Conformational analysis of 2,3 - dibromobutane

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INTRODUCTION:

Conformational analysis is the study of the different energy levels associated with the different conformations of a molecule. **Conformations** are the different 3-dimensional arrangements that the molecule can acquire by freely rotating around σ-bonds. One must keep in mind that **conformations are not isomers**. Isomers are different molecules. Conformations are simply different structural arrangements of the same molecule.

WHAT IS CONFORMATIONAL ANALYSIS:

Terms **conformation** and **conformational analysis** will be defined and illustrated. **Conformation** should be distinguished from the **configuration**.

configuration is normally taken to mean a fixed geometrical arrangement around an atom or several atoms and which is prevented from exchanging with other configurations at "chemical temperatures" by the presence of high kinetic barriers, normally resulting from the need to actually break bonds to do so. This normally means that geometrical and optical configurational isomers **can** be separated at room temperatures.

In contrast, any one **conformation** is more likely to easily exchange with other conformations as part of an equilibrium process, due to much smaller kinetic barriers which are normally the result of not needing to break any bonds. These changes normally occur at one or more **single bonds** which are presumed to rotate about their axes with relatively low kinetic barriers. This means that, except for a few special cases called '**atropisomers'**, we cannot separate and isolate individual conformational isomers at room temperature (although it might be possible at low temperatures). A **conformer** of a molecule is thus regarded as synonymous with a **rotamer** about one or more bonds.

NEED FOR CONFORMATIONAL ANALYSIS:

- The major objective of conformational analysis is to gain insight on conformational characteristic of drugs and also to identify the relation between the role of conformational flexibility and their activity.
- Conformational analysis is an important step in molecular modeling as it is necessary to reduce time spent in screening of compounds for activity. Most drugs are flexible molecules with the ability to adopt different conformations by means of rotation about single bonds.
- To know the mechanism and orientation of molecules in many chemical reactions.

FIELDS IN WHICH CONFORMATIONAL ANALYSIS IS USED:

- **Organic Chemistry:** Conformational analysis helps in understanding the spatial arrangement of atoms and bonds within organic molecules, which is crucial for predicting reactivity, stability, and reaction mechanisms
- **Biochemistry**: In biochemistry, conformational analysis is vital for understanding the structure and function of biomolecules like proteins, nucleic acids, and carbohydrates. It's used to study protein folding, enzyme-substrate interactions, and drug binding sites.
- **Pharmaceuticals**: Conformational analysis plays a significant role in drug design and development. By analyzing the different conformations of drug molecules and their interactions with target proteins, researchers can optimize drug potency, selectivity, and pharmacokinetic properties.
- **Materials Science**: Conformational analysis is important for studying the structure-property relationships in materials such as polymers, liquid crystals, and supramolecular assemblies. It helps in designing materials with specific mechanical, optical, or electronic properties.

- **Computational Chemistry**: In computational chemistry, conformational analysis is used to predict the energetically favorable conformations of molecules and study their dynamics. This information is valuable for virtual screening, molecular modeling, and understanding molecular behavior in different environments.

- **Medicinal Chemistry**: Conformational analysis aids medicinal chemists in optimizing the structure of drug candidates to improve their bioavailability, efficacy, and safety profile. It helps in designing molecules that can adopt the desired conformation for optimal interactions with biological targets.

- **Agrochemicals**: In the field of agrochemicals, conformational analysis is used to study the structure and activity of pesticides, herbicides, and fungicides. Understanding the preferred conformations of these molecules can guide the design of safer and more effective agrochemicals.

THREE STEPS OF CONFORMATIONAL ANALYSIS:

1. **Newman Projections:**
   Newman projection is a drawing that illustrates the 3D structure of a molecule by showing the conformation of a chemical bond from front to back

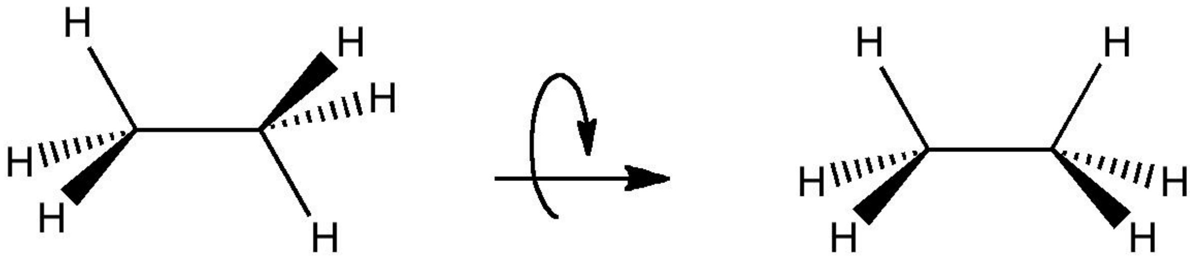
2. **Sawhorse Projections**:
   sawhorse projection is a graphical representation of an alkane molecule's structure from an oblique angle

3. **Molecular Modelling Software**:

Molecular modeling software is a computer program that simulates and explores the behavior of molecules. It uses quantum and classical physics equations to represent molecular structures numerically and simulate their behavior. Scientists use molecular modeling software to study the properties and interactions of molecules, predict their structures, and understand their behavior in different chemical reactions.

<u>CONFORMATIONAL ANALYSIS</u>

- The C-C bond is formed by the sp^3-sp^3 orbitals overlapping and the bond is cylindrically symmetrical, so rotation about the bond can occur easily and the molecule does not seem to change. However, a closer look indicates that the rotation of the C-C bond **does** result in a different spatial arrangement of hydrogen atoms in the molecule, as shown below:

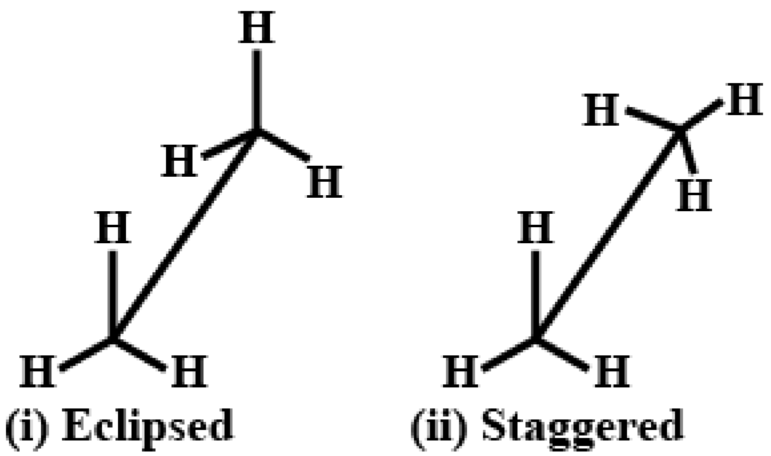


Staggered Eclipsed

- The different spatial arrangements of the atoms/groups that result from the single bond rotation are called **conformations**. Molecules with different conformations are called **conformational isomers** or **conformers.** The two extreme conformations of ethane coming from the C-C rotation shown above are: the ***staggered conformation*** with all of the H atoms spread out and the ***eclipsed conformation*** with all of the H atoms overlapped.

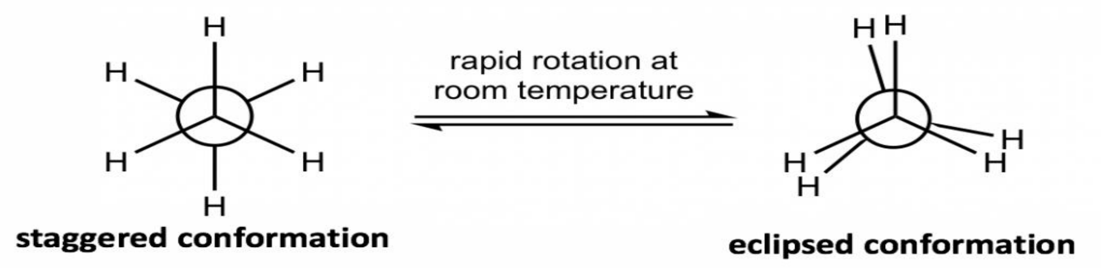
- In the study of conformation, it is convenient to use certain types of structural formulas. The formula used in the drawing above is the **perspective formula** that shows the side-view of the molecule. In perspective formulas, solid and dashed wedges are used to show the spatial arrangement of atoms (or groups) around the sp^3 carbons.

- Another structural formula is the **sawhorse formula** which shows the tilted top-view of the molecule.



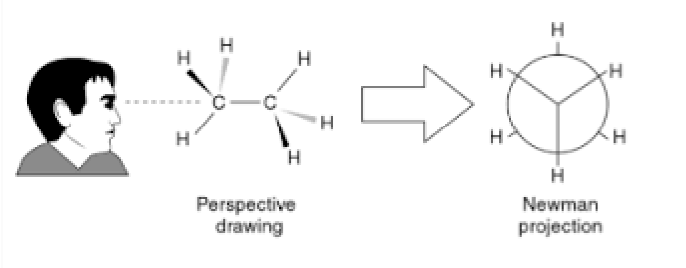
Sawhorse projections of ethane

- The most commonly applied formula in conformation analysis is the **Newman projection** formula.



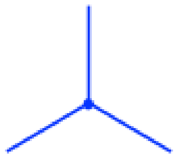
Two conformers of ethane in Newman projections

- To draw a **Newman projection,** we will imagine **viewing** the molecule from one carbon to the next carbon atom directly along a selected C–C bond, as shown below, and follow the rules:

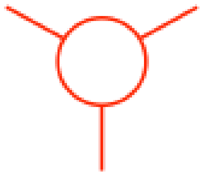


Viewing of the molecule

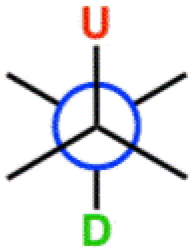
- The front carbon atom is shown as a point with three other bonds(C1)



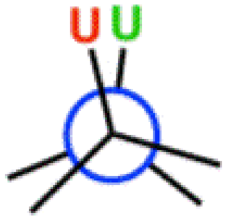
- The rear carbon atom is shown as a circle with three other bonds(C2)



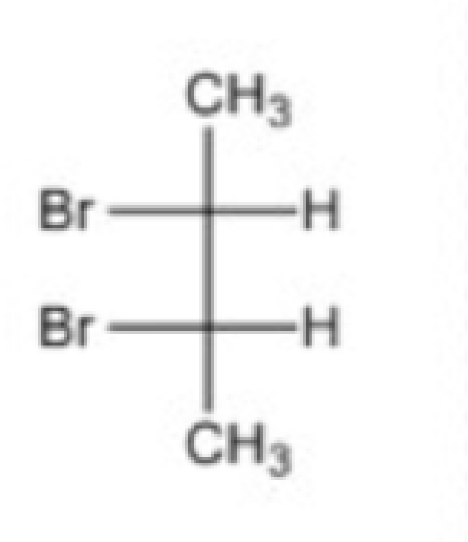
- Put the two carbons together to get the Newman projection of the staggered conformation:



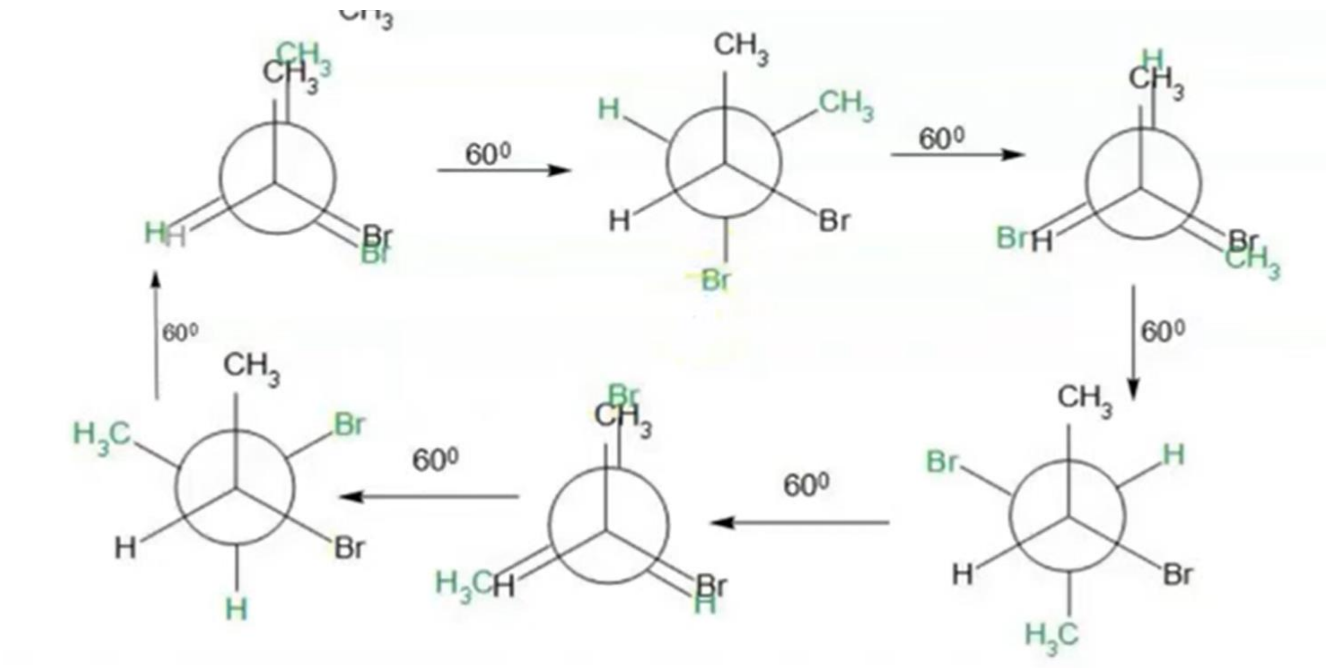
- From the staggered conformation, fix the front carbon in place and rotate the rear carbon by 60° to get the eclipsed conformation:



FISHER PROJECTION OF 2,3-Dibromobutane:

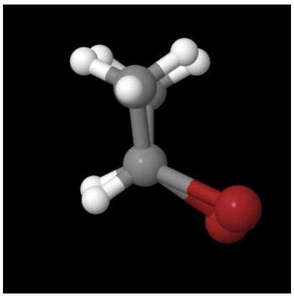


NEWMAN PROJECTIONS OF CONFORMERS OF 2,3-Dibromobutane



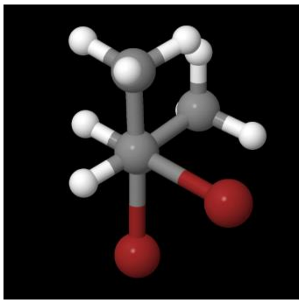
3D PROJECTIONS OF CONFORMERS OF 2,3-Dibromobutane

D



ECLIPSED

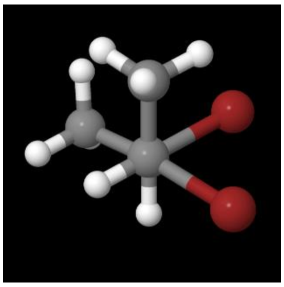
E



STAGGERED

(GAUGE)

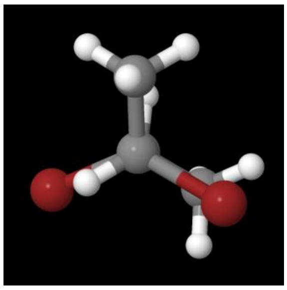
C



STAGGERED

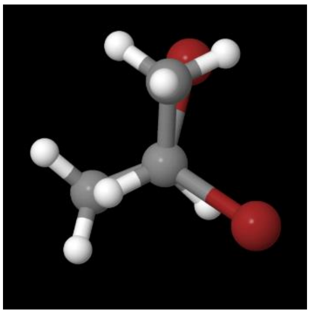
(GAUGE)

F



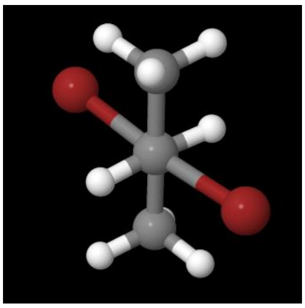
ECLIPSED

B



ECLIPSED

A

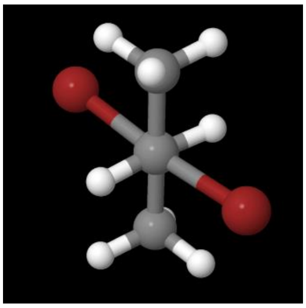


STAGGERED

(ANTI)

TYPE,ANGLE OF ROTATION AND ENERGY OF EACH CONFORMER

A.

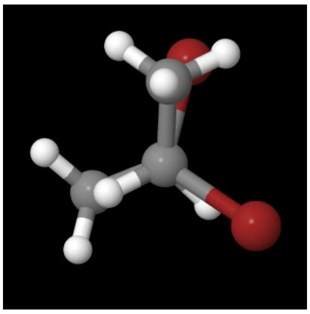


Type of conformation : Staggered (Anti)

Angle of rotation : 0 degree

Energy : 1.6 kJ/mol

B.

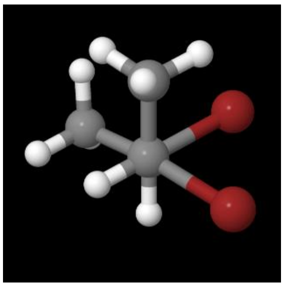


Type of conformation : Eclipsed

Angle of rotation : 60 degree

Energy : 26 kJ/mol

C.

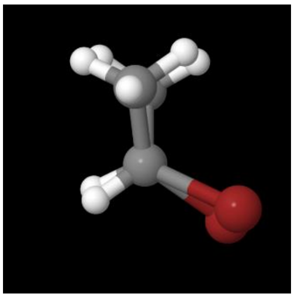


Type of conformation : Staggered (Gauge)

Angle of rotation : 120 degree

Energy : 7.1 kJ/mol

D.

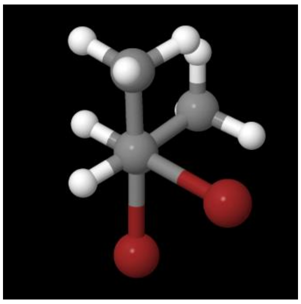


Type of conformation : Eclipsed

Angle of rotation : 180 degree

Energy : 22 kJ/mol

E.

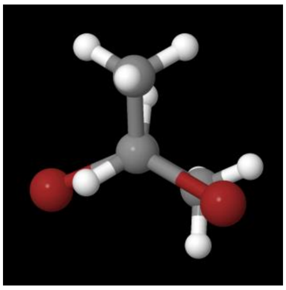


Type of conformation : Staggered (Gauge)

Angle of rotation : 240 degree

Energy : 7.1 kJ/mol

F.

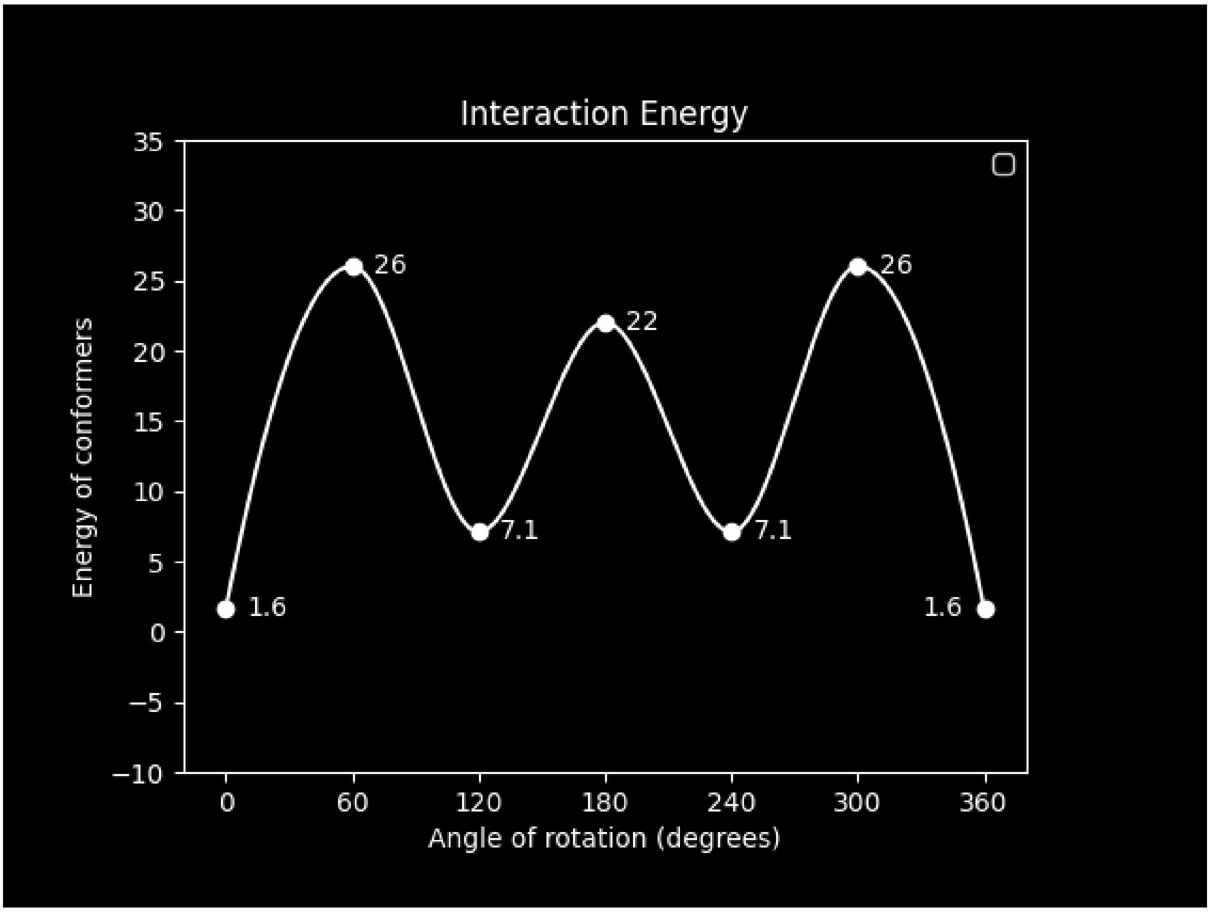


Type of conformation : Eclipsed

Angle of rotation : 300 degree

Energy : 26 kJ/mol

GRAPH SHOWING INTERACTION ENERGY IN EACH CONFORMER



OBSERVATION:

meso-2,3-Dibromobutane exists in three staggered conformations, none of which has a plane of symmetry. Yet the compound is optically-inactive. Indeed, the only conformation that has a plane of symmetry is quite unstable. Because Gauche 1 and 2 form a racemic pair (external comparison). The anti-conformation has a centre of symmetry at the centre of the C2-C3 bond (internal comparison).

CONCLUTION:

Conformational analysis of 2,3-dibromobutane shows that the molecule adopts various spatial arrangements, with the most stable conformation being staggered (anti). This conformation minimizes torsional strain and steric repulsion between the bulky bromine atoms. The less stable conformations, like gauche and eclipsed, have higher energy due to increased strain and steric hindrance. These differences in stability and energy impact the molecule's reactivity and other chemical properties, providing a basis for understanding its behavior in various contexts.

- The most stable conformation is generally the staggered anti-form, where the bulky bromine atoms are positioned as far apart as possible, minimizing steric repulsion and torsional strain.
- The gauche conformations, where the bromine atoms are separated by a smaller dihedral angle (typically around 60 degrees), are less stable than the anti-form but more stable than the eclipsed conformations due to reduced torsional strain.
- The eclipsed conformations, where the bromine atoms align directly behind each other, are the least stable due to increased torsional strain and steric repulsion.

STABILITY:

A > C > E > B > F > D

Most stable **least stable**

ACKNOWLEDGEMENT:

We wish to express our gratitude to our KARE Management for providing the facilities for fabrication. We also wish to express our heartfelt thanks to Dr. Sivarajana, Director Academics, Dr. N. Rajini, Dean Freshman Engineering for their encouragement and support