USER GUIDE

LigParGen 3.0

OPLS-AA parameters for organic molecules, on your own computer. Jorgensen Research Group, Yale University.

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What LigParGen does

You give LigParGen a molecule. BOSS, the Jorgensen group's simulation program, assigns each atom its OPLS-AA atom type and computes the partial charges with the CM1A model. LigParGen then writes the complete parameter set — charges, Lennard-Jones terms, bonds, angles, dihedrals and impropers — in the files of eleven simulation programs, so the same molecule has the same energy in each.

Everything runs on this computer. Nothing is sent anywhere, except a message you choose to send with Help.

1 · Installing

MAC (APPLE SILICON: M1 AND LATER)

1. Open `LigParGen-3.0.0-arm64.dmg` and drag LigParGen to Applications.
2. Open it from Applications. The first time, macOS may say it cannot check the developer: open **System Settings** → **Privacy & Security** and choose **Open Anyway**.

WINDOWS (10 AND 11, 64-BIT)

1. Run `LigParGen Setup 3.0.0.exe` and follow the steps. It installs for you only, so no administrator rights are needed.
2. If Windows SmartScreen says it protected your PC, choose **More info** → **Run anyway**.

LINUX (X86-64)

1. Make the file runnable and start it: `chmod +x LigParGen-3.0.0.AppImage`, then `./LigParGen-3.0.0.AppImage`.
2. Some distributions need the FUSE 2 library to open AppImages (on Ubuntu: `sudo apt install libfuse2`).

Nothing else is needed: BOSS, Python and RDKit are inside the program.

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2 · Giving a molecule

DRAW

Draw the molecule in the editor (Ketcher, the same as on jorgensenresearch.com). Hydrogens are added for you.

SMILES

Paste a SMILES string, such as `CC(=O)Oc1ccccc1C(=O)O` for aspirin. Hydrogens are added for you; write charges in the SMILES (`CC(=O)[O-]`).

FILE

Drop a **MOL**, **MOL2** or **PDB** file on the window, or choose one. A file must contain **every hydrogen**, at the protonation state you want. LigParGen keeps your file's atom order and atom names in every output file.

NAME, RESIDUE AND CHARGE

- **Name** is only a label: it names the files (`aspirin.gmx.itp` …) and their folder.
- **Residue** is the three-letter residue name written inside the files.
- **Charge** is the molecule's net charge. For a SMILES, drawing or MOL file it follows the structure by itself; for a PDB file, set it yourself.

Before you run, LigParGen checks the molecule and says **Ready**, or what needs fixing.

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3 · Charges

- **1.14*CM1A-LBCC** — for neutral molecules (the default). CM1A charges scaled by 1.14, with localized bond-charge corrections.
- **1.14*CM1A** — for charged molecules. For an ion the 1.14 scale is not applied, as in the method.

The charges come from BOSS's own charge cycle: charges, then an OPLS-AA optimization with them, three times. Your structure keeps its own coordinates in the output files.

SINGLE ATOMS AND IONS

A single atom or ion runs with BOSS's own OPLS-AA parameters for it: He, Ne, Ar, Kr, Xe; F^-, Cl^-, Br^-, I^-; Li^+, Na^+, K^+, Rb^+, Cs^+; Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}; La^{3+}, Nd^{3+}, Eu^{3+}, Gd^{3+}. Other ions are not supported: use your force field's ion parameters.

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4 · The files for each program

Results are saved in **Documents › LigParGen › *name*** (or the folder you chose), with `CITE.txt` and a log. In the **Files** tab you can drag any file, or a program's title for all its files, out of the window: onto the Desktop, into a folder, or into another program.

OpenMM — `.openmm.xml`, `.openmm.pdb`, `.openmm.py`. Build the system with `from NAME.openmm import build`; `pdb, system = build()`. The loader keeps OPLS's geometric combining rule and BOSS's impropers, which the XML alone cannot express.

GROMACS — `.gmx.itp`, `.gmx.gro`. Put `#include "NAME.gmx.itp"` in your `topol.top`.

AMBER — `.amber.prmtop`, `.amber.inpcrd`. Use with sander, pmemd or ParmEd. sander reports about 0.3 kcal/mol more per straight (180°) angle, as it cannot measure an angle that close to 180°.

CHARMM / NAMD — `.charmm.rtf`, `.charmm.prm`, `.charmm.pdb`. For NAMD, build the PSF with psfgen from the .rtf; the .prm carries NBFIX lines so NAMD mixes Lennard-Jones as OPLS does.

LAMMPS — `.lammps.lmp` (data), `.lammps.in` (settings): `include NAME.lammps.in`.

TINKER — `.tinker.key`, `.tinker.xyz`.

X-PLOR / CNS — `.xplor.top`, `.xplor.param`, `.xplor.pdb` (atom names in capitals, as X-PLOR reads them).

Q — `.q.lib`, `.q.prm`, `.q.pdb`. Desmond — `.desmond.cms`. PQR — `.pqr`.

BOSS / MCPRO — `.z`, the Z-matrix with its parameters, ready for BOSS and MCPRO.

> LigParGen writes the molecule's parameters only: no water, no box and no run settings. Build those in your program as usual.

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5 · Limits

- **Elements:** H, C, N, O, F, Cl, Br, I, P, S, B, Si, Al.
- **Size:** about 110 non-hydrogen atoms (250 atoms with hydrogens) for BOSS's charge calculation.
- **Optimization:** molecules over about 150 atoms are past BOSS's optimizer, so their charges are computed once, on the shape given.
- **One molecule at a time:** no salts, counter-ions or mixtures; remove counter-ions first.
- **Not supported:** two-atom molecules (N_2, O_2, CO, HCl…: OPLS-AA types are for atoms in larger molecules — use a model made for small gases), proteins, boranes and carboranes, perchlorate-type halogens, polymer repeat units with open attachment points (*).

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6 · Messages, and what to do

The file is missing hydrogen atoms.

Add hydrogens at the right protonation state (PyMOL: `h_add`; Open Babel: `obabel in.pdb -O out.pdb -h`), or give the molecule as SMILES.

The structure has a net formal charge of +1, but the net charge is set to 0.

Set the Charge to the structure's charge, or fix the structure.

1.14*CM1A-LBCC is for neutral molecules only.

Choose 1.14*CM1A for ions.

Some atoms are missing a bonded partner / an odd number of electrons / unpaired electrons.

Usually a missing hydrogen or a missing formal charge. Check the atoms named in the message.

Unbonded atoms closer than a bond length, as in a 2D drawing.

The file has flat or overlapping coordinates. Give it as SMILES, or save a 3D structure.

This structure contains several separate molecules / counter-ions / only ions.

Keep the one molecule you want parameters for.

Too large for BOSS.

See the limits above; parameterize a smaller fragment.

RDKit cannot read this SMILES or file.

Check the SMILES, or export the file again from your drawing program.

LigParGen stopped unexpectedly.

Use Help and attach the run: we will look at it.

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7 · From the command line

For scripts and long lists, the same LigParGen runs in a terminal. Set it up once: **About → Set up the ligpargen command**, then open a new terminal. (On Linux you can also run `./LigParGen-3.0.0.AppImage ligpargen …` directly.)

ONE MOLECULE — LIGPARGEN 2.1'S OWN OPTIONS

```
ligpargen -s "CC(=O)Oc1ccccc1C(=O)O" -n ASP -r ASP -c 0 -cgen CM1A-LBCC -p aspirin
ligpargen -i mymolecule.mol -n LIG -r LIG -p results/lig
```

Every option of LigParGen 2.1 works as before (`-s`, `-i`, `-n`, `-r`, `-c`, `-cgen`, `-o`, `-p`, `-f`, and the alchemical `-sb`, `-ib` …), so existing scripts keep running. Before a run the molecule gets the same check as in the window; `--no-check` skips it and `--json` prints a result a script can read.

A WHOLE LIST

`ligpargen batch molecules.csv -o results -j 4` — a CSV with the columns `name`, `smiles` or `file`, and optionally `charge` and `cgen`; or a folder: `ligpargen batch my_mol_files/ -o results`. One folder per molecule, and `summary.csv` with what ran and why anything did not.

ONLY THE CHECK

`ligpargen check -s "[Na+]" -c 1` says **Ready** or what to fix. `ligpargen --help` lists everything.

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8 · Getting help

Press **Help**, give your name and email and say what happened. Leave **Attach the last run** ticked so we can see the molecule, the settings and the log. We answer by email from support@jorgensenresearch.com. If this computer is offline, your email program opens with the message instead.

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9 · Citing LigParGen

If LigParGen helped your work, please cite (the **Copy citations** button copies them; each run also saves them in `CITE.txt`):

1. Dodda, L. S.; Cabeza de Vaca, I.; Tirado-Rives, J.; Jorgensen, W. L. LigParGen Web Server: An Automatic OPLS-AA Parameter Generator for Organic Ligands. *Nucleic Acids Res.* **2017**, 45, W331–W336.
2. Dodda, L. S.; Vilseck, J. Z.; Tirado-Rives, J.; Jorgensen, W. L. 1.14*CM1A-LBCC: Localized Bond-Charge Corrected CM1A Charges for Condensed-Phase Simulations. *J. Phys. Chem. B* **2017**, 121,

3864–3870. (for 1.14*CM1A-LBCC charges)
3. Jorgensen, W. L.; Tirado-Rives, J. Molecular Modeling of Organic and Biomolecular Systems Using BOSS and MCPRO. *J. Comput. Chem.* **2005**, 26, 1689–1700.