ENERGY MINIMISATION

In the field of computational chemistry, **energy minimization** (also called **energy optimization**, **geometry minimization**, or **geometry optimization**) is the process of finding an arrangement in space of a collection of atoms where, according to some computational model of chemical bonding, the net inter-atomic force on each atom is acceptably close to zero and the position on the potential energy surface (PES) is a stationary point. The collection of atoms might be a single molecule, an ion, a condensed phase, a transition state or even a collection of any of these. The computational model of chemical bonding might, for example, be quantum mechanics.

As an example, when optimizing the geometry of a water molecule, one aims to obtain the hydrogen-oxygen bond lengths and the hydrogen-oxygen-hydrogen bond angle which minimize the forces that would otherwise be pulling atoms together or pushing them apart.

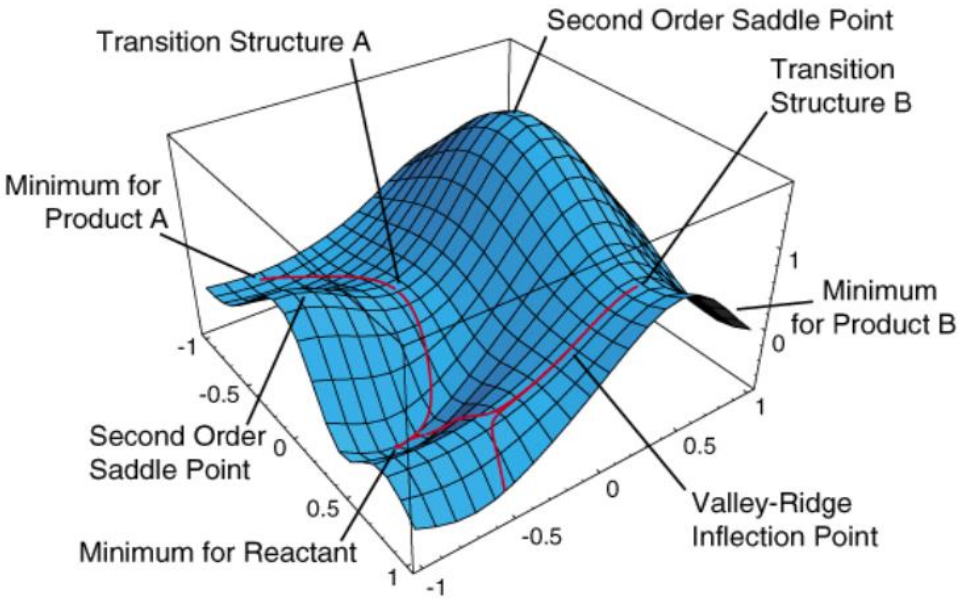
The motivation for performing a geometry optimization is the physical significance of the obtained structure: optimized structures often correspond to a substance as it is found in nature and the geometry of such a structure can be used in a variety of experimental and theoretical investigations in the fields of chemical structure, thermodynamics, chemical kinetics, spectroscopy and others.

Typically, but not always, the process seeks to find the geometry of a particular arrangement of the atoms that represents a local or global energy minimum. Instead of searching for global energy minimum, it might be desirable to optimize to a transition state, that is, a saddle point on the potential energy surface. Additionally, certain coordinates (such as a chemical bond length) might be fixed during the optimization.

- Energy minimization methods can precisely locate minimum energy conformations by mathematically "homing in" on the energy function minima (one at a time).
- The goal of energy minimization is to find a route (consisting of variation of the intramolecular degrees of freedom) from an initial conformation to the nearest minimum energy conformation using the smallest number of calculations possible.
- The way in which the energy varies with the coordinates is usually referred to as PES or hyper surface
- Energy of any conformation is a function of its internal or cartesian coordinates
- N atoms – energy is a function of 3N-6 internal coordinates or 3N cartesian coordinates

- Changes in the energy are a function of its nuclear coordinates.

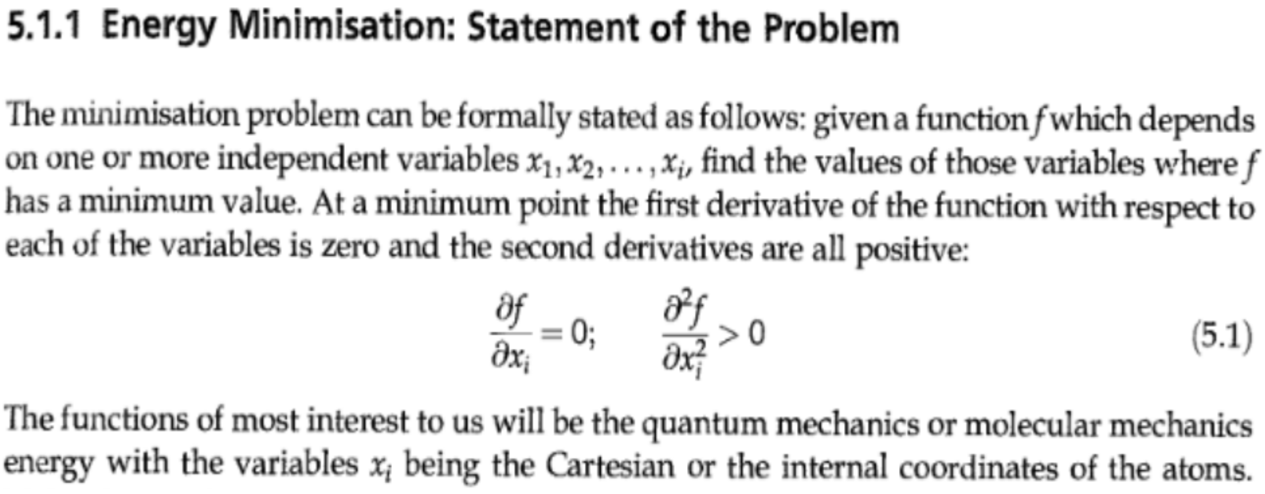
Potential energy surface

- Changes in the energy of a system can be considered as movements on a multidimensional surface called energy surface.
- Changes in the energy ➔ funtion of its nuclear coordinates.
- Movement of the nuclei influences change in energy
- Mathematical function that gives the energy of a molecule as a function of its geometry
- Energy is plotted on the vertical axis, geometric coordinates (e.g bond lengths, valence angles, etc.) are plotted on the horizontal axes
- A PES can be thought of it as a hilly landscape, with valleys, mountain passes and peaks
- Real PES have many dimensions, but key feature can be represented by a 3 dimensional PES
- 

- Equilibrium molecular structures correspond to the positions of the minima in the valleys on a PES
- Energetics of reactions can be calculated from the energies or altitudes of the minima for reactants and products
- A reaction path connects reactants and products through a mountain pass
- A transition structure is the highest point on the lowest energy path

- Reaction rates can be obtained from the height and profile of the potential energy surface around the transition structure
- The shape of the valley around a minimum determines the vibrational spectrum
- Each electronic state of a molecule has a separate potential energy surface, and the separation between these surfaces yields the electronic spectrum
- Properties of molecules such as dipole moment, polarizability, NMR shielding, etc. depend on the response of the energy to applied electric and magnetic fields

- Minima, lowest – global energy minima
- Minimization algorithms
- Highest point in the pathway between 2 minima is saddle point represents the transition state
- Minima and saddle points are stationary states on PES where the first derivative of energy function is 0
- E = f(x)
- E is a function of coordinates either cartesian or internal
- At minimum the first derivatives are zero and the second derivatives are all positive



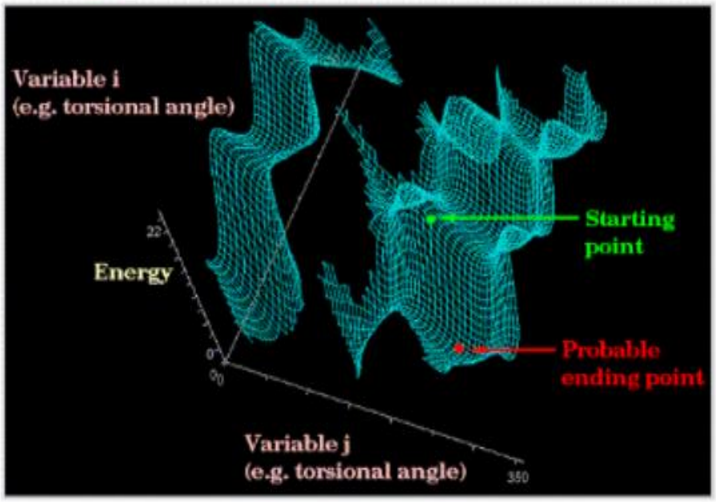
5.1.1 Energy Minimisation: Statement of the Problem

The minimisation problem can be formally stated as follows: given a function *f* which depends on one or more independent variables $x_1, x_2, \ldots, x_i$, find the values of those variables where *f* has a minimum value. At a minimum point the first derivative of the function with respect to each of the variables is zero and the second derivatives are all positive:

$$\frac{\partial f}{\partial x_i} = 0; \qquad \frac{\partial^2 f}{\partial x_i^2} > 0 \tag{5.1}$$

The functions of most interest to us will be the quantum mechanics or molecular mechanics energy with the variables x_i being the Cartesian or the internal coordinates of the atoms.

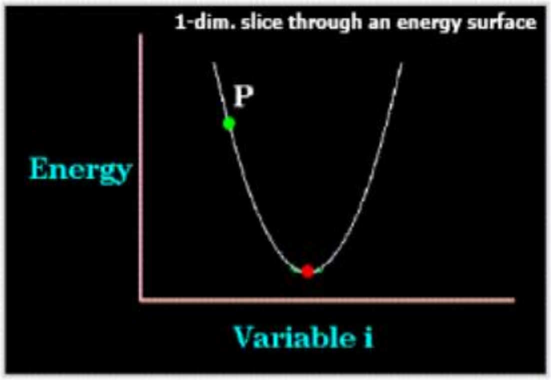
Energy minimisation



Minimisation algorithms are designed to head down-hill towards the nearest minimum.

Remote minima are not detected, because this would require some period of up-hill movement.

Minimisation algorithms monitor the energy surface along a series of incremental steps to determine a down-hill direction.



The local shape of the energy surface around a given conformation en route to a minimum is often assumed to be quadratic so as to simplify the mathematics.

An energy minimum can be characterised by a small change in energy between steps and/or by a zero gradient of the energy function.

Energy minimization algorithms

- Two types
  - Uses the derivatives of energy with respect to coordinates
  - Those that donot use derivatives

Derivatives are useful – provide info on the shape of the energy surface, enhance the efficiency of minima location

Best algorithm – provide quick answer using the least amount of memory

- Minimization algorithm can go down hill on the energy surface and hence locate minima that is nearest to starting point

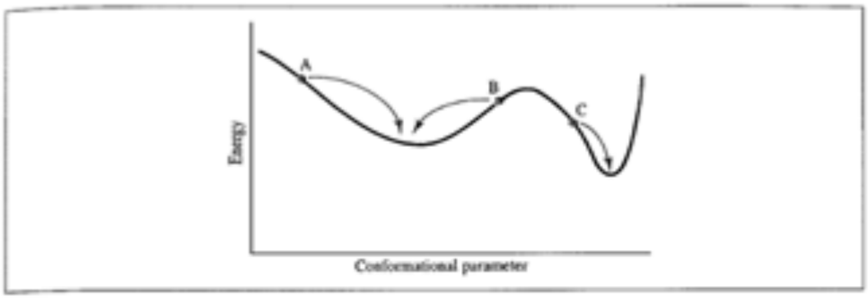


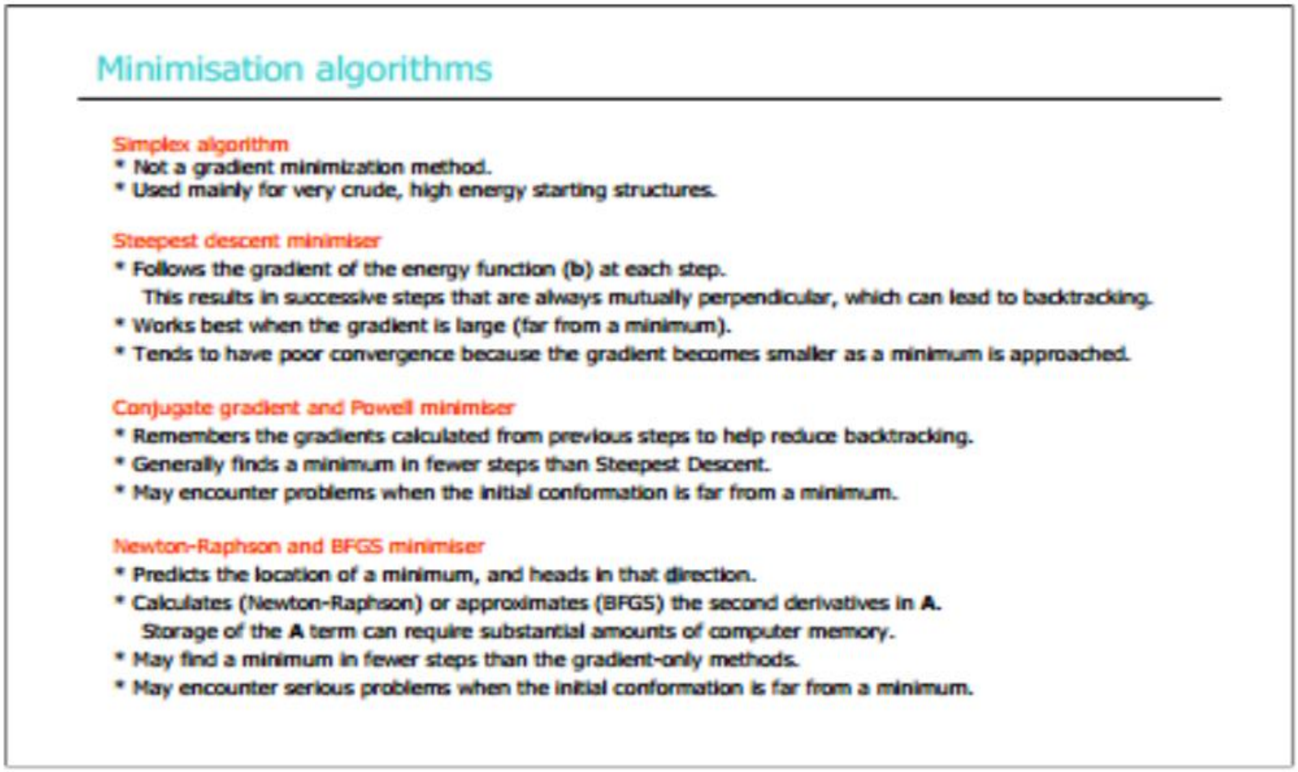
Fig. 5.3: A schematic one-dimensional energy surface. Minimisation methods move downhill to the nearest minimum. The statistical weight of the narrow, deep minimum may be less than a broad minimum which is higher in energy

The input to a minimisation program consists of a set of initial coordinates for the system. The initial coordinates may come from a variety of sources. They may be obtained from an experimental technique, such as X-ray crystallography or NMR. In other cases a theoretical method is employed, such as a conformational search algorithm. A combination of experimental and theoretical approaches may also be used. For example, to study the

Minimization Methods

- Non Derivative methods
  - Require energy evaluation only and may require many energy evaluations
  - Storage required ~ N^2
  - Simplex Method (Nelder and Mead)
  - Powell's Method (assumes quadratic function)
- Derivative Methods
  - Require evaluation of energy and first derivatives
  - Steepest Descent and Conjugate Gradient
  - Quasi-Newton Methods – DFP, BFGS
  - Full Newton-Raphson requires second derivatives
  - Storage requirements vary from 5N to ~N^2

- First-order minimization: Steepest descent, Conjugate gradient minimization
- Second derivative methods: Newton-Raphson method
- Quasi-Newton methods: L-BFGS



Minimisation algorithms

Simplex algorithm
* Not a gradient minimization method.
* Used mainly for very crude, high energy starting structures.

Steepest descent minimiser
* Follows the gradient of the energy function (b) at each step.
  This results in successive steps that are always mutually perpendicular, which can lead to backtracking.
* Works best when the gradient is large (far from a minimum).
* Tends to have poor convergence because the gradient becomes smaller as a minimum is approached.

Conjugate gradient and Powell minimiser
* Remembers the gradients calculated from previous steps to help reduce backtracking.
* Generally finds a minimum in fewer steps than Steepest Descent.
* May encounter problems when the initial conformation is far from a minimum.

Newton-Raphson and BFGS minimiser
* Predicts the location of a minimum, and heads in that direction.
* Calculates (Newton-Raphson) or approximates (BFGS) the second derivatives in **A**.
  Storage of the **A** term can require substantial amounts of computer memory.
* May find a minimum in fewer steps than the gradient-only methods.
* May encounter serious problems when the initial conformation is far from a minimum.

Minimisation algorithms

The **steepest descent** minimiser uses the numerically calculated first derivative of the energy function to approach the energy minimum. The energy is calculcated for the initial geometry and then again when one of the atoms has been moved in a small increment. This process will be repeated for all atoms which finally are moved to new positions downhill on the energy surface. The optimisation process is slow near the minimum. Usually used as a first run (e.g. start of crystallographic refinement).

The **conjugate gradient** method accumulates the information about the function from one iteration to the next. With this proceeding, the reverse of the progress made in an earlier iteration can be avoided. Computational effort and storage requirements are greater than for steepest descent, but conjugate gradient is the method of choice for larger systems.

The **Powell** method is very similar to the conjugate gradient approach. It is faster in finding convergence and suitable for a variety of problems. However, torsion angles may sometimes be modified dramatically.

The **Newton-Raphson** minimiser also uses the curvature of the energy function to identify the search direction. Its efficiency increases as convergenc eis approached. Main disadvantage is the computational effort and large storage requirements for calculating larger systems. Also, for structures with high starin, the minimisation process can become instable. This method is thus not recommended as the first method in a refinement procedure.

Computer simulation

A computer simulation is a simulation, run on a single computer, or a network of computers, to reproduce behavior of a system. The simulation uses an abstract model (a computer model, or a computational model) to simulate the system. Computer simulations have become a useful part of mathematical modelingof many natural systems in physics (computational physics), astrophysics, climatology, chemistry and biology, human systems in economics, psychology, social science, and engineering. Simulation of a system is represented as the running of the system's model. It can be used to explore and gain new insights into new technology and to estimate the performance of systems too complex for analytical solutions.

These are smaller replications of larger macromolecules with manageable number of atoms or molecules. A simulation generates representative configurations of these small replications in such a way that accurate values of structural and thermodynamic properties can be obtained with a feasible amount of computation. Simulation techniques also enable the time-dependent behaviour of atomic and molecular systems to be determined, providing a detailed picture of the way in which a system changes from one conformation or configuration to another. Simulation techniques are also widely used in some experimental procedures, such as the determination of protein structures from X-ray crystallography.

Time Averages, Ensemble Averages and Some Historical Background

Suppose we wish to determine experimentally the value of a property of a system such as the pressure or the heat capacity. In general, such properties will depend upon the positions and momenta of the N particles that comprise the system The instantaneous value of the property A can thus be written as $A(\mathbf{p}^N(t)\ \mathbf{r}^N(t))$, where $\mathbf{p}^N(t)$ and $\mathbf{r}^N(t)$ represent the N momenta and positions respectively at time t (i.e. $A(\mathbf{p}^N(t), \mathbf{r}^N(t)) \equiv A(p_{1x}, p_{1y}, p_{1z}, p_{2x}, \cdots, x_1, y_1, z_1, x_2, \ldots, t)$ where p_{1x} is the momentum of particle 1 in the x direction and x_1 is its x coordinate). Over time, the instantaneous value of the property A fluctuates as a result of interactions between the particles. The value that we measure experimentally is an average of A over the time of the measurement and is therefore known as a *time average* As the time over which the measurement is made increases to infinity, so the value of the following integral approaches the 'true' average value of the property:

$$A_{\text{ave}} = \lim_{\tau \to \infty} \frac{1}{\tau} \int_{t=0}^{\tau} A(\mathbf{p}^N(t), \mathbf{r}^N(t))\, dt \tag{6.1}$$

To calculate average values of the properties of the system, it would therefore appear to be necessary to simulate the dynamic behaviour of the system (i.e. to determine values of $A(\mathbf{p}^N(t), \mathbf{r}^N(t))$, based upon a model of the intra- and intermolecular interactions present).

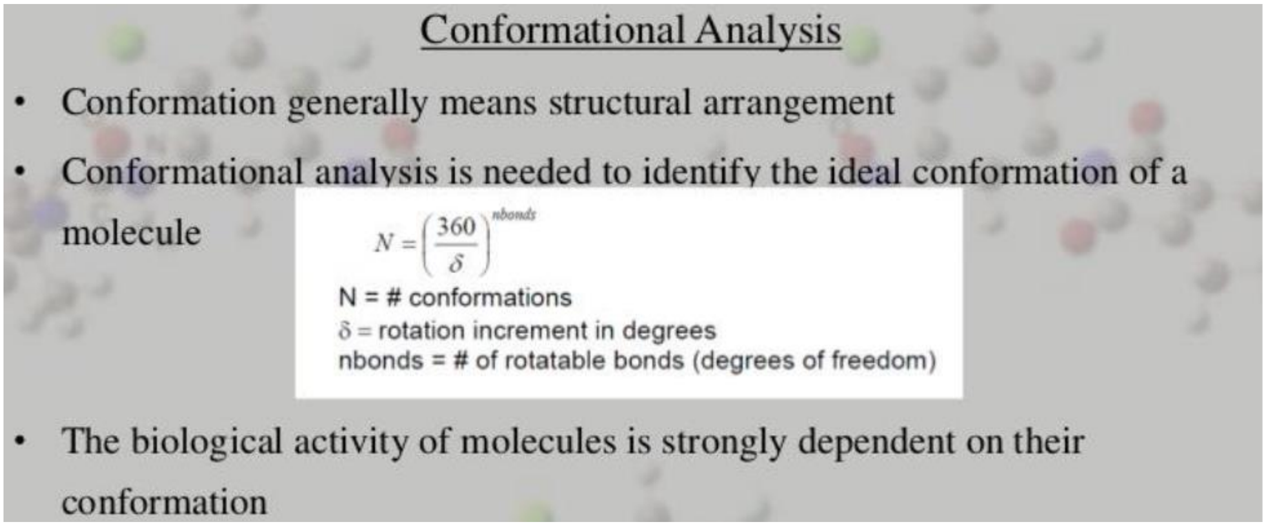
Two simulation techniques – Molecular dynamics and Monte carlo

Molecular dynamics

- Calculates the real dynamics of the sys from which time averages s of a property can be calculated
- Deterministic method – state of a system at any future time can be predicted from current state
    - Time dep of the properties of the system
    - Any configuration can be predicted
    - Has KE
    - Constant no of particles (N), V, E

Monte carlo

- Each configuration is dependent only upon the predecessor
- Generated configurations randiomly and uses a special set of criteria to decide whether or not to accept the config
    - Time independent
    - Config depends on predecessor
    - PE
    - Constant N, V, T



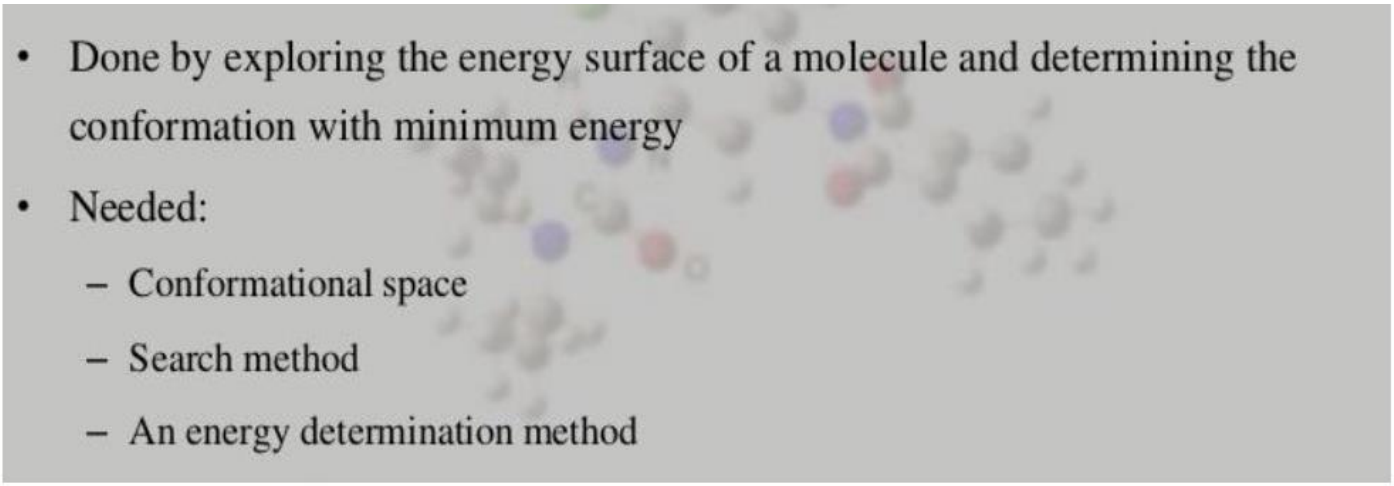
Conformational Analysis

- Conformation generally means structural arrangement
- Conformational analysis is needed to identify the ideal conformation of a molecule

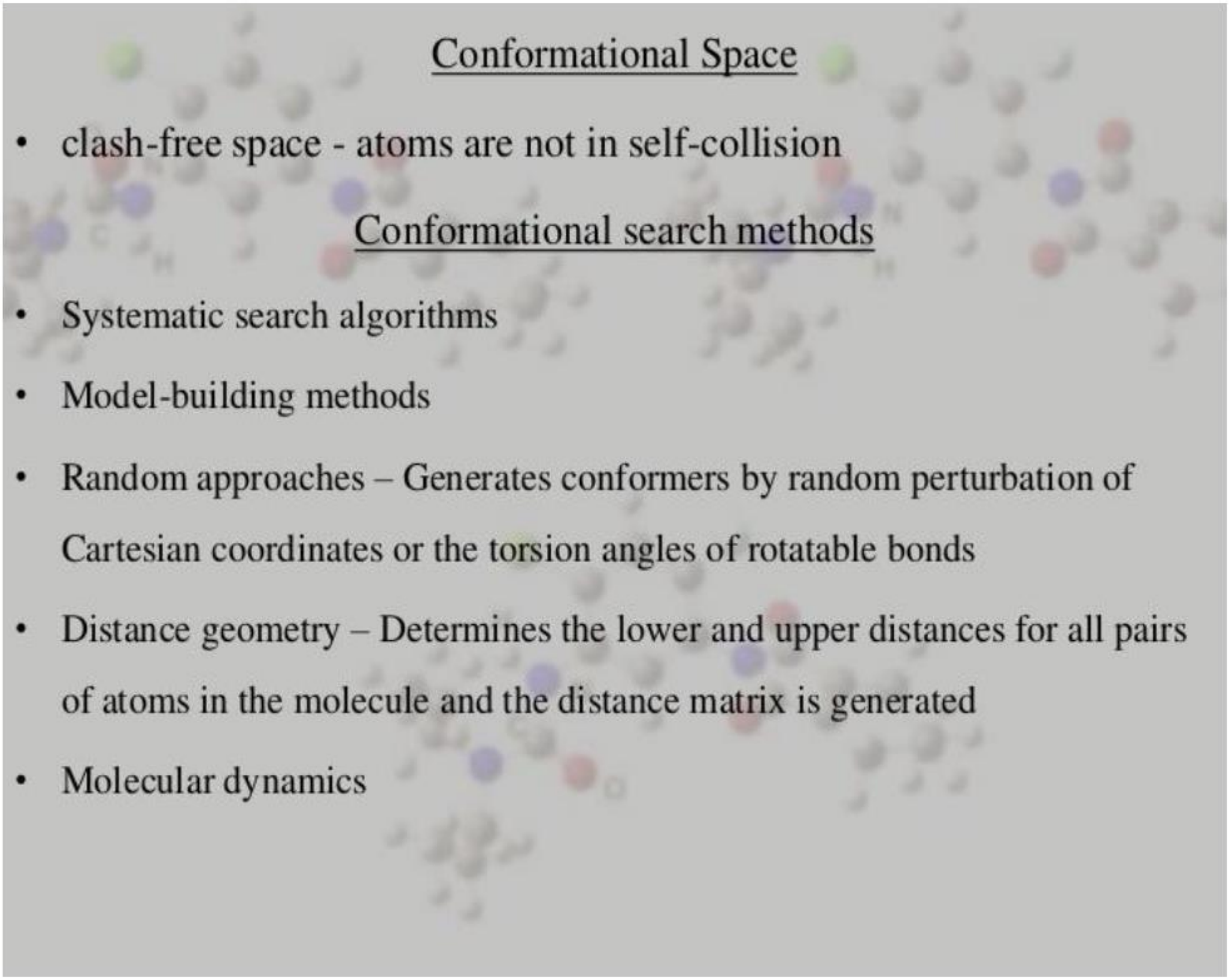
$$N = \left(\frac{360}{\delta}\right)^{nbonds}$$

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

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

- Simplest
- Deterministic
- *Grid search*

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

Identify all rotatable bonds

Rotate bonds through 360degrees by fixed increments

Generate a new conformation

Energy minimization

Minimum energy conformation

All possible torsion angles combinations have been generated and minimized

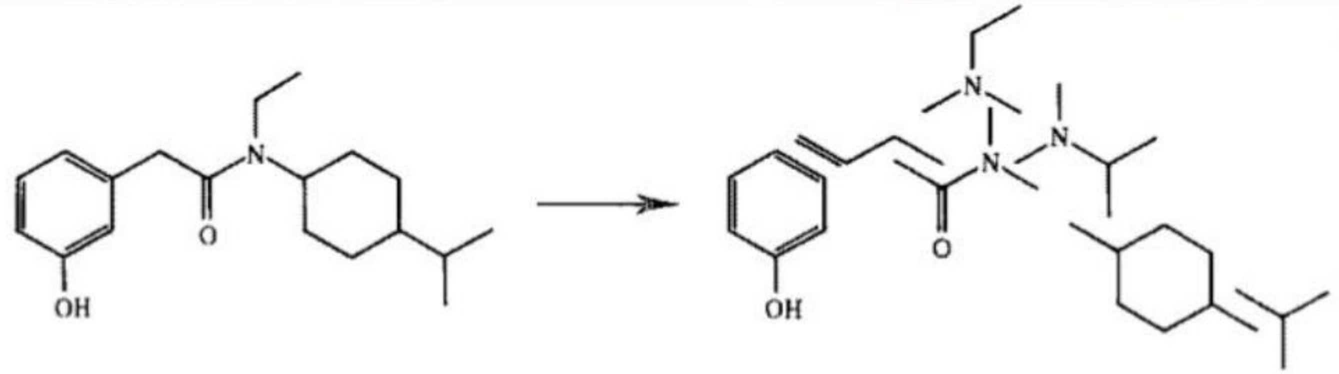
Advantages

- A deterministic approach, hence a systematic exploration of conformational space

- Can be used for small molecules or systems with 10-15 bonds

Model-building method

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



- 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.