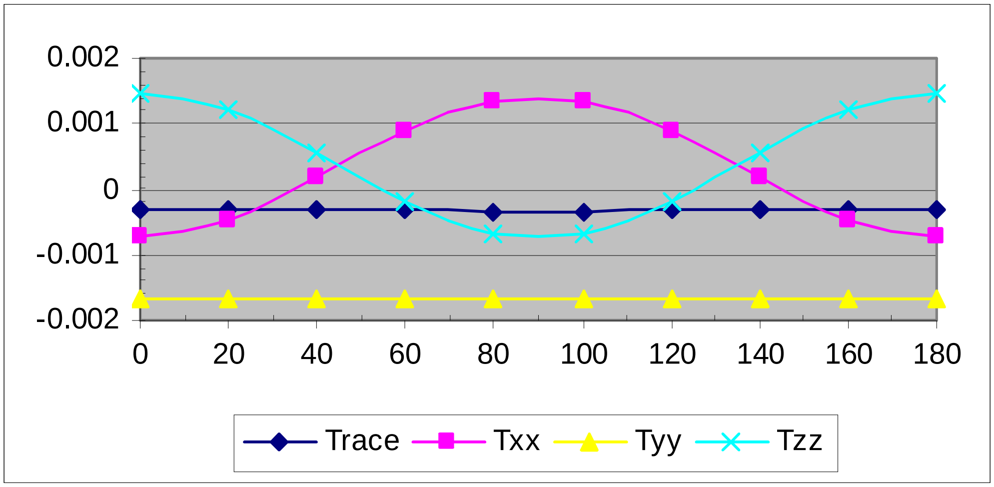
Graph_2



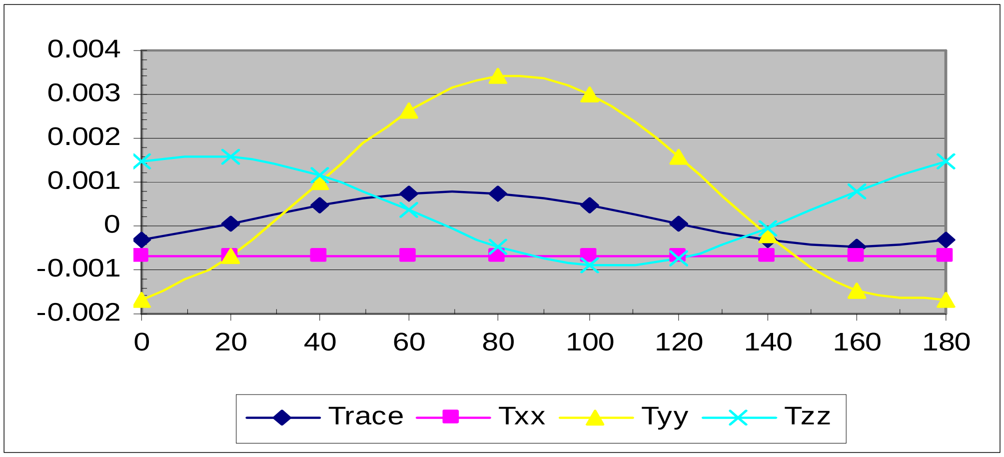
Graph_3



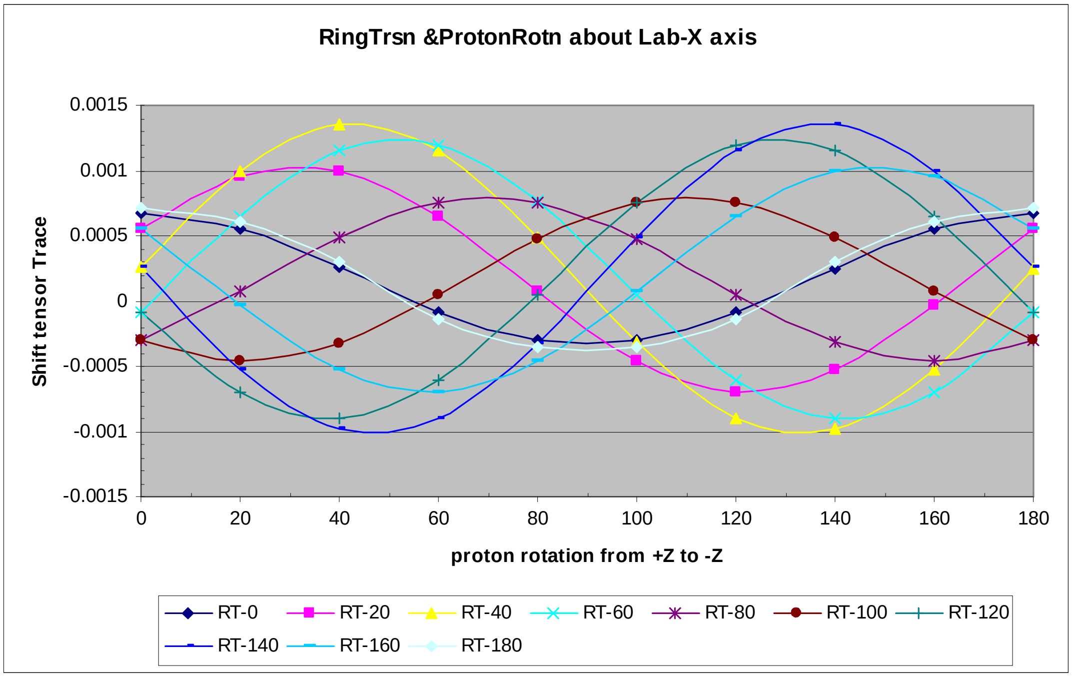
Graph_4

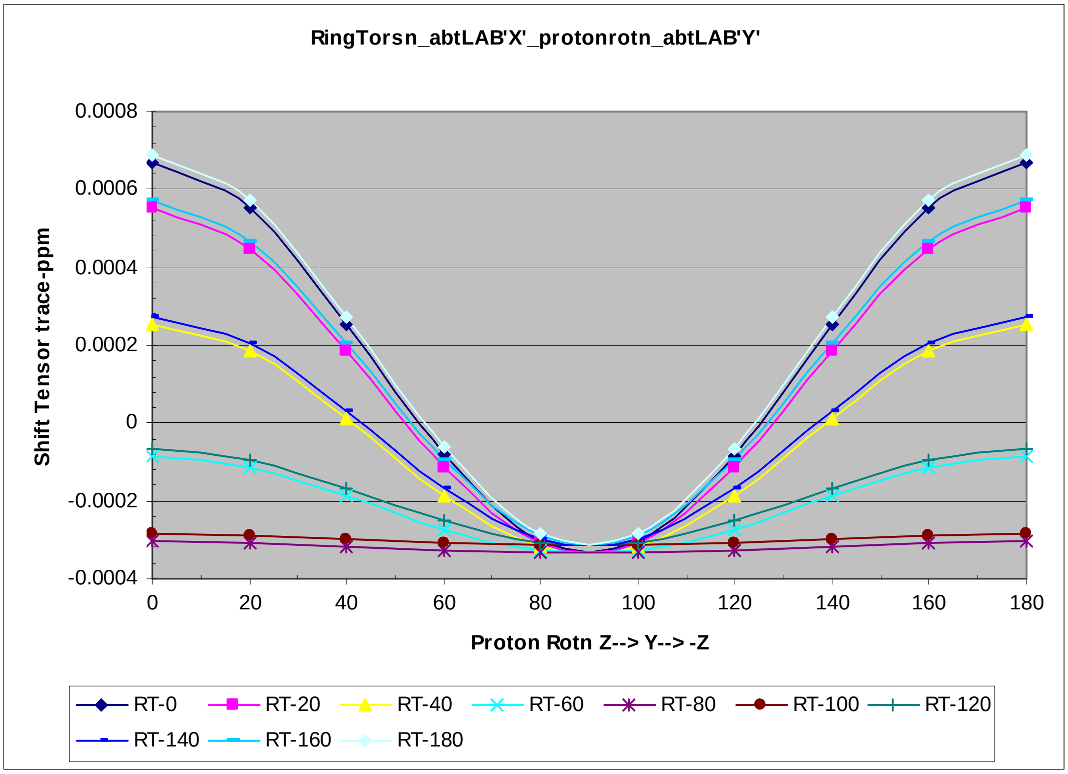


Graph_5

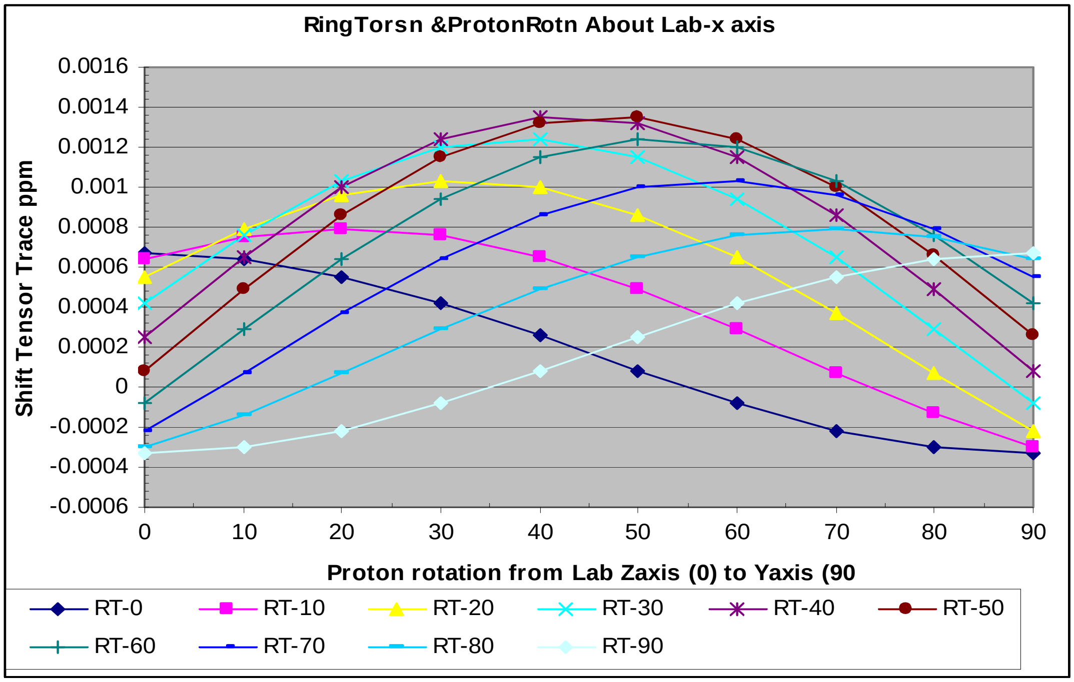


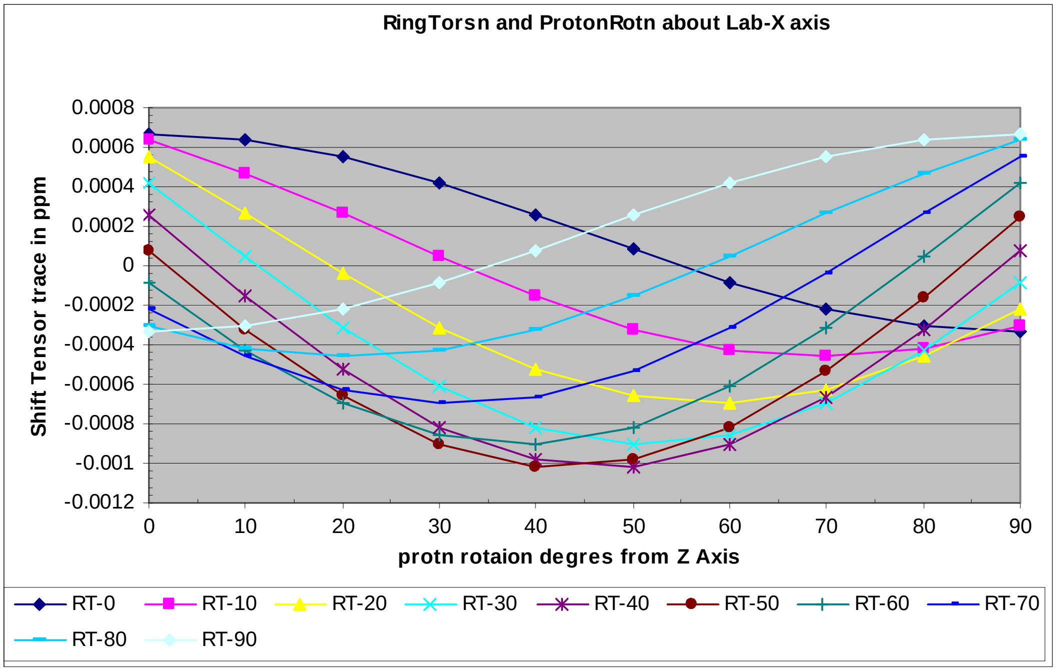
Graph_6

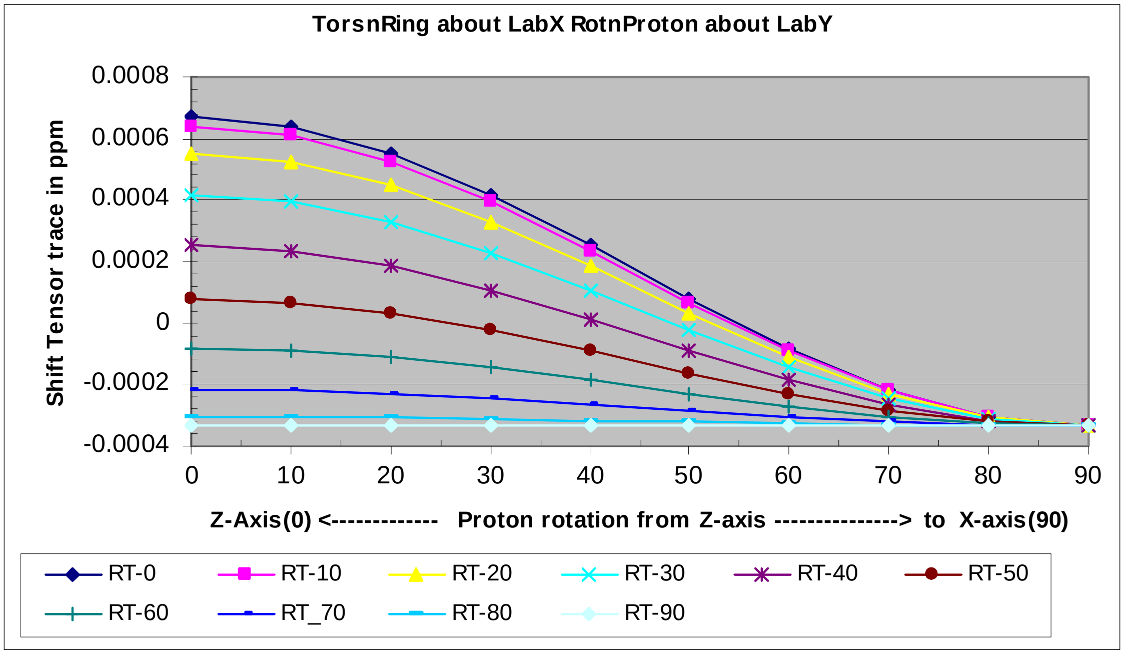


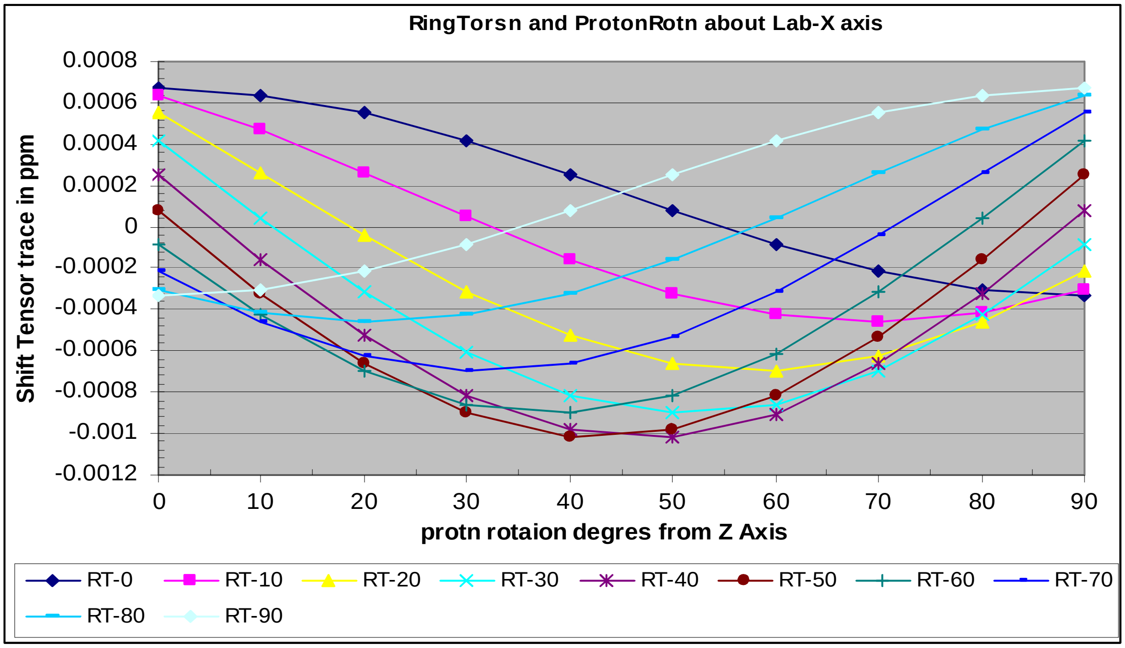


Display of only 'trace' (the isotropic shift values) as a function of the variation a parameters for the variation in proton position vector (by rotation 0-180 degrees in steps of 20 deg.) and in the ring disposition (termed torsion; 0-180 in steps of 20 degrees) can be seen above for a comprehension of the trends, ranges and distinctions.


RingTorsn &ProtonRotn About Lab-x axis
Shift Tensor Trace ppm
0.0016
0.0014
0.0012
0.001
0.0008
0.0006
0.0004
0.0002
0
-0.0002
-0.0004
-0.0006
0
10
20
30
40
50
60
70
80
90
Proton rotation from Lab Zaxis (0) to Yaxis (90
RT-0
RT-10
RT-20
RT-30
RT-40
RT-50
RT-60
RT-70
RT-80
RT-90


RingTorsn and ProtonRotn about Lab-X axis
Shift Tensor trace in ppm
0.0008
0.0006
0.0004
0.0002
0
-0.0002
-0.0004
-0.0006
-0.0008
-0.001
-0.0012
0
10
20
30
40
50
60
70
80
90
protn rotaion degres from Z Axis
RT-0
RT-10
RT-20
RT-30
RT-40
RT-50
RT-60
RT-70
RT-80
RT-90


TorsnRing about LabX RotnProton about LabY
Shift Tensor trace in ppm
0.0008
0.0006
0.0004
0.0002
0
-0.0002
-0.0004
0
10
20
30
40
50
60
70
80
90
Z-Axis(0) <------------- Proton rotation from Z-axis ---------------> to X-axis(90)
RT-0
RT-10
RT-20
RT-30
RT-40
RT-50
RT-60
RT_70
RT-80
RT-90


RingTorsn and ProtonRotn about Lab-X axis
Shift Tensor trace in ppm
0.0008
0.0006
0.0004
0.0002
0
-0.0002
-0.0004
-0.0006
-0.0008
-0.001
-0.0012
0
10
20
30
40
50
60
70
80
90
protn rotaion degres from Z Axis
RT-0
RT-10
RT-20
RT-30
RT-40
RT-50
RT-60
RT-70
RT-80
RT-90