

# CONFLEX<sup>®</sup> 6

## Conformation Analysis System

Conflex Corporation  
AIOS Meguro 6F  
2-15-19, Kami-Osaki  
Shinagawa-ku, Tokyo 141-0021  
Japan  
Tel: +81-3-6380-8290  
FAX: +81-3-6380-8299  
<http://www.conflex.co.jp>

For inquires outside Japan:

Conflex USA  
5631 Palmer Way, Suite C  
Carlsbad, CA 92130  
USA  
Tel: +1 (760) 930-9277  
USA: 1 (800) 298-0054  
Fax: +1 (509) 692-4541  
[info@conflex.us](mailto:info@conflex.us)  
<http://www.conflex.us>

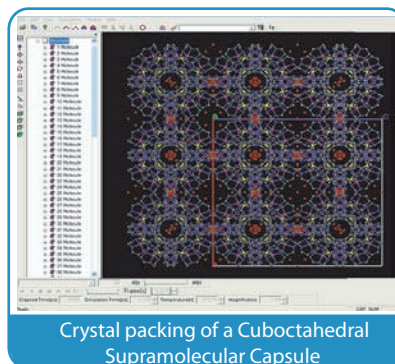
**CONFLEX<sup>®</sup> 6** permits fast, accurate, automated conformation searching and analysis critical to drug discovery and chemical engineering. Unique to CONFLEX 6 is its capability to completely search the conformational space of a flexible molecule to find every optimal structure of chemically significant conformers.

Utilizing several unique strategies, CONFLEX 6 exhaustively searches conformational space to identify the most stable structures using:

- Stepwise, one-at-a-time perturbations
- Three perturbation modes to mimic thermal vibration
- User-selectable force fields calculations
- User-variable search limit

CONFLEX 6 calculation results can be output in a variety of formats permitting their use in applications for ab initio calculations or visualization applications such as BARISTA<sup>™</sup>.

**PARALLEL CONFLEX** performs geometry optimization by distributing to multiple computers multiple starting structures generated by means of perturbations that alter the initial structure. Molecules of interest in post-genomic research and materials research frequently are extremely large, so accurate conformational searches cannot be performed easily on one PC. PARALLEL CONFLEX is an effective tool for reducing the research time in analyzing conformations of these large molecules, and it also has application for multi-conformation bio-macromolecules (e.g., proteins, DNA, RNA) with diverse three-dimensional structures.



### Key Features & Benefits

- Exhaustive conformation searches
- Fast and highly accurate
- Handles small & large molecules
- Single and Parallel CPU options
- GRID-compatible via OmniRPC
- CD/UV/VIS Spectra Prediction
- Reads PDB files
- Available as stand-alone engine or with BARISTA interface
- Affordable licensing plans

### New in this Release

- Crystal Packing - explore energies of crystal polymorphism
- Enhanced NQEq force field for greater accuracy
- Improved GBSA model for:
  - structure optimization
  - conformational search
  - vibrational analysis
  - LogP calculations
- Residue Substitution for homology modeling
- Improved MMFF94s parameters
- Frontier mode-Following Method (FMF)
  - new transitions state search method

### CONFLEX 6 Force Fields

- MM2
- EMM2
- MM3
- MMFF94s
- MMFF/NQEq

### File Formats

CONFLEX 6 handles these commonly used file formats:

- mol - MDL molfiles
- sdf - MDL SD file
- pdb - Protein data bank file

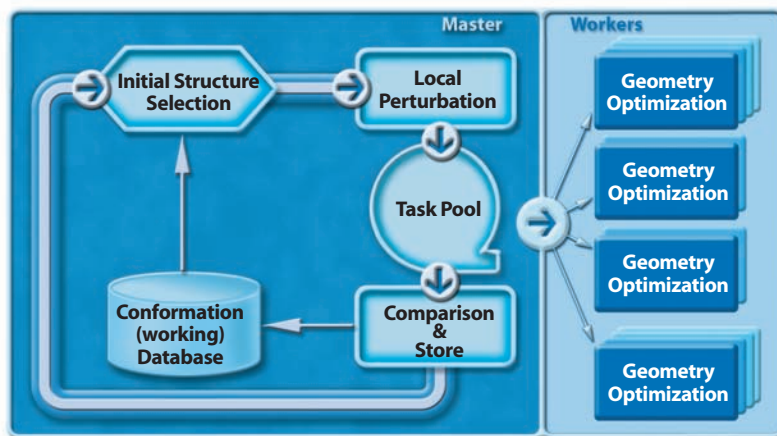
### System Requirements

#### CONFLEX 6

Mac OS X 10.2 & up  
Redhat Linux 8 & up  
Windows XP  
1.0 GHz Processor & up  
40 GB Disk Space  
Memory 1 GB minimum

#### PARALLEL CONFLEX

Redhat Linux 8 & up  
Mac OS X 10.2 & up  
Grid compatible  
1.0 GHz Processor & up  
40 GB Disk Space  
Memory 1 GB minimum

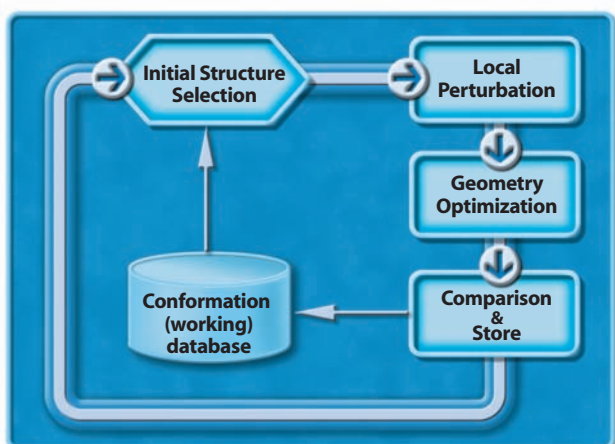


Part of PARALLEL CONFLEX was developed under a "Grant-in-Aid for Project Costs Associated with Innovation Creation with the Collaboration of Industry, Government, and Universities" of the Japan Ministry of Education, Culture, Sports, Science and Technology.

### Overview of the CONFLEX Algorithm

The basic concept behind CONFLEX is to examine the conformational space of a structure using an exhaustive step-wise approach:

1. The initial structure is perturbed using one of the three perturbation methods in CONFLEX
2. The resulting structure's geometry is measured using any one of a number of force-field algorithms, e.g. MM3, MMFF94s, MMFF/NQEQ
3. A comparison is made to determine whether or not the conformation is a new low energy conformer in which case it is stored in the working database for the experiment
4. Additional perturbations are made on the initial structure and steps 1-3 are repeated until all possible combinations of perturbations for the structure have been examined
5. The lowest energy conformer stored in the working database is then selected and steps 1-4 are repeated
6. Steps 1-5 are repeated until all possible conformers for the structure of interest have been examined



In such a way we can exhaustively explore the conformational space, and, with the CONFLEX perturbation algorithms, we can expect a high degree of accuracy in the conformers found.

#### CONFLEX Perturbation Algorithms

**Corner Flap** is the perturbation operation that moves one of the ring-skeleton atoms to the side opposite the average plane of the peripheral atoms. Corner Flap may be considered an operation that mimics thermal vibration, which is the actual motivation for interconversion between conformations. Various starting structures can be generated by applying this operation to successive ring-skeleton atoms.

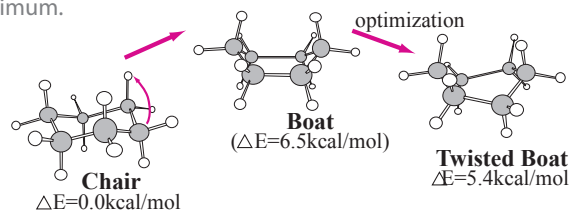
**Edge Flip** (ring-skeleton) and **Stepwise Rotation** (main-chain and side-chain skeleton). The concept is basically the same in that actual thermal vibrations are mimicked. The important point here is that it is possible to successfully find conformations directly related to the conformation of the initial structure by means of interconversion.

#### Structure Selection

As a general rule for replacing the initial structure, the conformation with the lowest energy is selected preferentially from among the obtained conformations stored in the working database. However, once a conformation is selected as the initial structure it is possible to find all conformations directly related to it so it will not be reselected again during the experiment.

If the molecule is large enough, the perturbation operation (e.g. Corner Flap) alters only a part of the molecule so that the structure obtained by this perturbation is more likely to retain a low-energy structure. Although this is not yet proven mathematically, it has been verified by the results we have obtained to date.

As an example, assume a molecular model of the chair conformation of cyclohexane, which is easily converted to the boat conformation. Unfortunately, the boat conformation is not the energy minimum; however, by twisting the model in small increments, it is possible to create the twisted-boat conformation, which is the energy minimum.



A new energy-minimum structure (twisted-boat type) is obtained by creating another conformation (boat type) by moving one ring-skeleton atom of an initial structure (chair-type) to the side opposite the average plane created by the skeleton atoms at its periphery, and by using this as the starting structure to optimize the geometry (by twisting in small increments) along the molecular force field potential. The results are stored in the working database.

The perturbation operations and geometry optimizations are performed for all ring-skeleton atoms and a comparison is made to determine whether or not the conformation is new, in which case it is stored. By selecting another conformation (twisted-boat) from the working database and repeating the same operations, it is then possible to obtain a new energy-minimum structure (chair-type in the case of cyclohexane), depending on the geometry optimization.

Therefore, it is evident that, in the CONFLEX conformation space search algorithm, the initial structure periphery is searched thoroughly by means of the perturbation operations and geometry optimizations, and the search area is expanded comprehensively by replacement of the initial structure. Even if the search starts from a somewhat unstable input structure, the search space decreases rapidly each time the initial structure is replaced. Once the most stable conformation is found, the search space gradually moves in the high-energy direction.



Reservoir-Filling Algorithm

We call this CONFLEX search algorithm a reservoir-filling algorithm as it evokes a natural scene in which water flows into all the lowest points of a reservoir, and the reservoir fills as the water level rises.

#### References:

- J. Am. Chem. Soc., 1989, 111, 8950-8951.
- J. Chem. Soc., Perkin Trans. 2, 1993, 187-198.