FACULTY OF ENGINEERING AND TECHNOLOGY

Department of Biotechnology

XYZ Conformational Analysis

- Conformation generally means structural arrangement

abc

- Conformational analysis is needed to identify the ideal conformation of a molecule

$$N = \left(\frac{360}{\delta}\right)^{nbonds}$$

N = # conformations

δ = rotation increment in degrees

nbonds = # of rotatable bonds (degrees of freedom)

- The biological activity of molecules is strongly dependent on their conformation
- Done by exploring the energy surface of a molecule and determining the conformation with minimum energy
- Needed:
  - Conformational space
  - Search method
  - An energy determination method

Conformational Space

- clash-free space - atoms are not in self-collision

abc

Conformational search methods

- Systematic search algorithms
- Model-building methods
- Random approaches – Generates conformers by random perturbation of Cartesian coordinates or the torsion angles of rotatable bonds
- Distance geometry – Determines the lower and upper distances for all pairs of atoms in the molecule and the distance matrix is generated
- Molecular dynamics

Systematic Method

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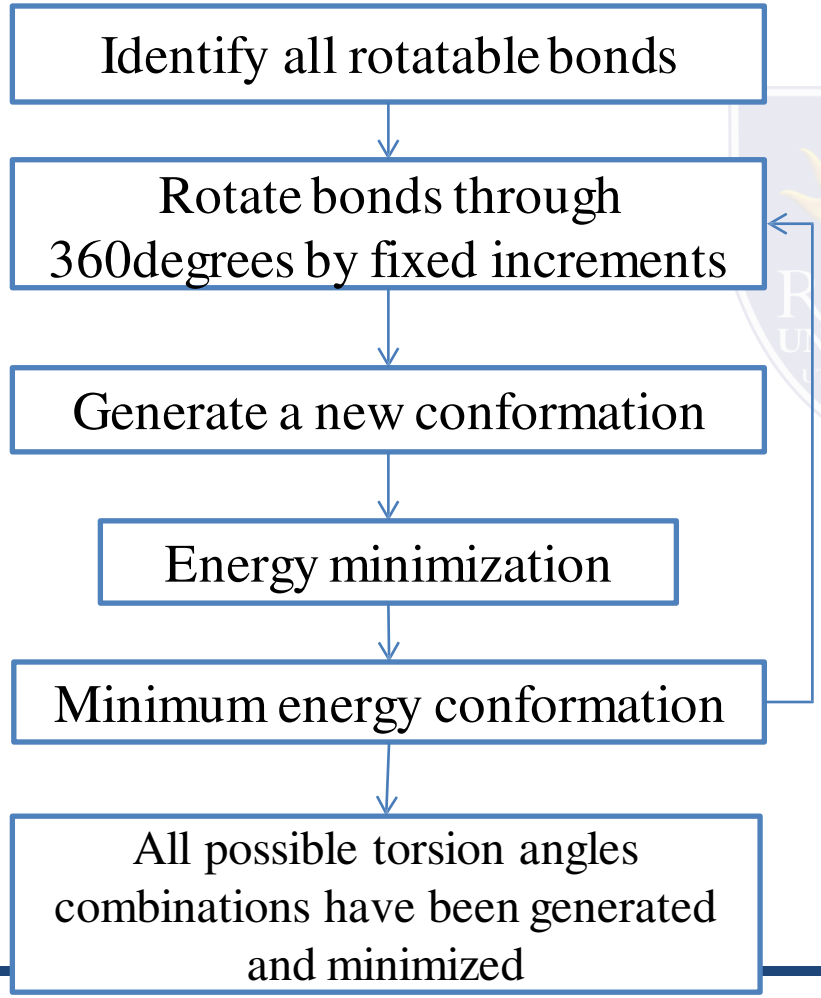
- Simplest
- Deterministic
- abc
- *Grid search*

Assumption: All bond lengths and angles remain fixed throughout the calculation



Advantages

- A deterministic approach, hence a systematic exploration of conformational space
- Can be used for small molecules or systems with 10-15 bonds

Shortcomings

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Combinatorial explosion:

$$\text{Total number of conformations} = \prod_{i}^{N} \frac{360}{\theta_i}$$

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Θ is the dihedral angle chosen for the bond i

Example –

- 3 rotatable bonds
  - 30 degree increment
  - Conformers generated = 1728
  - Time = 29 min
- 5 rotatable bonds
  - 30 degree increment
  - Conformers = 248832
  - Time = 69 hours
- Time for 7 rotatable bonds = 415 days
- Explores large regions with high energy
- Not good for highly flexible molecules

❖ Therefore its time consuming and cannot be used for large system

Search tree

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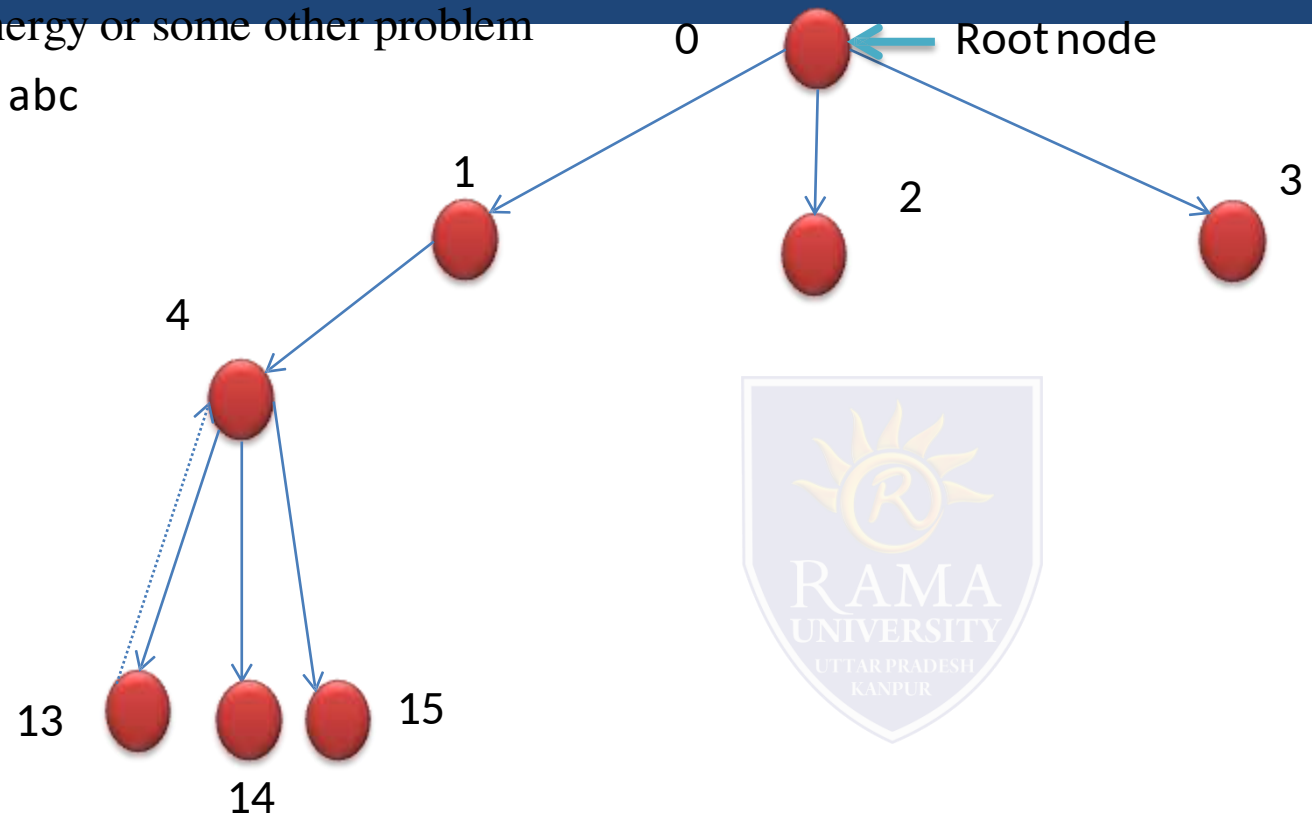
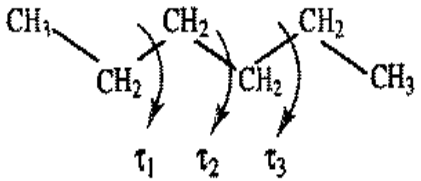
Eliminates the time consuming energy minimization stage for structures that have a very high energy or some other problem





Conformers with severe intra-molecular clashes, i.e. interatomic van der Waals contact energy greater than 10 kcal/mol are removed.

Model-building method

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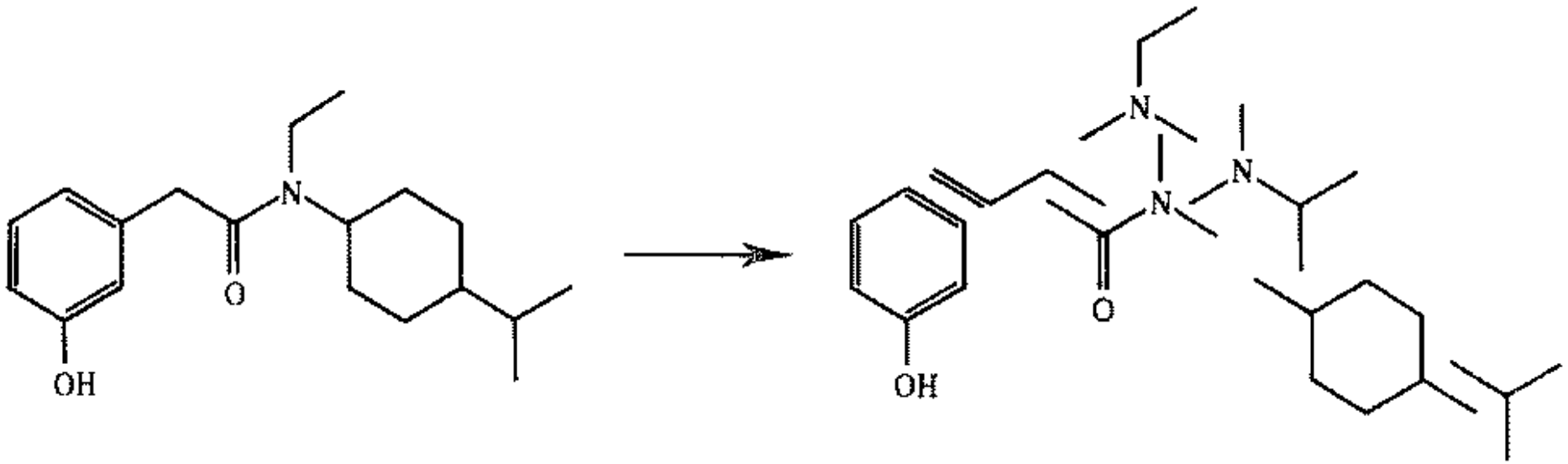
- Construct conformations of molecules by joining together three-dimensional structures of molecular fragments

abc



- Substructure search algorithm
  - Substructure searching is finding a mapping for a query to a target molecule.
  - In other words, no bonds are broken and no new bonds are formed.

fast (systematic search) and *best* (distance geometry) .

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- The program systems **CORINA** and **ROTATE** available from Molecular Networks.
- **OMEGA** from OpenEye Scientific Software is a fast systematic, knowledge-based method.
- **MacroModel** from Schrodinger is a very well-known and widely used force field-based molecular modeling package and offers a variety of methods for conformation generation.
- **CONFORT** was developed by Prof. Pearlman, University of Texas, Austin and is distributed by Tripos. CONFORT performs an exhaustive conformational analysis of a molecule.
- Some open source packages, such as **Open Babel** (http://openbabel.org) or

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MCQs

1. A
2. A
3. A
4. A
5. A
6. A
7. A
8. A
9. A
10. A