Conformational Analysis of 1,2:3,4-Di-O-isopropylidene-\(\alpha\)-D-galactopyranose

Six-membered rings play an important part in organic chemistry and the six-membered heterocyclic monosaccharides (sugars) play an important role in biological chemistry. The conformation of the six-membered ring (chair or boat) is critical to the arrangement of substituents on the ring. In this experiment, you will investigate the preference for the chair or boat conformation of a substituted monosaccharide. The reaction of D-Galactose with acetone using FeCl\(_3\) catalyst to produce 1,2:3,4-Di-O-isopropylidene-a-D-galactopyranose greatly increases the steric strain of the ring. You will use Spartan to investigate the ring conformation and the location of the various protons with respect to the rest of the molecule.

![Molecular Structure](image)

**Experimental Procedures**

**Di-O-Isopropylidene-\(\alpha\)-D-galactopyranose**

A 250-mL round-bottom flask containing a magnetic stir bar is charged with anhydrous FeCl\(_3\) (0.60 g, 3.7 mmol), D-galactose (2.0 g, 11 mmol) and acetone (100 mL). A condensing column is attached to the round bottom flask and the mixture stirred and brought to a gentle reflux for 1.5 h using a heating mantle. The solution initially appears as a cloudy, light-brown color with the sugar being insoluble. The sugar should eventually dissolve. Trace amounts of the sugar may be noticed after 1.5 h. The heating mantle is then removed and the solution cooled while being stirred. Potassium carbonate (10%, 20 mL) is then gradually added. A brown oil will form on the bottom. The reaction is stirred for ~1 min and then the stir bar is removed and the solution concentrated via rotary evaporation until a brown sludge is apparent. The sludge is diluted with ether (ca. 40 mL) and transferred to a 250-mL separatory funnel. The brown aqueous layer is separated. The organic layer is transferred to a separate Erlenmeyer flask and the aqueous layer extracted two more times with ether (2 X ~40 mL). The organic layers are combined and transferred into the separatory funnel. The organic layer is washed with water (2 X 20 mL). The organic layer is dried over Na\(_2\)SO\(_4\), gravity filtered into a tared RBF and concentrated by rotary evaporation. An NMR spectrum (in CDCl\(_3\)) may be obtained and the crude product purified by bulb-to-bulb distillation (4). Note: The final product is a clear, colorless thick oil, BP \(\sim\)115 °C at 0.025 mmHg. The final yield after distillation is 1.78 g (6.85 mmol, 62%).

**Molecular Modeling**

First, you will optimize the starting material, D-Galactose. Open a new molecule and use the rings menu to select “cyclohexane.” Once you have cyclohexane, use the “Delete Atom” function to remove the carbon at the appropriate position to substitute the oxygen. Now click on the Oxygen button with two single bonds. Add the oxygen to one of the two carbons that was previously bonded to the carbon you deleted. Then use “Make Bond” to connect the oxygen to the other free carbon to close the ring. Now, use the Oxygen button with two single bonds again to add the hydroxyl groups as shown in the figure. In this chiral molecule, stereochemistry is important, so you will need to carefully add the oxygens in the “up” or “down” position as shown in the figure. Notice that the hydroxyl on carbon 5 has a hydroxymethyl group.
(-CH$_2$OH) and not simply a hydroxyl group. Once you have D-Galactose drawn, minimize it and save it. Now you will submit a Geometry Optimization at the AM1 level with charge as neutral and multiplicity as singlet (Setup/Calculation). Setup a Surface by adding surface = density, property = potential. Now submit the job.

You will now build the chair form of 1,2,3,4-Di-O-isopropylidene-$\alpha$-D-galactopyranose using your optimized form of D-galactose. Select the tetrahedral carbon and bond a carbon to the oxygen on carbon 1 (see figure below). Then use “Make Bond” to bond this carbon to the oxygen on carbon 2. You will then use the tetrahedral carbon to add the two methyl groups in place of the two yellow lines coming from the central carbon of the iso-propyl group. Now, repeat these steps for the iso-propyl diester on carbons 3 and 4. Then, select the ice cube from the menu at left. Freeze the 6 atoms making up the ring by clicking on each of them. Each of them should now be marked. Now minimize this structure (you may wish to do so a few times), save it under a different name in your folder (for example, “chair 1,2:3,4-Di-O-isopropylidene-$\alpha$-D-galactopyranose”), and exit the builder. Now, setup an AM1 geometry optimization with “Frozen Atoms” checked. Submit this job. The frozen atoms force the molecule to retain the chair conformation.

After awhile of computation, the chair form of 1,2,3,4-Di-O-isopropylidene-$\alpha$-D-galactopyranose should be optimized. Unfreeze the ring atoms by selecting “Freeze Center” and clicking on each ring atom again. Minimize the unfrozen structure, and save this molecule under a third name (“boat 1,2:3,4-Di-O-isopropylidene-$\alpha$-D-galactopyranose”). Then setup and submit an AM1 calculation on the molecule.

Once both of the chair and boat forms of the molecule have been optimized, there are a number of geometrical parameters you will want to extract from the geometries. Spartan will easily allow you to get the atom-to-atom distances, the angle values, and the dihedral angle values. A dihedral angle (sometimes called a strain angle) is an angle defined by four atoms. The rotation of the fourth atom out of the plane of the first three atoms is the dihedral angle value. (The concept of the dihedral angle is easier to understand when you select the four atoms in Spartan.)

In the MacSpartan workspace (not the builder), select the optimized chair molecule. Then select Measure Distance under the Geometry menu. You want to look for the closest hydrogen of each isopropyl group to each other and to the ring atoms. You want to measure the steric hindrance by comparing this distance separation. So, select two atoms (which are not bonded to each other) and the value Spartan gives you in the bottom of the window is the distance (in Angstroms) separating the two atoms. Record the various sterically hindered atom distances in the chair formation (those that look awkward and constrained). Select the Boat conformation and select Meausrue Distance under the Geometry menu again to measure the distances between those same sets of atoms (they will be numbered the same) that you measured in the chair conformation. Comparing these values will enable you to assess the strain in the two conformations.

Measuring the angles of the 6-membered and two five-membered rings will also help you understand the strain involved in the chair and boat conformations. After selecting the chair molecule, select Measure Angle under the Geometry menu. You need to select three atoms before Spartan will give you a value. To analyze the ring strain in these molecules, select three atoms that are bonded consecutively. You should expect an unstrained angle to be very close to 109° (tetrahedral carbon). Measure all six angles in the cyclohexyl ring and all five angles in each of the 5-membered rings. Open up the Boat molecule and measure the same angles for comparison.

Measuring the dihedral angles of the ring hydrogens in each molecule will allow you to compare with the experimental results obtained by NMR spectroscopy. Measure the dihedral angles using Measure Dihedral under the Geometry menu just like before only now you need to select 4 atoms which are bonded consecutively. Measure the dihedral angle of H1-C1-C2-H2 (H1 is bonded to C1, etc.) by selecting these atoms in this exact order (see diagram on the preceding page for the numbering scheme). Measure the dihedral angle for the following hydrogen pairs for both the Chair and Boat molecules:

$$\begin{align*}
1,2 & \quad 2,3 & \quad 3,4 & \quad 4,5
\end{align*}$$

Now you have all of the geometric measurements you will need to assess the preference of this system for either the Chair or Boat conformations. You should obtain one more value, the heat of formation for each molecule so that you can compare their overall stabilities. The geometry values help you to isolate the specific locations that affect the stability of each molecule, but the energy value of heat of formation gives an overall comparison. Under the Display menu, select Properties. Record the energy value for each molecule.
Questions:
1) Which conformation (Chair or Boat) is more sterically hindered with the addition of the di-O-isopropylidene structures? Which atoms are closest (have the greatest steric interaction) in each conformation? How does this compare to the steric reasons for the preference for the chair conformation in D-Galactose?

2) What do the angle values for the three rings in 1,2:3,4-Di-O-isopropylidene-\(-\)-D-galactopyranose tell you about the stability of the Chair and Boat conformations?

3) Use the following equation to calculate the coupling constant (J) between each pair of hydrogens (1-2, 2-3, 3-4, 4-5) for comparison to your NMR spectrum:
   \[ J = 7.76(\cos^2 \theta) - 1.1(\cos \theta) + 1.4 \]

4) Using the steric distances, the ring angle strain values, the J-value comparison to your NMR spectrum, and also the heat of formation of the Chair and Boat conformations, explain which conformation is preferred in 1,2:3,4-Di-O-isopropylidene-\(-\)-D-galactopyranose and why.