

INTRODUCTION

- In 1885 Adolf von Baeyer proposed that if carbon prefers to have a tetrahedral geometry with bond angles of 109.5 degrees, then ring sizes other than 5 and 6 may be too strained to exist. The basis for this proposal was that all ring systems are planar, clearly this is not the case. Ring systems can adopt many different conformations just as easily as acyclic compounds do.
- The Cambridge Structural Database is a unique resource providing a wealth of information on the preferred conformations of rings. Indeed, the database has been used extensively to map the conformational space of medium ring-sized cyclic and heterocyclic compounds (*Acta Cryst.*, **B49**, 910, 1993) and of macrocyclic ether and thioether ligands (*Acta Cryst.*, **B53**, 241, 1997).
- By examining crystal structures we can and understand why the observed conformations are adopted in terms of the strain present in these systems

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OBJECTIVES

- To investigate and understand the reason for angle strain in fully saturated planar carbocyclic rings.
- For cyclohexane, determine the angle strain in actual compounds by analysing experimental crystal structure data.
- To compare the predicted angle strain (in planar rings) against that observed in actual compounds and account for the differences.
- To closely examine the conformations of 3- to 6-membered carbocyclic rings and understand why these conformations are adopted in terms of the strain present in these systems.

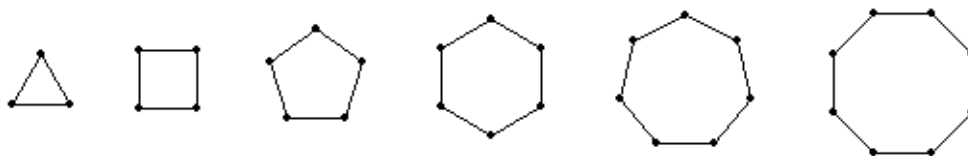
GETTING STARTED

- If you do not subscribe to the Cambridge Structural Database (CSD) System:
 - Open *free* Mercury (the free version of Mercury can be downloaded from http://www.ccdc.cam.ac.uk/free_services/mercury/)
 - Open the free teaching subset of the CSD (downloadable from http://www.ccdc.cam.ac.uk/free_services/teaching/downloads) by selecting **File** from the top-level menu, followed by **Open** in the resulting menu, and then selecting the database file `teaching_subset.ind`
 - Database reference codes (*refcodes*) of the structures in the teaching database will appear in a list on the right hand side of the main Mercury window. To view a structure select the corresponding *refcode* in the list.
- If you subscribe to the Cambridge Structural Database (CSD) System:
 - Open MercuryCSD.
 - The full database should be detected and opened within the *Structure Navigator* on the right hand side of the main Mercury window. To view a structure select, or type in, the corresponding *refcode*.

1 STEPS REQUIRED

1.1 Investigate angle strain in planar rings.

- Ideally the sp^3 hybridised carbon atoms of fully saturated carbocyclic rings would adopt bond angles of 109.5 degrees. However, in planar rings the internal bond angles will depend on the number of atoms in the ring.



- The table below gives values for the internal angles for the regular planar polygons shown above and an indication of angle strain per carbon atom due to deviation from the ideal sp^3 angle of 109.5 degrees.

No. atoms in ring	Internal angle in planar ring (degrees)	Measure of angle strain abs(internal angle - 109.5)
3	60	49.5
4	90	19.5
5	108	1.5
6	120	
7	128.5	
8	135	

- Complete the table above by calculating the angle strain (angle strain = internal angle - 109.5) for 6- to 8-membered rings.
- This data is best presented as a graph. Plot the predicted angle strain against ring size (for three- to eight-membered planar rings). What conclusions can you draw?
- Strain is predicted to be largest for three-membered rings but rapidly decreases and reaches a minimum for a five-membered ring. In fact, a planar five-membered ring is predicted to be virtually free of angle strain. After the minimum at five, angle strain increases steadily as the rings get larger.

1.2 Calculating angle strain in actual compounds

- So far we only have a predicted value of angle strain in planar rings. We need a measure of angle strain in actual compounds, so that we can compare this to the predicted values.
- The preferred angle in actual compounds can be determined, for an n-membered carbocyclic ring, by taking the average internal angle across a large number crystal structures. Angle strain can then be calculated as the difference between this average internal angle and the ideal sp^3 angle of 109.5.
- Calculate, from crystal structure data, the actual angle strain in cyclohexane. For this task you are provided with 5 structures each containing a cyclohexane ring (CSD refcodes: *ALIPIU*, *AZANUK*, *CYCHEX*, *CHXDCA* and *BCYHAC*). To view a structure click on its refcode in the *Structure Navigator* on the right hand side of the main Mercury window. For each structure measure all six internal C-C-C angles, then calculate the average internal angle of each structure and the overall average across the whole set.

To measure angles in Mercury

1. Set Picking Mode in the tool bar (near the top of the main Mercury window) to the required parameter type, viz. **Measure Distance**, **Measure Angle** or **Measure Torsion**
 2. Geometrical measurements (intramolecular or intermolecular) can now be made by clicking on e.g., two atoms for a distance, three atoms for an angle or four atoms for a torsion angle.
 3. To remove all geometrical measurements from the display click on the **Clear Measurements** button in the tool bar near the top of the main Mercury window.
- *Note: For the purpose of this task only a small number of representative structures are provided. However, if you have full access to the Cambridge Structural Database (CSD) the average internal angle can be calculated across a large number of cyclohexane fragments (see SUPPLEMENTARY MATERIAL: DETERMINING THE PREFERRED INTERNAL BOND ANGLE IN CYCLOHEXANE USING THE FULL CSD, page 11).*

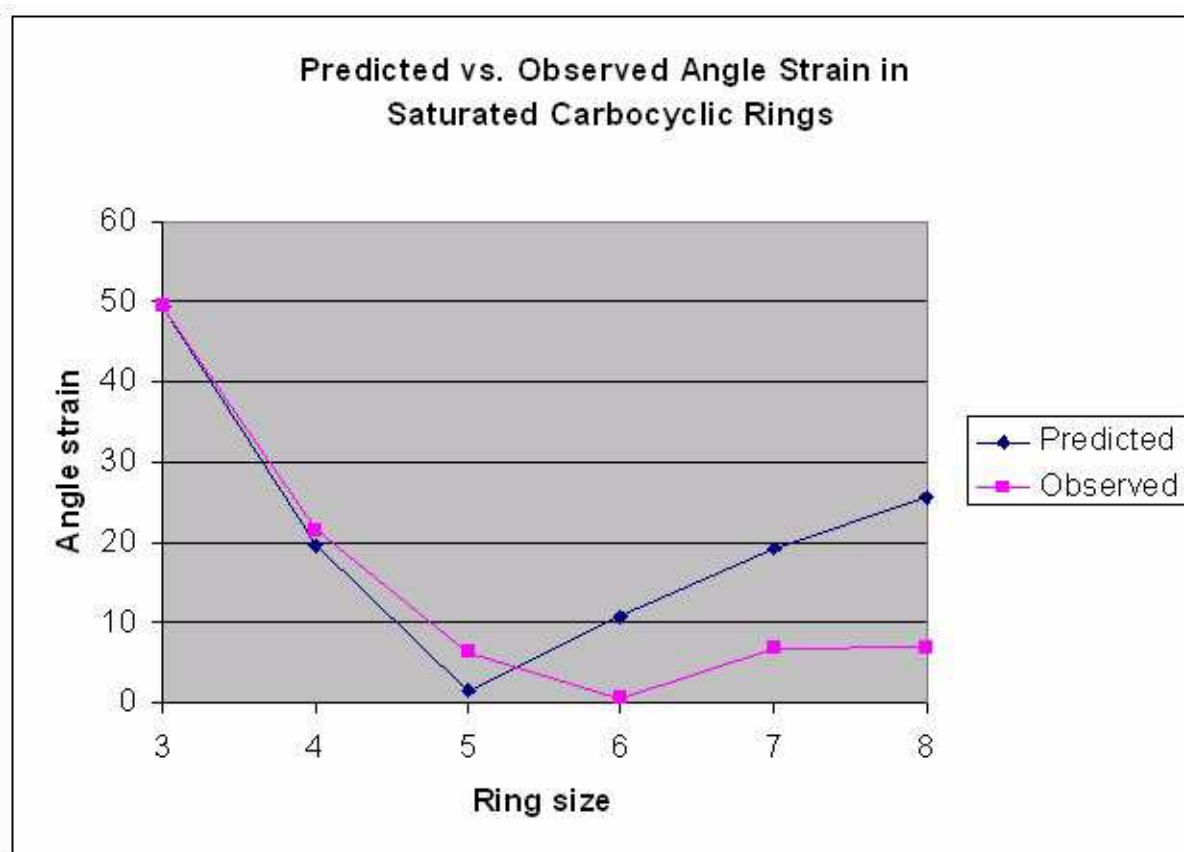
1.3 Compare predicted angle strain against that calculated from actual compounds

- The table below shows both the predicted angle strain (in planar rings) and the angle strain calculated from actual compounds.
- Complete the table by entering the angle strain in cyclohexane calculated from actual

compounds. Angle strain = average internal angle across all 5 structures - 109.5.

No. Atoms in Ring	Measure of Angle Strain (internal angle - 109.5)	
	Predicted (in planar rings)	Calculated (crystal structure data)
3	49.5	49.5
4	19.5	21
5	1.5	6
6	10.5	
7	19	6.5
8	25.5	7

- Add the angle strain data calculated from actual compounds to the graph we plotted previously. This will allow us to easily compare the predicted angle strain against that observed in actual compounds.



Plot comparing predicted angle strain in planar rings against that calculated from actual compounds

- Compare the two data series. What conclusions can we draw?
- The observed angle strain is greatest in cyclopropane. Angle strain then decrease rapidly with ring size but reaches a minimum for cyclohexane, not cyclopentane (as predicted for the planar structure). Angle strain then increases again but not nearly as quickly as predicted.
- Why are six-membered rings essentially free of angle strain? and why is there some angle strain in five membered rings even though the bond angles in the planar structure are almost 109.5 degrees?
- The answer, at least to the first question, is that rings in actual compounds are not planar, they can adopt many different conformations just as easily as acyclic compounds do. To help answer the second question, let's look at some ring conformations in more detail.

1.4 Examine the conformation of cyclopropane

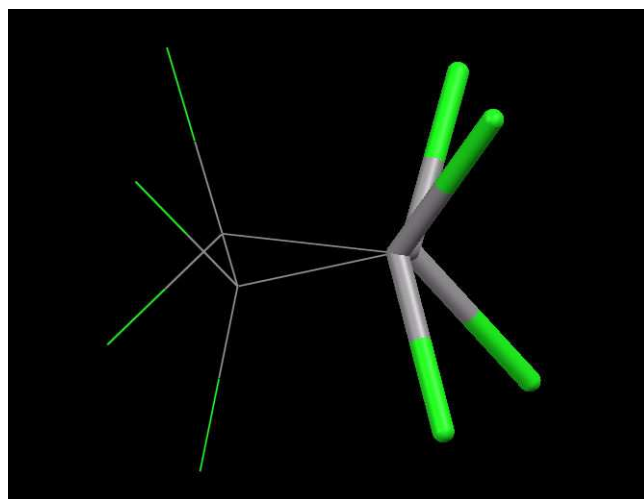
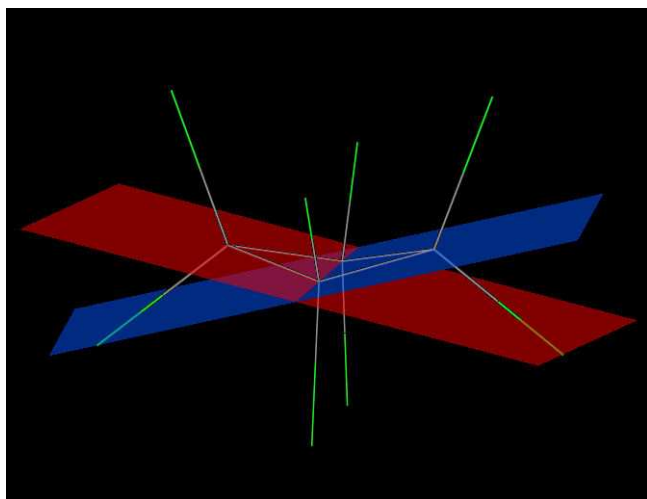
- Display the structure of cyclopropane by clicking on the refcode *QQQCIS01* from the *Structure Navigator* on the right hand side of the main Mercury window.
- Examine the structure. The three carbon atoms of cyclopropane lie in a plane. Three membered rings must be planar since it is always possible to draw a plane through any three points.
- We know already that there is considerable angle strain in this planar molecule. This is due to the bond angles deviating from the ideal tetrahedral value of 109.5 degrees. However, there is a further cause of strain in cyclopropane. Can you identify what this is? (*hint*: it may help to view along one of the C-C bonds).

To view along bonds in Mercury

- 1. The view direction in Mercury can be changed so that you are looking down a particular bond.*
 - 2. To view along a bond, right-click on the bond and select View along bond from the resulting pull-down menu.*
 - 3. At any stage the display area can be returned to the default view by hitting the Reset button at the bottom of the window*
- All the C-H bonds in cyclopropane are eclipsed. This is energetically unfavourable and any rotation would lead to a more stable conformation. However, C-C bond rotation is impossible and so all the C-H bonds are forced to eclipse their neighbours. The strain resulting from eclipsed conformations is called *Pitzer* strain.

1.5 Examine the conformation of cyclobutane

- Display the structure of octachlorocyclobutane by clicking on the refcode *CLCBUT* from the *Structure Navigator* on the right hand side of the main Mercury window.
- Examine the structure. In octachlorocyclobutane the ring distorts from a planar conformation in order to reduce the eclipsing interactions, even though this increases the angle strain. Octachlorocyclobutane therefore adopts a *wing-shaped* conformation, with an angle between the planes of about 26 degrees.
- View along one of the C-C bonds in order to see how this deviation from planarity relieves the C-Cl eclipsing interactions.



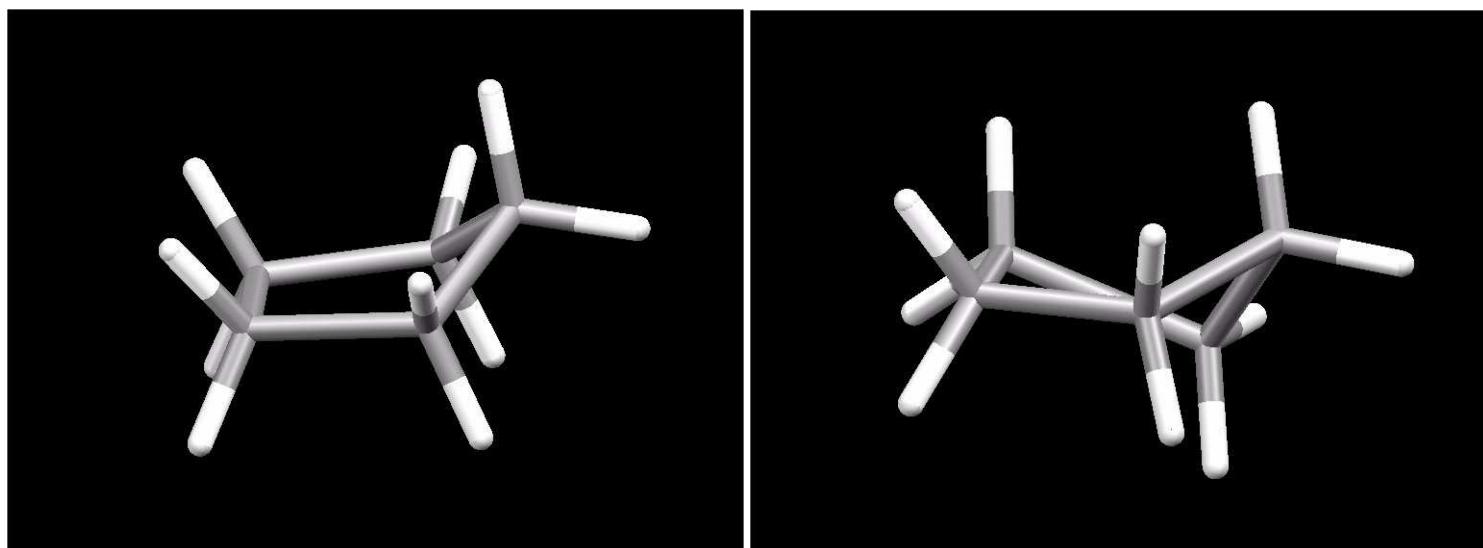
left: wing-shaped conformation of octachlorobutane (CLCBUT) showing angle between planes; right: this wing-shaped conformation relieves the C-Cl eclipsing interactions.

- By comparison, oxetane (*CIVXIO10*), in which eclipsing is less, is closer to planarity. Measure the distance between the two C-C-C planes in oxetane.

1.6 Examine the conformation of cyclopentane

- This eclipsing effect explains why there is some angle strain in five membered rings even though the bond angles in the planar structure are almost 109.5 degrees.
- We now know that in the planar molecule there would be considerable strain caused by eclipsing of adjacent C-H bonds. Therefore the ring distorts (as in cyclobutane) to reduce these eclipsing interactions, but this increases the angle strain. Whatever happens there will always be some strain present. The minimum energy conformation adopted is therefore a balance of the two opposing types of strain.

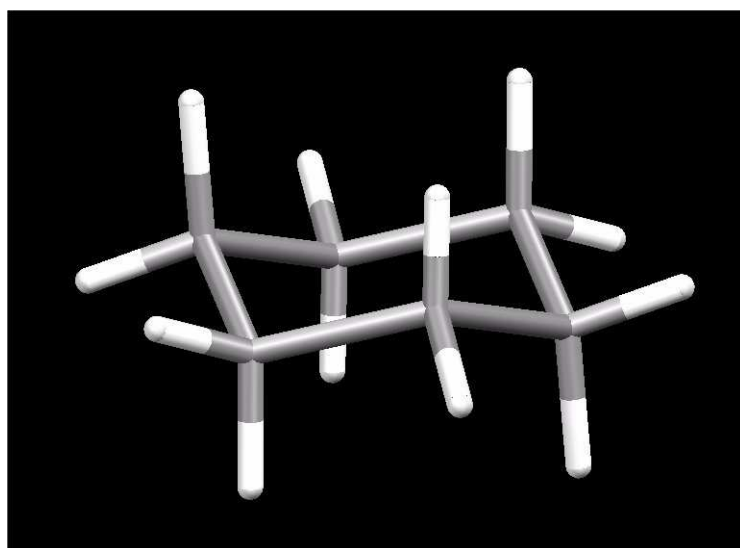
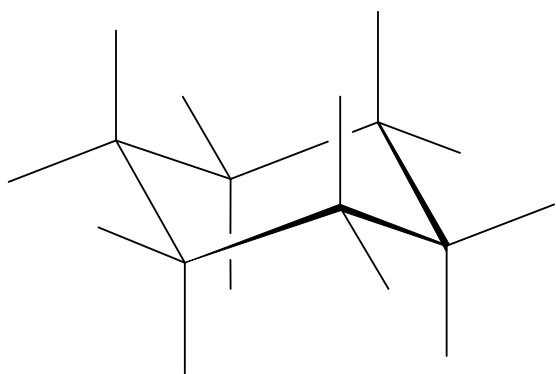
- There are two puckered conformations of cyclopentane, the *envelope* (*IHIPOE*, *ACUHUB*) and the *half-chair* (*LISLOO*, *ABIKUR*). There is little energy difference between the two forms and many five-membered ring systems adopt conformations somewhere between the two.



conformations of cyclopentane, left: *envelope* (*IHIPOE*); right: *half-chair* (*LISLOO*)

1.7 Examine the conformation of cyclohexane

- Display the structure of cyclohexane by clicking on the refcode *CYCHEX* from the *Structure Navigator* on the right hand side of the main Mercury window.
- From our analysis of crystal structure data we have determined that six-membered rings are essentially free of angle strain. Inspect the structure of cyclohexane and explain why this is.
- Cyclohexane adopts a puckered conformation that relieves all strain. This conformation is called the *chair*.
- In the *chair* conformation of cyclohexane all bond angles are close to the ideal tetrahedral angle of 109.5 degrees. In addition, viewing along any of the C-C bonds clearly shows that there are no eclipsing C-H interactions. All bonds are fully staggered, i.e. in a *gauche* arrangement, giving the lowest possible energy. This is why cyclohexane is essentially strain-free.
- In the vast majority of compounds containing a cyclohexane ring, the molecule exist almost entirely in the *chair* form. However, other cyclohexane conformations are know. These conformations and substituted cyclohexanes are dealt in detail elsewhere (*CSD teaching module #n*).



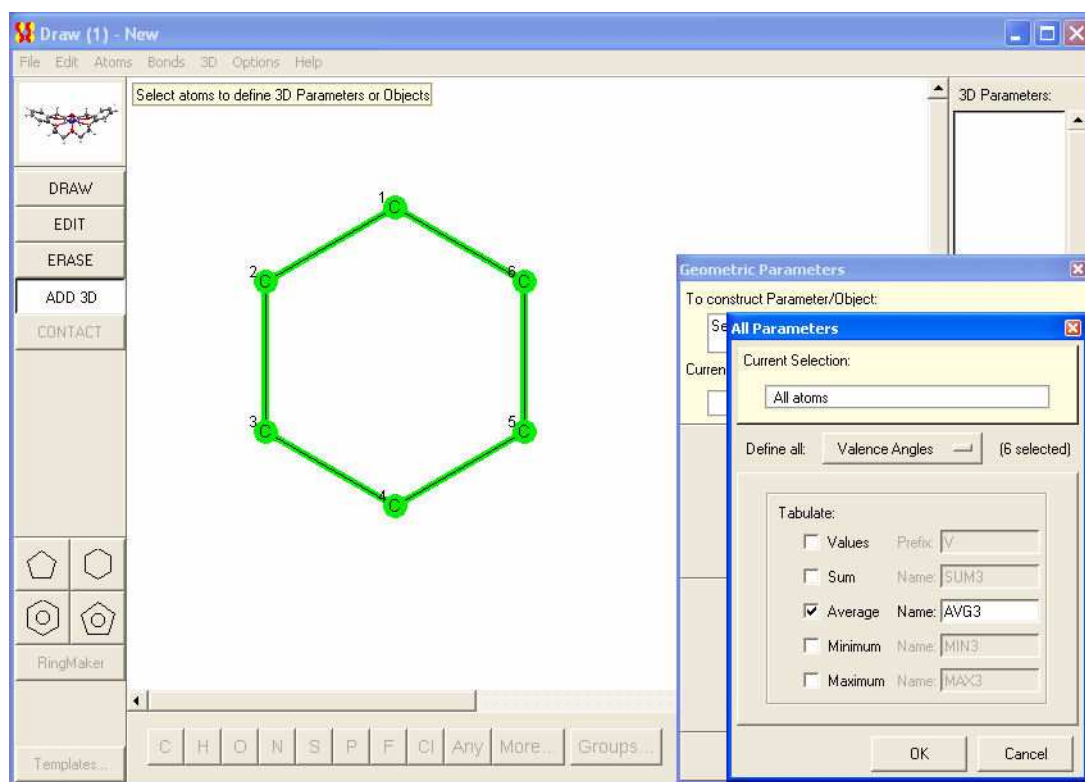
Chair conformation of cyclohexane (CYCHEX)

SUMMARY OF KEY CONCEPTS

- Angle strain can occur in cycloalkanes due to deviation from the ideal sp^3 angle of 109.5 degrees.
- Strain can also occur when neighboring bonds are forced to be eclipsed, or partially eclipsed. The strain resulting from eclipsed conformations is called *Pitzer* (or *torsional*) strain.
- Cyclopropanes are forced to be planar and are highly strained because of both angle strain and the eclipsing of C-H bonds.
- Cyclobutanes adopt a *wing-shaped* conformation. This deviation from planarity occurs in order to relieve the eclipsing of neighboring bonds.
- Cyclopentanes are not planar even though the bond angles in the planar structure would be almost 109.5 degrees. Again, this distortion occurs in order to relieve eclipsing of adjacent C-H bonds. The minimum energy conformation adopted is therefore a balance between the two opposing types of strain.
- Cyclohexane is strain free because of its puckered *chair* conformation, in which all bond angles are close to 109.5 degrees and all neighboring C-H bonds are staggered. Cyclohexane rings are the most important of all ring sizes because of their wide occurrence. As such, cyclohexanes are dealt with in detail elsewhere (*CSD teaching module #n*).

SUPPLEMENTARY MATERIAL: DETERMINING THE PREFERRED INTERNAL BOND ANGLE IN CYCLOHEXANE USING THE FULL CSD

- Start *ConQuest* and hit the **Draw** button to open the *Draw* window.
- Draw a cyclohexane substructure (*hint*: this can be done quickly by selecting the appropriate ring template from the bottom left-hand corner of the *Draw* window and then clicking in the white drawing area). Since we also want to retrieve substituted cyclohexanes don't include any hydrogen atoms when sketching your search substructure.
- For each hit structure retrieved by the search we need to record the average of the six internal bond angles in the cyclohexane fragment. To define the required geometric parameters click on the **Add 3D** button. This will open the *Geometric Parameters* window. Click on the **All Parameters...** button, then in the resultant dialogue box select **Define all: Valence Angles** from the drop down menu. Choose to tabulate the average of these angles by enabling the tick-box next to the word **Average**.



- Hit **OK**, to define the selected parameters and then **Done** to close the *Geometric Parameters* window.
- Hit **Search**, then in the *Search Setup* window set the filters **R factor ≤ 0.1** , **Not disordered** and **No errors**, and then hit **Start Search**.
- As soon as you start the search, the ConQuest interface moves to the *View Results* pane. After a few moments, the refcodes of hit structures will start to appear in the list on the right-hand side.

Click on any structures refcode to see its chemical diagram, the cyclohexane substructure will be highlighted and the average value of the internal valence angles will also be displayed.

- The blue progress bar indicates how much of the CSD has been searched so far. There is no need to allow the search to go to completion, you can stop it after about 20% by hitting the **Stop Search** button in the bottom right-hand corner.
- Geometric parameters retrieved from a *ConQuest* search can be exported to *Vista* for statistical analysis. Select **File** from the top-level menu followed by **View in Vista...**, then in the resulting window click on the **View in Vista** button. The main *Vista TABLE SPREADSHEET* window should appear:

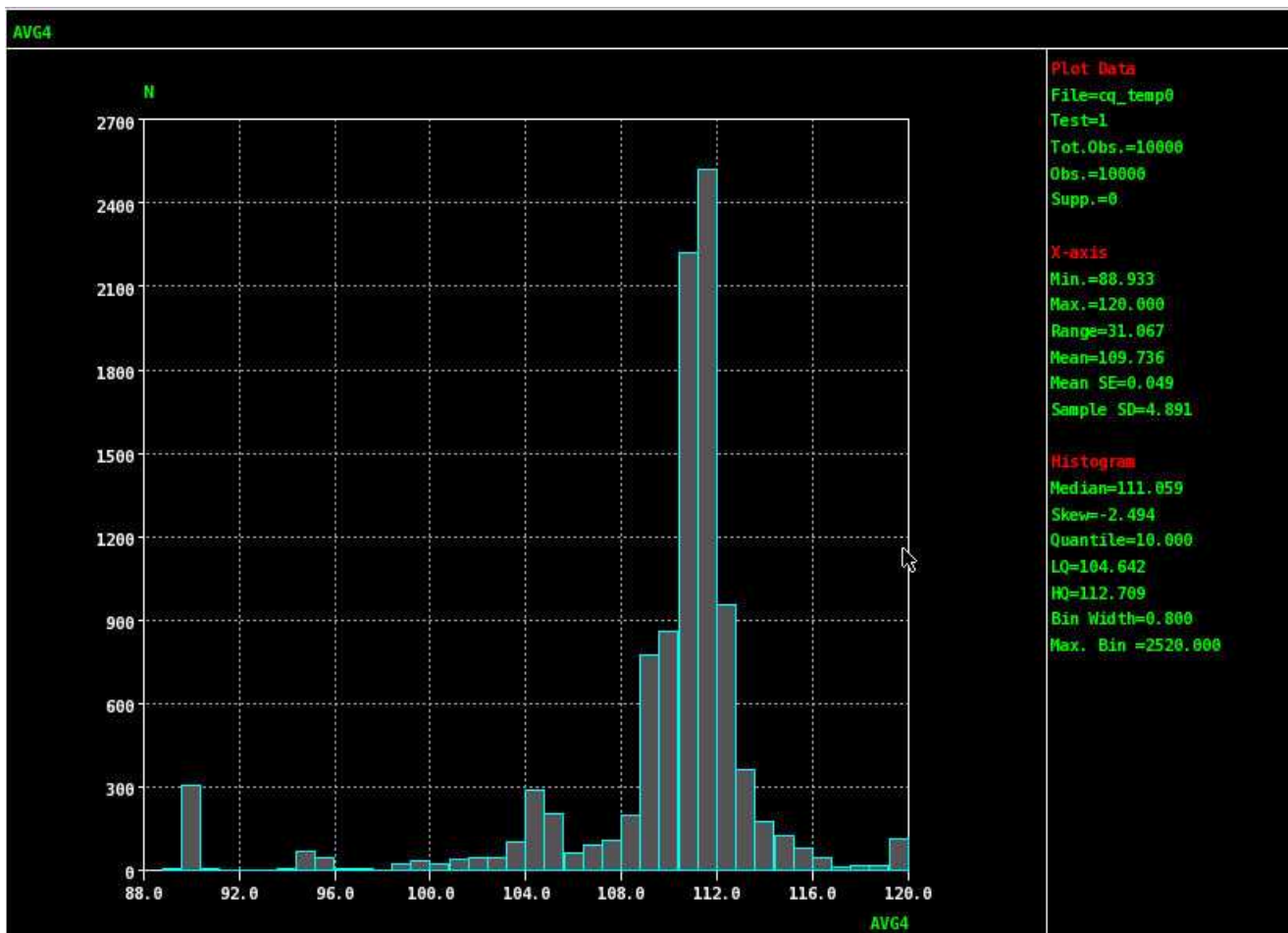
Quest File : C:\DOCUME~1\battle\CSDS_D-1\searches\temp\cq_temp0

Test : 1 of 1

	Total	Selected	Suppressed
Parameters	3	0	n/a
Refcodes	4551	n/a	n/a
Fragments	10000	0	0

REF COD	PARAMS	1	2	3	4	5	6	7	8	9	10	11
1	AACHX10	1	AACHX10	111.262								
2	AADAMC	2	AADAMC	109.609								
3	AADAMC	3	AADAMC	109.481								
4	AADAMC	4	AADAMC	109.257								
5	AADAMC	5	AADAMC	109.599								
6	AADMPY10	6	AADMPY10	109.450								
7	AADMPY10	7	AADMPY10	109.203								
8	AADMPY10	8	AADMPY10	110.368								
9	AADMPY10	9	AADMPY10	109.418								
10	ABAFEP	10	ABAFEP	111.400								
11	ABAFEP	11	ABAFEP	111.618								
12	ABATRG	12	ABATRG	111.059								
13	ABATRG	13	ABATRG	111.833								
14	ABATRG	14	ABATRG	109.288								
15	ABATUT	15	ABATUT	109.487								
16	ABATUT	16	ABATUT	109.439								
17	ABATUT	17	ABATUT	109.516								

- To determine the mean value of the average internal angle across all hit structures select the parameter *AVG4* by clicking on the grey numbered button at the top of the relevant column, then select **Histogram** from the *Data Visualization* options on the right hand side of the window.
- The resulting histogram shows the distribution of the average internal cyclohexane valence angle across a large number of crystal structures.



- The mean value is given on the right hand side of the plot. Calculate the angle strain by subtracting this value from 109.5 (the ideal sp^3 angle). The angle strain should be close to zero.

