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Structures, Stability and Hydrogen Bonding in Inositol Conformers

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DOI: 10.1039/x0xx00000x

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Various *ab initio* calculations using the density-functional (DFT), the second order Moller-Plesset perturbation (MP2) and self-consistent reaction field (SCRF) theories were performed on thirteen theoretically possible inositol stereoisomers. Gas phase calculations reveals that the *myo*- and *neo*- isomers of inositol (bearing one and two axial hydroxyl groups, respectively) are marginally more stable (by 0.5 kcal mol^{-1}) than the all equatorially substituted *scyllo*-inositol. The calculations when done in different polar solvents shows that the scyllo-inositol becomes most stable inositol isomer, a fact attributed to weaker intramolecular hydrogen bonds. The individual hydrogen bond energy in all the isomers of inositol was also estimated using molecular tailoring approach (MTA). The calculated hydrogen bond energies in these isomers are in excellent agreement with reported O-H...H bond distances and ν_{O-H} strectching frequencies. The estimated H-bond energy values suggest that the order of the intramolecular hydrogen bonding strength follows: axial-axial>equatorial-axial>axial-equatorial>equatorial-equatorial hydrogen bonds.The intramolecular hydrogen bonds in *scyllo* isomer are much weaker than those in other conformers, thus making this isomer more stable in polar solvents.

Introduction

Inositol is a sixfold alcohol of cyclohexane. The most abundant derivatives of inositol include its methyl esters and phosphate esters. Inositol derivatives function as intracellular signal transduction molecules[1-4] and thus play important roles in various biological activities.[5-8] Amino or substituted amino derivatives of inositol also occur in many antibiotics.[9-10] Inositol derivatives are extensively used in treatments of panic disorders[11], polycystic ovary syndrome (PCOS)[12], cancer[13], metabolic syndrome[14] etc. Inositols serve as a building block for the synthesis of natural products[15-21] and molecular crystals with unusual properties.[22-23] "Insoamino acids" are new class of inositol derivatives composed of inositol and β- or γ- amino acids, used for the construction of peptide nanotubes with hydrophobic cavities.[24-25]

The maximum number of stereoisomers for a molecule with more than one stereogenic centres is given by 2^n rule (where, n= number of stereogenic centers), which in the case of inositol should be sixty four (2^6). The symmetry inherent in inositol, as it is cyclic six membered ring, reduces the possible distinct stereoisomers to sixteen. Of these six are made of three enantiomeric pairs while the rest are meso compounds leading to only thirteen theoretically possible isomers of inositol as enantiomeric pairs(i.e., *dl*(4e/2a), *allo*(3e/3a) and *1,2eq*(2a/4e)) have identical energies (Figure 1). A survey of the literature reveals that all previous theoretical studies consider only eight stereoisomers, ignoring the more axially substituted inositols.[26-28] The conformational study of inositols is thus important as they provide a simple model system for investigating conformational effects in other substituted cyclohexane systems.[29-30] Important theoretical studies were mostly performed on phosphate derivatives of *myo*-inositol. Other than that, NMR analysis of O-methyl-inositol isomer,[28] crystal structure for *myo*-[31] and *epi*-[32] inositols, vibrational spectral study of all inositols[33] were also reported. *Ab inito*

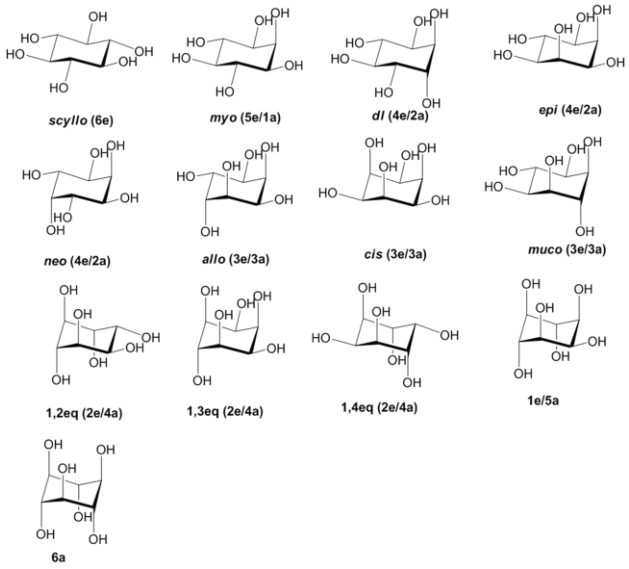

Figure 1: The thirteen possible Inositol isomers, e and eq stands for equatorial and a stands for axial hydroxyl groups.

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† The C-C-C-C ring torsion angle is reported in Table S1 supplementary information. Authors wish to dedicate this work to Professor Shridhar R. Gadre on his 65th birthday.

calculations on *scyllo*, *myo*, *dl*, *epi* and *neo* isomers of inositols has already been reported, which shows that *myo*- and *neo*-inositols are much lower in energy as compared to *scyllo*-inositol.[27]

In this work, we investigate the structures and the relative stability of all thirteen possible inositol isomers by employing DFT and MP2 levels of theory. The effect of solvent on the relative stability of these conformers is also discussed. Importantly, we show here that the intramolecular O-H…O hydrogen bonding patterns and the strength of these interactions in terms of the hydrogen bond (H-bond) energy calculated by molecular tailoring based approach (MTA),[34-39] in these inositol conformers make scyllo- inositol more stable in polar media.

Computational methods

The geometries of all theoretically possible thirteen stereoisomers of inositol were constructed and optimized considering the concerted intramolecular hydrogen bonding arrangement of the hydroxyl groups at the second order Möller-Plesset perturbation (MP2) level[40-41] employing the 6-311+G(d,p)[42-43] basis set. During optimization of the geometries, no symmetry was imposed. Frequency calculations were performed to characterize the optimized structures as true minima (no imaginary frequency found). In order to evaluate the changes in energy of inositol isomers in solvent media, we also carried out the single point calculations in various solvents at the B3LYP[44-46] density functional theory (DFT) and the 6-311+G(d,p) basis set using Polarizable continuum model (PCM)[47-51] method. Intramolecular hydrogen bond energies in inositol isomers were obtained using the molecular tailoring approach (MTA).[34-39]All quantum chemical calculations mentioned above were carried out using the GAUSSIAN 09 program packages.[52]

Results and discussion

Geometry of inositol isomers

Figure2 represents the MP2/6-311+G(d,p) optimized structures of thirteen inositol isomers. As seen in Figure 2, the hydroxyl groups in these isomers were oriented to maximize internal hydrogen bonding which is retained in these final optimized structures. Individual C-C bond lengths in all these optimized structures do not show any systematic variation; See Table 1. The C-C bond distances are in general relatively shorter than those in cyclohexane optimized at MP2/6-311+G(d,p) level of theory. This is may be due to the substitution by electronegative hydroxyl groups as predicted by the Bent's rule,[53-54] (electron withdrawing substituent's tend to reduce the covalent radius of carbon). In general, it is observed that the average C-C bond length increases as the number of axial hydroxyl groups increases from *6e* to *6a* inositol isomers; See Table 2 for the axial (ax) and equatorial (eq) orientations of hydroxyl groups in these inositol conformers. This increment in bond lengths can be accounted on the basis of size of the hydrogen bonded ring in inositols. In general, a five membered H-bonded ring is more strained than a six membered ring. For example, in inositols up to *3e/3a* isomers, hydrogen bonding between hydroxyl groups mainly lead to formation of five membered H-bonded rings making them more strained thus resulting in shortened bond lengths (cf. Table 1 and Figure 2). From *2e/4a* to *6a* isomers, the number of six membered H-bonded rings increases from two to six because of increase in number of axial-axial hydrogen bonds, which makes the cyclohexane ring slightly pucker away from the normal chair form resulting in lengthening of C-C bond lengths.

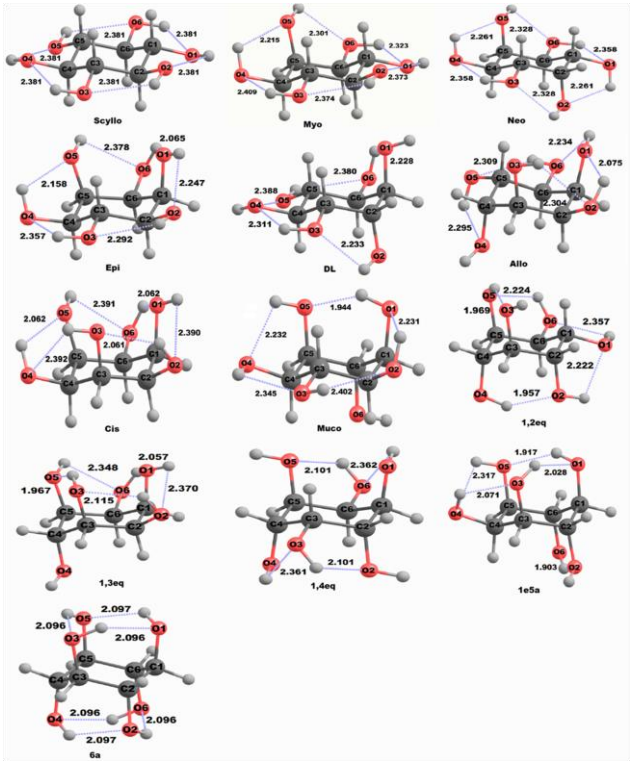

Figure 2: The MP2/6-311+G(d,p) optimized structures for all thirteen inositol conformers.

In inositols, CCC angle values do not show any dependence on the position of hydroxyl groups (cf. Table 3). The average CCC angle in *scyllo* inositol is smaller compared to other inositol isomers by 0.3 to 3.0 degree. The above results indicate the small degree of planarity in all isomers except *scyllo* inositol (in consideration of planner cyclohexane ring whose CCC angles are at 120 degree). Whereas, the orientation of hydroxyl groups in inositols shows correlation with the values of OCC angles. Inositol isomers shows wide range of adjoining OCC angles varying from 0.4 to 6.1 degree, depending upon the orientation of two –OH groups on adjacent carbons and the strength of intramolecular hydrogen bonding among them. An OCC angle on the same side of the OC bond as a hydroxyl group is about 4.4 to 5.2 degree larger than that on the opposite side in *scyllo*, *myo* and *neo* isomers. The intramolecular hydrogen bonding is likely to be the reason for the deviation of OCC angles from regular tetrahedral angle of 109.5 degree, analogous to that observed in 1,2- ethanediol.[55-56] The average C-C-C-C (ring torsion) angles in all inositol isomers range between 1.2 to 9.3 degree and are smaller than that observed

for *scyllo*- inositol; See supporting information Table S1. Above results are consistent with the CCC angles showing

Inositol isomers	Average C-C bond lengt(in Å)
Scyllo(6e)	1.518
Myo(5e/1a)	1.520
Neo(4e/2a)	1.522
Epi(4e/2a)	1.524
Dl(4e/2a)	1.521
Muco(3e/3a)	1.525
Allo(3e/3a)	1.525
Cis(3e/3a)	1.528
1,3eq(2e/4a)	1.529
1,2eq(2e/4a)	1.529
1,4eq(2e/4a)	1.528
1e/5a	1.533
6a	1.533

Table 1 : Average C-C bond lengths of inositol isomers calculated by MP2/6-311+g(d,p) level of theory. e and eq stands for equatorial and a stands for axial hydroxyl groups.

slightly planner cyclohexane ring in all isomers other than *scyllo* inositol. Thus, the flattening of ring torsion angles, differences in C-O bond lengths and CCC angles in all inositol isomers are in accordance with stereorepulsion involving axial OH group(s).

It is seen that on going from *6e scyllo* to *6a* isomers of inositol, the orientation of the -OH groups vary considerably, See Figure 2. For instance, in the *scyllo*, *myo*, *neo*, *epi*, *dl*, and *cis* isomers, the orientation of –OH groups are in clockwise direction, that is, it forms a network of OH(1) → OH(2) → OH(3) → OH(4) → OH(5) → OH(6) → OH(1) hydrogen bonds. However, in *dl* isomer, H-bond network starts from OH(2) group and there is no H-bond between OH(1) and OH(2) hydroxyl groups due to their axial and adjacent positions. In *allo* isomer, hydroxyl groups are oriented in counterclockwise direction forming OH(3) → OH(2) → OH(1) → OH(6) → OH(5) → OH(4) network of H-bond. Orientation of –OH groups are in an counterclockwise direction in the *muco* isomer, in sequence of OH(1) → OH(5) → OH(4) → OH(3) → OH(2) → OH(1), with OH(6) and OH(1) groups at axial positions. In *1,2eq* isomer, –OH groups are in an counterclockwise direction in the sequence OH(4) → OH(2) → OH(1) → OH(6) → OH(5) → OH(3) with OH(1) and OH(6) hydroxyl groups occupying the equatorial positions. *1,3eq* isomer have OH(1) → OH(2) → OH(3) → OH(5) → OH(6) → OH(1) H-bond network with clockwise direction of –OH groups, where OH(1), OH(3), OH(4) and OH(5) groups are at axial positions. *1,4eq* isomer forms two short OH(1) → OH(6) → OH(5) and OH(4) → OH(3) → OH(2) H-bond networks in a counter-clockwise direction, where OH(1), OH(2), OH(4) and OH(5) groups are at axial positions. The isomers *1e/5a* and *6a* show the orientation of –OH groups in clockwise direction. In 1e/5a isomer, OH(1) → OH(5) → OH(4) → OH(3) → OH(1) H-bond network contains all –OH groups at axial position except OH(4). Also, OH(6) → OH(1) axial-axial H-bond is present in *1e/5a* isomer. Two H-bond networks OH(1) → OH(5) → OH(3) → OH(1) and OH(2) → OH(6) → OH(4) → OH(2) are present in *6a* isomer with all –OH groups at axial positions.

Conformers	O^1H	O^2H	O^3H	O^4H	O^5H	O^6H
Scyllo (6e)	eq	eq	eq	eq	eq	eq
Myo (5e/1a)	eq	eq	eq	eq	ax	eq
Neo (4e/2a)	eq	ax	eq	eq	ax	eq
Epi (4e/2a)	ax	eq	eq	eq	ax	eq
DL (4e/2a)	ax	ax	eq	eq	eq	eq
Allo (3e/3a)	ax	eq	ax	ax	eq	eq
Cis (3e/3a)	ax	eq	ax	eq	ax	eq
Muco(3e/3a)	ax	eq	eq	eq	ax	ax
1,2eq(2e/4a)	eq	ax	ax	ax	ax	eq
1,3eq(2e/4a)	ax	eq	ax	ax	ax	eq
1,4eq(2e/4a)	ex	ax	eq	ax	ax	eq
1e/5a	ax	ax	ax	eq	ax	ax
6a	ax	ax	ax	ax	ax	ax

Table 2: The axial (ax) and the equatorial (eq) orientation of hydroxyl group in 13 possible inositol isomers.

The presence of intramolecular hydrogen bonding in inositols is supported by various studies like H^1 NMR, infrared spectra, study of 1,3,5-trideoxy-1,3,5-tris(dimethylamino)-cis inositol (TDCI),[57] NMR dynamics study of chair-chair interconversion of cis-inositol.[58] In order to understand the differences in the intramolecular hydrogen bonds between these inositol isomers, we discussed here the intramolecular O-H…O H-bond distances in these MP2 optimized inositol isomers; See Table 4 and Figure 2 for details. As seen in Table 4, the OH…O hydrogen bond distances are in the range of 1.9 to 2.4 Å in these inositol isomers. The OH…O distances in the hydrogen bond involving two equatorial hydroxyl groups are found to be about 2.2 to 2.4 Å and 1.9 to 2.3 Å for those involving axial –OH groups. This indicates that the intramolecular hydrogen bond involving axial hydroxyl groups is stronger than that involving equatorial hydroxyl groups. Thus, axial hydroxyl group actually provides a stabilizing effect, which may be the reason for lower internal energies obtained for certain inositol isomers as compared to *scyllo*-inositol. The order of strength of intramolecular hydrogen bonding follows:

Angles	6e	5e/1a	4e/2a			3e/3a			2e/4a			1e/5a	6a
	Scyllo	myo	neo	epi	dl	allo	cis	muco	1,2eq	1,3eq	1,4eq		
$C_5C_6C_1$	110.4	111.5	111.3	110.3	111.0	112.2	114.7	111.0	111.2	111.4	114.5	112.4	112.0
$C_6C_1C_2$	110.4	110.4	111.7	111.9	111.8	114.9	112.2	112.1	111.9	112.0	112.3	111.9	112.0
$C_1C_2C_3$	110.4	109.5	110.6	115.1	111.6	111.8	114.7	111.4	112.2	111.4	112.4	112.0	112.0
$C_2C_3C_4$	110.4	110.6	111.3	111.9	111.3	111.6	112.2	110.9	111.2	113.9	114.5	111.1	112.0
$C_3C_4C_5$	110.4	111.3	111.7	111.1	110.1	110.5	114.7	111.3	111.7	113.1	112.3	112.9	112.0
$C_4C_5C_6$	110.4	111.2	110.6	109.8	109.9	111.0	112.2	110.9	111.5	113.9	112.4	115.0	112.0
average	110.4	110.7	111.2	111.7	110.9	112.0	113.4	111.2	111.6	112.6	113.0	112.5	112.0

Table 3: The C-C-C bond Angles (in degree) in the various MP2/6-311+G(d,p) optimized inositol isomers.

O_{axial}-H…O_{axial} > $O_{equtorial}$-H…O_{axial} > O_{axial}-H…$O_{equatorial}$ > $O_{equatorial}$-H…$O_{equatorial}$.

In Table 5 the unscaled O-H stretching frequencies calculated at MP2/6-311+G(d,p) level are listed. The unscaled O-H frequencies lie between 3882 and 3729 cm^{-1}. In these inositols, the –OH groups that are not involved in H-bonding are seen to show a high stretching frequency; For instance, the O1H group of *dl(4e/2a*) conformer has the highest O-H stretching frequency of 3882 cm^{-1}. The average O-H stretching frequency of the –OH groups forming O-H…O hydrogen bond between the equatorial hydroxyl groups is about 3849 cm^{-1}. The O-H stretching frequency decreases further when OH groups are involved in either equatorial-axial or axial-equatorial hydrogen bonded interactions (~3800 cm^{-1}). Further decrease in O-H stretching frequency up to 3729 cm^{-1} are observed when hydroxyl group involved in the axial-axial hydrogen bonds. These decreased in frequency (red shift) is in agreement with the shortening of O-H…O distances on moving from equatorial-equatorial to axial-axial O-H…O H-bonds.

Thus, from the above discussion about the H-bond distances and O-H stretching frequencies, it is conjectured that stronger O-H…H bonds are formed when there are more axial-axial O-H…O interactions. Besides this, the axial-equatorial O-H…O bonds also emerge to be stronger than the equatorial-equatorial ones. The above gas phase observations regarding strength of hydrogen bonds in inositol isomers is supported by various reports present in literature.[59, 60]

Relative stability of the inositol isomers

The absolute energy of *scyllo* isomer and the relative energies of all inositol isomers with respective to *scyllo* isomer, calculated at MP2 and B3LYP levels employing 6-311+G(d,p) basis sets are reported in Table 6. In general, it is believed that in case of substituted cyclohexanes, there is a large steric strain if a substituent is present at the axial position due to butane gauche interactions than when it is present at the equatorial position. Thus, axial substitution makes the molecule generally less stable (or higher energy) than an equatorially substituted molecule. But, here the trend in energies obtained at MP2/6-311+G(d,p) level reveals that *neo*-inositol (with 2 axial hydroxyl groups) is most stable followed by *myo*-inositol (with 1 axial hydroxyl group) and then by *scyllo*-inositol (with all 6 equatorial hydroxyl groups). However, the energy difference in these conformers is very marginal (~0.5 kcal mol^{-1}). There may be other reasons (such as strong intramolecular hydrogen bonding due to axial–OH groups) that may provide the slightly higher stability of two and one axial -OH groups containing inositols (*-neo* and *–myo*) over all equatorial –OH groups containing *scyllo*-inositol. Thus, the above discussed generalization works in these inositol isomers as well with exceptions of *–neo* and *–myo* isomers. These results calculated at MP2 level are similar to those calculated at B3LYP level, except that the *myo* isomer becomes less stable as *scyllo* at B3LYP level (cf. Table 6).

Free energies

Calculation using MP2/6-311+G** molecular structures of the corresponding free energies (at 298.15 K) of inositols were also performed. Table 7 presents various thermodynamic quantities including zero-point vibrational energy (ZPE), thermal energy (E) and entropy contributions. The trend in ZPE reveals that the all equatorially substituted *scyllo* (6e) inositol is more stable relative to other isomers. However, other isomers are favour over *scyllo*-inositol when the entropy is considered. All inositol isomers shows stability over the *scyllo*- inositol except *1,4 eq* isomer, in terms of the thermal energies. But, if we consider overall energies by inclusion of electronic energies along with thermal energies, then, it shows only *myo* (with 1 –OH group) and *neo* (with 2 –OH groups) inositols to be more relatively stable than *scyllo*- inositol. In case of free energies of inositols, *scyllo*- isomer shows stability over all other isomers. Thermodynamic quantities of inositol at B3LYP level in gas phase and free energies of all isomers relative to *–scyllo* isomer in various solvents are also listed in supplementary material as table S2 and S3, respectively.

	Scyllo	Myo	Neo	Epi	Dl	Allo	Cis	Muco	1,2eq	1,3eq	1,4eq	1e/5a	6a
$O_1H\ldots O_2$	2.381	2.373	2.261	2.247	-	2.075	2.390	2.231	2.222	2.370	-	-	-
$O_2H\ldots O_3$	2.381	2.374	2.328	2.292	2.233	2.304	2.061	2.402	-	2.115	2.101	-	2.096
$O_3H\ldots O_4$	2.381	2.409	2.358	2.357	2.311	-	2.392	2.345	-	-	2.361	2.071	-
$O_4H\ldots O_5$	2.381	2.215	2.261	2.158	2.388	2.295	2.062	2.232	-	-	-	2.317	2.096
$O_5H\ldots O_6$	2.381	2.301	2.328	2.378	2.380	2.309	2.391	-	2.224	2.348	2.101	-	-
$O_6H\ldots O_1$	2.381	2.323	2.358	2.065	2.228	2.234	2.062	-	2.357	2.057	2.362	-	-
$O_4H\ldots O_6$	-	-	-	-	-	-	-	-	-	-	-	-	-
$O_5H\ldots O_3$	-	-	-	-	-	-	-	-	1.969	1.967	-	-	-
$O_2H\ldots O_4$	-	-	-	-	-	-	-	-	1.957	-	-	-	-
$O_5H\ldots O_1$	-	-	-	-	-	-	-	1.944	-	-	-	1.917	2.096
$O_3H\ldots O_1$	-	-	-	-	-	-	-	-	-	-	-	2.028	-
$O_6H\ldots O_2$	-	-	-	-	-	-	-	-	-	-	-	1.903	2.096
$O_1H\ldots O_4$	-	-	-	-	-	-	-	-	-	-	-	-	2.096
$O_3H\ldots O_6$	-	-	-	-	-	-	-	-	-	-	-	-	2.096

Table 4. The intramolecular O-H...O H-bond distances (in Angstrom) in the MP2/6-311+G(d,p) optimized inositol conformers.

Solvent effects on the relative stabilities of inositols

Gas phase calculations of inositols shows that certain axial inositols (*neo*- and *myo*-inositols in case of MP2 level and *neo*-inositol in case of B3LYP level) are more stable than all equatorial *scyllo*-inositol because of presence of a more favorable intramolecular hydrogen bonding in the former. But, in the presence of solvent, competition with intermolecular hydrogen bonding could alter the strength of intramolecular hydrogen bonding, which in turn could depend on the polarity of the solvents. In nonpolar solvents, intramolecular hydrogen bonding is likely to dominate but, in polar solvents, competition from intermolecular hydrogen bonding could be more favorable. A study of the solvent effect on the closely related glucose molecule shows that aqueous solution favors all equatorially substituted β-isomer over the α-isomer.[59] Studies on other similar carbohydrates, which are related to inositol structure, also show significant differences in gas and condensed phases.[60] Thus, we performed calculations in presence of various solvents using self-consistent reaction field (SCRF) with Polarizable continuum method (PCM) at B3LYP level of theory.

PCM calculations suggests that all equatorially substituted *scyllo*-inositol as the most stable inositol as compared to others isomers especially, -*myo* and –*neo* inositols, in all 3 polar solvents (water, dmso, ethanol); See Table 6 for details. This may be attributed to favorable intermolecular solute-solvent interaction present in -*scyllo* relative to other axial –OH groups containing inositols, where the intramolecular hydrogen bonding is expected to be more dominant. Also, the hydroxyls in the all equatorial scyllo-inositol are better positioned to form intermolecular hydrogen bonds, supported by the study of solvent effects on closely related glucose molecule.[59]

The comparison of energy of these isomers in the gas phase and solvents obtained by B3LYP method shows that overall energy gets lowered in condensed phases. Thus, the presence of polar solvent stabilizes all isomers of inositols more than when they are present in vacuum. Also, the *scyllo*-inositol becomes most stable in all polar solvents because of favorable intermolecular solute-solvent interaction.

Strength of intramolecular O-H…O hydrogen bonds in inositol isomers

As discussed earlier, the hydroxyl groups in inositol are involved in the formation network of intramolecular OH...O H-bonds. Here, we discuss the energy of each individual hydrogen bond and the effect of the cooperative networking on their strength estimated with the molecular tailoring approached proposed in recent past.[34,61-64] The estimated hydrogen bond energy of each individual hydrogen bond in presence of the cooperative H-bonded network at the MP2 level is reported in Table 8. In this table, the individual hydrogen bond are labelled based on the hydroxyl groups involved and the exact directionally is not considered. For example, the hydrogen bond between O^1H and O^2H in *allo* isomer is labelled as $O^1H...O^2$ in Table 8 although it is should have been as $O^2H...O^1$ as per the Figure 2. As seen in Table 8, the estimated hydrogen bond energies are in the range of 1.9 to 3.9 kcal mol^{-1} suggesting that the variable strengths of hydrogen bonds are found in these inositol isomers. As one move across Table 8, the H-bond strength increases; In other words, the hydrogen bond in inositol isomers involving more equatorial groups are relatively much weaker. In general, the estimated hydrogen bond energy follows: O_{axial}-H…O_{axial} > $O_{equtorial}$-H…O_{axial} > O_{axial}-H…$O_{equatorial}$ > $O_{equatorial}$-H…$O_{equatorial}$. Thus the estimated hydrogen bond energies are in agreement with the previously discussed H-bond strength based on hydrogen bond distances and vibrational frequency. For instance, the average hydrogen bond energy of one H-bond in *scyllo* isomer is about 2.2 kcal mol^{-1} as compared to *6a* isomer wherein the average hydrogen bond energy is largest (3.02 kcal mol^{-1}). There are

certain exceptions to this average hydrogen bond energies; there hydrogen bonds in some of these isomers wherein the H-bond energy is smaller than the *scyllo* isomer and lager than those in *6a* isomer despite the fact that the number of hydroxyl groups are less in equatorial and axial positions with respective *scyllo* and *6a* isomers, respectively. For Instance, the strength of some of the hydrogen bond in *myo* ($O^4H...O^5$), neo ($O^1H...O^2$ and $O^4H...O^5$) etc. is smaller than in *scyllo* isomer despite less number of equatorial groups in *myo*, *neo*, *dl* and *allo* isomers. Also the hydrogen bond strength in *muco* ($O^5H...O^1$), 1,3eq ($O^2H...O^3$,$O^5H...O^3$) and 1e/5a ($O^3H...O^4$, $O^5H...O^1$) is large than the average hydrogen bond energy in *6a*(6axial groups) isomer despite lesser number of axial groups in *muco*, *1,3eq*, and *1e/5a*. There is one major exception to the above discussed trend in H-bond energies is *1,4eq* isomer. In *1,4eq* isomer, the hydrogen bond energy is much smaller (1.7 to 1.9 kcal mol^{-1}) than *scyllo* isomer despite of four axial hydroxyl groups in *1,4eq* inositol. The reason for this weaker strength of hydrogen bond in *1,4eq* conformer is cleared if one look at the structure of this isomer (See Figure2). As seen in *1,4eq* isomers, despite the four axial groups, there are in total four hydrogen bonds which involves two equatorial...axial and two axial...equatorial interactions. Thus the smaller hydrogen bond energy in *1,4eq* isomer may be attributed to weaker axial...equatorial (or equatorial...axial) interaction than those in axial...axial interaction in *6a* isomer. However, as discussed earlier, axial...equatorial (or equatorial...axial) are in general stronger than equatorial-equatorial interaction thus we expect that hydrogen bond strength in *1,4eq* isomer to be stronger than those in *scyllo* isomer. The reason for the weaker hydrogen bond strength in *1,4eq*and other isomers of inositol than in *scyllo* isomer may be attributed to loss of cooperativity due to networking of hydrogen bond in *1,4eq* as is discussed in the next section.

The effect of cooperativity on the strength of the intramolecular O-H…O hydrogen bonds in inositol isomers

In general, it is accepted fact that the strength of individual hydrogen bond is enhanced due to presence of an interconnected network of hydrogen bonds. The phenomenon is well known as cooperativity effect in Chemistry and Biology. In this work, we quantified this effect on the strength of individual hydrogen bond by estimating their energy by isolating such bond from the network keeping the overall geometry to be same as that in presence of network of cooperative network. We have applied this methodology in recent past for various systems of interest. For details of the general methodology for estimation of hydrogen energy and cooperative contribution see reference 34 and 61-64. In Table 9, we present the intramolecular OH...O hydrogen bond energy of the individual H-bond in the absence of cooperative network of hydrogen bonds at the MP2 level. The difference between the sum of H-bond energy in the presence of cooperative network (cf. Table 8) and in the absence of cooperative network of H-bonds is also presented in Table 9 as the total cooperative contribution. As seen in the Table 9, the hydrogen bond energy estimated in the absence of cooperative network of H-bond is smaller than the respective ones in the presence of network. In general the cooperative

Conformers	O^1H	O^2H	O^3H	O^4H	O^5H	O^6H
Scyllo (6e)	3849.5	3849.5	3849.7	3849.9	3849.9	3849.9
Myo (5e/1a)	3849.6	3849.8	3842.0	3817.9	3839.4	3841.1
Neo (4e/2a)	3821.0	3840.9	3833.2	3820.9	3840.8	3832.9
Epi (4e/2a)	3834.4	3839.2	3837.2	3810.1	3802.6	3808.6
DL (4e/2a)	3882.6	3822.9	3840.7	3851.2	3839.7	3818.7
Allo (3e/3a)	3832.6	3806.0	3848.2	3881.6	3821.3	3828.6
Cis (3e/3a)	3859.8	3797.9	3860.6	3798.4	3860.0	3798.1
Muco(3e/3a)	3735.3	3795.5	3838.1	3843.8	3812.6	3877.0
1,2eq(2e/4a)	3827.0	3805.9	3866.0	3768.6	3786.8	3790.1
1,3eq(2e/4a)	3849.0	3772.5	3729.2	3878.3	3841.6	3806.7
1,4eq(2e/4a)	3857.3	3877.3	3808.6	3857.0	3877.4	3808.8
1e/5a	3739.9	3868.8	3765.9	3777.0	3836.7	3790.3
6a	3794.8	3771.3	3794.6	3791.9	3772.0	3791.7

Table 5: The unscaled O-H stretching frequency (cm^{-1}) in the MP2/6-311+G(d,p) optimized inositol conformers.

contribution is indeed substantial (2 to 5 kcal mol^{-1}) in these inositols isomers and is seen to be increases across the Table 9 apart from some exceptions which are discussed separately. This increased in the cooperative contributions is seems to depend on two factors (a) the number of hydrogen bonds in the network and (b) the strength of each of these bonds. As discussed in previous sections, the equatorial-equatorial hydrogen bonds are weaker than the equatorial-axial (or axial-equatorial) and the axial-axial hydrogen bonds are strongest. In case of scyllo isomer, there is pleasant symmetric network of hydrogen bond, the cooperative contribution is although substantial but is not large enough as compared to other isomers. This may be attributed to the weaker equatorial-equatorial (six) H-bonds (evident from the H-bond energy in Table 8) in this isomer. The cooperativity contribution is seen to increases in myo isomer and may be attributed to stronger equatorial-axial and axial-equatorial interaction. The cooperative contribution in neo and epi isomers is similar to that in scyllo isomer and may be due to some of the weak hydrogen bond in the network. In dl and allo isomers, there are only five H-bonds in the network and hence the cooperative contribution is smaller than that in scyllo, myo, neo and epi isomers. The cooperative contribution is substantially large (5 kcal mol^{-1}) in cis isomer and may be attributed to nice alternate three axial-equatorial and three equatorial-axial (total six) H-bonds in the network. In muco, 1,2eq, and 1,3eqisomers, although there are stronger axial-axial H-bonds in the network, it is expected that increase in the cooperative contribution is compensated by much weaker equatorial-equatorial hydrogen bond/s in the networks. More importantly, there are only five H-bonds in the network and the total contribution is smaller in these isomers. The cooperative contribution is almost null (0.1 kcal

mol^{-1}) in 1,4eq isomer is apparently due to the absolutely no networking (only two hydrogen bond in the network) of the H-bonds as discussed in previous Section. This is the reason although there are equatorial-axial and axial-equatorial H-bonds in 1,4eq isomer, the estimated H-bonds energies are smallest in these isomer. The cooperative contribution is highest (5.4 kcal mol^{-1}) in 6a isomer wherein there are stronger axial-axial H-bonds (3 above and 3 below the cyclohexane ring).

In summary, the intramolecular hydrogen bond strengths in all the inositol isomers studied in the present work are substantially enhanced or altered due to the interconnected networking of H-bond. In general, the strength of stronger (axial-axial) hydrogen bond is enhanced substantially than the weaker equatorial-equatorial bonds. Further the total cooperativity contributions depend on the number and strength of individual H-bonds in the network.

Conclusions

In the present work, the geometries of all the thirteen theoretical possible conformers of isomers of inositol are explored at the correlated MP2 level of theory for the first time. Earlier studies in the literature reports only some of the lower energy conformers and ignored the conformers with axial orientation of hydroxyl groups. We studied the relative stability of these conformers in both gas as well as solvent phase. It is seen that in gas phase, the conformers -*neo* and –*myo* conformers with two axial hydroxyl group is marginally stable (by 0.5 and 0.3 kcal mol^{-1}) than that with all equatorial hydroxyl groups (*scyllo*-inositol). The gas phase stability of the conformers with increase in number of axial hydroxyl group decreases substantially. For instance, the *6a* conformer (six axial hydroxyl groups) is destabilized by 11.5 kcal mol^{-1} than the *scyllo* conformer (six equatorial hydroxyl groups).

	6e	5e/1a	4e/2a			3e/3a			2e/4a			1e/5a	6a
Method	**Scyllo**	**Myo**	**neo**	**epi**	**dl**	**allo**	**cis**	**muco**	**1,2eq**	**1,3eq**	**1,4eq**		
MP2(gas)	-685.69545	-0.54	-0.36	2.52	5.62	4.47	9.80	1.26	2.80	5.28	11.30	7.21	11.40
B3LYP(gas)	-687.42282	0.01	-0.38	3.01	6.45	5.27	9.81	2.26	3.60	6.00	11.50	7.34	11.70
B3LYP(Water)	-687.45997	0.32	1.42	4.50	16.51	4.70	9.74	2.57	4.86	6.49	6.73	9.53	19.35
B3LYP(DMSO)	-687.45667	0.95	0.86	4.53	14.56	4.64	8.57	2.71	4.47	6.11	7.07	8.93	17.18
B3LYP(Ethanol)	-687.45596	0.90	1.22	4.06	14.39	3.60	9.21	2.45	4.40	6.21	7.34	9.05	17.02

Table 6: The computed absolute energies of *scyllo*-isomers (in Hatree) and that of other isomers of inositols (in kcal/mol) relative to *scyllo*-inositol in gas and solvent phase at various levels of theory and employing 6-311+G(d,p) basis sets.

	5e/1a	4e/2a			3e/3a			2e/4a			1e/5a	6a
quantities	**Myo**	**neo**	**epi**	**dl**	**allo**	**cis**	**muco**	**1,2eq**	**1,3eq**	**1,4eq**		
ΔZPE[b]	0.40	0.80	0.55	0.41	0.54	0.30	0.85	1.13	0.78	0.09	0.94	0.46
ΔE[c]	-0.16	-0.31	-0.24	-0.15	-0.21	-0.11	-0.35	-0.51	-0.33	0.002	-0.44	-0.13
-TΔS[d]	-0.39	-0.72	-0.58	-0.37	-0.52	-0.30	-0.84	-1.23	-0.83	0.06	-1.11	-0.36
ΔG[e]	0.61	1.18	0.88	0.62	0.84	0.46	1.33	1.84	1.27	0.02	1.59	0.68

[a]Calculated at 298.15 K using the MP2/6-311+G** method, in kcal/mol. [b]For *scyllo*, ZPE= 125.65 kcal/mol. [c]Sum of rotational, translational, and thermal vibrational energies (excluding ZPE).For *scyllo*, E_t= 7.68 kcal/mol. [d]For *scyllo*, TS= 31.45 kcal/mol. [e]For *scyllo*, G= 102.47 kcal/mol.

Table 7. Thermodynamic quantities[a] of Inositols relative to the *scyllo* isomer

	Scyllo	Myo	Neo	Epi	Dl	Allo	Cis	Muco	1,2eq	1,3eq	1,4eq	1e/5a	6a
$O_1H…O_2$	-2.19	-2.17	-1.80	-2.85	-	-1.90	-2.33	-2.91	-3.03	-2.58	-	-	-
$O_2H…O_3$	-2.19	-2.13	-2.62	-2.24	-2.76	-3.43	-2.13	-2.49	-	-3.49	-1.92	-	-3.02
$O_3H…O_4$	-2.19	-2.56	-2.64	-2.72	-2.27	-	-2.32	-2.03	-	-	-1.67	-3.49	-
$O_4H…O_5$	-2.19	-1.90	-1.80	-2.03	-1.98	-1.87	-2.13	-2.82	-	-	-	-2.50	-3.02
$O_5H…O_6$	-2.19	-2.71	-2.62	-2.45	-2.56	-2.67	-2.33	-	-3.00	-1.98	-1.92	-	-
$O_6H…O_1$	-2.19	-2.96	-2.64	-2.05	-2.03	-2.89	-2.13	-	-2.61	-1.69	-1.67	-	-
$O_4H…O_6$	-	-	-	-	-	-	-	-	-	-	-	-	-
$O_5H…O_3$	-	-	-	-	-	-	-	-	-3.01	-3.36	-	-	-
$O_2H…O_4$	-	-	-	-	-	-	-	-	-3.16	-	-	-	-
$O_5H…O_1$	-	-	-	-	-	-	-	-3.84	-	-	-	-3.66	-3.02
$O_3H…O_1$	-	-	-	-	-	-	-	-	-	-	-	-2.44	-
$O_6H…O_2$	-	-	-	-	-	-	-	-	-	-	-	-3.03	-3.02
$O_1H…O_4$	-	-	-	-	-	-	-	-	-	-	-	-	-3.02
$O_3H…O_6$	-	-	-	-	-	-	-	-	-	-	-	-	-3.02
		-	-	-	-	-	-	-	-	-		-	-
SUM	**-13.14**	**14.43**	**14.13**	**14.35**	**11.61**	**12.76**	**13.37**	**14.09**	**14.80**	**13.10**	**-7.18**	**15.13**	**18.12**

Table 8: Intramolecular O-H…O hydrogen bond energy for individual hydrogen bond in presence of the OH…H hydrogen bond network various inositol isomers calculated at the MP2/6-311+G(d,p) level of theory.

	Scyllo	Myo	Neo	Epi	Dl	Allo	Cis	Muco	1,2eq	1,3eq	1,4eq	1e/5a	6a
$O_1H…O_2$	-1.73	-1.66	-1.46	-2.22	-	-1.42	-1.98	-2.40	-2.57	-2.01	-	-	-
$O_2H…O_3$	-1.73	-1.61	-2.20	-1.68	-2.54	-2.09	-1.82	-2.02	-	-2.76	-1.90	-	-2.12
$O_3H…O_4$	-1.73	-2.23	-2.40	-2.27	-1.78	-	-1.97	-1.50	-	-	-1.64	-2.78	-
$O_4H…O_5$	-1.73	-1.55	-1.46	-1.70	-1.41	-1.79	-1.82	-2.35	-	-	-	-2.10	-2.12
$O_5H…O_6$	-1.73	-2.23	-1.63	-2.14	-2.20	-2.37	-1.15	-	-2.48	-1.85	-1.90	-	-
$O_6H…O_1$	-1.73	-1.83	-2.40	-1.59	-1.95	-2.24	-1.81	-	-2.21	-1.41	-1.64	-	-
$O_4H…O_6$	-	-	-	-	-	-	-	-	-	-	-	-	-
$O_5H…O_3$	-	-	-	-	-	-	-	-	-3.01	-2.81	-	-	-
$O_2H…O_4$	-	-	-	-	-	-	-	-	-2.61	-	-	-	-
$O_5H…O_1$	-	-	-	-	-	-	-	-3.20	-	-	-	-	-2.12
$O_3H…O_1$	-	-	-	-	-	-	-	-	-	-	-	-2.47	-
$O_6H…O_2$	-	-	-	-	-	-	-	-	-	-	-	-1.57	-2.12
$O_1H…O_4$	-	-	-	-	-	-	-	-	-	-	-	-3.03	-2.12
$O_3H…O_6$	-	-	-	-	-	-	-	-	-	-	-	-	-2.12
SUM	**-10.38**	**-11.11**	**-11.56**	**-11.60**	**-9.86**	**-9.91**	**-10.54**	**-11.47**	**-12.88**	**-10.83**	**-7.07**	**-11.95**	**-12.75**
cooperativity	**-2.76**	**-3.34**	**-2.57**	**-2.75**	**-1.75**	**-2.85**	**-5.12**	**-2.63**	**-1.92**	**-2.28**	**-0.10**	**-3.17**	**-5.37**

Table 9: Intramolecular O-H…O hydrogen bond energy for individual hydrogen bond in absence of the OH…H hydrogen bond network various inositol isomers calculated at the MP2/6-311+G(d,p) level of theory.

These gas phase results are also seen to be consistent with those in the solvent phase. The *scyllo* isomer becomes the most stable and 6a isomer is least stable in solvents. The hydroxyl groups in these inositol isomers are involved in the formation of a network of intramolecular OH...O hydrogen bonds. In general, it follows that the OH...O hydrogen bond distances are longer when two hydroxyl groups involved in the formation of hydrogen bond are in equatorial positions. The hydrogen bond distances with hydroxyl groups with axial-equatorial or equatorial-axial orientations are generally shorter than those with equatorial-equatorial orientations and are longer than those observed for axial-axial orientations. These geometrical parameters suggest that the strength of hydrogen bond in these inositol isomers follows: O_{axial}-H…O_{axial} > $O_{equtorial}$-H…O_{axial} > O_{axial}-H…$O_{equatorial}$> $O_{equatorial}$-H…$O_{equatorial}$. This trend in hydrogen bond strength is reflected in the corresponding O-H stretching frequencies. For instance, the hydroxyl groups that are not involved in formation of hydrogen bond have the highest O-H stretching frequency. The O-H stretching frequency decreases (red shift) substantially when OH groups are involved in the formation of stronger hydrogen bond. The decrease in frequency (red shift) is in agreement with the shortening of OH…O distances on moving from equatorial-equatorial to axial-axial O-H…O hydrogen bonds. In order to get further insight into the strengths of these hydrogen bonds, we quantified the individual bond strengths and the effect of formation of cooperative network on the hydrogen bond strengths in all inositol isomers. For this purpose, the hydrogen bond energies were estimated in the presence and absence of cooperative networking using molecular tailoring approach. The estimated hydrogen bond energy in presence of cooperative network of hydrogen bonds is in the range of 2.2 to 3.8 kcal mol^{-1}. The estimated hydrogen bond energies are in qualitative agreement with the above discussed trend in their bond strength based on bond distances and vibrational frequency. The estimated cooperative contribution is substantial (2 to 5 kcal mol^{-1}) in most of these inositols isomers and is seen to increase as we go from isomers with more equatorial hydroxyl groups to isomers with more axial hydroxyl groups. This increase in the cooperative contributions seems to depend on two factors (a) the number of hydrogen bonds in the network and (b) the strength of each of these bonds. In general, it is seen that the strength of hydrogen bond increases substantially due to cooperative interaction when hydroxyl groups are involved in the formation of stronger axial-axial H-bonds.

We also wish to attribute the highest stability of the *scyllo* isomer in solvent to weaker intramolecular OH...O hydrogen bonds between equatorial hydroxyl groups, which in turn, may facilitate favourable intermolecular interaction. This stability correlates well with the natural abundance in inositol isomers. On the contrary, the inositol isomers with axial hydroxyl groups are involved in the formation of relatively much stronger H-bonds (for example, *6a* isomer) and hence are less stable due to overpowering steric factors in gas phase and unfavourable intermolecular interaction in solvent phase. It is indeed of great importance to understand this competition between the intermolecular and intramolecular interactions which effectively governs the relative stability of these inositol isomers in solvent phase. We hope that such a study would provide insights into the physicochemical properties of these important biological systems.

Acknowledgements

NS is thankful to the Indian Institute of Technology Kanpur (IITK), for a senior research fellowship. VS is thankful to the Dr. Harisingh Gour University for research fellowship. MMD is thankful to University Grant Commission for the initial start-up grant (No. F. 30-56/2014/BSR).

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