CYCLIC STEREOCHEMISTRY

SEM-5, CC-12 PART-1, PPT-1

Lecture material menander with the second menander of the second second

Cyclic Stereochemistry (PART-1, PPT-1)

Conformation-I

Introduction

Though the nonplanar arrangement of cyclic compounds such as cyclohexane is predictable from the tetrahedral theory (1874) of van't Hoff and Le Bel, its acceptance was delayed due to the popularity of Baeyer's strain theory (1885). According to this all-ring compound are assumed to be planar and suffer from angle strain to a greater or lesser extent arising out of deviation from the normal valency angles.

The strain theory was supported by the facts that 3- and 4-membered ring compounds in which the angle strain is maximum are most unstable (also most reactive), compounds containing 5- and 6-membered rings in which angle strain is small or negligible are readily formed, and rings of higher members (> 7) in which angle strain is again appreciably high are difficult to form.

The stability of a ring is controlled by thermodynamics but ease of ring formation is explained on the basis of kinetic property. Therefore, the ease of ring formation is not necessarily pertinent to thermodynamic stability of the ring. A 3-membered ring is easy to make because the geometry of the acyclic precursor (planar with two terminal atoms are very close to each other) is favourable for cyclisation (entropy effect). It is also easy to break because of the inherent Baeyer (angle) and Pitzer (torsional) strains in the system.

The formation of a 4-membered ring is difficult because of its unfavorable transition state with all the hydrogens as well as the terminal carbons on both sides of the incipient ring eclipsed. The nonbonded interaction and torsional strain are considerably reduced in the transition states leading to 5- and 6-membered rings due to the puckering/non-planarity of the chain which explains their easy formation.

The larger ring compounds are difficult to make because of an unfavorable entropy factor, the probability of having both ends of acyclic intermediate within bonding distance being very small. The overall strain in a cyclic molecule is, thus, in the absence of electronic effects and secondary linkages, originated from three factors: Baeyer (angle) strain, Pitzer strain, and non-bonded interactions.

Classification and Strains of Monocyclic Systems

Prelog and Brown have classified monocyclic compounds into four families. This classification is based on the number of carbon atoms in the ring: small rings, 3-4 membered; common/normal rings, 5-7 membered; medium rings, 8-11 membered, and large rings, 12-membered and higher. Many chemical properties depend on the class of the cycloalkane, and these differences in behavior have been explained largely in terms of total strain the molecule assumes.

Since strain affects chemical stability, measurement of the latter will indicate the presence of the former. Chemical stability may be measured in various ways, e.g., by the heat of formation, heat of combustion, dipole moment, absorption spectra, etc.

Ring Strains of Monocyclic Systems

For hydrocarbons, one easy way to work with is the heat of combustion study. This gives a measure of thermodynamic stability which is related to the total strain, i.e., the sum of the Baeyer strain (bond angle deformation only) and other sources of strain (steric repulsions, etc.) that a cycloalkane suffers. If the strain in a ring change with the size of the ring, then this can be observed by changes in the heat of combustion. From the experimental point of view, the heat of combustion of a ring compound per methylene group may be taken as a reliable guide to the relative stability of different ring systems.

Total strain in the molecule = (number of C atoms in ring) \times (observed heat of combustion/CH₂ - observed heat of combustion/CH₂ for *n*-alkanes)

According to the results shown in Table 1, stability increases up to the 6-membered ring, then decreases from 7-11 membered rings, and from the 12-membered onwards attains the stability of the 6-membered ring. These conclusions have been reached from heats of combustions obtained experimentally.

Table 1: Heat of Combustion and Ring Strain for Cycloalkanes					
Number of C- atoms in the ring	Angle between valency bonds	Distortion	Heat of combustion in kJ/CH2	Total strain (kJ)	
3	60°	24° 44'	697	120	
4	90°	9° 44'	685	112	
5	108°	0° 44'	664	35	
6	120°	-5° 16'	659	12	
7	128° 34'	-9° 33'	662	35	
8-11	135° - 147° 16'	-12° 46' – (-18° 54')	661-665	32-88	
12-00	150°-	-20° 16'	657-661	0-48	
<i>n</i> -Alkanes	109° 28'	0°	657	0	

Baeyer's Strain Theory

Baeyer (1885) was the first to point out that the angle subtended by the corners and centre of a regular tetrahedron is 109° 28' which lies between the values of the angles in a regular pentagon (108°) and a regular hexagon (120°). Baeyer strain theory was based on this observation. According to the strain theory, the valency angle can be altered from the normal

value of 109° 28', but when altered, a strain is set up in the molecule, and the greater the deviation from the normal value, the greater is the strain.

Thus, according to Baeyer, 5- and 6-membered rings form most readily, and are the most stable because they involve the least strain (or distortion) from the normal valency angle. The distortion for each ring-size can be readily calculated if all the rings are assumed to be planar. Baeyer pointed out that the construction of a small ring compound involves strain. For example, in cyclopropane the angle between the carbon-carbon bonds must, for geometrical reasons, be 60°. This is because in cyclopropane the three carbon atoms each occupy a corner of an equilateral triangle.

Therefore, in cyclopropane the angle between lines connecting the nuclei, i.e., the internuclear angle and the interorbital angle (the normal tetrahedral bond angle at carbon is $109^{\circ} 28'$) differ to a large extent. Since there is a deviation of $49^{\circ} 28'$ from the normal, the distortion in cyclopropane will be $\frac{1}{2} (109^{\circ} 28' - 60^{\circ}) = + 24^{\circ} 44'$. Since three points are required to form an angle, the distortion of the bond angle has been assumed to be equally shared between the two bonds (Figure 1).



Table 1 gives a list of distortions, and it can be seen that these decreases rapidly from cyclopropane to cyclopentane and then decrease more slowly. Thus, the smaller rings suffer large distortion and this was believed to be the cause of their enhanced reactivity. Therefore, according to Table 1 small rings are highly strained. There is relatively little strain in the common rings which abound in natural as well as synthetic products. Strain increases again in the medium rings and the large rings are nearly strainless.

Baeyer's strain theory is based on a mechanical concept of valency and on the assumption that all the rings are planar. This is proved to be wrong. Physical methods have shown that all rings, except cyclopropane (it is a three-point system and consequently must be planar), are not planar.

Stability of Cyclic Molecules

Strain introduced in a molecule may be of different types, such as bond strain, angle strain, torsional strain, and van der Waals compression. Thus, the strain in cycloalkanes is actually not purely angle strain. Strain is the excess of observed over "calculated" heat of formation (or more conveniently from heat of combustion). For a cycloalkane, this is conveniently taken as the heat of formation or heat of combustion of a CH₂ group multiplied by the number of carbon atoms in the ring.

The value for a CH₂ group, in turn, is obtained by taking the difference between a large straight-chain hydrocarbon, CH₃(CH₂)_nCH₃, where n > 5, and its next lower homologue. The strain thus calculated, expressed either as total strain or as strain per CH₂ group, is high for cyclopropane, drops to near zero as one proceeds to cyclohexane, increases again to a maximum in the cyclooctane to cycloundecane (11-membered) region and then drops again, reaching values near zero from 14-membered rings on up. The strain in 3-, 4-, and 5-membered rings indeed runs parallel with Baeyer's prediction, but the 6-membered ring is nearly strainless.

A puckered (chair or boat shaped) form of cyclohexane can be constructed that is free from angle strain. The bond angles in a non-planar ring are always smaller than those in a planar one; thus, puckering reduces the angle in cyclohexane from 120° to near tetrahedral. Sachse (1890) pointed out that nonplanar cyclohexane can be strainless, or at least has no angle strain.

Even though the medium-sized rings are free of angle strain (Baeyer strain) due to puckering, they are highly strained. This is because they have large numbers of pairs of eclipsed hydrogen atoms on adjacent CH₂ groups; moreover, with rings in the C₈-C₁₁ range, such hydrogen atoms will tend to "bump" each other across the ring, leading to so-called "*transannular strain*"; this strain arises from the van der Waals compression (nonbonded energy, V_{nb}) term.

Transannular strain: In medium-sized ring compounds, the strain due to repulsive nonbonded interactions between substituents or hydrogen atoms attached to non-adjacent ring atoms.



Geometry of Cyclopropane

If cyclopropane were an equilateral triangle with bonds directed along the lines joining the carbon atoms, then the ring valency angle of each carbon atom would be 60° . This value is impossible, since the carbon valency angle can never be less than 90° (when they are pure *p*-orbitals). Furthermore, mixture of *p* with *s*-orbitals opens the valency angle. The smallest carbon valency angle that can be reasonably expect to have been 104° . Thus, in cyclopropane, the carbon hybridized orbitals are not pointing towards one another in the same straight line, and consequently there is a loss of overlap. It is this loss of overlap that gives rise to instability, the cyclopropane molecule being in a state of 'strain' due to 'bent' bonds as shown in Figure 2.

 σ bonding involves 'end-on-overlap' and π bonding involves 'lateral' overlap. σ bonding is stronger than π bonding. Bent bonding is intermediate between σ and π bonding, the overlap being neither end-on or lateral. This makes the overlap less efficient than σ overlap, and the cyclopropane C-C bonds are weaker than normal C-C σ bonds. This is described as angle strain.



The cause of the bent overlap is that the internuclear angle (the angle between the bond lines connecting the nuclei) is forced to be much smaller (60°) than the interorbital angle (the angle between the axis of the two AO's on a given carbon), which is $109^\circ 28'$.

Geometry of Cyclobutane

Cyclobutane has also 'bent' bonds, but loss of overlap is less in this case than for cyclopropane, and so the former will be more stable than the latter. Cyclobutane has less angle strain than cyclopropane but more torsional strain because of its larger number of ring hydrogens. Cyclobutane is slightly bent out of plane-one carbon is about 25° above.



Cyclobutane may be represented by two extreme conformations: a planar one (I, point group D_{4h}) and a puckered one (II, point group D_{2d}). The former has the pairs of adjacent H's eclipsed and suffers from torsional as well as angle strain. The puckering of the ring with one carbon atom either above or below the plane of the other three relieves some of the torsional strain and nonbonded interaction at the expense of angle deformation (increased angle strain).

Raman spectra and electron diffraction experiments confirm the puckered conformation with an angle of puckering α (the angle between C₁-C₂-C₃ and C₃-C₄-C₁ planes) of approximately 35° (the torsion angles are alternately + 25° and - 25°).

Geometry of Cyclopentane

The planar conformation of cyclopentane (D_{5h} point group) is highly strained because of eclipsing interactions among adjacent H's even though angle strain is almost nil. Two puckered conformations which retain some residual symmetry, one known as envelope (IV) and the other known as half-chair (V) are preferred. The former has a plane of symmetry (C_s point group) and the latter has a C₂ axis (C_2 point group) as shown in Figure 4. The C_s conformation has four carbon atoms in a plane with the fifth either above or below the plane. The C_2 conformer has three carbon atoms in a plane with the fourth and fifth either above or below the plane.



Internal Strain (I-Strain)

Chemical reactions involving change of hybridized state of carbon from sp^3 to sp^2 or viceversa are facilitated or retarded if steric strains are released or enhanced respectively. This fact is called *I-strain*. The concept of I-strain was proposed (Brown 1951) to explain the relative ease with which a change of bond hybridization, sp^2 to sp^3 (addition to C=O) or sp^3 to sp^2 (oxidation of -CHOH- to C=O, S_N1 and S_N2 reactions) takes place in cyclic compounds.

The strain energy changes in rings as a result of the change of bond hybridisation. The change may refer to the formation of a transition state or of a product leading to a kinetic effect or a thermodynamic effect respectively. In addition to angle strain and torsional strain, steric strain arising out of transannular interactions may also contribute to *I-strain*.

The angle strain is most important in 3- and 4-membered rings and that it is larger in rings with unsaturated (sp² hybridized) atoms than in saturated (sp³ hybridized) rings, because the "normal" angle is larger in the former situation than in the latter (120° vs. 109° 28'), and therefore the angle deformation incurred in forming the ring is also larger.

Therefore, in 3- and 4-membered rings, reactions which involve a change from sp^2 to sp^3 is favourable. In these cases, angle strain is relieved at the expense of some torsional strain. If the ground state is sp^2 and the transition state more nearly sp^3 hybridized, the reaction should be more favoured than in acyclic analogues, and *vice-versa*. Therefore, the energy differences between ground and transition states also play important roles in these transformations.

Hydrolysis of cyclopropanone (Figure 5) involves a change of bond hybridization of carbonyl carbon from sp^2 to sp^3 and, therefore, the reaction is favoured.



In 5-membered ring, a change from sp^3 to sp^2 is easier because it removes considerable amount of torsional strain with a slight increase in angle strain. On the contrary, 6-membered ring is nearly perfectly *staggered* in the *chair* conformation. Therefore, in the *chair* conformation of cyclohexane, there is little torsional strain and angle strain is also negligible. As a result, the change from sp^2 to sp^3 is very facile.

Example of *I-strain* controlling the rate of reaction is the cyanohydrin formation of cyclopentanone and cyclohexanone. In the case of cyclopentanone, the rate is much slower for conversion of sp^2 to sp^3 hybridization of carbonyl carbon because that will increase torsional strain but in case of cyclohexanone the cyanohydrin formation will not increase any torsional strain.



In 7- to 11-membered rings, angle strain plays a minor part, but eclipsing strain is important. The major source of *I-strain* in these rings is *transannular* interactions with concomitant deformation of bond angles and torsion angles which may be removed at least partly in a change from sp^3 to sp^2 due to a decrease in the number of intraannular H's. The configuration, with its lesser number of C-H bonds, is therefore, favoured over sp^3 .

The situation of *I-strain* in different ring systems is summed up in Table 2. To illustrate the effect of *I-strain* in medium ring compounds, it may be pointed out that while cyclohexanone cyanohydrin hardly dissociates, cyclodecanone does not form a cyanohydrin at all. The rate of reduction of cyclodecanone (sp^2 to sp^3) with sodium borohydride is the lowest among cyclic ketones.

The rates of solvolysis of the tosylates derived from cycloalkanols, which goes through the carbocation intermediate (sp³ to sp²) are highest for medium ring compounds. The rates of S_N2 reaction (sp³ to sp²) between cycloalkyl bromides and lithium iodide also follow the same trend. The large ring compounds resemble open chain compounds and are not amenable to *I-strain* treatment.

Table 2: Prediction of I-strain in different ring size				
Ring size	Facile process	Relief of major strain		
3- and 4-membered	$sp^2 \rightarrow sp^3$	Angle strain		
5-membered	$sp^3 \rightarrow sp^2$	Torsional strain		
6-membered	$sp^2 \rightarrow sp^3$	Angle strain, Torsional strain		
7- and 11-membered	$sp^3 \rightarrow sp^2$	Transannular strain		
12-membered and higher	No appreciable difference in either change			

The reaction of cycloalkyl bromides with iodide is a notable exception; this is an S_N2 reaction and steric hindrance in the transition state due to other causes may overwhelm any predictions based solely on *I-strain*. Exceptions may also occur when other factors are more important than *I-strain*, for example, steric hindrance to rearward attack, as mentioned above for cycloalkyl halides, or neighboring group participation (with anchimeric assistance), which leads to a high solvolysis rate in cyclobutyl halides and tosylates.

Figure 7 illustrates the reactions included in Table 2 with an indication of the appropriate change in hybridization between starting material and product (equilibrium-controlled reactions) or starting material and transition state (rate-controlled reactions).

