

Drug Design Package Software
with In Silico Drug Discovery

MolDesk Basic
Ver. 1.1.89

Quick Manual

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1. Quick Manual

1.1. project

MolDesk processes data on a project-by-project basis.

As a general rule, one project will be created for each file entered with [File]-[Open Molecular File].

The project should be in the directory set in the Default Project Directory of [Help] - [Preference] - [8. Other].

MoldeskProject00000

MoldeskProject00001

MoldeskProject00002

. . .

Is created as.

The above Default Project Directory directory is the system default tmp directory, which differs for Windows, Linux, and MAC, so check where it is stored.

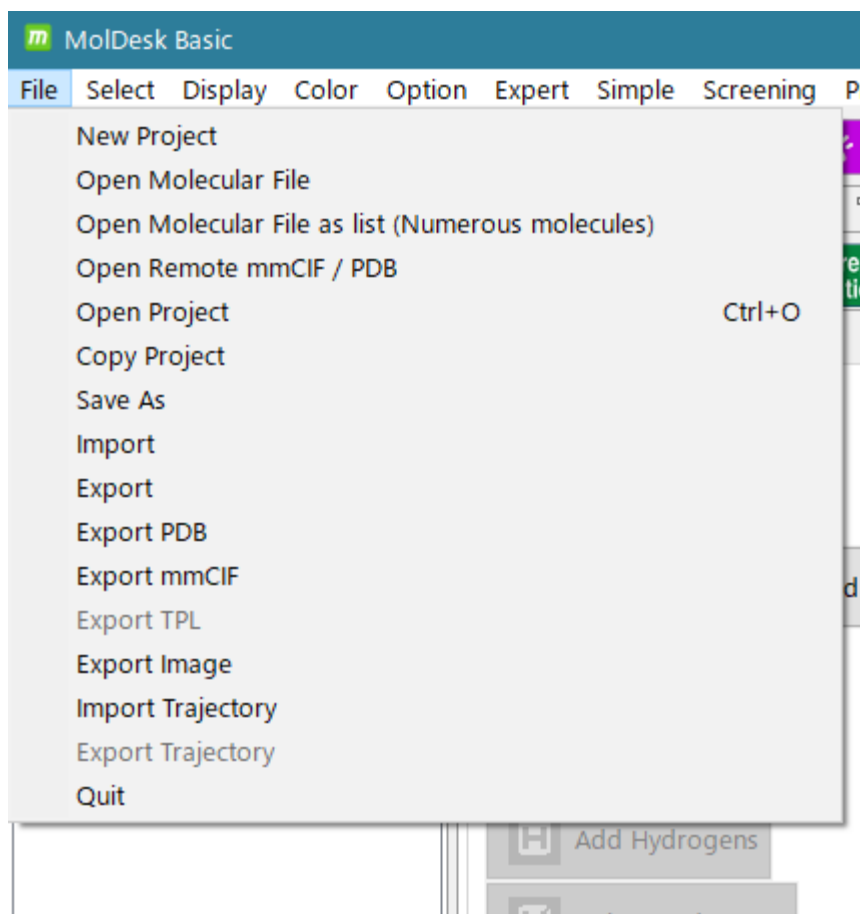
[Help]-[Preference]-[8. Other]

Please verify.

[Help] - [Preference] - [8. If the user changes the Default Project Directory in Other, the program will no longer prompt you to save the project.

It is recommended that you change to a directory (folder) with sufficient disk space.

1.2. Create a project



There are seven menus for creating a project:

[File] - [New Project]

[File] - [Open Molecular File]

[File] - [Open Molecular File as list (Numerous Molecules)]

[File] - [Open Remote mmCIF / PDB]

[File] - [Open Project]

[File] - [Import]

[File] - [Import Trajectory]

of which

[Open Molecular File]

[Open Molecular File as list (Numerous Molecules)]

[Open Remote mmCIF / PDB]

[Open Project]




Describes .

1.2.1. [File] - [Open Molecular File]

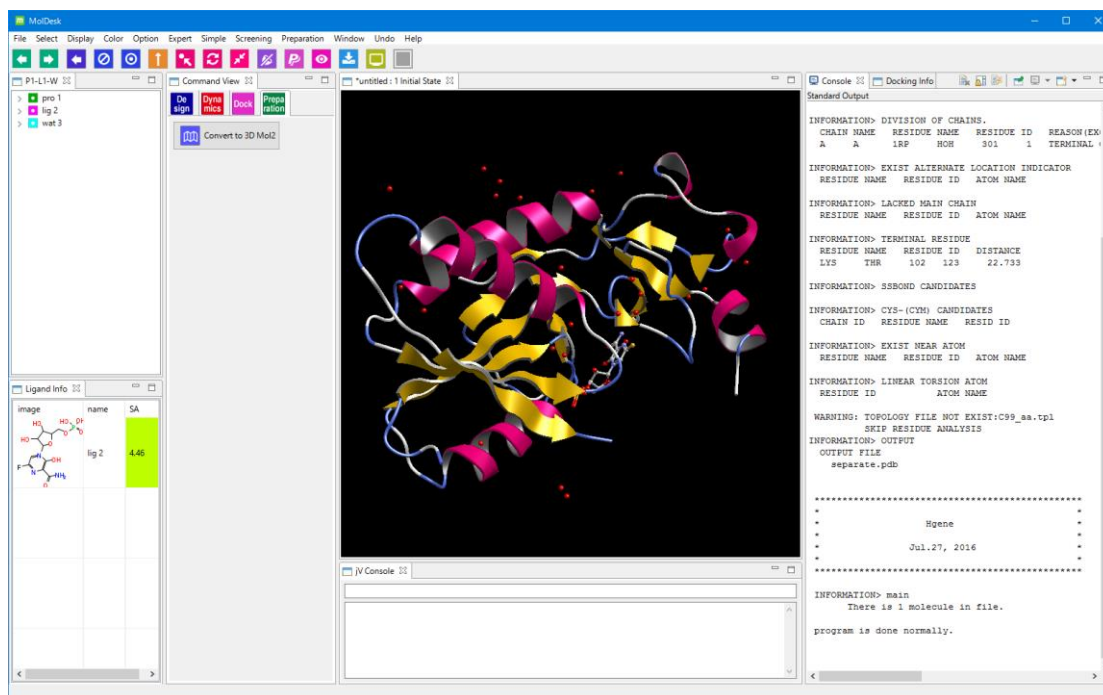
Load the specified file to create a new project.

There are five file formats that can be entered: PDB / mmCIF / Sybyl Mol2 / MDL SDF / MDL MOL / SMILES. The file extensions should be as shown in the table. If the extension is different, change the extension before entering.

file	File extension
PDB	. pdb / . ent
mmCIF	. cif
Sybyl Mol2	.mol2 / .sm2 / . SM2 / .ml2
MDL SDF	. sdf
MDL MOL	.mol / .mdl
SMILES	. smi / . SMI / .smiles / . SMILES

- If the input file is a mmCIF file or pdb file, hydrogen atoms are missing, so you need to add hydrogen atoms with  [Add Hydrogens] as appropriate.
 - If you want to detect and process the terminal residues of a protein molecule, perform  [Cap with ACE and NME] before adding a hydrogen atom. If a hydrogen atom is added first, an OXT atom will be added to the N-terminal and the NME terminal cannot be added.
- If the file you entered is a mol2 file, read the charge information if the mol2 file contains it, but it does not automatically calculate the charge even if the charge information is not included.
 - If you read a mol2 file that does not have charge information, use  [Partial Charge] to calculate the charge as appropriate.

When you load the file, the structure of the molecule is displayed on the 3D screen.



The project name is not yet attached at this time.

When saving the project name with "1.3.1 [File] - [Save As]" described later, save it with the project name.

1.2.2. [File] - [Open Molecular File as list (Numerous Molecules)]

Fast loading of files containing more than 10,000 molecules. It can be used as a molecular viewer for files with large numbers of molecules.

Because a large number of molecules are read as a list, no new project is created when loaded.

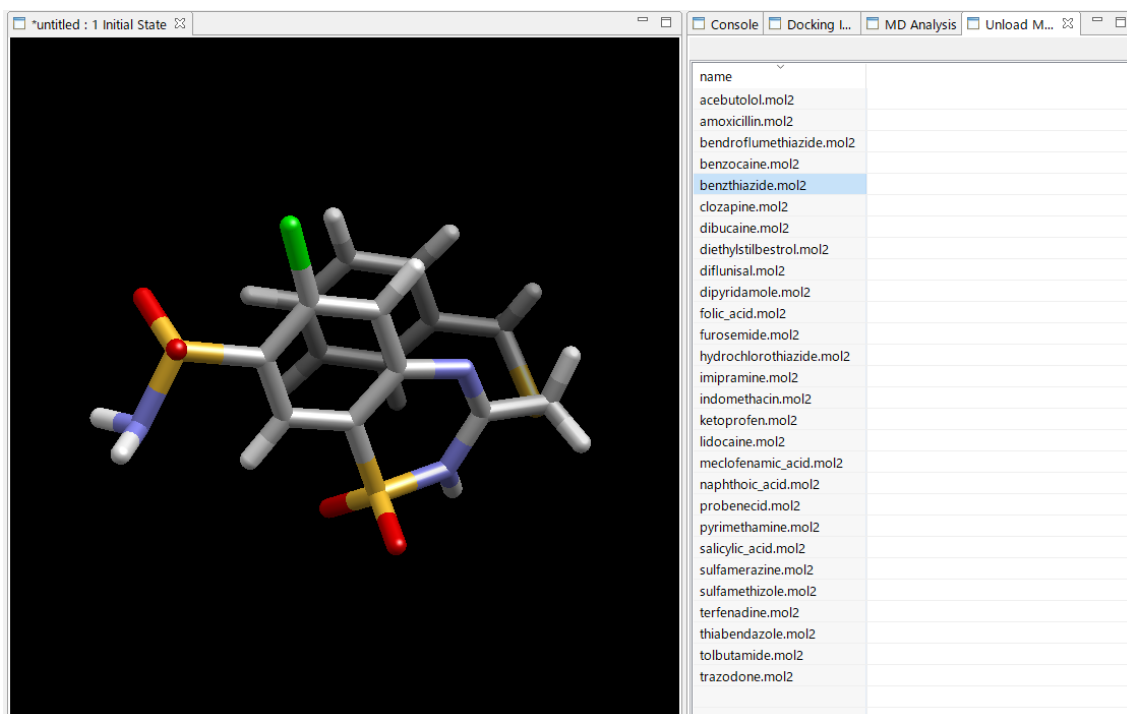
There are four file formats that can be entered: PDB / Sybyl Mol2 / MDL SDF / MDL MOL.

file	File extension
PDB	. pdb
Sybyl Mol2	.mol2
MDL SDF	. sdf
MDL MOL	.mol

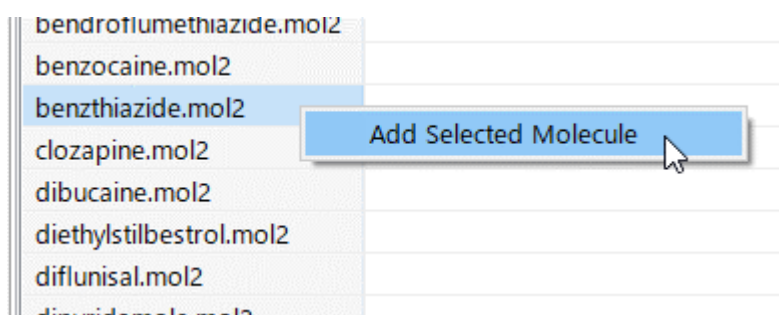
- The file extension must be as shown in the table. If the extensions are different, change the extension before entering them.

Example of loading MolDesk Basic -> sample -> mol2 -> multi28.mol2.

This file contains only 28 molecules, but reads it as a list as follows:



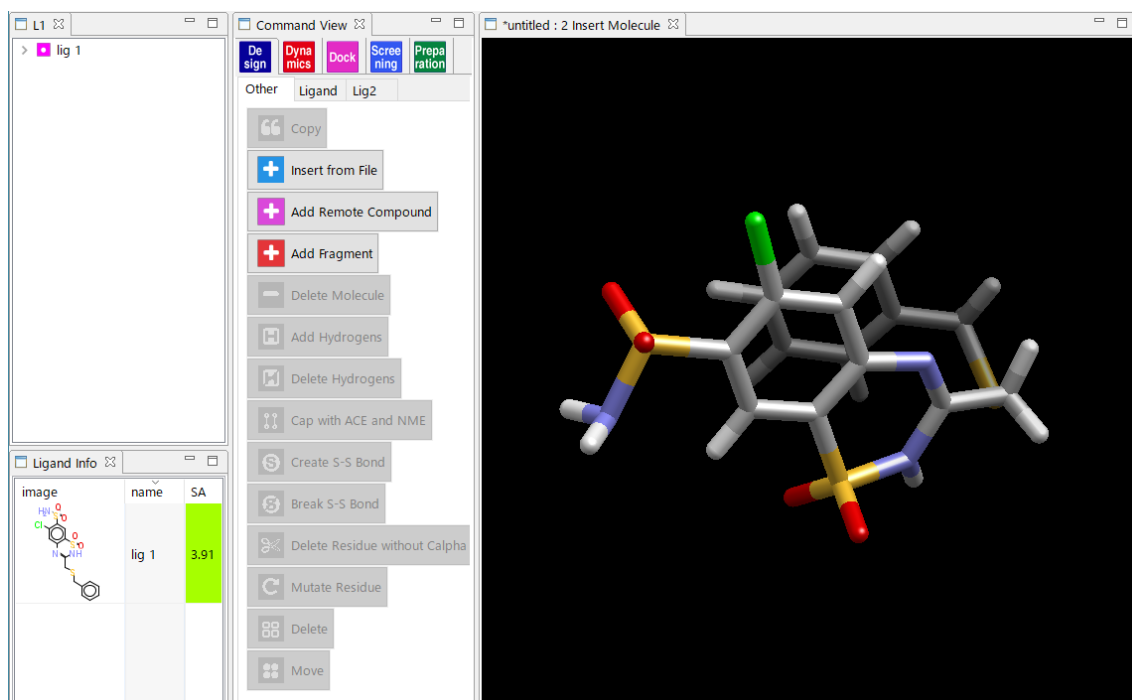
Click the name of the molecule in the list to display the molecule in 3D, as shown above.



Right-click on the molecule name in the list to display the [Add Selected Molecule] menu. If you click this, you can import the molecule as a project, and the molecule you imported will be added to the tree display.

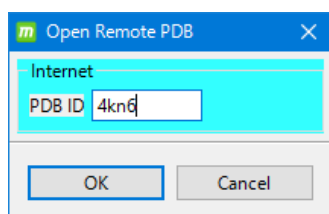
This is the first time a project is created.

* Before importing molecules in the [Add Selected Molecule] menu, you can only view the molecules and not generate a project.



1.2.3. [File] - [Open Remote mmCIF / PDB]

Download mmCIF and PDB files via the internet. Import the mmCIF file and create a new project.



Example: Load PDBID 4kn6

1.2.4. [File] - [Open Project]

It is in the project saved by [File] - [Save As] in the past,
or in the directory set in the Default Project Directory of [Help]-[Preference]-[8. Other].

MoldeskProject00000

MoldeskProject00001






MoldeskProject00002

. . .

Open.

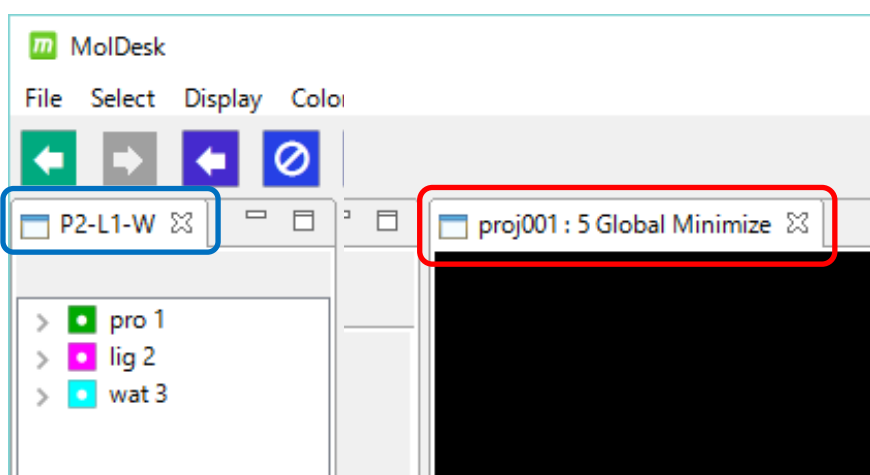
Select the existing project folder (including the original and work folders directly under it) and click "OK".

The tab name on the tree display screen (blue frame "P2-L1-W" in the figure below) indicates the number of proteins and compounds. P is a protein chain, L is a compound, W is water of crystallization, and M is a metal / ion.

On the tree display screen,  is a protein,  is a compound,  is water,  is glycan and  is a metal / ion.

The last command you operated can be confirmed from the tab name on the 3D screen (red frame "proj001: 5 Global Minimize" in the figure below).

The tab name indicates **[project name: history number execution command name]**.



The executed command can be re-executed by clicking



[UNDO] and



[REDO].

1.3. Save project

There are three menus for saving projects:

[File] - [Save As]

[File] - [Copy Project]

[File] - [Export]

Let's talk about this [Save As].

1.3.1. [File] - [Save As]

Save the system you are displaying with the project name. The history of the command is also saved.

Run [File] -[Save As], select [Create New Folder] in the [Make PROJECT directory] dialog, and enter the folder name. This folder name will be the new project name.

In the folder you created, all data (including command history) of the system being displayed is saved.

Please note that if you specify an existing folder without performing [Create new folder], the following folders and files will be output directly under the folder.

original folder

work folder

cif and pdb files downloaded via internet

* If you are interested in the details of the files stored in the project, please refer to the MolDesk Basic Manual.

1.4. 3D display of molecular structure

1.4.1. Mouse operation

On the 3D screen, you can control the rotation and movement of molecules with the mouse.

behavior	Mouse operation
X-axis (left-right axis) rotation Y-axis (vertical axis) rotation	Left drag
Z-axis (depth direction axis) rotation	Shift + Right Drag (Left/Right)
Move in the X-axis (left and right) direction Move in the Y-axis (up and down) direction	Right drag
Move in the Z-axis (depth) direction (scale)	Shift + Left Drag Or wheel rotation

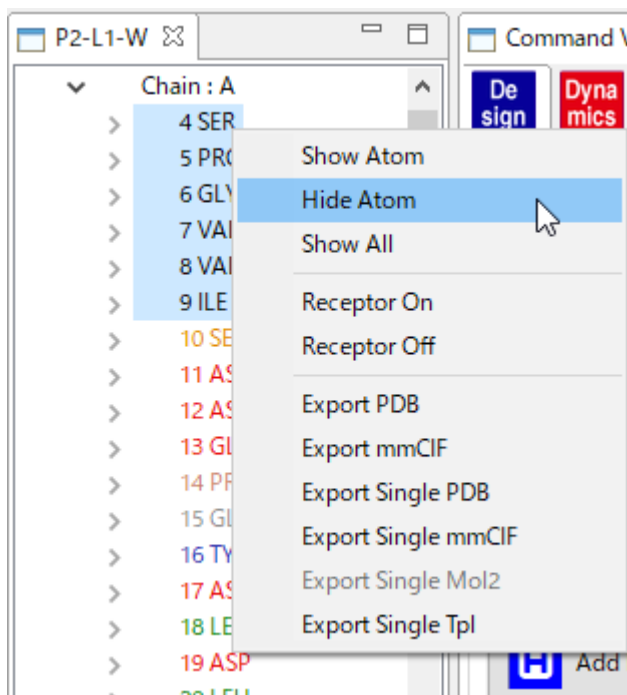
※ For MAC, left-click = click

Right-click =[Command] + Click

1.4.2. Selection of molecules, chains, afterts, and atoms

The selection of molecules, chains, rests, and atoms is done with the mouse, but the operation is different onthe 3D screen and the tree display screen.

operation	3D screen	Tree display screen
Multiple selection	Ctrl + Click	Ctrl + Click
Continuous multiple selection	—	Shift + Click
Base selection	Double-click	Click the base name
Chain selection	Triple Click	Click the chain name
Molecular selection	—	Click on the name of the molecule

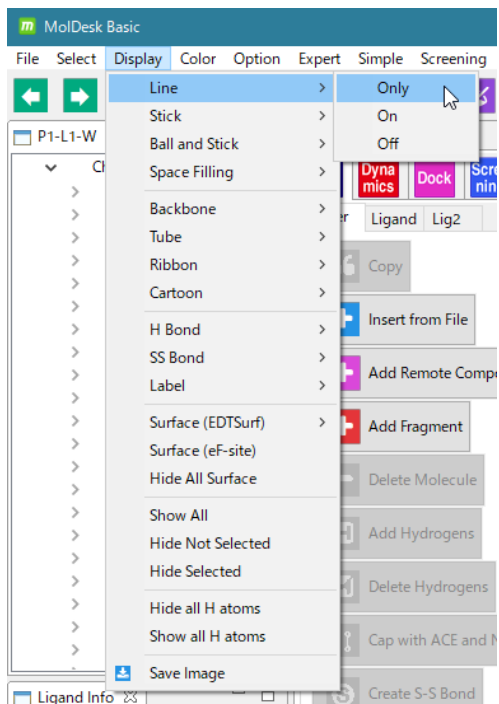


Multiple molecules, chains, afterts, and atoms are grouped together. It is possible to show and hide.

Select multiple items on the tree display screen, right-click and select [Show Atom] or [Hide Atom].

Unhide with Show All to show everything.

1.4.3. Select display model



You can change the display model to Line, Stick, etc. by selecting the molecule / chain / residue / atom and selecting the model from the [Display] menu.

The meanings of the options are as follows.

[Only] : Only this display model is displayed in 3D.

[On] : Overwrites this display model on other display models.

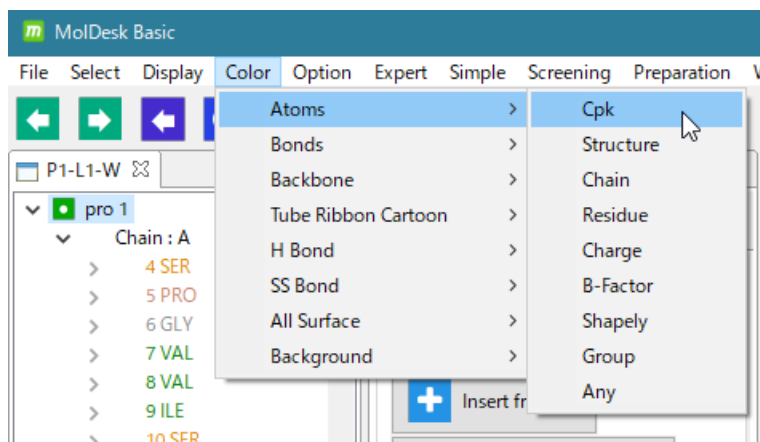
[Off] : Turns off this display model.

For more display models, visit MolDesk at:

<https://www.moldesk.com/moldesk-basic-commands/#Display>

1.4.4. How to color

You can change the color of molecules, chains, rests, and atoms.



Select a molecule, chain, residue, or atom, and then select a color from the [Color] menu to change the color.

You can also change the color and transparency of all molecular surfaces at the same time with [Color] - [All Surface].

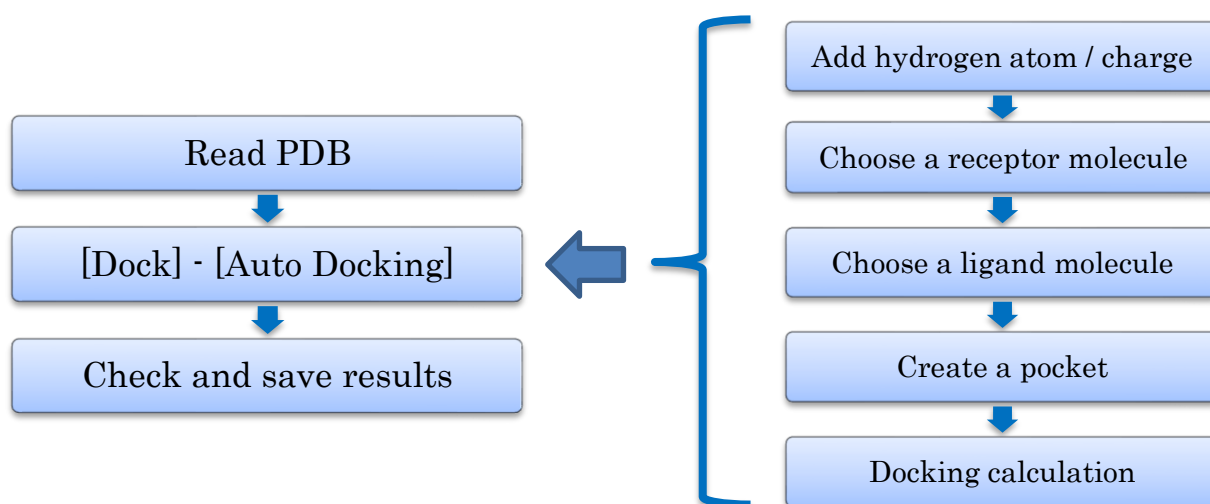
[Color] For more information about each item in the menu, visit the following sites in MolDesk:

<https://www.moldesk.com/moldesk-basic-commands/#Color>

1.5. Docking

Here is an example of performing the simplest docking calculation using fully automatic docking.

The procedure is as follows.



※ In addition to proteins, docking to nucleic acid molecules is available in ver. 1.1.89 and later.. You can specify a protein or a nucleic acid molecule as a receptor.

A pocket (probe point) must be generated before docking calculations can be performed. There are the following methods for pocket generation:

How pockets are generated:

1. How to make the coordinates of a molecule the probe point of a pocket itself
Use when you know the correct structure of the join state. The regand molecule is the probe point.
Select a molecule other than a protein. Multiple selections allowed.
2. How to generate a pocket probe point on the surface of a molecule
Select a molecule containing a protein or nucleic acid molecule. Multiple selections are allowed.
The user can specify the position or the search can be done automatically.

To generate a pocket, you must select a molecule who creates the coordinates of the probe point (or the probe point on its surface).

After the pocket generation is finished, specify the molecules of the receptors and the molecules of the regando to be used in the docking calculation.

Multiple molecules of receptors can be selected from molecules containing proteins or nucleic acid molecules. The molecules of the ligand are one compound or glycan.

MolDesk allows you to specify and calculate exactly the receptor molecule group (must contain at least one protein or nucleic acid molecule) and the ligand molecule (one compound or glycan).

1.5.1. Load PDB files over the Internet

Refer to "1.2.3 [File]-[Open Remote mmCIF / PDB]" and read PDB ID 1m17 from the Internet as test data.

This protein is the EGFR tyrosine kinase domain, to which the molecule of the anticancer drug Erlotinib is added.

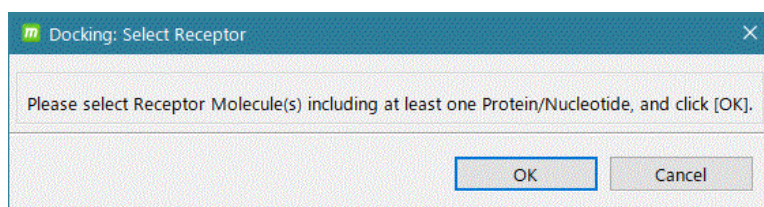
1.5.2. Fully automatic docking


Select  [Dock] -  [Auto Document].

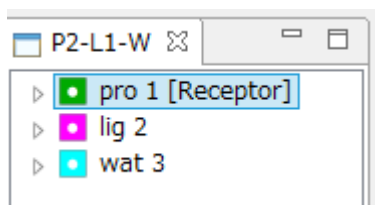
Initially, missing hydrogen atoms (in the dissociated state in water) will be automatically added to all molecules, and charges will be added to all compounds or glycans with Gasteiger. Molecules other than compounds or glycans will have charges added based on the force field selected in [Help] - [Preference] - [Molecule] - [tplgeneX].




1.5.3. Choosing receptor and regand molecules

When the charge addition is complete, a message dialog is displayed to encourage the selection of receptors.



In this example, select  pro1 on the tree view screen and click OK.

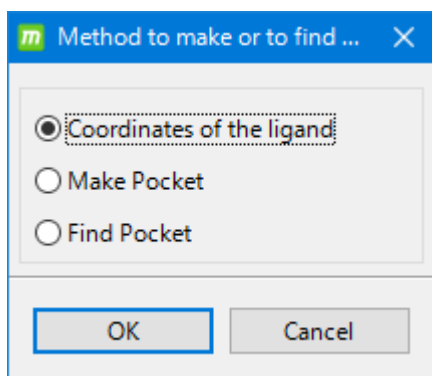


Since  pro1 has been recognized as a receptor, the notation of  pro1 changes to  pro1 [Receptor].

The receptor molecule must contain at least one protein or nucleic acid molecule. It can also contain compounds, glycans or metals.

- ✖ You can select a receptor molecule other than a protein or nucleic acid molecule, but make sure to leave a space in the pocket for the ligand to bind. Docking calculations are performed for the available space.

1.5.4. Create a pocket



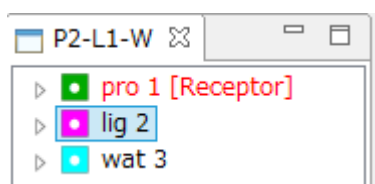
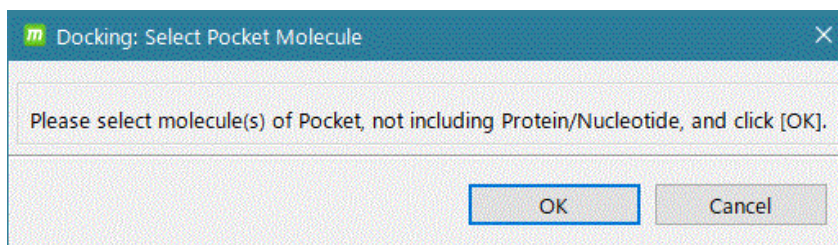
After specifying the receptor, a dialog for selecting the pocket generation method is displayed.


In this example, we know the correct structure, so select [Coordinates of the Ligand] and make the coordinates of the selected ligand itself the probe point of the pocket.

The items in the dialog for selecting a pocket generation method are described below.

item	explanation
[Coordinates of the ligand]	Makes the coordinates of the selected molecule the probe point of the pocket. You can select multiple molecules other than proteins or nucleic acid molecules and use them as probe points at once.
[Make Pocket]	Place the pocket sphere on the surface of the selected receptor to generate a pocket probe point inside the sphere.
[Find Pocket]	Pocket search is performed on the surface of the selected receptor to automatically generate multiple probe points in order of score.

A dialog box will appear to select a molecule (other than protein or nucleic acid molecule) to be the probe point of the pocket.




In this example, on the tree view screen, select  lig2 and click OK.

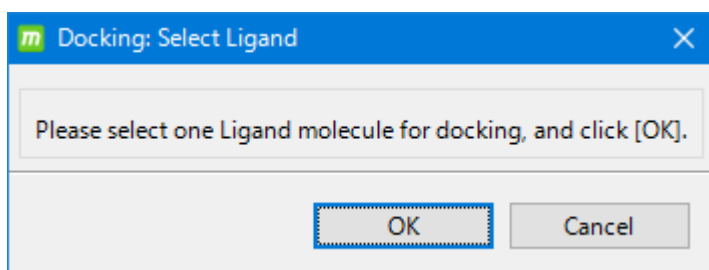
The atoms of the ligand molecule will be circled in red.


This indicates that all atoms of the regand molecule have become probe points in the pocket.



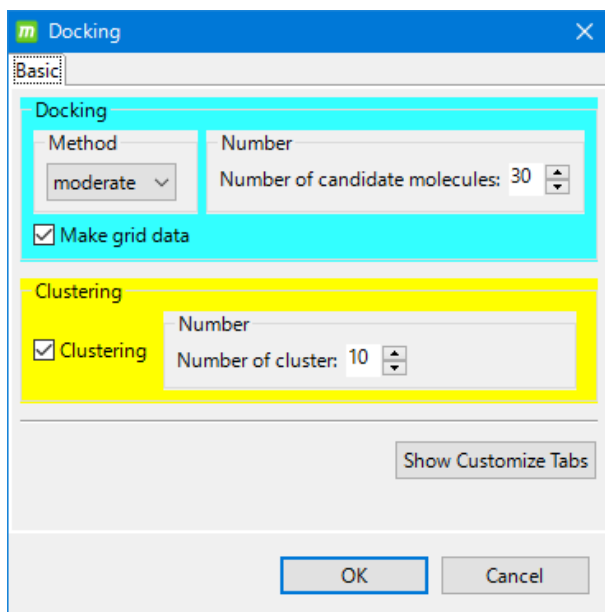
You can also see  point4 on the tree display screen that the probe point in the pocket has been added to the system.

A message dialog prompts you to select a regand.



In this example, select  lig2 on the tree view screen and click OK.

For the ligand, it is possible to specify a molecule different from the molecule used as the probe point of the pocket.



The docking calculation condition setting dialog is displayed.

In this example, leave the default conditions and click OK.

Click [Show Customize Tabs] to set detailed parameters for docking calculation.

The items in the docking calculation condition setting dialog are described below.

item		explanation
Docking	Method	fast fast and low accuracy Medium accuracy at moderate medium speed (default) precise high accuracy at low speed
	Number of candidate molecules	Number of outputs of candidate molecular structures
	Make grid data	Grid calculation Required for the first calculation, but can be omitted if the same receptor name and pocket are used repeatedly
Clustering	Clustering	Structural clustering
	Number of cluster	Make the regand atom the probe point of the pocket
Show Customize Tabs		Displays a tab for setting detailed parameters. ※ Please note that when this tab is displayed, some items on the [Basic] tab cannot be changed. (Cancel and re-execute to change)

1.5.5. Review results

When the docking calculation is completed, the Docking Info screen lists the compound (lig3) used in the docking calculation and the 10 molecular structures predicted by the docking calculation in descending order of score.

The values of the attributes of the molecular structure are as follows:

ΔG value (deltaG, free energy)

Score (score, docking score)

RMSD (value for the regand used to enter docking calculations)

image	SA	deltaG	score	RMSD
	4.62	-8.45	-3.4996	3.09
	4.62	-7.79	-3.286	2.19
	4.62	-7.85	-3.2882	4.53
	4.62	-6.11	-2.5939	5.41
	4.62	-6.86	-2.9077	1.63
	4.62	-6.7	-2.8133	8.81
	4.62	-7.86	-3.1996	9.8
	4.62	-7.14	-2.8879	8.8

Click the molecule on the Docking Info screen and click the $\uparrow\downarrow$ key to
Appears one at a time on the 3D screen.

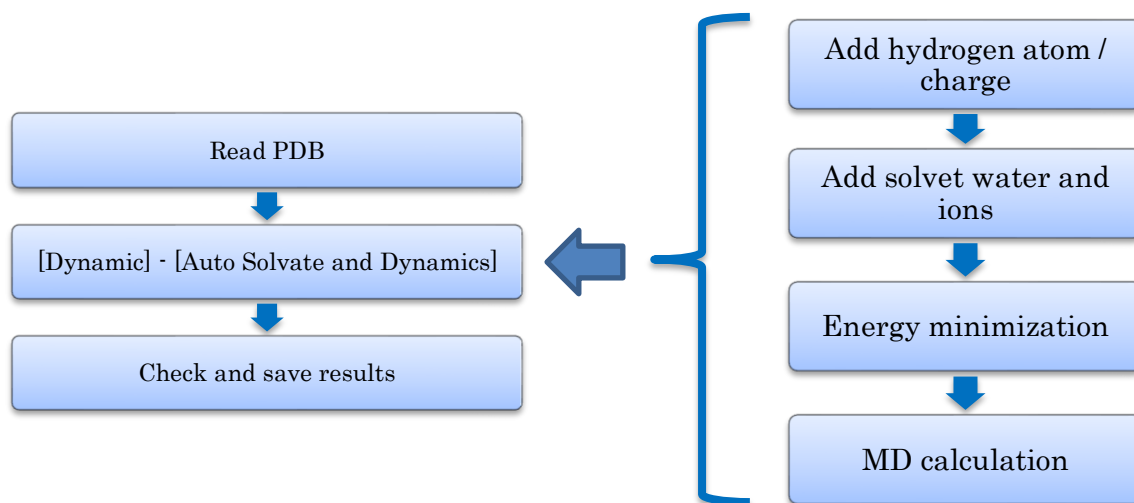
image	SA	deltaG	score	RMSD
	4.06	-8.23	-3.9681	0.88

You can add the candidate structure to the Ligand Info screen by selecting the candidate structure on the Docking Info screen (Ctrl + click for multiple selection), right-clicking, and selecting "Add Selected Docking Result".

1.6. MD calculation in water

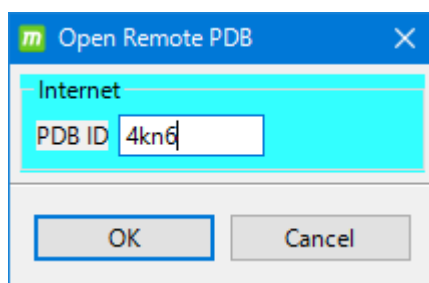
Provides an example of performing the simplest MD calculation with automated calculations.

The procedure is as follows.



1.6.1. Load mmCIF/PDB files over the Internet

Refer to "1.2.3 [File] - [Open Remote mmCIF / PDB]" and read PDB ID 4kn6 from the Internet as test data.



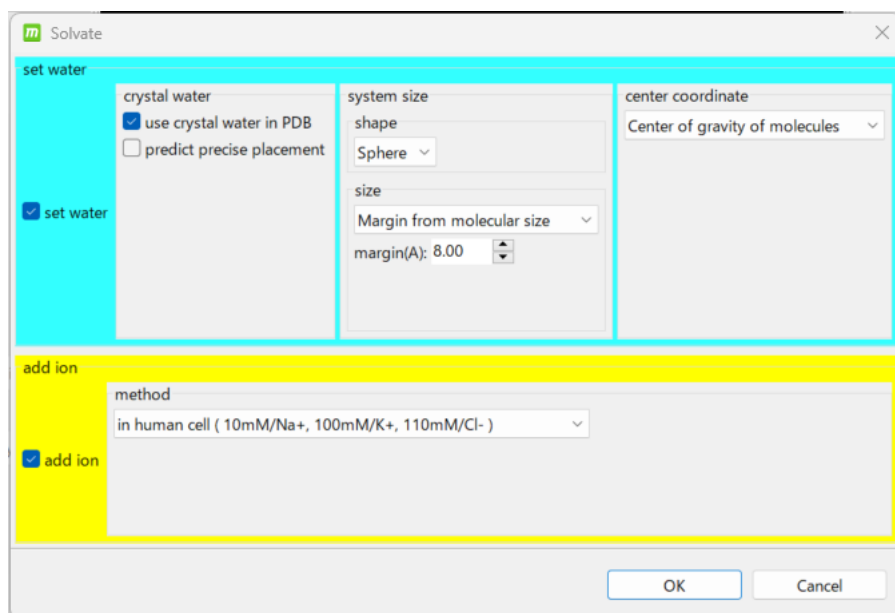
"4kn6" used in the example is a compound in which ribose-5'-1 phosphate is bound to HGPRT (hypoxanthine-guanine phosphoribosyl transferase), which is one of the purine-metabolizing enzymes, and favipiravir, a candidate for the treatment of Ebola fever. It is included.

1.6.2. Fully automatic MD calculation

Select  [Dynamics] -  [Auto Solvate and Dynamics]

The operations are performed in the following order:

- Missing hydrogen atoms are added to all molecules (default is the dissociated state in water).
- All compounds or glycans are charged with Gasteiger.
- Molecules other than compounds or glycans add charge based on the force field selected in [Help] - [Preference] - [Molecule] - [tplgeneX].
- A dialog for selecting the water solvent and ion addition method is displayed.



This example runs with the default settings.

About aero solvents,

- The center of gravity of the system is the center of solvent, and the size is a sphere of 8Å from the boundary of the soe blend.

About ions,

- Ion concentrations in human cells, adding Na⁺, K⁺ and Cl⁻.

The description of the setting items is as follows.

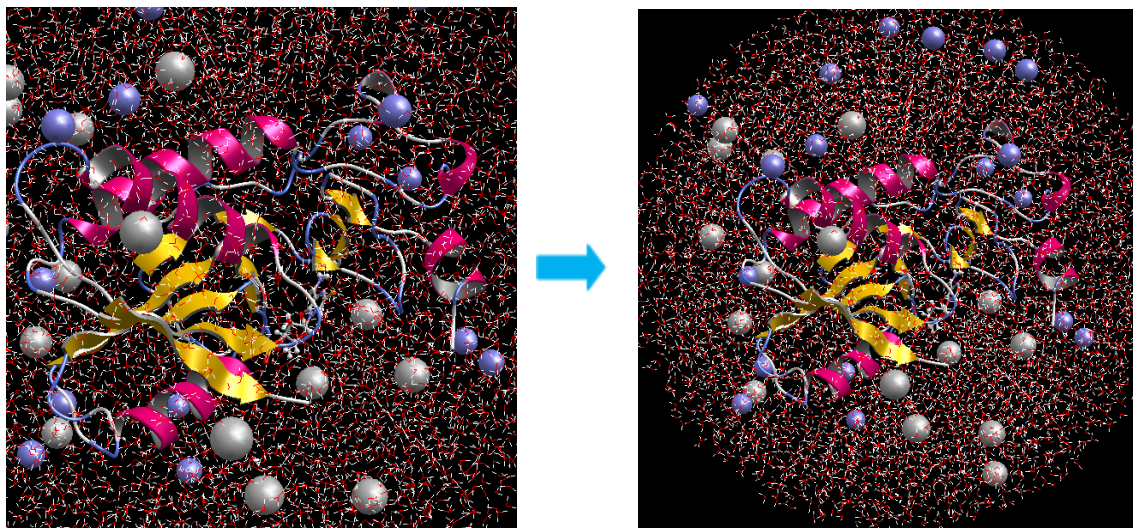
Select whether or not to set water (addition of water solvent) with the check box.

crystal water	use crystal water in PDB	Include PDB water of crystallization in the system
	predict precise placement	Produces accurate water of crystallization
shape size	Sphere	margin (Distance from solute Å)
		Radius Å
	Cube	margin (Distance from solute Å)
		x,y,z (Length directions Å)
center coordinate		Center of gravity of solute
		Setting of the central coordinate (User-specified coordinates
		Specify the central atom with a mouse click)

Select whether to add ion (Na⁺, K⁺ and Cl⁻ ion addition) or not with the check box.

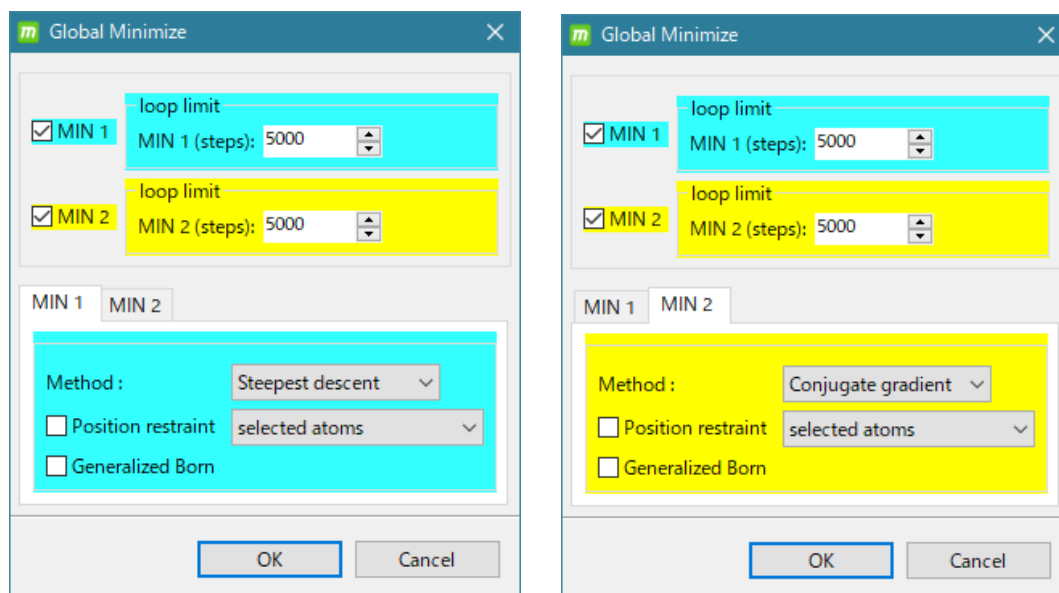
method	direct input of number of ions
	minimum number of ions to neutralization
	saline solution (0.00277/Na ⁺ , 0.00006/K ⁺ , 0.00283/Cl ⁻)
	in human blood plasma (154mM/Na ⁺ , 4mM/K ⁺ , 158mM/Cl ⁻)
	in human cell (10mM/Na ⁺ , 100mM/K ⁺ , 110mM/Cl ⁻)
	in bacteria (10mM/Na ⁺ , 200mM/K ⁺ , 210mM/Cl ⁻)
	in densities of Na ⁺ , K ⁺ and Cl ⁻ in mM
	in % densities of Na ⁺ , K ⁺ and Cl ⁻ (100mM=0.18015%)

Specify the method of adding a water solvent and ions, and click"OK"to add solvent water and ions.



to display all systems in the center of the screen.

A condition setting dialog for energy-to-the-ion calculations is displayed.



In this example, the default is used. The meaning is as follows.

- Energy minimization calculation by cosgene is performed twice in succession.
- The first time is the steepest descent method, 5000 steps, no position constraint, no Generalized Born method
- The second time is the conjugate gradient method, 5000 steps, no position constraint, no Generalized Born method.

The explanation of the setting items is as follows.

The energy minimization calculation can be performed twice in a row (uncheck MIN 1 or MIN 2 if you do not want to run it continuously).

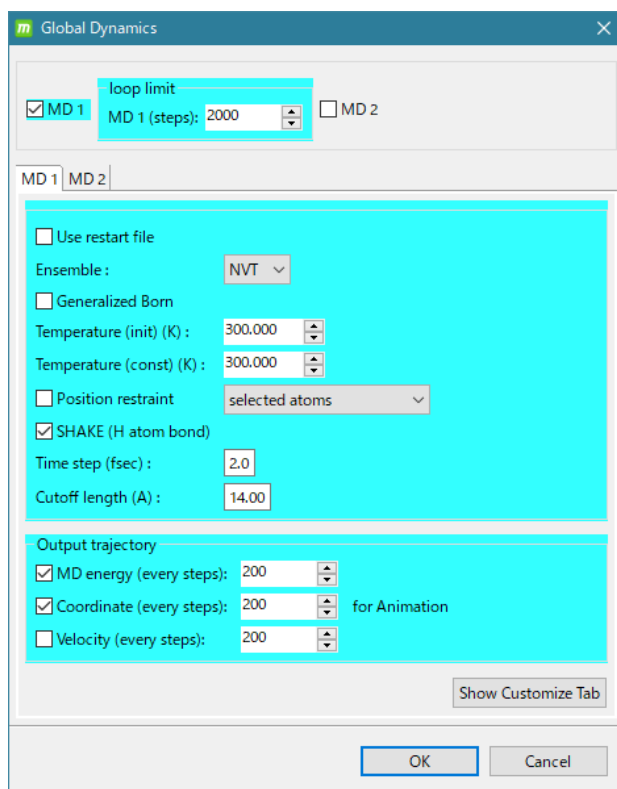
Set MIN 1 for the first run and MIN 2 for the second run.

The explanation of the setting items is as follows.

loop limit (Number of time steps) Default 5000	
Method	Steepest descent
	Conjugate gradient
Position restraint	Selected atoms (Position constrains the atom (group) specified by the user with the mouse)
	Main chain (proteins & DNA/RNA)
	Heavy atoms (proteins & DNA/RNA)
Calculated by the Generalized Born method	

When the energy minimization calculation is completed, the MD calculation condition setting dialog is displayed.

In this example, the default settings are used.



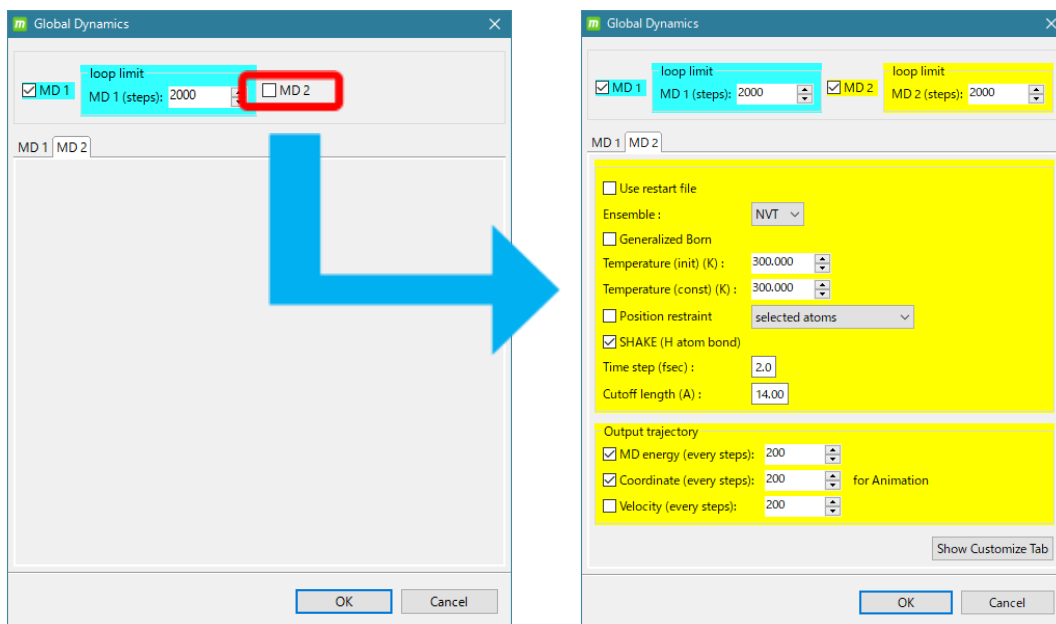
- Execute only once
- The number of steps is 2000
- NVT ensemble
- No Generalized Born method
- Initial temperature 300K
- 300K temperature constant
- No position constraint
- SHAKE calculation
- Time step is 2.0 fsec
- Cutoff radius is 14.0Å
- There is energy file output (Every 200 steps)
- Trajectory file output available (Every 200 steps)
- Long-distance Coulomb force calculation by FMM method (Because the shape of the solvent water is a sphere)

- In MolDesk, the force field used by cosgene is set to AMBER GAFF2 for compounds or glycans and AMBER ff99SB for others (such as proteins).
(The force field can be changed with [Help] - [Settings] - [Molecules] - [tplgeneX].)

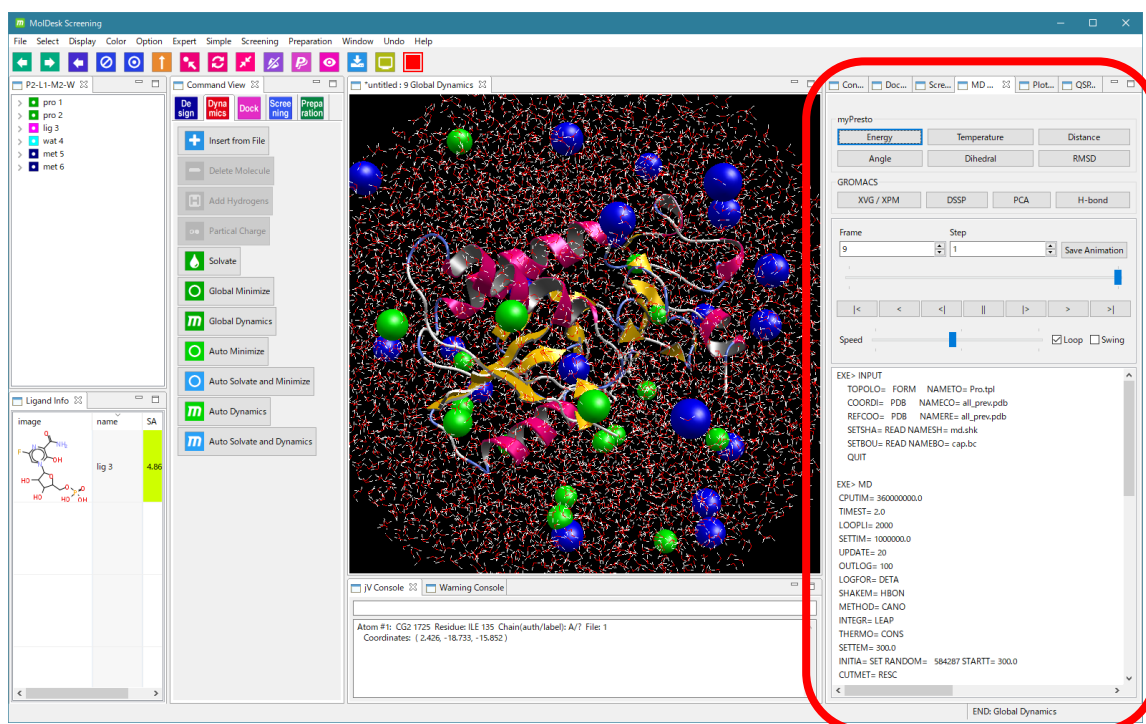
The explanation of the setting items is as follows.

Loop limit (number of time steps) Default 2000	
Use restart file Default : OFF	
Ensemble	NVT (Canonical ensemble)
	NPT (NPT ensemble)
	NVE (Microcanonical ensemble)
Calculated by the Generalized Born method	
Temperature (init)	Initial temperature K
Temperature (const)	Constant temperature K (NVE ensemble is not set)
Position restraint	Selected atoms (Position constrains the atom (group) specified by the user with the mouse)
	Main chain (proteins & DNA/RNA)
	Heavy atoms (proteins & DNA/RNA)
SHAKE Fixing hydrogen atom bonds	
Time step (fsec)	
Cutoff length (Å)	
Output trajectory	MD energy (interval between output steps for each energy value)
	Coordinate (interval between output steps of coordinates)
	Velocity (Interval between x, y, z speed output steps)

MD calculations can be performed twice in a row. Set the settings for the first run in MD 1 and the second run in MD 2.



When the MD calculation is finished, the button on the command button screen becomes executable.



Refer to "1.3 Saving the project" and save the project with a name of your choice.

1.6.3. Review MD calculation results

MD Analysis screen (red frame above) myPresto

Click the **Energy** button to display a time-varying graph of each energy.

Click the **Temperature** button to display the temperature change graph over time. You can display a two-dimensional graph in which the video and the time axis are linked. Also, by clicking the 2D graph, you can see the video (structure) of the time of the click point.

Click the **Distance** button and then select two atoms with the mouse to display a time-varying graph of the selected two-atom distance. You can display a two-dimensional graph in which the video and the time axis are linked. Also, by clicking the 2D graph, you can see the video (structure) of the time of the click point.

Click the **Angle** button and then select 3 atoms with the mouse to display a time-varying graph of the angles formed by the selected 3 atoms. You can display a two-dimensional graph in which the video and the time axis are linked. Also, by clicking the 2D graph, you can see the video (structure) of the time of the click point.

Click the **Dihedral** button, then select 4 atoms with the mouse, and in the order you selected, 2 planes between the planes of the 1st and 2nd atoms and the planes of the 3rd and 4th atoms. Display the time change graph of the corner. You can display a two-dimensional graph in which the video and the time axis are linked. Also, by clicking the 2D graph, you can see the video (structure) of the time of the click point.

After clicking the **RMSD** button, select one molecule on the tree display screen with the mouse to display the RMSD time change graph with respect to the initial coordinates of the selected molecule. You can display a two-dimensional graph in which the video and the time axis are linked. Also, by clicking the 2D graph, you can see the video (structure) of the time of the click point.

By working with the Animation controller on the MD Analysis screen, the 3D screen animates the time change (trajectory) of the atomic movement.

By clicking the [Save Animation] button, you can output the file to an animated GIF as it is displayed. At that time, you can also set the frame time interval.

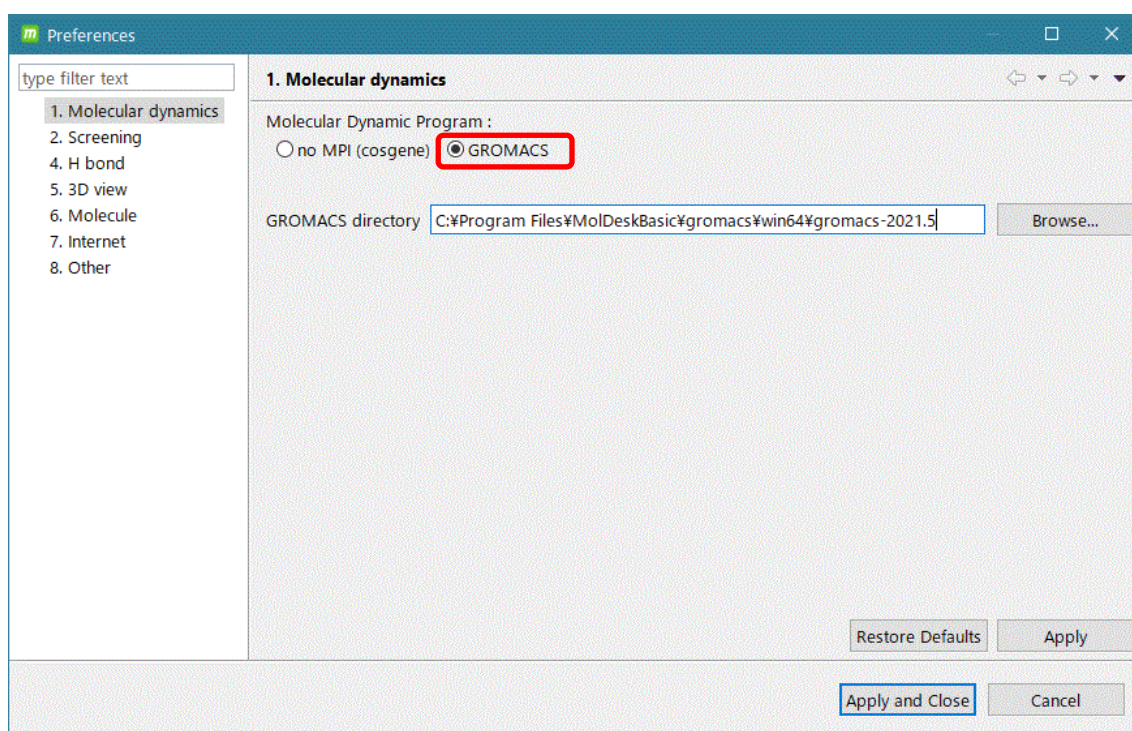
Click the [Save PDB] button to save each snapshot of the trajectory of the entire system to a PDB file.

The MD Analysis screen displays the contents of the input file for MD programs (such as cosgene).

1.7. GROMACS : MD calculation Trajectory Analysis

1.7.1. [Preference] - [Molecular dynamics] settings

On the [Help]-[Preference]-[Molecular dynamics] screen, select [GROMACS] under [Molecular Dynamic Program :] to run the GROMACS energy minimization calculations and MD calculations by GROMACS.



Here, except for Windows 10 and Windows 11, Linux and MAC, the user must install GROMACS and set the [GROMACS directory] of the installed GROAMCS. Windows 10 and Windows 11 do not require this setting since the GROMACS executable program has been implemented beforehand.

The [GROMACS directory] should be set to the directory where **share** and **bin** exist.

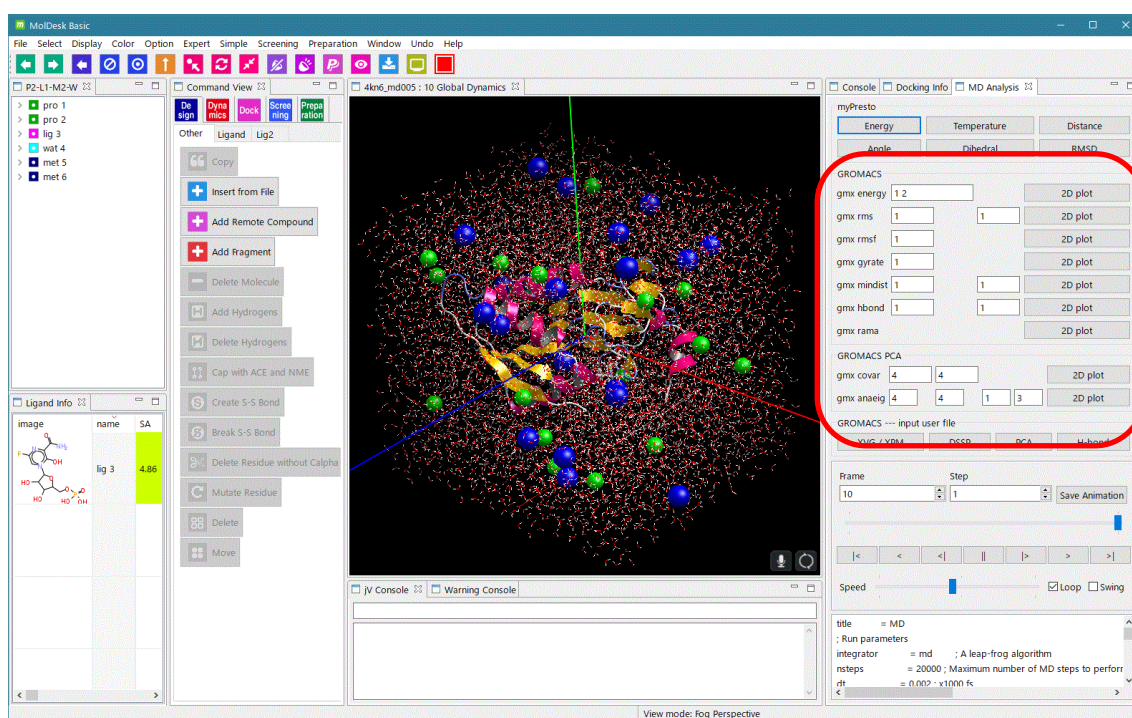
※In the current version, GROMACS is executed in **bin/gmx** without specifying the number of parallels.

If **bin/gmx** does not exist in the installation directory, GROMACS cannot be executed.

The parallel number of OpenMP and thread MPI depends on the automatic parallel number specification function of GROMACS. MPI is not used.

1.7.2. Trajectory Analysis

Perform the following trajectory analysis to display graphs with time axis linked to the video.



General

- (1) gm energy
- (2) gm rms
- (3) gm rmsf
- (4) gm gyrate
- (5) gm mindist
- (6) gm hbond
- (7) gm rama

PCA relationship

- (8) gm covar

(9) gmx anaeig

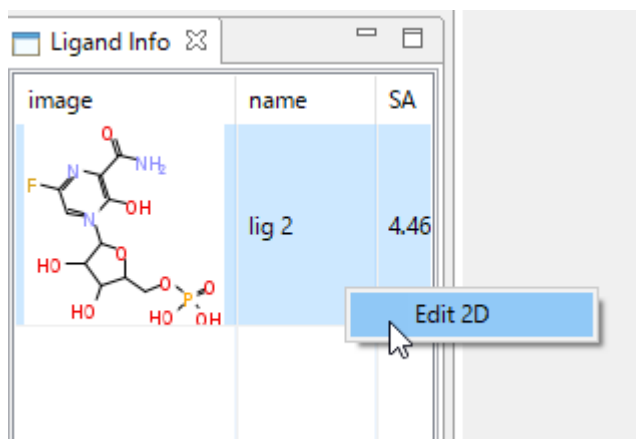
* Please refer to the "MolDesk Basic Manual" for details on usage.

* For details on trajectory analysis with GROAMCS, refer to the GROMACS manual.

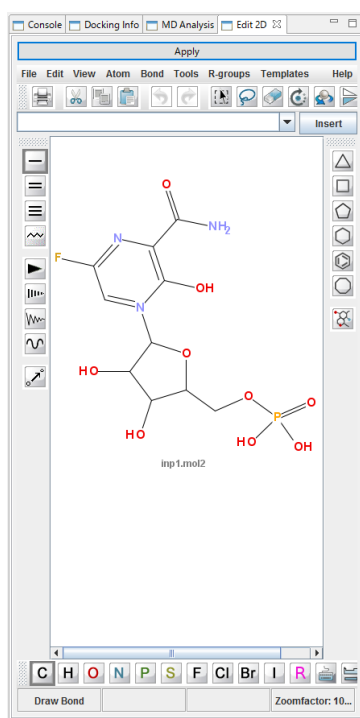
1.8. Compound 2D Editor

Right-clicking on a compound or glycan on the Ligand Info screen will bring up the Edit 2D menu. Click this to enter the selected compound or glycan and launch the 2D editor JChemPaint. The version is 3.3-1210.

1.8.1. Start JChemPaint



The 2D editor JChemPaint starts with the selected compound or glycan as the input.



✖ When the screen is small, you can use the tab with the mouse to drag it outside the MolDesk screen to take out the screen and make the screen larger.

After editing, click the [Apply] button at the top of the menu to make the edited molecule three-dimensional and import it into MolDesk.

For information on how to use JChemPaint, refer to the JChemPaint Help menu.